ASCO 2016 Update: What Will Effect Treatment In Clinic Now

CAGPO Conference

Sept 29, 2016

Dr. Simon Yu

Disclosures

In compliance with accreditation, we require the following disclosures to the session audience:

Research Support/P.I.	N/A
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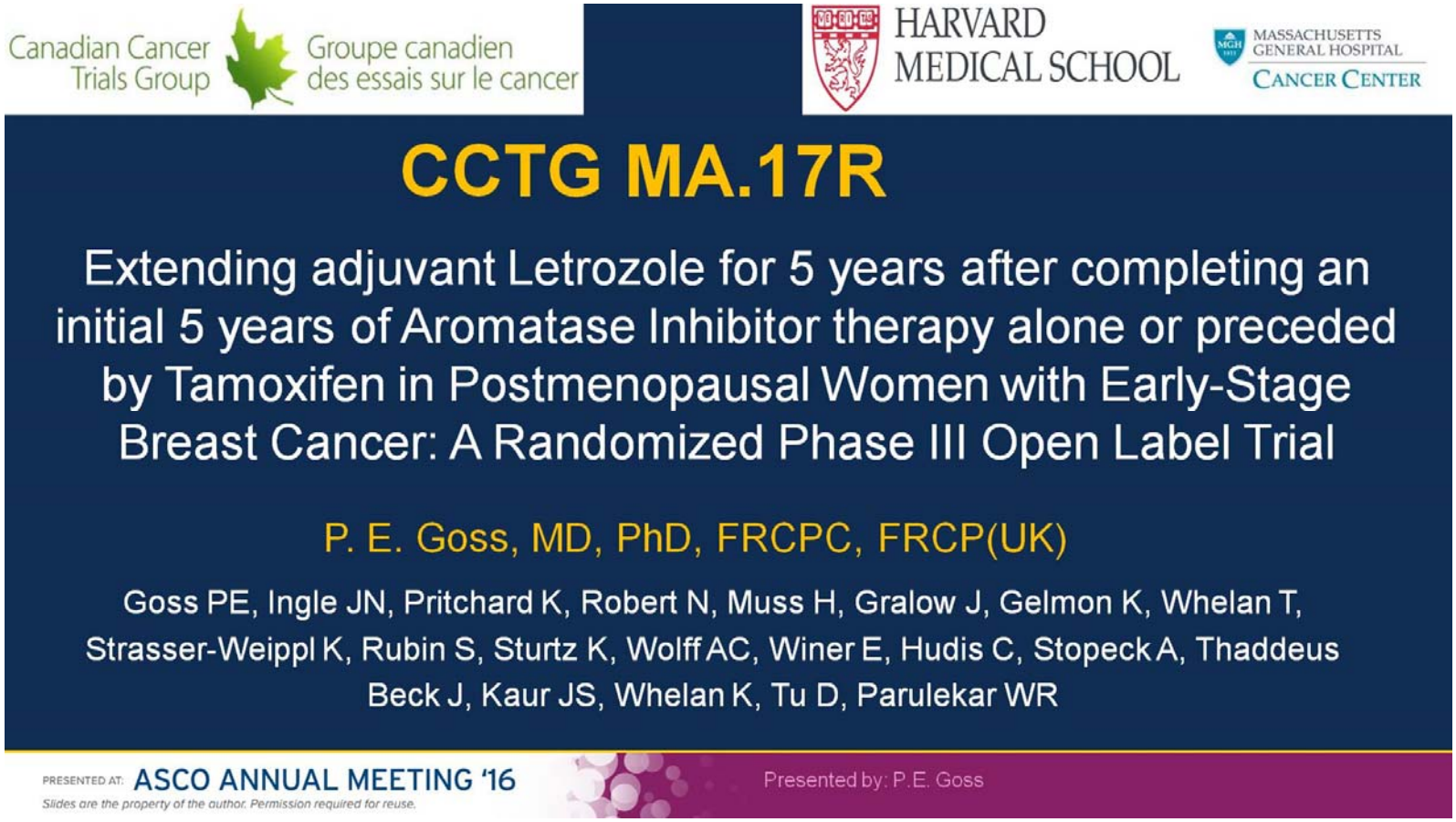
Consultant	N/A
Major Stockholder	N/A
Speakers Bureau	N/A
Honoraria	Roche, Novartis
Scientific Advisory Board	N/A

