ASCO　2011の話題

(1)　PARP　阻害剤の　最新情報

(2)　乳房温存術後の　領域リンパ節照射

(3)　転移性乳癌に対するゼローダ「持続」対「間欠」投与

(4)　exemestaneによる乳癌予防研究

PARP 阻害剤理解のために　①

DNAダメージ

通常の細胞分裂でも起きるし紫外線、放射線、抗がん剤治療などでも起きる

PARP　：　poly(ADP-ribose) polymerase

ダメージを受けたDNAを修復する酵素（核酸切り出し）

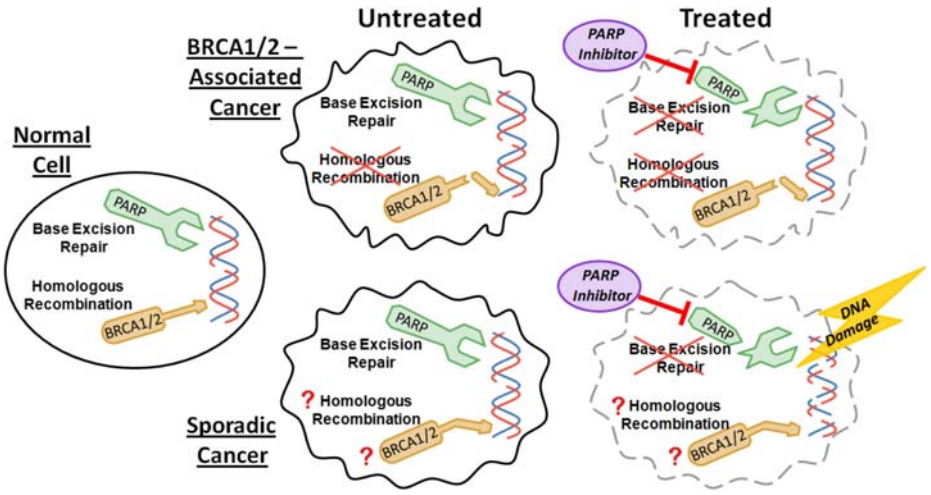
傷んだDNA を修復するもう一つの酵素BRCA1/2

BRCA1/2（breast cancer susceptibility gene)とは、がん抑制遺伝子の一種であり、その変異により遺伝子不安定性を生じ、最終的に乳癌を引き起こす。

BRCA1/2はDNA損傷に伴って活性化されDNA修復蛋白と協調してDNA損傷を修復する（相同組み換え）

PARPとBRCA1、両方が働かないとどうなるか?

PARP 阻害剤理解のために ②



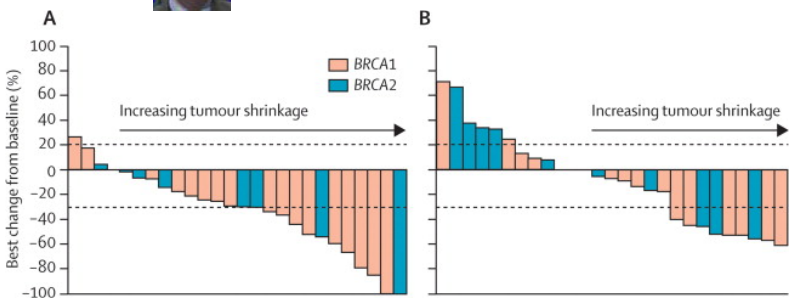
開発中のPARP阻害剤

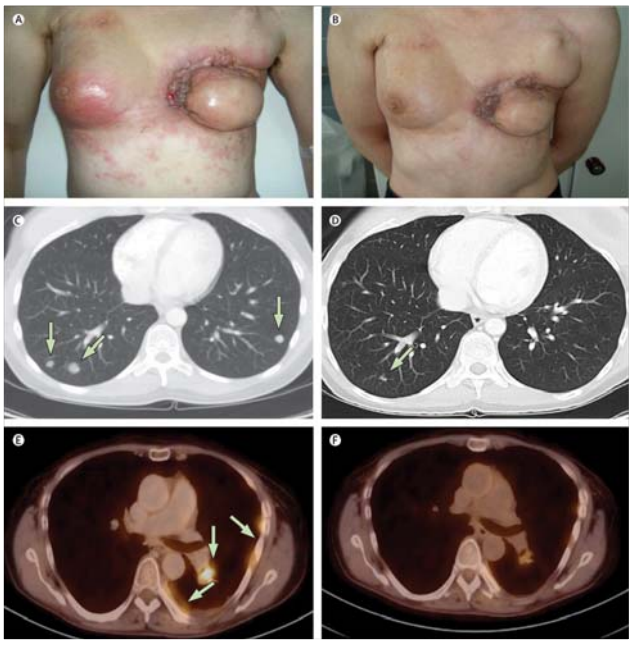
薬剤	開発企業	投与経路	
KU59436 AZD2281 Olaparib	AstraZeneca/ Kudos	経口	phase II
AG014699	Pfizer	静注・経口	
Veliparib ABT888	Abott	経口	phase I
Iniparib BSI-201	BiPar/ Sanofi-Aventis	静注	phase III
INO-1001	Inotek	静注	
CEP-9722	Cephalon	経口	
MK4827	Merck & Co	経口	
E7016	Eisai	経口	

Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial

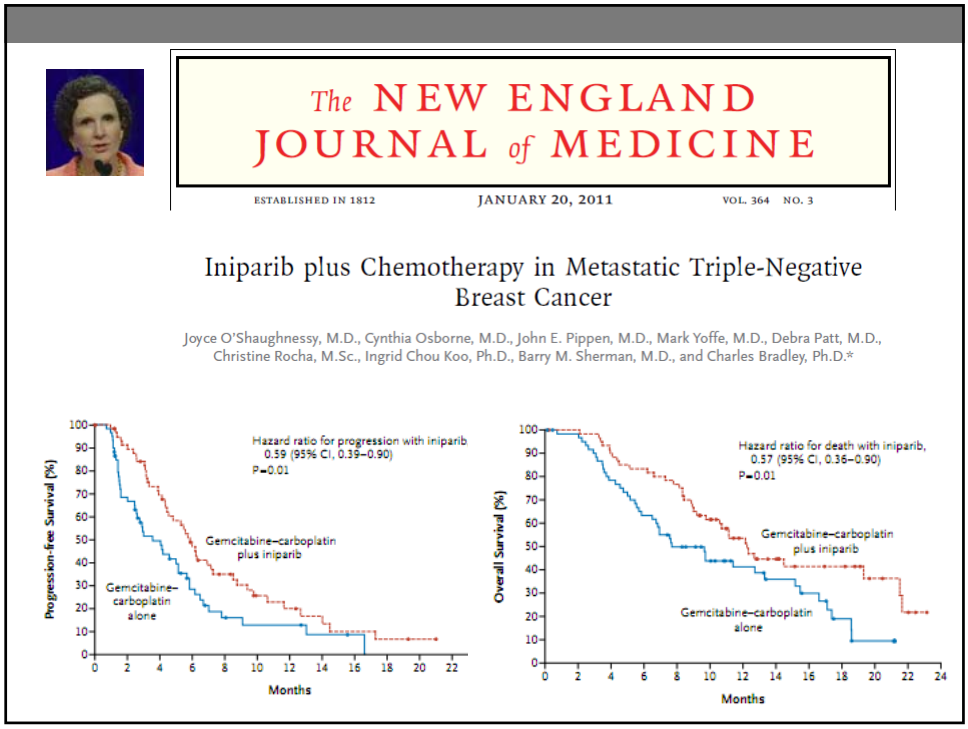
Andrew Tutt, Mark Robson, Judy E Garber, Susan M Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, Banu Arun, Niklas Loman, Rita K Schmutzler, Andrew Wardley, Gillian Mitchell, Helena Earl, Mark Wickens, James Carmichael

The Lancet 2010; 376:235-244





The Lancet 2010; 376:235-244

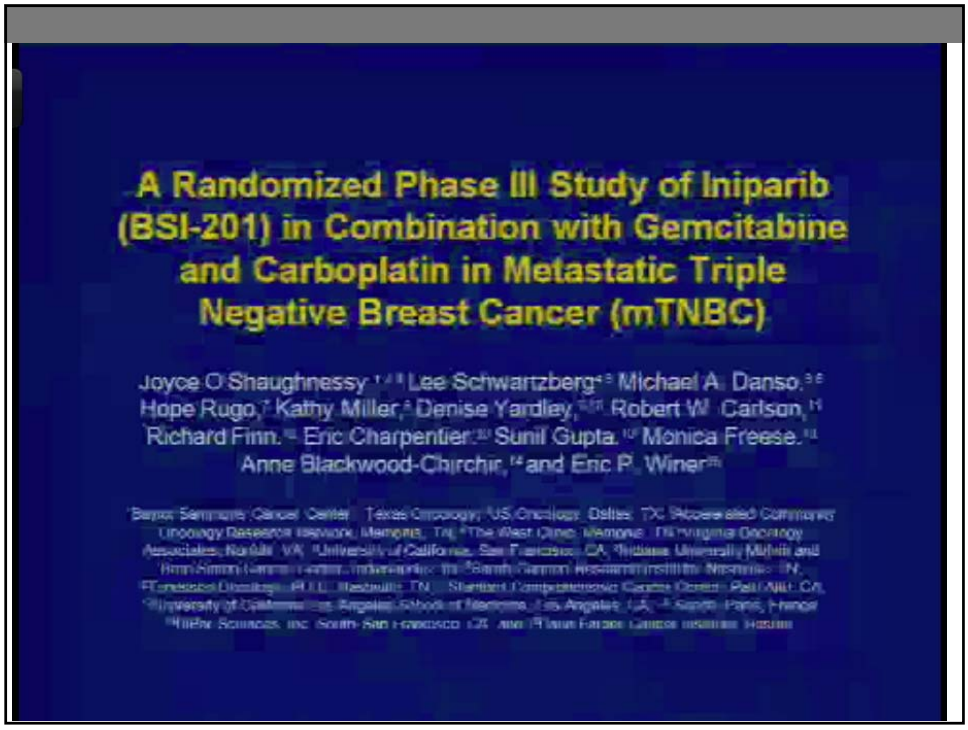


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 20, 2011 VOL. 364 NO. 3

Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.*



A Randomized Phase III Study of Iniparib (BSI-201) in Combination with Gemcitabine and Carboplatin in Metastatic Triple Negative Breast Cancer (mTNBC)

Joyce O'Shaughnessy, Lee Schwartzberg, Michael A. Danso, Hope Rugo, Kathy Miller, Denise Yardley, Robert W. Carlson, Richard Finn, Eric Charpentier, Sunil Gupta, Monica Freese, Anne Blackwood-Chirchir, and Eric P. Winer

Metastatic Triple Negative Breast Cancer (mTNBC)

- 15% of breast cancers; clinically defined as ER-negative, PR-negative and HER2- non-overexpressing
- Heterogeneous disease with generally virulent natural history
- Shares gene expression profiles with basal-like, claudin-low, and other molecular subtypes
- No clinical implications of molecular subtypes at present

Lin NU et al. Cancer. 2008;113:2638-45; Rody A et al. Breast. 2007; 16:235-49; Kassam F et al. Clin Breast Cancer. 2009; 9:29-33; Lill and Russell CA. Oncology. 2004; 18:12; Lueach D et al. Clin Breast Cancer. 2008; 8:178; Hoelak K et al. Cancer Res. 2010;70:7970-7980.