Discussion Topics

- MA-17R – Extended letrozole beyond 5 years of aromatase inhibitors in early post-menopausal hormone sensitive breast cancer
- PALOMA-2 – Letrozole +/- palbociclib in first line treatment of hormone sensitive metastatic breast cancer
- ESPAC-4 – Adjuvant Capecitabine/Gemcitabine for resected pancreatic adenocarcinoma
- CRITICS – Peri-operative chemotherapy vs chemoradiation for early resectable stomach cancer
- SWISH – Prophylactic oral steroid mouth rinse for patients undergoing exemestane + everolimus treatment in metastatic breast cancer



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MA.17R - Faculty Disclosures

Dr. Goss: None
Dr. Ingle: None
Dr. Pritchard: Fees for serving on advisory boards from AstraZeneca, Pfizer, Roche, Amgen, Novartis, GlaxoSmithKline and Eisai, consulting fees from Pfizer and Novartis, and lecture fees from Novartis.
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Dr. Muss: Uncompensated consultant and advisor to Pfizer and HarborPath, and serves on the board of directors of HarborPath.
Dr. Gralow: DSMC for Novartis and Roche/Genentech and on a steering committee for Roche/Genentech.
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Dr Sturtz: None
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Kate Whelan: None
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MA.17R Trial Schema and Design

AI x 5 yrs - Following Prior 5 years of AI - preceded or not by Tamoxifen

Any duration of prior Tamoxifen

4.5-6 yrs of Aromatase Inhibitor

Letrozole 2.5 mg po od

- ER+ and/or PR+ breast cancer
- Postmenopausal and disease-free
- Completed 4.5-6 years of adjuvant AI
- Any time of prior TAM
- Minimum life expectancy ≥5 years (no exclusion for age alone)

RANDOMIZE

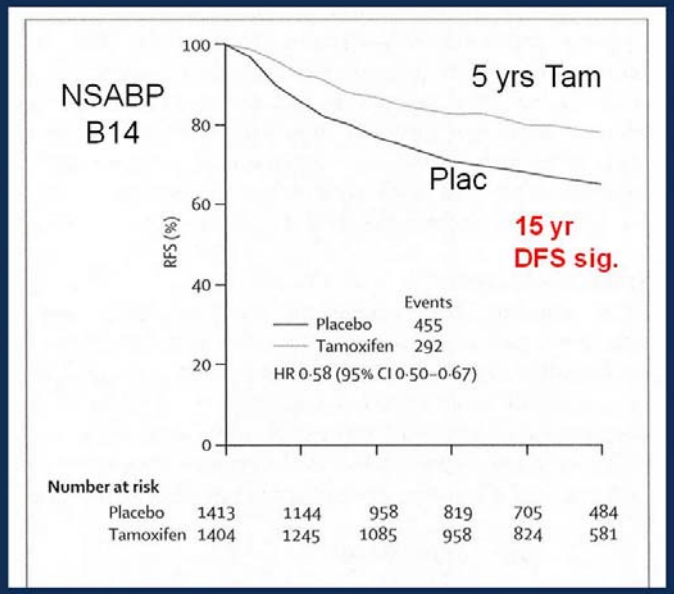
Oct 2004 - May 2009
n = 1918

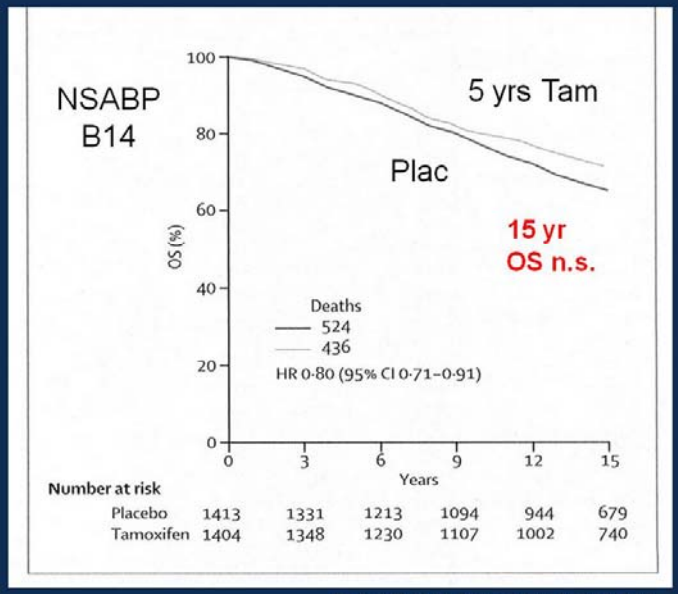
Letrozole 2.5 mg po od

Placebo

5 yrs

(NSABP B14): The 15 year DFS and OS curves with/without 5 yrs of adjuvant tamoxifen in ER+ node -ve breast cancer





Fisher B et al. Lancet 2004; 364: 858 – 68.

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MA.17 (Years 5-10 post Tam): AI better than Placebo

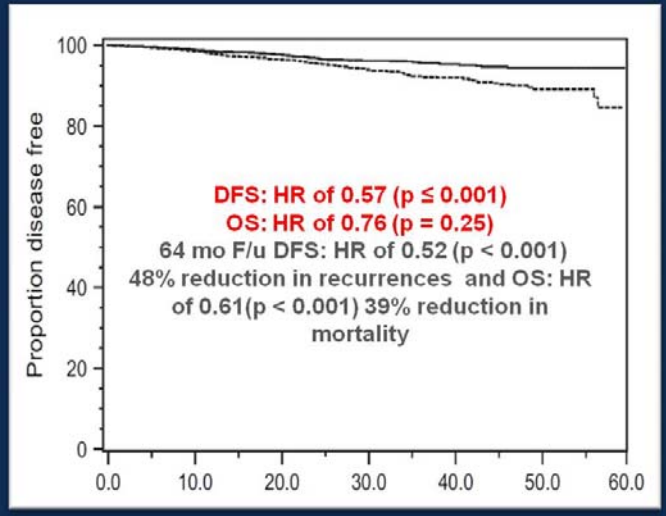
5 yrs of prior Tamoxifen

RANDOMIZE

Letrozole 2.5 mg po od

Placebo

5 yrs



Goss et al, N Engl J Med. 2003;349(19):1793-802.

Jin H, Goss p et al. J Clin Oncol. 2012 Mar 1;30(7):718-21.

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MA.17R – Hypothesis and Trial Objectives

Hypothesis: The question being posed in MA17R is: Does extending AI therapy from 5 to 10 years further improve patient outcomes?