Iniparib* (BSI-201)

A novel, investigational, anti-cancer agent

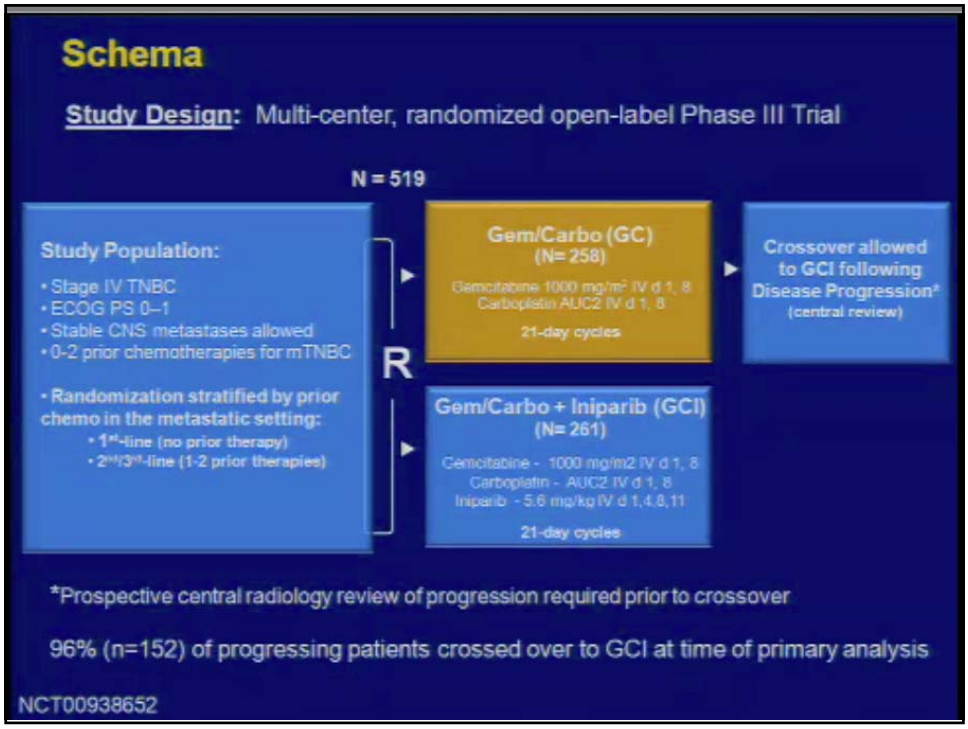
- In triple negative breast cancer cell lines[1-4]:
  - Induces cell cycle arrest in the G2/M phase
  - Induces double strand DNA damage γ–H2AX foci but does not inhibit PARP 1 and 2 at physiologic drug concentrations
  - Potentiates cell-cycle arrest induced by DNA damaging agents, including platinum and gemcitabine
- Physiologic targets of iniparib and its metabolites are under investigation

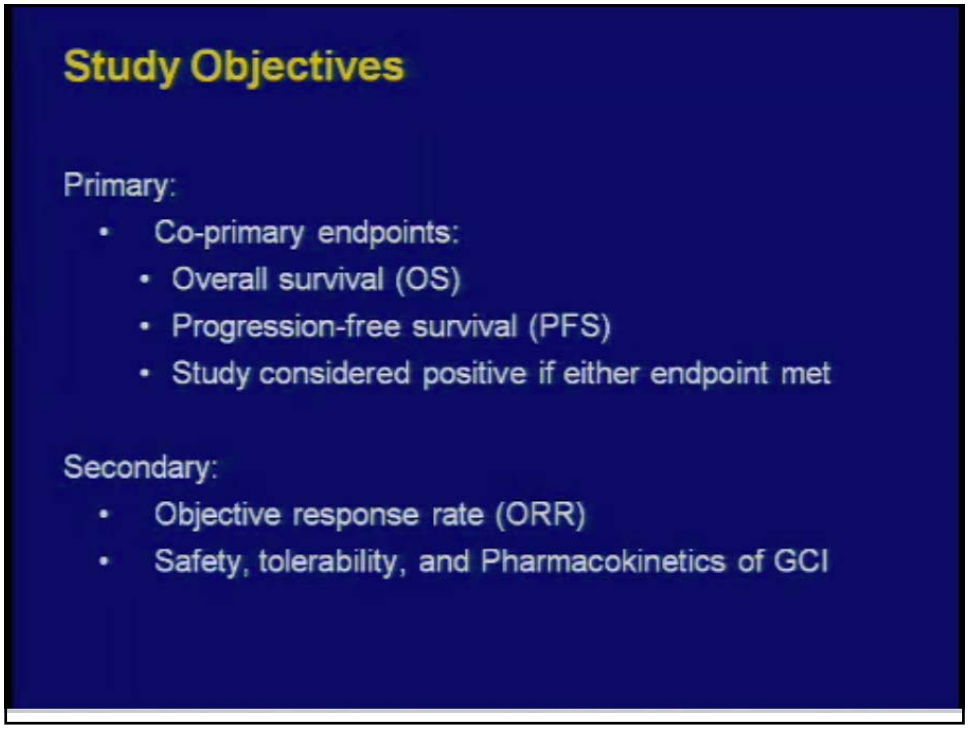
Clinical Data:

- In a randomized phase 2 study, addition of iniparib to gemcitabine/carboplatin improved CBR, ORR, PFS and OS in patients with mTNBC[5]
- No potentiation of chemotherapy-related toxicities when iniparib is combined with gemcitabine/carboplatin

*Iniparib is the United States Adopted Name (USAN) for the investigational agent BSI-201.

1. Ostrovskaya V, et al. SABCS 2010, San Antonio, TX. Poster P5-06-09; 2. Ostrovskaya V, et al. AACR 2009, Denver, CO. Abstract 5552; 3. Ostrovskaya V, et al. AACR 2011, Orlando, FL. Abstract LB-001; 4. Ji et al. AACR 2011, Orlando, FL. Abstract 4524; 5. O'Shaughnessy J, et al. N Engl J Med 2011; 364:205-214.


Schema
Study Design: Multi-center, randomized open-label Phase III Trial
N = 519
Study Population:
• Stage IV TNBC
• ECOG PS 0–1
• Stable CNS metastases allowed
• 0-2 prior chemotherapies for mTNBC
• Randomization stratified by prior chemo in the metastatic setting:
• 1st-line (no prior therapy)
• 2nd/3rd-line (1-2 prior therapies)
R
Gem/Carbo (GC)
(N= 258)
Gemcitabine 1000 mg/m2 IV d 1, 8
Carboplatin AUC2 IV d 1, 8
21-day cycles
Gem/Carbo + Iniparib (GCI)
(N= 261)
Gemcitabine - 1000 mg/m2 IV d 1, 8
Carboplatin - AUC2 IV d 1, 8
Iniparib - 5.6 mg/kg IV d 1,4,8,11
21-day cycles
Crossover allowed to GCI following Disease Progression*
(central review)
*Prospective central radiology review of progression required prior to crossover
96% (n=152) of progressing patients crossed over to GCI at time of primary analysis
NCT00938652


Study Objectives
Primary:
• Co-primary endpoints:
• Overall survival (OS)
• Progression-free survival (PFS)
• Study considered positive if either endpoint met
Secondary:
• Objective response rate (ORR)
• Safety, tolerability, and Pharmacokinetics of GCI

Statistical Considerations

Type-I error adjustment for co-primary endpoints
- Total alpha level = 0.05 split: 0.04 for OS and 0.01 for PFS

Planned sample size and hypothesis:
- Total number of planned patients: 420
- OS: HR = 0.66, power = 90%, alpha = 0.04 (2-sided)
  - Total 260 deaths
- PFS: HR = 0.65, power = 90%, alpha = 0.01 (2-sided)
  - Total 322 PFS events

Efficacy analyses:

ITT- population based on treatment group assigned at randomization

N = 519 (over enrolled due to very rapid enrollment 7/09 – 3/10)

Safety population:

All patients who received at least 1 dose of any study drug

Baseline Characteristics

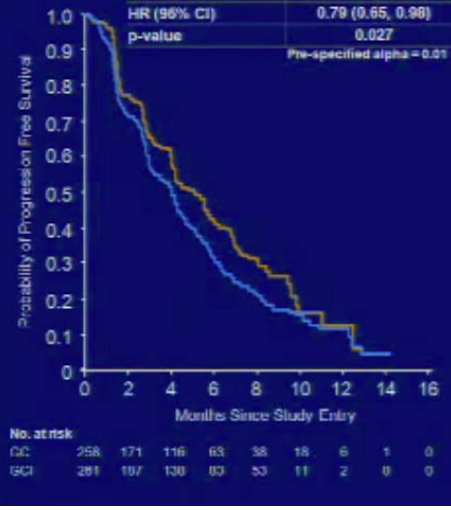
	GC (N=258)	GCI (N=261)
Age, years, median	54	53
ECOG PS, %		
0 / 1	53 / 45	57/ 42
No. metastatic sites, %		
1	14	8
2	26	34
≥3	60	58
Metastatic site, %		
Lung	43	38
Liver	61	62
CNS/Brain	8	8
Bone	30	33
Skin/Soft Tissue	23	25
Lymph nodes	72	76
Breast	19	18

Baseline Characteristics (cont'd)

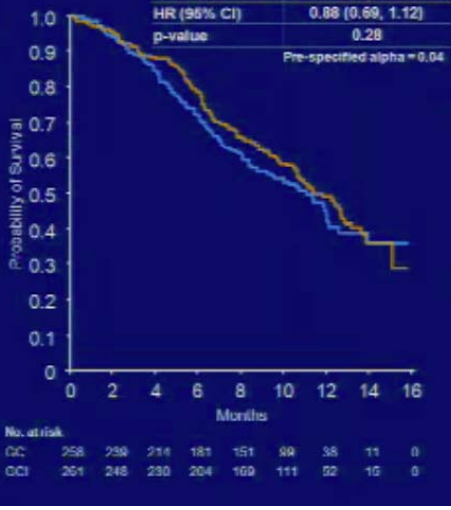
	GC N=258	GCI N=261
Patients with prior chemotherapies n, %	232 (90)	231 (89)
Prior neoadjuvant or adjuvant	204 (79)	201 (77)
Prior metastatic		
0	148* (57)	147* (56)
≥1	110* (43)	114* (44)
Prior Anthracycline	74	70
Prior Taxane	85	83
Prior Bevacizumab**	32	28
Disease Free Interval (DFI)†		
Median	15 months	12 months
≤ 12 months	44%	51%
> 12 months	56%	49%
DFI - 1st line	(n=149)	(n=148)
Median	15.9 months	9.5 months
DFI - 2nd/3rd line	(n=109)	(n =113)
Median	13.8 months	15.7 months

Efficacy Endpoints – ITT population

PFS	GC (N=258)	GCI (N=261)
Median PFS, mos (95% CI)	4.1 (3.1, 4.6)	6.1 (4.2, 5.8)
HR (96% CI)	0.79 (0.65, 0.98)	
p-value	0.027	
Pre-specified alpha = 0.01		



OS	GC (N=258)	GCI (N=261)
Median OS, mos (95% CI)	11.1 (9.2, 12.1)	11.8 (10.6, 12.9)
HR (96% CI)	0.88 (0.69, 1.12)	
p-value	0.28	
Pre-specified alpha = 0.04		



Overall Response Rate* – ITT Population

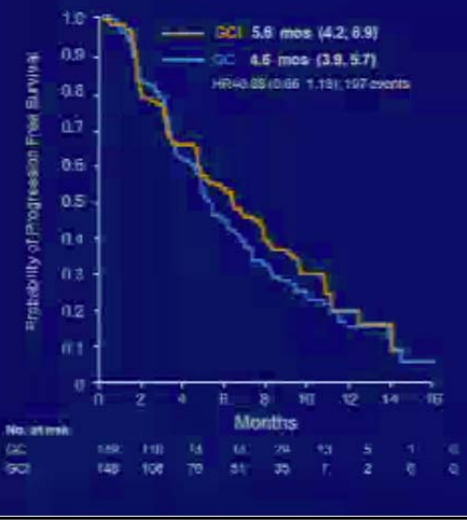
Response, n (%)	GC N = 258	GCI N = 261
Complete response	4 (1.6)	5 (1.9)
Partial response	74(29)	83 (32)
Stable disease	89 (35)	99 (38)
Progressive disease	62 (24)	62 (24)
Inevaluable	29 (11)	12 (4.6)
SD > 6 months	14 (5.4)	19 (7.3)
ORR, n (%) (95% CI)	78 (30) (25–36%)	88 (34) (28–40%)
Clinical Benefit Rate, n (%) [CR +PR +SD(> 6 mos)]	92 (36)	107 (41)