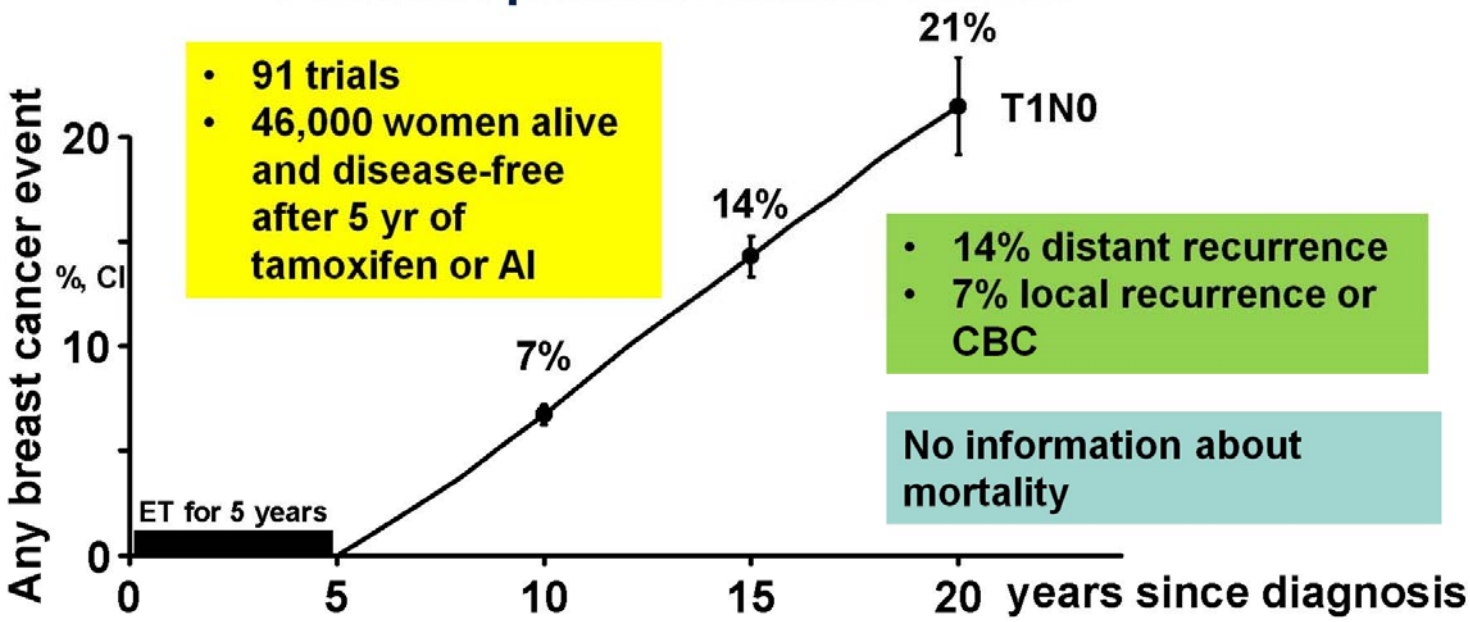
Primary Objective:

- DFS: from randomization → time of recurrence or development of CBC, whichever came first

Secondary Objectives:

- OS
- All CBC
- Safety
- Quality of life (Dr. Julie Lemieux tomorrow)

EBCTCG--Risk of ANY Breast Cancer Event at Years 5-20 in T1N0 ER-positive Breast Cancer



Annual event rate (and no. of events), by 5-year time period

T1N0 (n=16K): **1.4%** (807) **1.7%** (309) **1.8%** (54)

Pan et al, ASCO, 2016

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MA.17R - Stratification

- Lymph node status at diagnosis
- Prior adjuvant chemotherapy
- Interval between the last dose of AI and randomization
- Duration of prior tamoxifen (0; >0 to <2; 2 to 4.5; >4.5)

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MA.17R - Statistical Considerations

Hypothesis and Power:

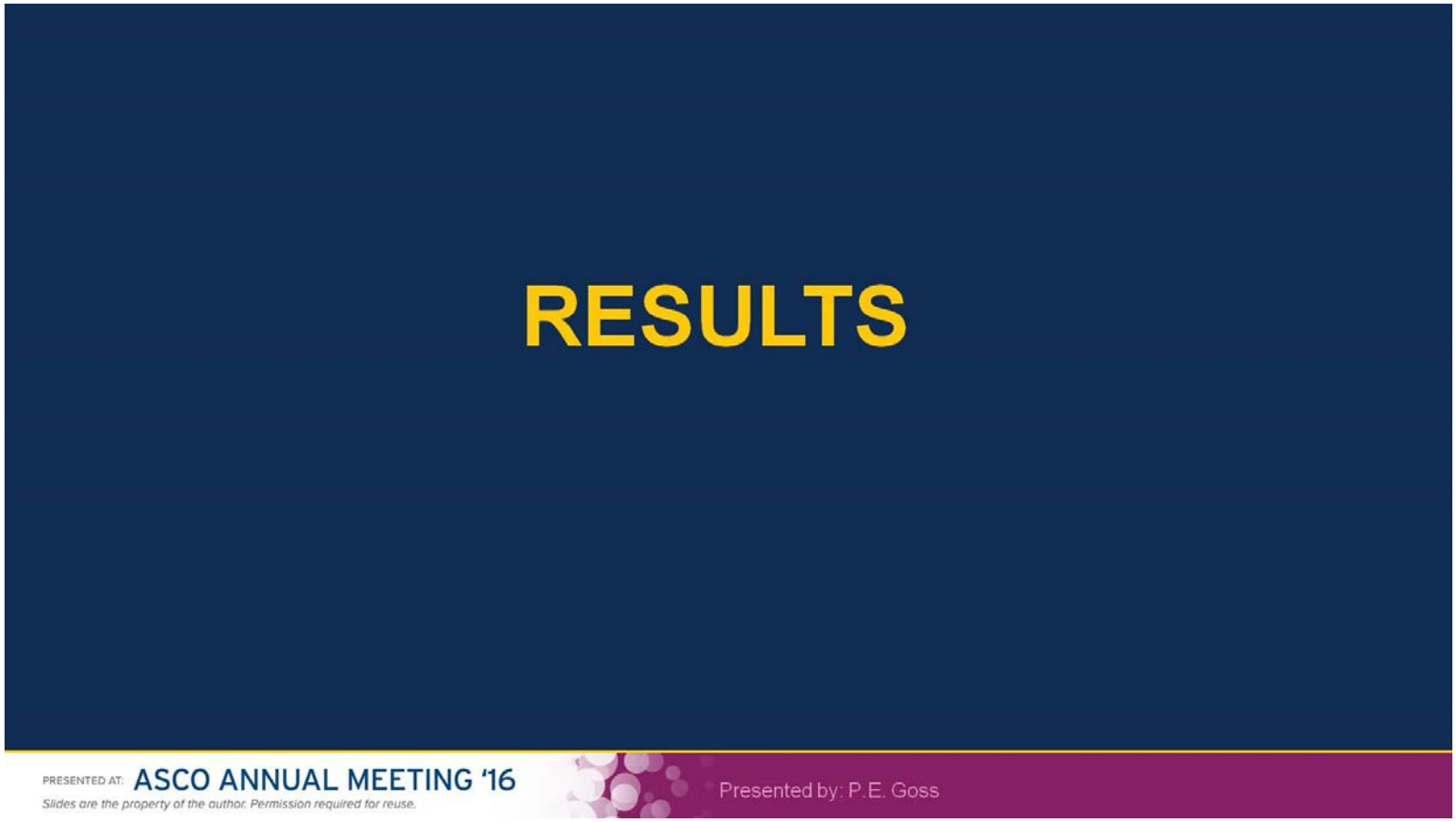
Our initial projection: 196 DFS events in 1800 patients would be needed to achieve a power of 80% to detect a HR of 0.67 (33% reduction in recurrences) at a 2-sided alpha of 5%

Study Amendment:

Based on a lower-than-expected event rate, the trial design was later amended from an event-based primary analysis to time-based. The final database provided an 80% power to detect a hazard ratio of 0.655 for disease-free survival

Interim analyses:

There were no interim analyses planned



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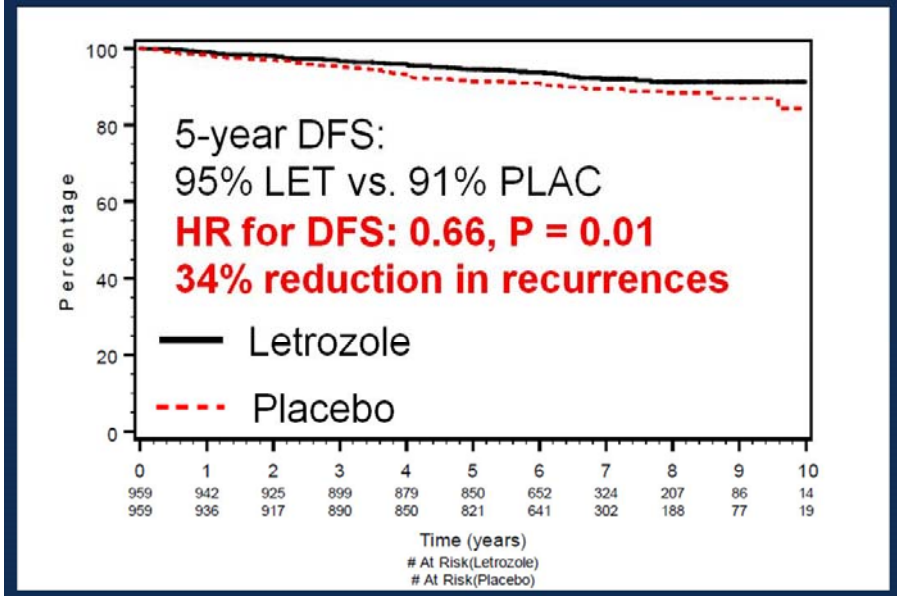
MA.17R – Key Baseline Characteristics