* Independent central review, RECIST 1.1 † confirmation of response

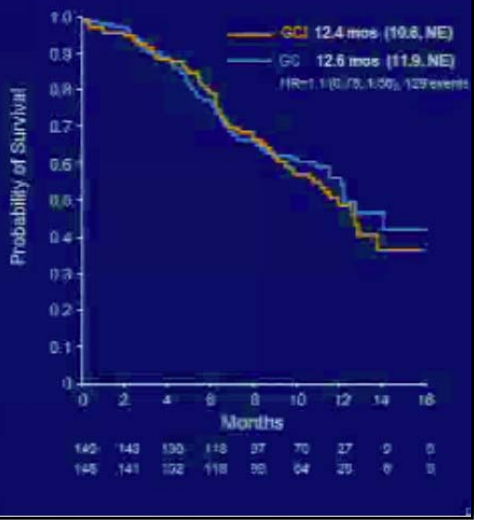
Exploratory Analysis 1st -line ITT Population

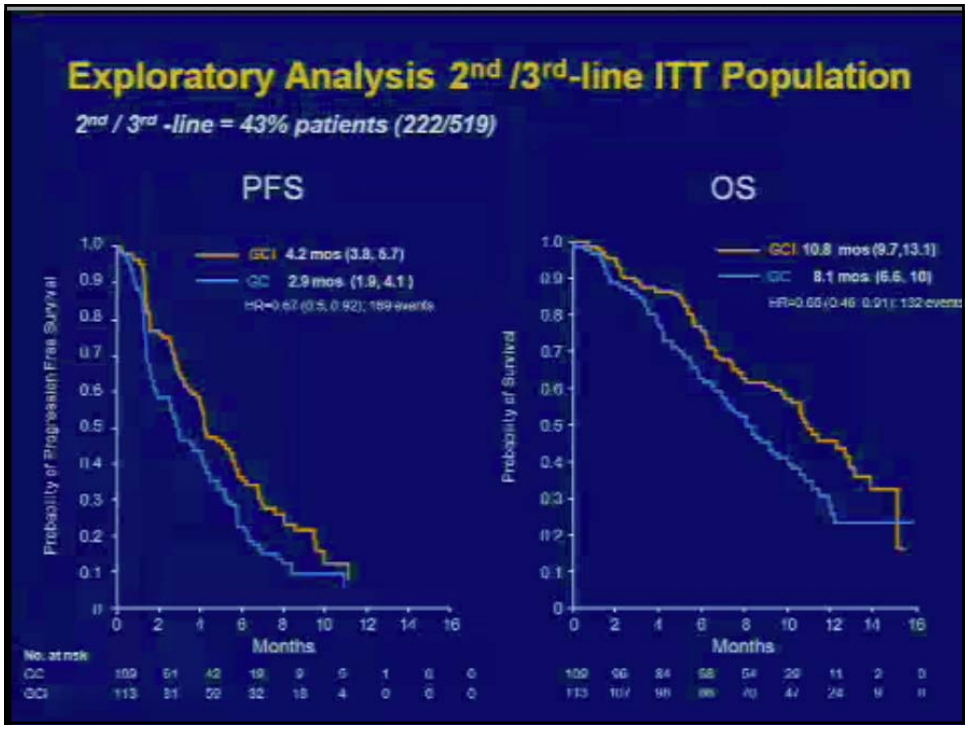
1st -line = 57% of patients (297/519)

PFS



OS





Multivariate Analysis - OS

Evaluate impact of imbalances in specific baseline characteristics on OS per multivariate analyses as specified in the statistical analysis plan (SAP)

Analyses based on :

1. Pre-specified baseline factors: age, disease burden, ECOG PS, line of therapy, race, time since diagnosis of mTNBC, visceral disease, and elevated alkaline phosphatase
2. Pre-specified baseline factors above - but replace time since diagnosis of mTNBC with Disease Free Interval from primary BC surgery to onset of metastatic disease

Treatment Estimates for OS determined using Multivariate Cox Model

	ITT Population		1st-line		2nd/3rd-line	
	HR	p	HR	p	HR	p
Unadjusted	0.88	0.28	1.1	0.56	0.65	0.012
Using pre-specified baseline factors	0.81	0.08*	0.91	0.62*	0.72	0.07*
Using pre-specified baseline factors with DFI replacement	0.78	0.05*	0.83	0.32*	0.71	0.05*

* p-value is Wald Chi-Square test

Multivariate Analysis - PFS

Evaluate impact of imbalances in specific baseline characteristics on PFS
Analyses as described

Treatment Estimates for PFS determined using
Multivariate Cox Model

	ITT Population		1st-line		2nd/3rd-line	
	HR	p	HR	p	HR	p
Unadjusted	0.79	0.027	0.88	0.37	0.67	0.011
Using pre-specified baseline factors	0.75	0.006*	0.81	0.15*	0.72	0.033*
Using pre-specified baseline factors with DFI replacement	0.74	0.004*	0.80	0.117*	0.71	0.031*

*p-value is Wald Chi-Square test

Conclusions

- The addition of iniparib to GC did not improve PFS or OS according to the pre-specified criteria for these co-primary endpoints
  - 96% of GC patients eligible for crossover at time of analysis crossed over to GCI and received median of 2 cycles of therapy
- Exploratory analyses of PFS and OS by prior therapy suggests:
  - Potential efficacy benefit among 2nd/3rd line patients
  - Confirmatory study needed
- GCI safety profile confirmed; toxicity comparable to GC arm
- mTNBC population is highly heterogeneous on intrinsic subtyping
- Biomarker analyses underway to evaluate patient populations that may benefit from iniparib

NCIC-CTG MA.20
An Intergroup Trial of Regional Nodal Irradiation (RNI) in Early Breast Cancer

TJ Whelan, I Olivotto, I Ackerman, JW Chapman, B Chua, A Nabid, KA Vallis, JR White, P Rousseau, A Fortin, LJ Pierce, L Manchul, P Craighead, MC Nolan, J Bowen, DR McCready, KI Pritchard, MN Levine, and W Parulekar

On behalf of the NCIC-CTG, TROG, RTOG, SWOG, NCCTG, and NSABP Cooperative Groups

NCIC Clinical Trials Group
ICNC Groupe des essais cliniques

Background and Rationale

Radiation to chest wall, and regional lymph nodes after mastectomy in women with node +ve breast cancer treated with adjuvant systemic therapy decreases the risk of recurrence and improves overall survival

Ragaz J et al. *NEJM* 1997; 337:956-962;
Overgaard M et al. *NEJM* 1997; 337:949-955;
Overgaard M et al. *Lancet* 1999; 353:1641-1648

NCIC CTG
ICNC GEC

Background and Rationale

- ASTRO (1999) and ASCO (2001) guidelines recommend locoregional radiation following mastectomy for :
  - tumors > 5cm
  - > 3 +ve axillary nodes
- For women with 1-3 +ve nodes, further study was advised

NCIC CTG
INCC GEC

Background and Rationale

- Women treated with breast conserving surgery (BCS) receive whole breast irradiation (WBI)
- WBI may involve radiation to the lower axilla and some of the internal mammary nodes
- RNI may provide added benefits to WBI but can be associated with pneumonitis, lymphedema and brachial plexopathy

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INCC GEC

Objective of MA.20

To compare relative effectiveness of RNI to the internal mammary (IM), supraclavicular (SC) and high axillary (AX) lymph nodes in addition to WBI after BCS for women with node +ve and high risk node –ve breast cancer treated with adjuvant systemic therapy

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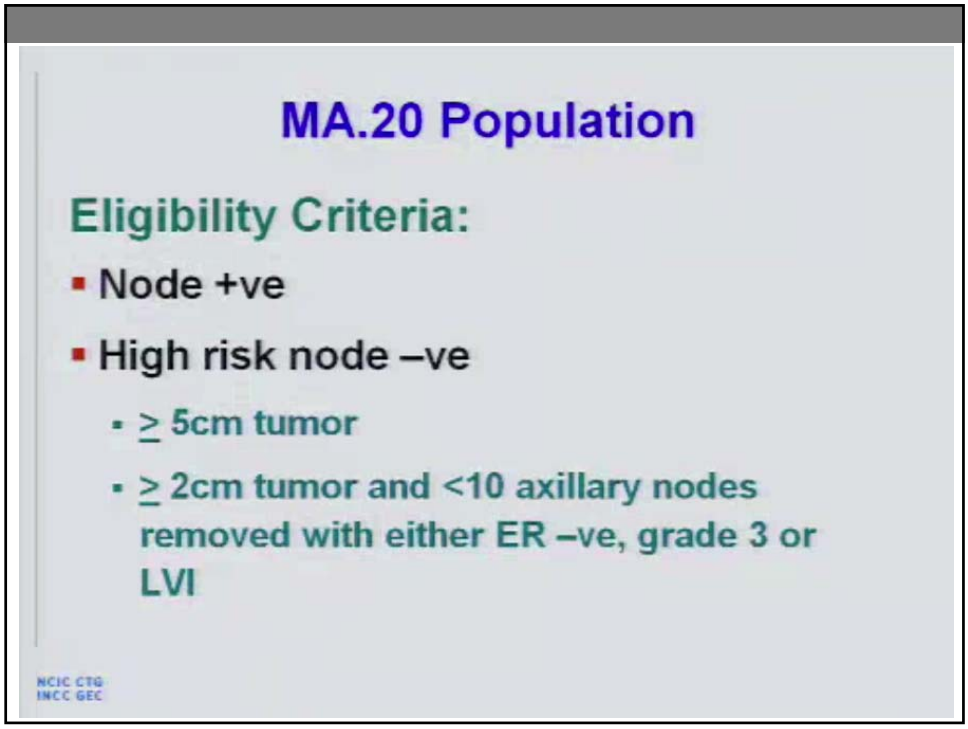
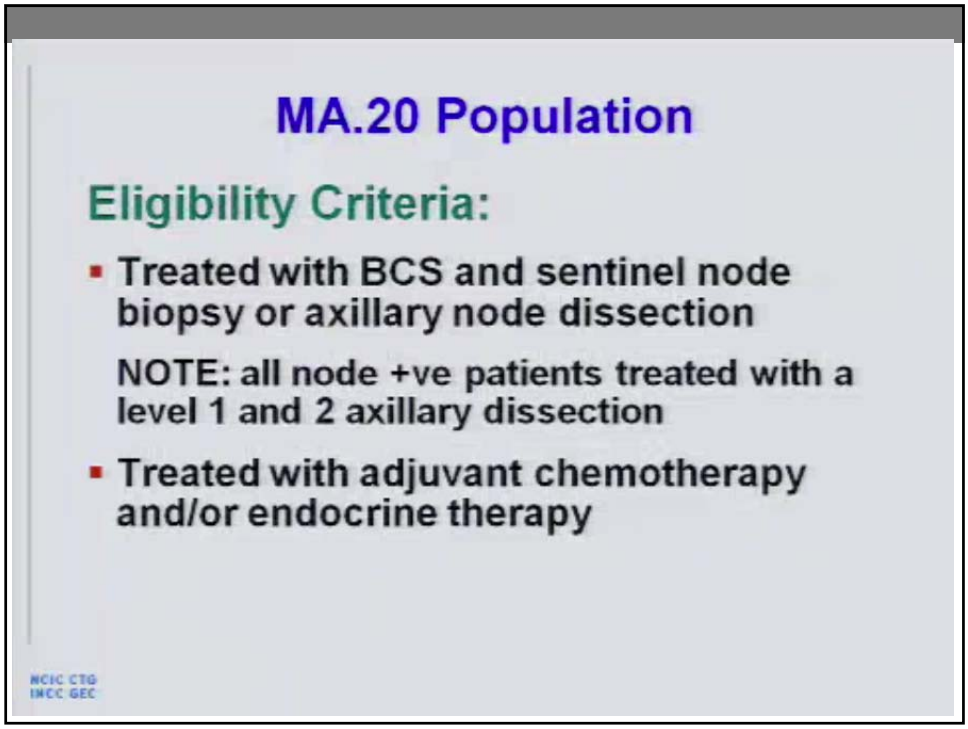
INCC GEC

Outcomes in MA.20

- Primary outcome: Overall Survival (OS)
- Secondary outcomes:
  - Disease-Free Survival (DFS)
  - Isolated Locoregional DFS
  - Distant DFS
  - Toxicity
  - Cosmetic outcome

NCIC CTG
INCC GEC


MA.20 Population
Eligibility Criteria:
Node +ve
High risk node –ve
≥ 5cm tumor
≥ 2cm tumor and <10 axillary nodes removed with either ER –ve, grade 3 or LVI
NCIC CTG
INCC GEC


MA.20 Population
Eligibility Criteria:
Treated with BCS and sentinel node biopsy or axillary node dissection
NOTE: all node +ve patients treated with a level 1 and 2 axillary dissection
Treated with adjuvant chemotherapy and/or endocrine therapy
NCIC CTG
INCC GEC

Study Design

Node positive or high risk node negative after BCS

R

- WBI
- WBI + RNI

Stratification

- Axillary nodes removed (<10, ≥10)
- Positive axillary nodes (0, 1-3, >3)
- Chemotherapy (anthracycline, other, none)
- Endocrine therapy (yes, no)

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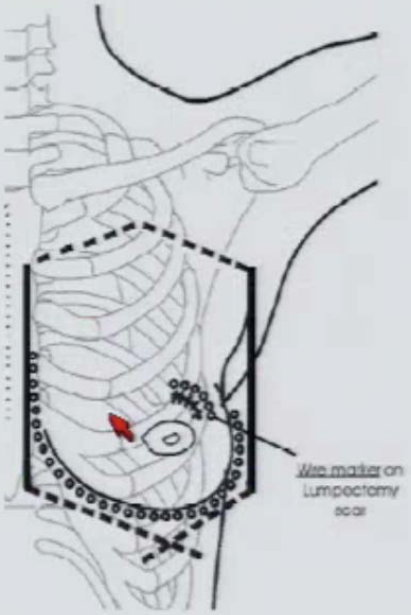
Methods

WBI

- Treat whole breast
- 4-18 MV
- CT planning recommended
- Wedges or compensators were used to ensure uniformity of dose +/- 7%
- Dose: 50 Gy/25 fractions
- Boost irradiation 10 Gy/5 fractions permitted



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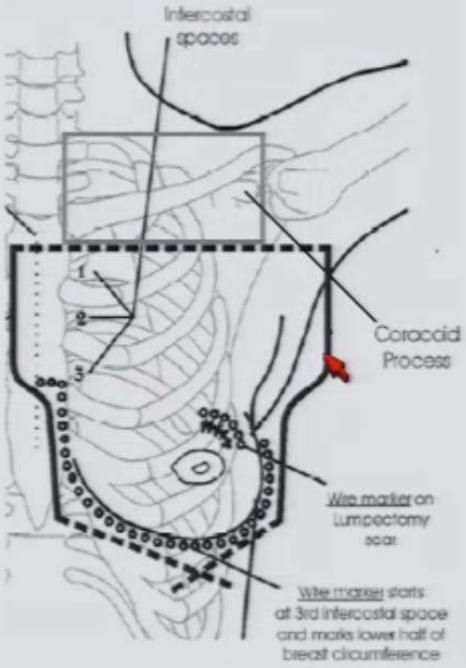
INCC GEC

Methods

WBI + RNI

- Treat breast + IM, SC and level 3 AX nodes
- IMN volume treated with a modified wide tangent technique or direct field matched to tangent fields
- SC and level 3 AX nodes treated with an anterior field
- Dose to the breast and boost irradiation same
- Dose to the regional nodes: 45 Gy/25 fractions



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Statistical Considerations

- Designed to detect a hazard ratio (HR) = 0.73 for OS with 80% power and two-sided α = 5%
- Requires a minimum of 312 deaths
- Interim analysis was planned after 156 deaths with early termination, or release of results if $p < 0.005$

NCIC CTG
INCC GEC

Study Progress

- Study accrued 1832 patients from Canada, US & Australia (2000–07)
- Specified interim analysis for OS planned for December 2010
- Spring of 2010: the Trial Committee requested the DSMC to expand the interim analysis to include locoregional recurrence and toxicity

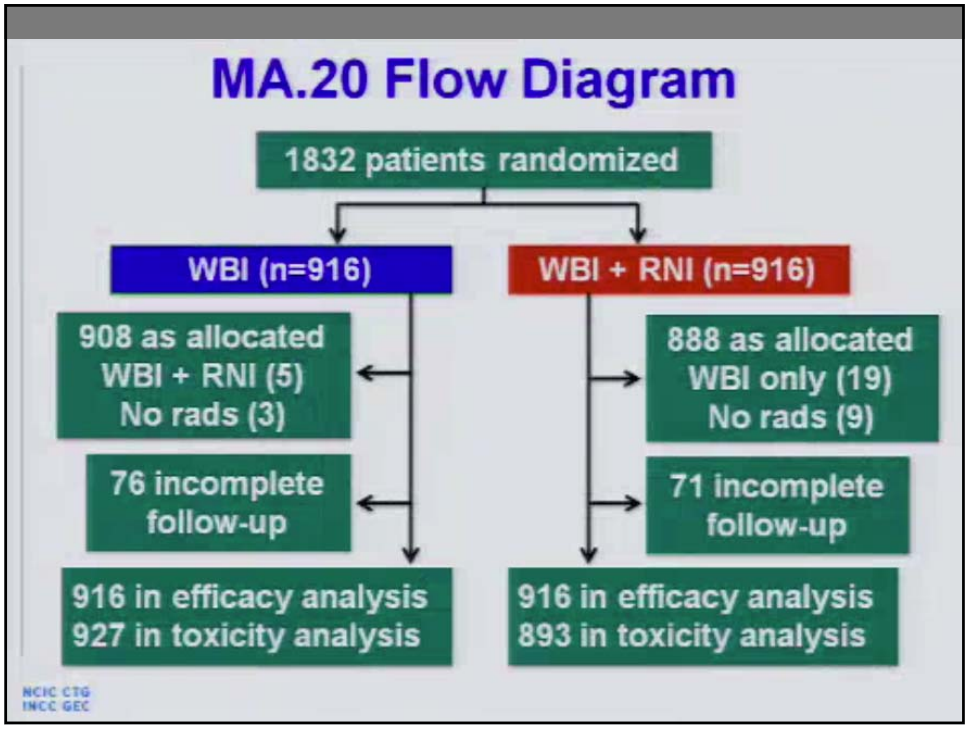
NCIC CTG
INCC GEC

Study Progress

Reasons for an expanded interim analysis:

- Because the death rate was low, there was concern that the trial was underpowered, and many more years of follow up would be required to have sufficient # of events
- EBCTCG (Oxford) Overview demonstrated a relationship between the reduction locoregional recurrence and survival
- Perception that RNI after BCS for 1-3 +ve nodes was being adopted in clinical practice based on subgroup analyses of the BC & Danish trials and the Oxford Overview

NCIC CTG
INCC GEC



Baseline Characteristics

	WBI N=916	WBI+RNI N=916
Age *(mean)*	53	54
Axillary nodes removed *(mean)*	12	12
Node Negative	10%	10%
Node Positive (1-3)	85%	85%
Tumor size > 2cm	45%	50%
Grade III	42%	43%
ER Negative	26%	25%
Adjuvant chemotherapy	91%	91%
Adjuvant endocrine therapy	77%	76%
Boost irradiation	24%	22%

NCIC CTG
INCC GEC

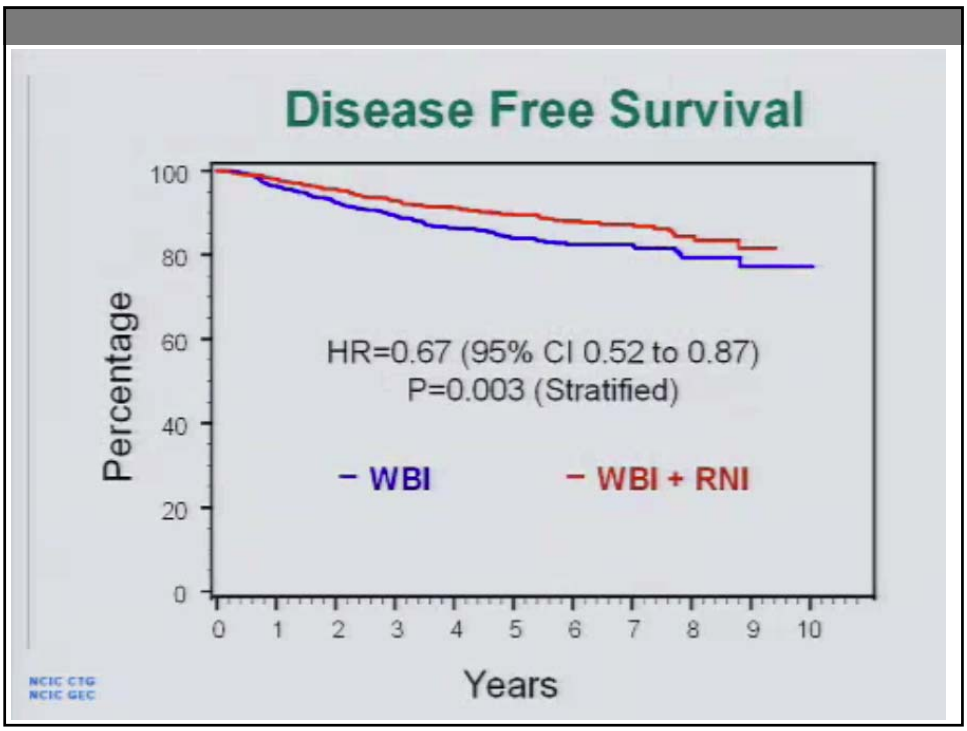
DFS*

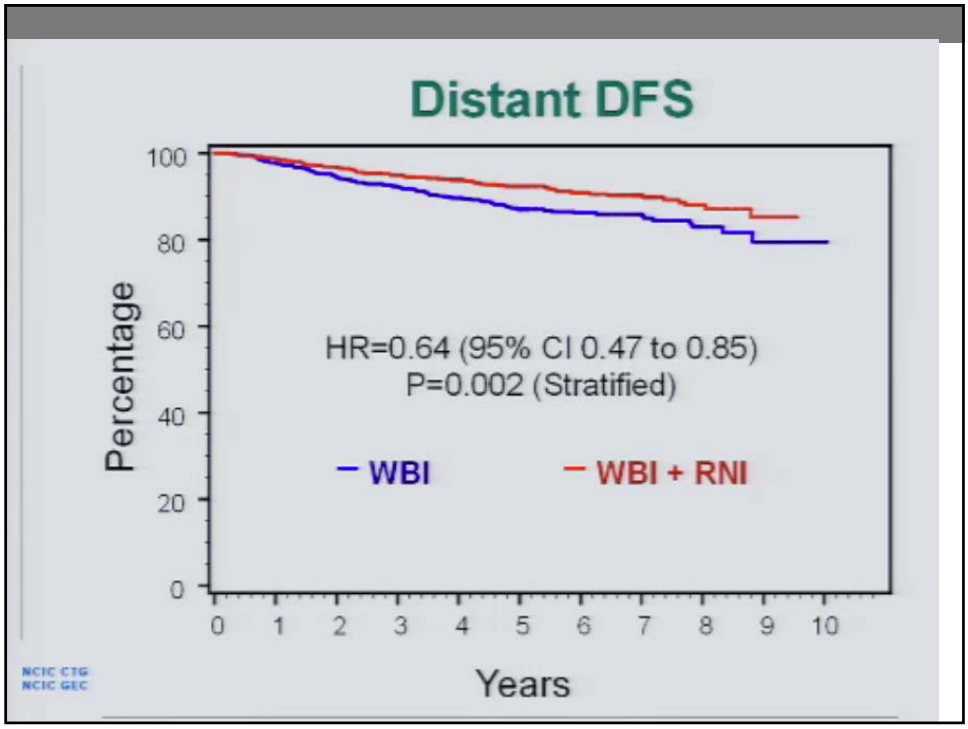
Any Recurrence, Contralateral Breast Cancer or Breast Cancer Death