n = 1918 pts	Letrozole (n = 959)	Placebo (n= 959)
	% [interquartile range]	% [interquartile range]
Age (median in years)	65.6 [60.3–72.0]	64.8 [59.6–71.1]
Caucasian (non-Hispanic)	92.2	91.6
ECOG PS 0	88.8	89.3
Time from diagnosis (median yrs)	10.6 [7.5-11.5]	10.6 [7.8-11.6]
Tumor Size T1	57.6	55.8
Nodal Status N0	46.5	46.7
Hormone receptor positive	98.5	99.1
> 4.5 years on prior tamoxifen	70.5	72.2
Adjuvant chemotherapy	58.5	58.1
Mastectomy	47.9	49.2

MA.17R Primary Endpoint: DFS at med F/U of 6.3 yrs



	LET	PLAC
DFS events	67 (7.0)	98 (10.2)
Distant recurrences	42	53
Loco-regional recurrences	19	30
Bone recurrences	28	37
New Contralateral breast cancers§ CBC	13 (1.4)	31 (3.2)

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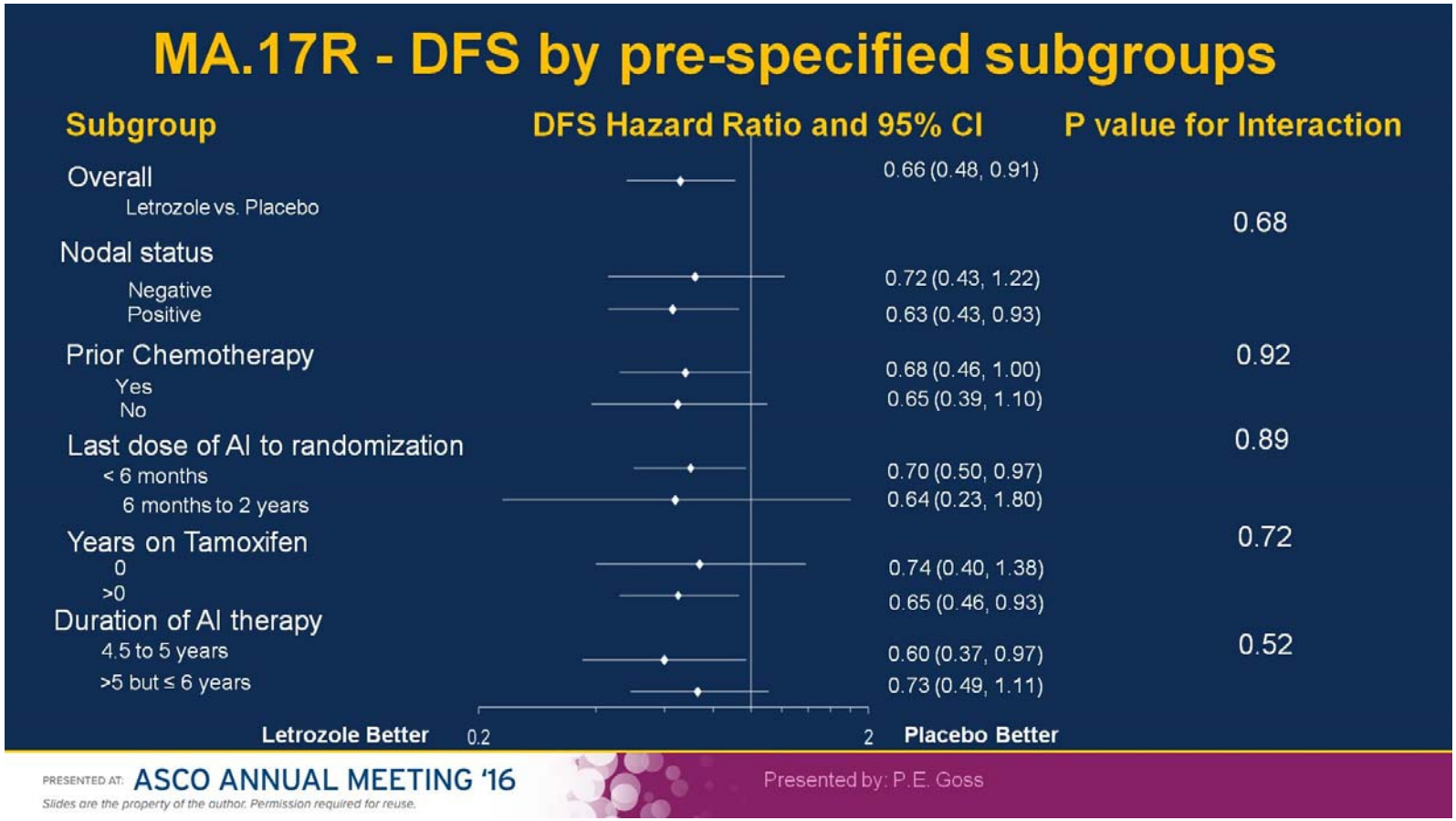