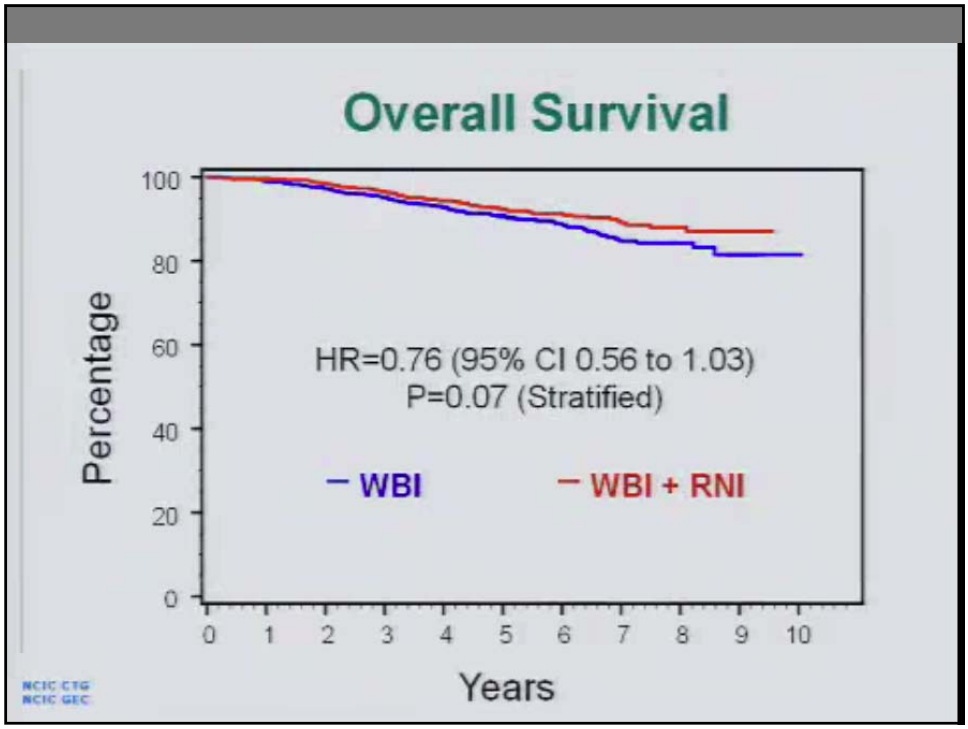
	WBI	WBI + RNI
N of Patients	916	916
Events	144	102
5-Yr DFS	84.0%	89.7%

*Median follow up of 62 months

NCIC CTG
INCC GEC




Distant DFS
Percentage
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10
Years
HR=0.64 (95% CI 0.47 to 0.85)
P=0.002 (Stratified)
WBI
WBI + RNI
NCIC CTG
NCIC GEC


Overall Survival
Percentage
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10
Years
HR=0.76 (95% CI 0.56 to 1.03)
P=0.07 (Stratified)
WBI
WBI + RNI
NCIC CTG
NCIC GEC

Adverse Events*
Grade ≥ 2

	WBI n=927				WBI + RNI n=893				
Grade ➡	2	3	4/5	Any	2	3	4/5	Any	P Value
Acute									
Radiation Dermatitis	349	23	-	40%	397	45	-	50%	<0.001
Pneumonitis	2	-	-	0.2%	12	-	-	1.3%	0.01
Delayed									
Lymphedema	34	3	1	4%	61	4	-	7%	0.004

*NCI Common Toxicity Criteria v.2 1998

NCIC CTG
INCC GEC

Adverse Cosmetic Outcome*

	WBI	WBI + RNI	P Value
Baseline	187 / 910 (21%)	197 / 876 (22%)	0.33
At 3 years	177 / 679 (26%)	195 / 670 (29%)	0.22
At 5 years	111 / 381 (29%)	142 / 396 (36%)	0.047

* Number (%) of Patients with fair or poor global assessment of cosmetic outcome using the EORTC cosmetic rating system

NCIC CTG
INCC GEC

Conclusions

- RNI, added to WBI, increased DFS at 5 years with a reduction in both locoregional and distant recurrence
- There was also a trend in improvement for overall survival, but this was not statistically significant
- RNI was associated with an increase in radiation pneumonitis and lymphedema

NCIC CTG
INCC GEC

Implications

- Women with node +ve breast cancer are treated WBI following BCS
- Women with large primary tumours or >3 +ve nodes are also offered RNI
- Results from MA.20 suggest that all women with node +ve disease be offered RNI provided they are made aware of the associated toxicities

NCIC CTG
INCC GEC

Results of NCIC CTG MAP.3 (ExCel)

Exemestane for breast cancer prevention in postmenopausal women

A double blind placebo-controlled Phase III Trial

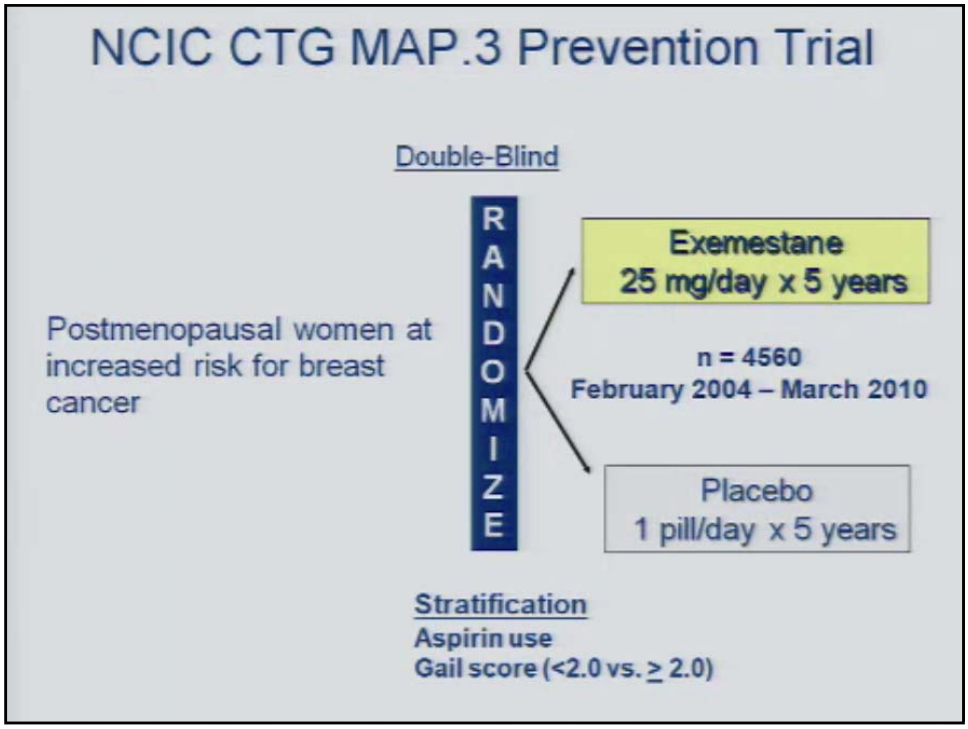
Paul E. Goss
Massachusetts General Hospital Cancer Center

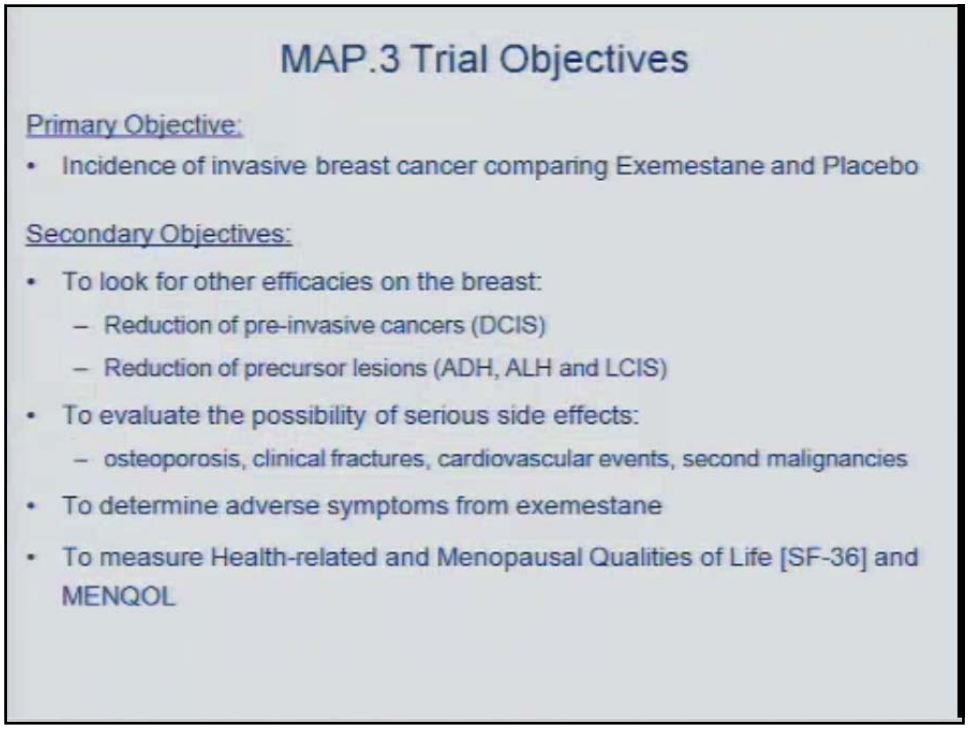
J.N. Ingle, J. Alés-Martínez, A.M. Cheung, R. T. Chlebowski, J. Wactawski-Wende, A. McTiernan, J. Robbins, K. Johnson, L. Martin, E. Winquist, G. Sarto, J. Garber, C. Fabian, P. Pujol, E. Maunsell, P. Farmer, K. Gelmon, D. Tu, H. Richardson, for the NCIC CTG MAP.3 Study Investigators

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Rationale for MAP.3

- Estrogens are associated with breast cancer risk
- Tamoxifen (Selective Estrogen Receptor Modulators SERMs)
  - Tamoxifen and raloxifene reduce breast cancer risk by ~38% and are approved in the US for breast cancer prevention.
  - Rare serious side effects (endometrial cancers, blood clots, strokes) have in part limited the use of tamoxifen to ~4% of women at increased risk.
  - Tamoxifen: the number needed to treat (NNT) is ~95 over 5 years.
- Aromatase (estrogen synthesis) Inhibitors (AIs)
  - AIs are superior to tamoxifen in early breast cancer, including reducing the occurrence of new cancers in the opposite breast (a prevention effect).
  - Exemestane is one of three AIs approved for breast cancer treatment. It causes less bone loss than other AIs and thus was our first choice for a breast cancer prevention trial.


NCIC CTG MAP.3 Prevention Trial
Double-Blind
Postmenopausal women at increased risk for breast cancer
RANDOMIZE
Exemestane
25 mg/day x 5 years
n = 4560
February 2004 – March 2010
Placebo
1 pill/day x 5 years
Stratification
Aspirin use
Gail score (<2.0 vs. ≥ 2.0)


MAP.3 Trial Objectives
Primary Objective:
• Incidence of invasive breast cancer comparing Exemestane and Placebo
Secondary Objectives:
• To look for other efficacies on the breast:
– Reduction of pre-invasive cancers (DCIS)
– Reduction of precursor lesions (ADH, ALH and LCIS)
• To evaluate the possibility of serious side effects:
– osteoporosis, clinical fractures, cardiovascular events, second malignancies
• To determine adverse symptoms from exemestane
• To measure Health-related and Menopausal Qualities of Life [SF-36] and MENQOL

Power Estimates

Hypothesis: Reduction in incidence of invasive breast cancer by 65% (Assuming an annual incidence rate of 0.60% in the placebo arm and 0.21% in the exemestane arm)

HR: 0.35, 90% power, 2-sided alpha of 5%

Interim analyses: None planned

Events: 38 invasive cancers required for the final analysis

MAP.3 Key Eligibility Criteria

- Postmenopausal and ≥ 35 years
- At least ONE of the following breast cancer risk factors:
  - Age ≥ 60 years
  - Gail score >1.66%
  - Prior ADH, ALH, LCIS
  - Prior DCIS with mastectomy
- BRCA 1 and 2 mutation carriers excluded
- Prior DCIS with lumpectomy excluded
- Women with a history of breast cancer or other malignancies excluded

MAP.3 Baseline Characteristics

Characteristics	Exemestane N=2285	Placebo N=2275
Age, median (range)	62.5 (38.5-88.2)	62.4 (37.1-89.9)
Caucasian-no. (%)	2138 (93.6)	2123 (93.3)
BMI, median (range)	27.9 (15.9-54.3)	28.1 (16.3-65.4)
Gail score Median (range)	*N=2171* 2.3 (0.6-21.0)	*N=2163* 2.3 (0.6-15.1)
Strongest Breast Cancer Risk Factor at study entry-no. (%)		
≥ 60 years	1114 (48.8)	1126 (49.5)
Gail score >1.66%	929 (40.7)	905 (39.8)
Prior ADH, ALH, LCIS on breast biopsy	185 (8.1)	188 (8.3)
Prior DCIS treated with mastectomy	56 (2.5)	56 (2.5)

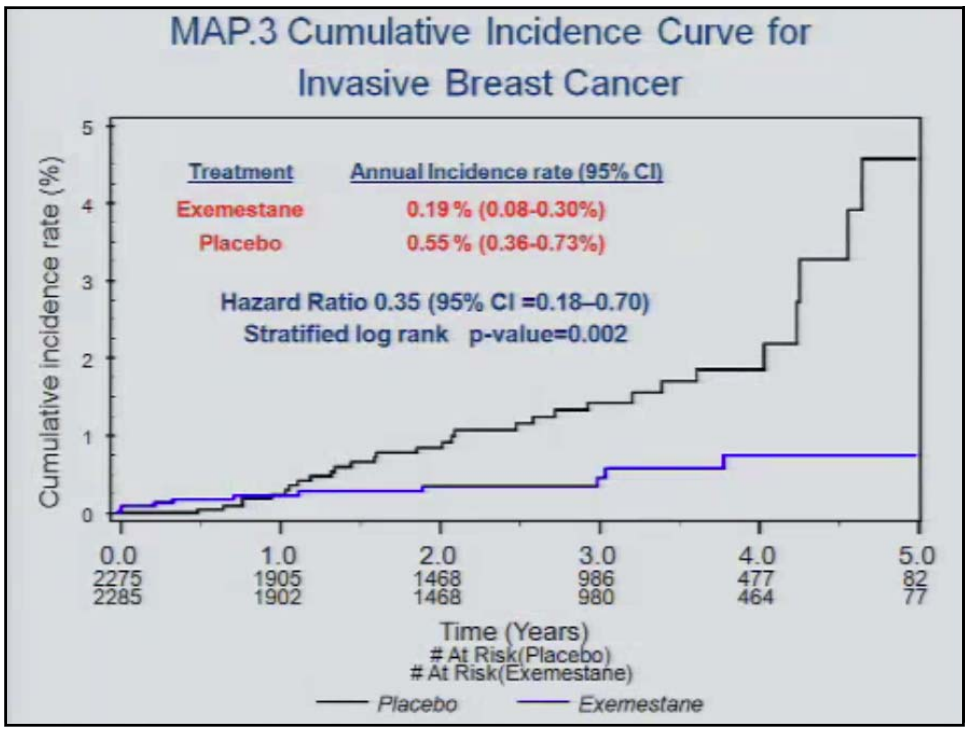
MAP.3 Baseline Characteristics

Characteristics	Exemestane N=2285	Placebo N=2275
Prior therapy-no. (%)		
Menopausal Hormone Therapy (HT)	1310 (57.3)	1327 (58.3)
Bisphosphonate medication	427 (18.7)	414 (18.2)
Lipid lowering drugs	738 (32.3)	696 (30.6)
Cardiovascular medications	955 (41.8)	973 (42.8)
Selective estrogen receptor modulators	104 (4.6%)	116 (5.1%)
Selected Medical history- no. (%)		
Prior clinical skeletal fracture	409 (17.9)	400 (17.6)
Baseline osteoporosis	303 (13.3)	293 (12.9)
Prior Cardiovascular event	267 (11.7)	255 (11.2)
Baseline BMD T-scores		
Total Hip BMD, Mean (SD)	- 0.38 (1.29)	- 0.39 (1.16)
L1-L4 PA Spine, Mean (SD)	- 0.54 (1.39)	- 0.49 (1.46)

RESULTS
Incidence of invasive breast cancer and tumor subtypes

Type of events	Exemestane		Placebo		HR (95% CI)	P-value
	No. events	Annual Incidence rate (%)	No. events	Annual Incidence rate (%)		
Incident invasive breast cancer	11	0.19	32	0.55	0.35 (0.18, 0.70)	0.002
ER +	7	0.12	27	0.46	0.27 (0.12, 0.60)	0.0008
ER -	4	0.07	5	0.09	0.80 (0.21, 2.98)	0.74
PgR+	5	0.09	20	0.34	0.26 (0.10, 0.69)	0.004
PgR-	6	0.10	12	0.20	0.50 (0.19, 1.33)	0.16
Her2/neu +	0	0.00	6	0.10	NE	NE
Her2/neu -	10	0.17	26	0.44	0.40 (0.19, 0.82)	0.01

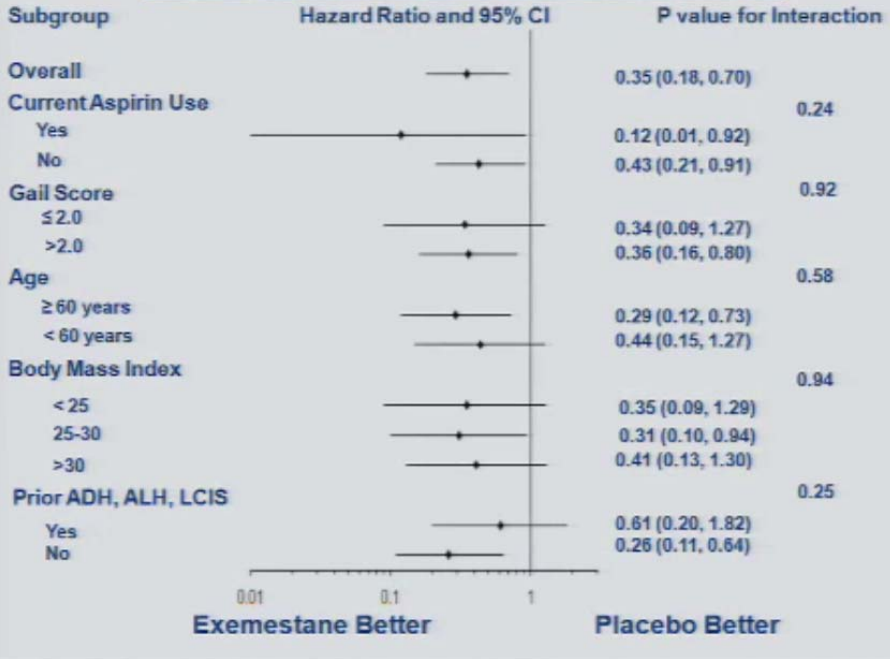
MAP.3 Cumulative Incidence Curve for Invasive Breast Cancer



Incidence of invasive & pre-invasive breast events

Type of events	Exemestane No. events	Exemestane Annual Incidence rate (%)	Placebo No. events	Placebo Annual Incidence rate (%)	HR (95% CI)	P-value
Combined incidence of invasive breast cancer and DCIS	20	0.35	44	0.77	0.47 (0.27, 0.79)	0.004
All DCIS	9	0.16	14	0.24	0.65 (0.28, 1.51)	0.31
All LCIS, ADH & ALH events	4	0.07	11	0.20	0.36 (0.11, 1.12)	0.08

Invasive breast cancer by risk categories



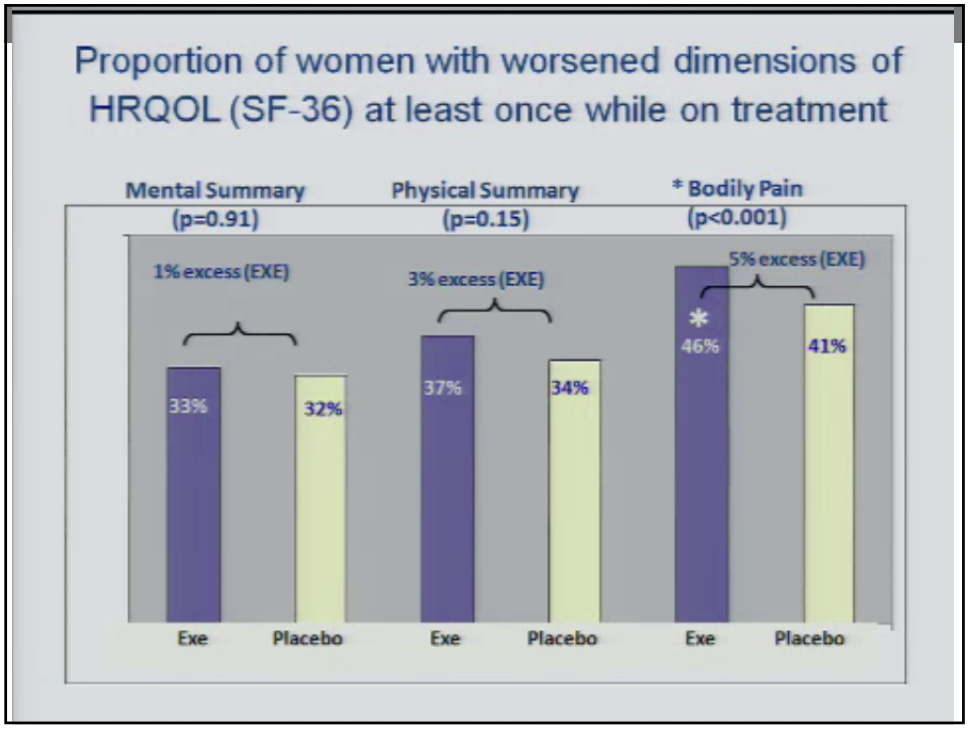
Side effects by severity and treatment arm

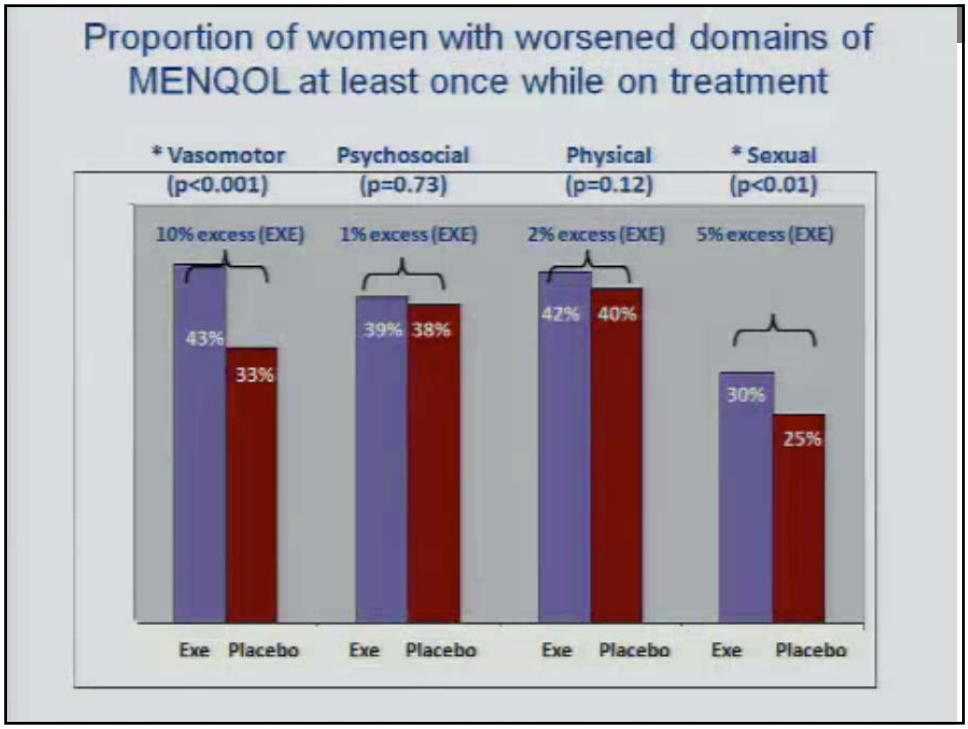
	Exemestane (n=2240)			Placebo (n=2248)			
Toxicity	≤ gr 2	≥ gr 3	Total (%)	≤ gr 2	≥ gr 3	Total (%)	P-value
Any	1395	568	1963 (88)	1434	467	1901 (85)	0.003
Hot flashes	833	67	900 (40)	742	43	718 (32)	<0.0001
Fatigue	492	33	525 (23)	440	25	465 (21)	0.03
Insomnia	215	15	230 (10)	182	7	189 (8)	0.04
Diarrhea	109	9	118 (5)	74	1	75 (3)	0.002
Nausea	149	3	155 (7)	120	2	122 (5)	0.04
Arthritis	215	32	247 (11)	179	17	196 (9)	0.01
Joint pain	587	78	665 (30)	572	34	606 (27)	0.04
Muscle pain	131	16	147 (7)	178	14	192 (9)	0.01
Depression	213	23	236 (11)	226	9	235 (10)	0.96
Vaginal dryness	351	1	352 (16)	343		343 (15)	0.68