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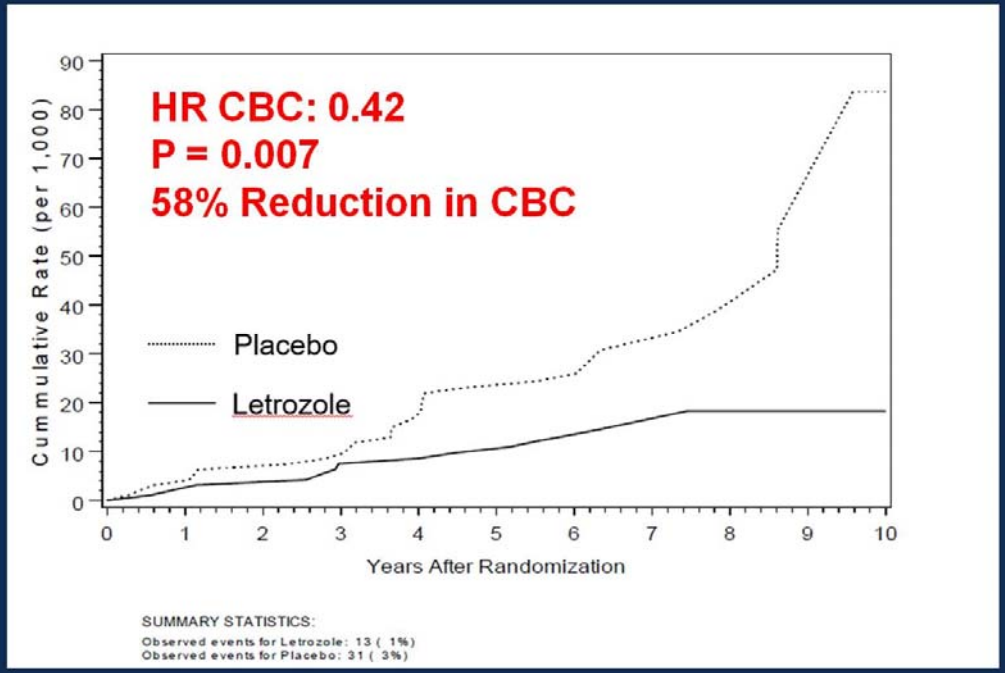
MA.17R - Contralateral Breast Cancer