NCI CTCAE version 3

Serious adverse effects by severity and treatment arm

Serious Toxicities	Exemestane n (%)	Placebo n (%)	P-value
Cardiovascular Disease	106 (4.7%)	111 (4.9 %)	0.39
Clinical skeletal fractures	149 (6.7%)	143 (6.4%)	0.72
Osteoporosis	37 (1.7%)	30 (1.3%)	0.39
Other malignancies	43 (1.9%)	38 (1.7%)	0.58


Proportion of women with worsened dimensions of HRQOL (SF-36) at least once while on treatment
Mental Summary (p=0.91)
Physical Summary (p=0.15)
* Bodily Pain (p<0.001)
1% excess (EXE)
3% excess (EXE)
5% excess (EXE)
*
33%
32%
37%
34%
46%
41%
Exe
Placebo
Exe
Placebo
Exe
Placebo


Proportion of women with worsened domains of MENQOL at least once while on treatment
* Vasomotor (p<0.001)
Psychosocial (p=0.73)
Physical (p=0.12)
* Sexual (p<0.01)
10% excess (EXE)
1% excess (EXE)
2% excess (EXE)
5% excess (EXE)
43%
33%
39%
38%
42%
40%
30%
25%
Exe
Placebo
Exe
Placebo
Exe
Placebo
Exe
Placebo

MAP.3 Conclusions

- Exemestane reduced the incidence of invasive breast cancer by 65% (from 0.55% to 0.19%)
- Exemestane also reduced pre-invasive DCIS and pre-cancerous ADH, ALH and LCIS
- Serious toxicities over 3 years were not seen, particularly fractures, self reported osteoporosis, cardiovascular toxicities or second cancers
- Minimal meaningful changes in health related QOL occurred

MAP.3 Strengths and Limitations of MAP.3

Strong Study Design

- Large double blind placebo-controlled trial
- Annual BrCa rates similar in placebo-controlled trials:
  - MAP.3 (0.55%) IBIS1 (0.68%) and NSABP P1 (0.61%)

Short median follow-up of ~3 years

- Efficacy: In EBC Trials CBC reductions continue beyond 3 years and longer treatment is better than shorter up to 5 years
- Toxicities: Absence of serious toxicities unlikely to change 3 through 5 years

Number needed to treat (NNT)

- MAP.3 NNT is 94 over 3 yrs; 26 over 5 yrs
- Plans to refine the target population: sub-studies, tumor biomarkers and host pharmacogenomic studies

Randomized, phase II trial comparing continuous vs intermittent capecitabine (X) monotherapy for metastatic breast cancer (MBC): results from the GEICAM 2009-05 study

Miguel Martìn
Hospital Universitario Gregorio Marañon, Madrid, Spain

Noelia Martínez-Jañez, Manuel Ramos, Lourdes Calvo, Ana Lluch, Pilar Zamora, Montserrat Munoz-Mateu, Daniela Caronia, Eva Carrasco, Jose Angel Garcia Saenz, Antonio Casado, Ignacio Chacón, Blanca Hernando, Manuel Ruiz-Borrego, Ana Gonzalez-Neira

Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.

ASCO Annual '11 Meeting

Background

GEICAM

- The current recommended schedule of capecitabine in MBC, 1,250mg/m^2 b.i.d., d1–14, q21d (intermittent; Xint), is based on data from a small phase II colorectal cancer trial
- This dose schedule produces unwanted side effects in a significant proportion of patients
- Alternative schedules in breast cancer should be evaluated in a prospective, randomized way
- We designed the randomized phase II GEICAM 2009-05 study to investigate whether continuous dosing of capecitabine (Xcont) would decrease the severity of side effects while maintaining the efficacy

MBC = metastatic breast cancer

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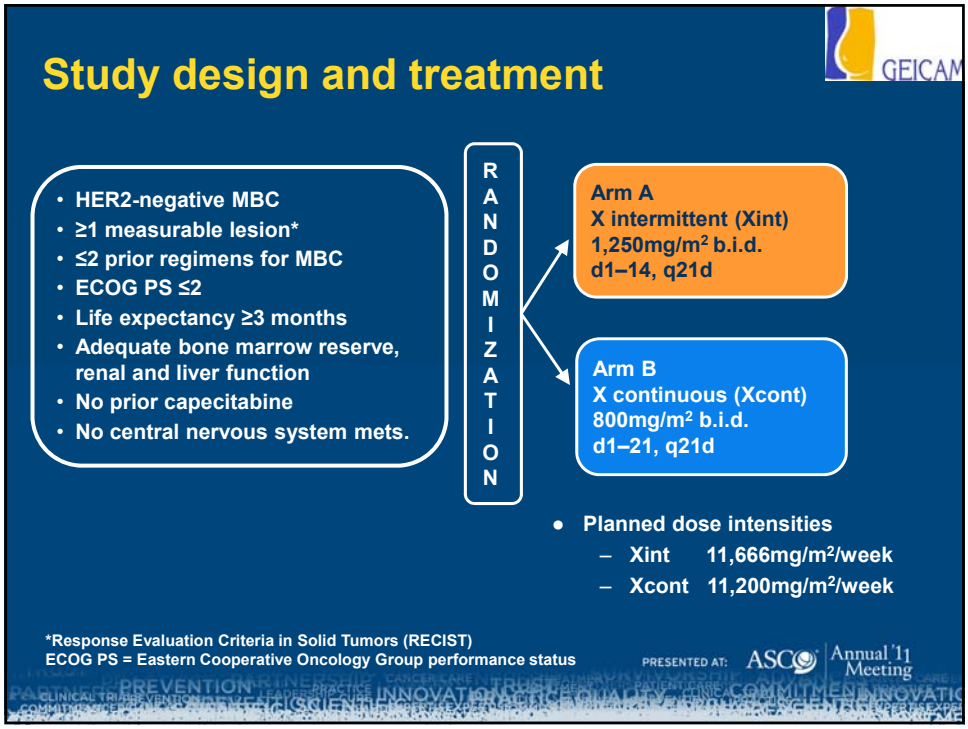
Study design and treatment
GEICAM
• HER2-negative MBC
• ≥1 measurable lesion*
• ≤2 prior regimens for MBC
• ECOG PS ≤2
• Life expectancy ≥3 months
• Adequate bone marrow reserve, renal and liver function
• No prior capecitabine
• No central nervous system mets.
RANDOMIZATION
Arm A
X intermittent (Xint)
1,250mg/m² b.i.d.
d1–14, q21d
Arm B
X continuous (Xcont)
800mg/m² b.i.d.
d1–21, q21d
• Planned dose intensities
– Xint 11,666mg/m²/week
– Xcont 11,200mg/m²/week
*Response Evaluation Criteria in Solid Tumors (RECIST)
ECOG PS = Eastern Cooperative Oncology Group performance status
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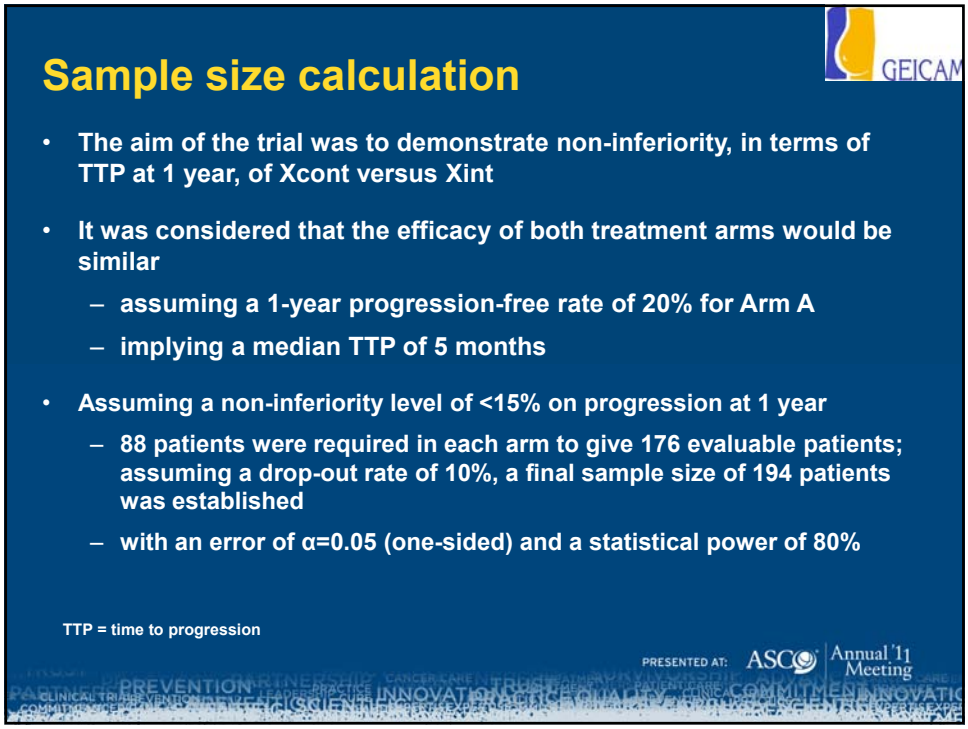
Sample size calculation
GEICAM
• The aim of the trial was to demonstrate non-inferiority, in terms of TTP at 1 year, of Xcont versus Xint
• It was considered that the efficacy of both treatment arms would be similar
– assuming a 1-year progression-free rate of 20% for Arm A
– implying a median TTP of 5 months
• Assuming a non-inferiority level of <15% on progression at 1 year
– 88 patients were required in each arm to give 176 evaluable patients; assuming a drop-out rate of 10%, a final sample size of 194 patients was established
– with an error of α=0.05 (one-sided) and a statistical power of 80%
TTP = time to progression
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Objectives

- Primary
  - to assess the non-inferiority, in terms of TTP at one year, of Xcont vs Xint
- Secondary
  - TTP differences between arms (Kaplan-Meier)
  - time to treatment failure, disease-free survival, overall survival
  - safety, particularly HFS
  - study of polymorphisms of CES2, CDD, TP, DPD, TS
  - ORR (complete plus partial responses)
  - clinical benefit (ORR plus stable disease >3 months)

ORR = objective response rate; HFS = hand-foot syndrome

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Polymorphisms

Gene	Polymorphism	rs	Method
CES2	intronic	rs2241409	Kaspar
	intronic	rs11568314	Kaspar
	intronic	rs11568311	Kaspar
	C823G (promoter)	rs11075646	Kaspar
CDD	A79C(Lys27Gln)	rs2072671	Kaspar
	-92A/G	rs602950	Kaspar
	943insC	rs3215400	Kaspar
	-205C/G	rs603412	Kaspar
	-451C/T	rs532545	Kaspar
TP	intronic	rs470119	Kaspar
	A324A	rs131804	Kaspar
	S471L	rs11479	Kaspar
DPD	IVS14+1G	rs3918290	Kaspar
TS	5'UTR 28 bp repetition		Sequencing
	3'UTR 6bp del		RFLP

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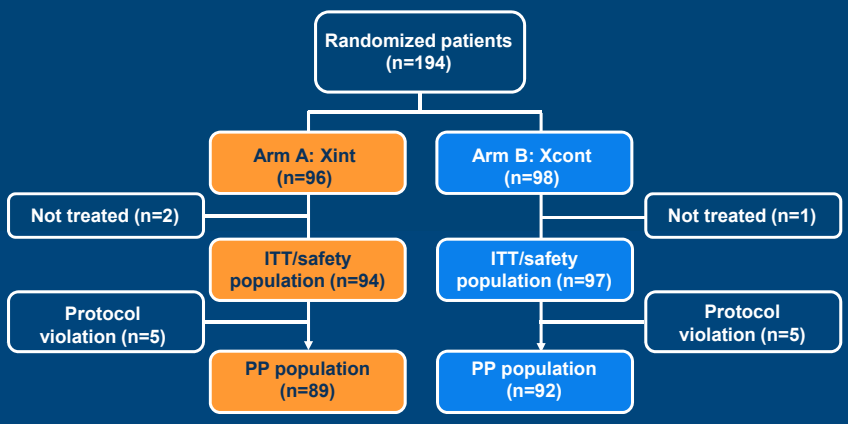
Patient disposition



ITT = intent-to-treat; PP = per protocol

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Baseline patient characteristics (ITT)

	Arm A Xint (n=94)	Arm B Xcont (n=97)
Median age, years (range)	61 (34–87)	59 (29–81)
Postmenopausal, n (%)	60 (64)	60 (62)
Prior chemotherapy exposure*, n (%)		
Anthracyclines	23 (25)	21 (22)
Taxanes	10 (11)	7 (7)
Anthracyclines and taxanes	44 (47)	52 (54)
Prior treatment for metastases, n (%)		
Chemotherapy	58 (62)	55 (57)
Hormone therapy	61 (65)	58 (60)

*Including (neo)adjuvant and first-line metastatic

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Baseline tumor characteristics (ITT)

	Arm A Xint (n=94)	Arm B Xcont (n=97)
Hormone receptor status, n (%)		
Positive*	74 (79)	76 (78)
Negative	18 (19)	16 (17)
Unknown	2 (2)	5 (5)
HER2 status, n (%)		
Negative	94 (100)	94 (97)
Positive/Unknown	0	1(1)/2 (2)
Sites of metastases, n (%)		
Liver	44 (47)	59 (61)
Lung	30 (32)	29 (30)
Other visceral	19 (20)	30 (31)**
Bone	48 (51)	46 (47)
Lymph nodes	44 (47)	36 (37)
Soft tissue, local recurrences	16 (17)	26 (27)
Metastatic sites, %		
1 / 2 / ≥3	44 / 29 / 27	51 / 27 / 22

*Including estrogen receptor and/or progesterone receptor positive
** including one patient with CNS metastasis

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Capecitabine exposure

	Arm A Xint (n=94)	Arm B Xcont (n=97)
Median number of cycles	7	6
Median duration of therapy, weeks	23	22
Median dose intensity, mg/m^2/week	9,448	9,193
Median relative dose intensity	0.81	0.82
Dose delays, %		
Patients	60	52
Cycles	16	14
Patients with dose reductions, %	63	49

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Grade 3–4 hematologic adverse events

Patients with event, %	Arm A Xint (n=94)	Arm B Xcont (n=97)
Hemoglobin	1	2
Absolute neutrophil count	5	1
Febrile neutropenia*	3	1
Platelets	3	0

*One of these patients was found to have DPD deficiency and presented with severe mucositis and diarrhea

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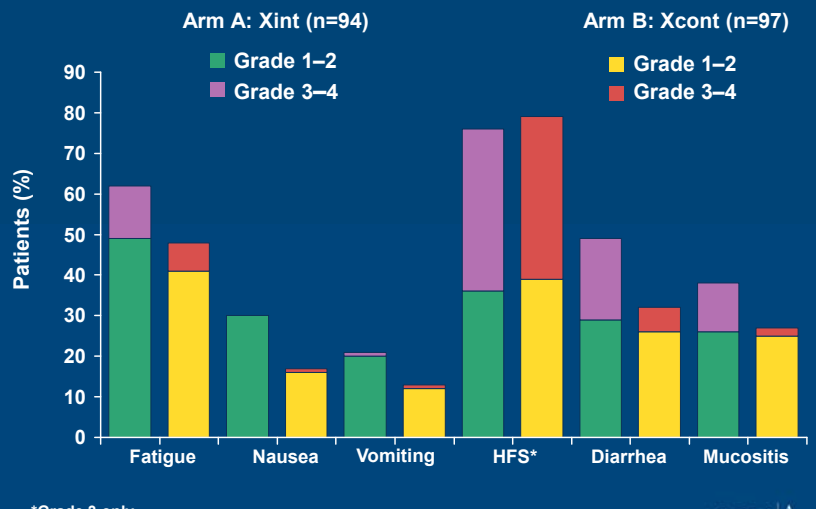
Non-hematologic adverse events



*Grade 3 only

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Hand-foot syndrome: grade 3 vs 0–2

- We found two polymorphisms associated with grade 3 HFS in TS and CES2 genes

TS 3'UTR			*CES2 C823G*		
Logistic regression analysis			Logistic regression analysis		
OR	95% CI	p-value	OR	95% CI	p-value
0.43	0.23–0.80	0.008	3.50	1.22–10.00	0.019
	No toxicity, %	Toxicity, %		No toxicity, %	Toxicity, %
Ins/ins	35 (14/40)	65 (26/40)			
Ins/del	67 (30/45)	33 (15/45)	CC	60 (51/85)	40 (34/85)
Del/del	67 (10/15)	33 (5/15)	GC	30 (6/20)	70 (14/20)

OR = odds ratio; CI = confidence interval

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Objective response rate

	ITT population		PP population	
n (%)	Arm A Xint (n=94)	Arm B Xcont (n=97)	Arm A Xint (n=89)	Arm B Xcont (n=92)
Complete response	2 (2)	1 (1)	2 (2)	–
Partial response	28 (30)	29 (30)	28 (31)	28 (30)
Stable disease	35 (37)	38 (39)	33 (37)	37 (40)
Progressive disease	19 (20)	23 (24)	16 (18)	21 (23)
Unknown	10 (11)	6 (6)	10 (11)	6 (7)
ORR	30 (32)	30 (31)	30 (34)	28 (30)
Clinical benefit rate	55 (59)	54 (56)	53 (60)	52 (57)

- No statistically significant differences between treatment arms

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TTP at 1 year (ITT population)

- 53 patients (29 in Arm A Xint; 24 in Arm B Xcont) were censored as they had been on study for <1 year and had not progressed or died
- 138 patients (65 in Arm A and 73 in Arm B) progressed or died during the first year
- TTP at 1 year
  - ITT population: 36% vs 31% (A vs B: -5%)
  - PP population: 35% vs 30% (A vs B: -5%)

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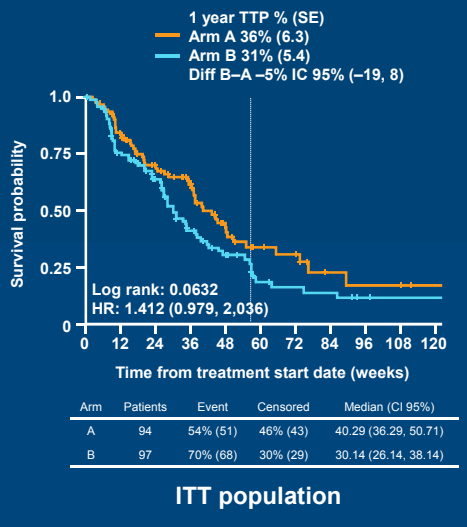
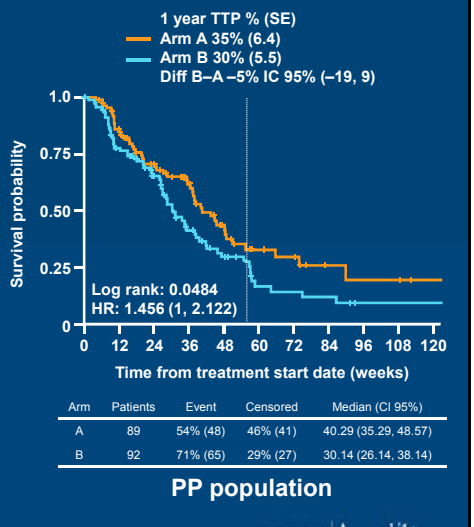
Time to progression



Arm	Patients	Event	Censored	Median (CI 95%)
A	94	54% (51)	46% (43)	40.29 (36.29, 50.71)
B	97	70% (68)	30% (29)	30.14 (26.14, 38.14)

ITT population



Arm	Patients	Event	Censored	Median (CI 95%)
A	89	54% (48)	46% (41)	40.29 (35.29, 48.57)
B	92	71% (65)	29% (27)	30.14 (26.14, 38.14)

PP population

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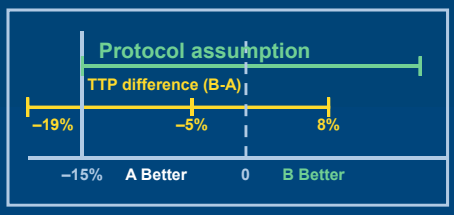
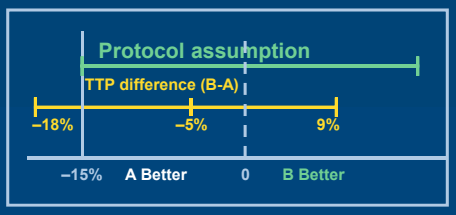
Analysis of non-inferiority

- Non-inferiority of Arm B (Xcont) versus Arm A (Xint) could not be demonstrated



ITT population



PP population

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Post-study treatment

n (%)	Arm A Xint (n=94)	Arm B Xcont (n=97)	Total (n=191)
Hormones	25 (27)	16 (16)	41 (21)
Chemotherapy	53 (56)	55 (57)	108 (56)
Taxanes	29 (31)	37 (38)	66 (35)
Vinorelbine	20 (21)	12 (12)	32 (17)
Anthracyclines	12 (13)	12 (12)	24 (13)
Capecitabine	5 (5)	6 (6)	11 (6)
Anthracyclines and taxanes	6 (6)	1 (1)	7 (4)
Other chemotherapy	19 (20)	17 (18)	36 (19)
Other biologics	2 (2)	2 (2)	4 (2)

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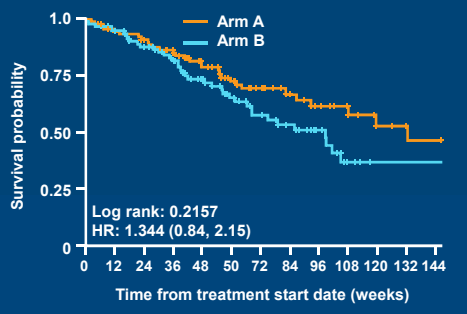
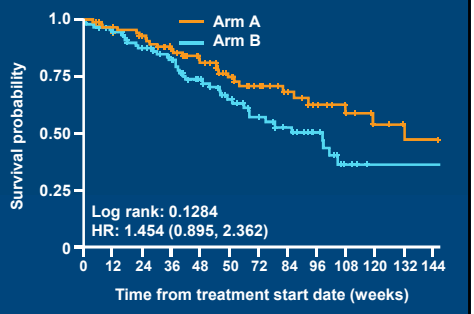
Overall survival



Arm	Patients	Event	Censored	Median (CI 95%)
A	94	35% (33)	65% (61)	132.1 (92.71, 210.4)
B	97	39% (38)	61% (59)	98.43 (66.29, N/A)

ITT population



Arm	Patients	Event	Censored	Median (CI 95%)
A	89	34% (30)	66% (59)	132.1 (92.71, 210.4)
B	92	40% (37)	60% (55)	98.43 (66.29, N/A)

PP population

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Conclusions

- This randomized phase II trial failed to demonstrate non-inferiority for continuous low-dose capecitabine (Xcont) versus the standard schedule (Xint), despite similar dose-intensity and cumulative dose
- TTP was significantly prolonged with Xint versus Xcont (PP population HR 1.412, p=0.0484), with a trend towards improved OS
- There was a similar incidence of hand-foot syndrome in both arms
- Two polymorphisms (TS 3'UTR, CES2 C823G) were associated with grade 3 HFS
- These data suggest that dose-density of capecitabine is more relevant than dose-intensity or total cumulative dose
- Newer, more dose-dense capecitabine schedules (e.g. weekly intermittent administration) should be explored in randomized trials to see whether efficacy and / or safety can be improved

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Long way to go