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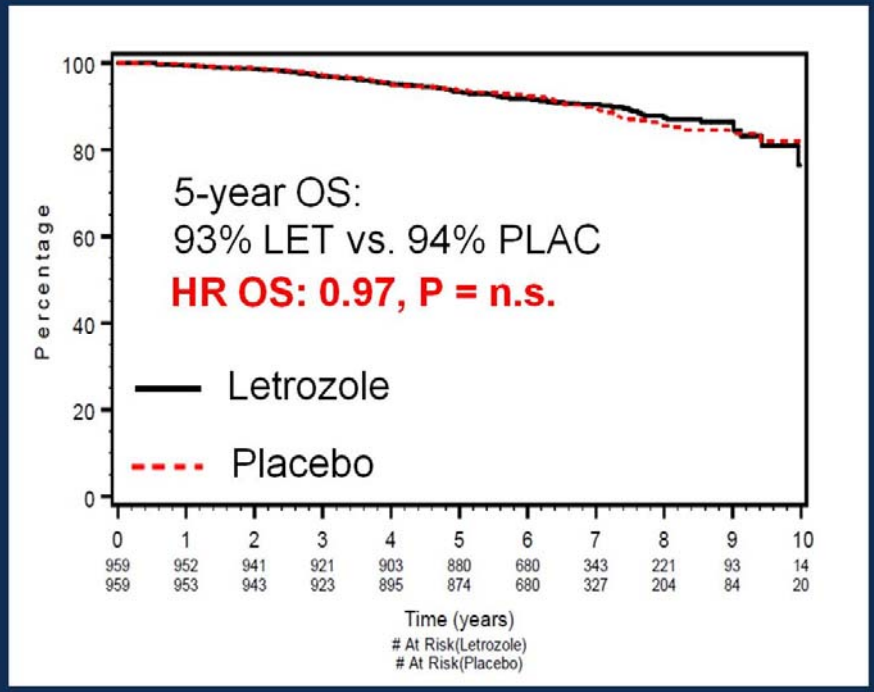
MA.17R – Overall Survival at med F/U of 6.3 yrs



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MA.17R – Toxicities During Treatment

N=1918 Patients	Letrozole (n=959)	Placebo (n=959)	
	N (%)	N (%)	P value
Compliance	62.5%	62.3%	n.s.
Hot flashes/flushes	360 (38)	354 (37)	n.s.
Arthralgia	513 (53)	475 (50)	n.s.
Myalgia	268 (28)	240 (25)	n.s.
Bone pain	174 (18)	133 (14)	0.01
Vaginal dryness	102 (11)	96 (10)	n.s.
Elevation of Alkaline Phosphatase	111(12)	78 (9)	0.01
Elevation of ALT	97 (11)	120 (14)	0.02
Cardiovascular event	116 (12)	98 (10)	n.s.

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MA.17R – Bone Health & Bone Protection at Baseline

	Letrozole	Placebo	Total
Fractures prior to randomization	15.8%	14.8%	15.3%
History of Osteoporosis	21.3%	20.4%	20.9%
Baseline T-score hip	-0.74	-0.73	-0.73
Baseline T-score lumbar spine	-0.73	-0.78	-0.76
Medications for Prevention or Treatment of Osteoporosis during study treatment			
Bisphosphonates	46.3%	46.7%	46.5%
Calcium	86.1%	86.1%	86.1%
Vitamin D	84.5%	84.6%	84.5%
SERMs (raloxifene)	0.3%	0.2%	0.3%

MA.17R – Toxicity: Fractures During Treatment

	Letrozole	Placebo	P-Value
	n (%)	n (%)	
Bone fractures	**133 (14)**	**88 (9)**	**0.001**
Location of bone fractures			
Spinal	17 (1.8)	9 (0.9)	0.12
Wrist	27 (2.8)	16 (1.7)	0.09
Pelvis	1 (0.1)	7 (0.7)	0.08
Hip	7 (0.7)	6 (0.6)	0.79
Femur	9 (0.9)	4 (0.4)	0.17
Tibia	5 (0.5)	4 (0.4)	0.74
Ankle	19 (2.0)	11 (1.2)	0.14
Other	68 (7.1)	48 (5.0)	0.06
New onset osteoporosis	**109 (11)**	**54 (6)**	**<0.0001**

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MA.17R – Quality of Life

Measurements:
MENQOL and SF-36 at baseline and at 12, 24, 36, 48, 60 months
Compliance >85% at each time point

Results:
No between-group **differences** for:
- SF-36 summary score
- Most SF-36 subscales
- No difference in any of the four MENQOL subscales

There was a difference in favor of placebo for SF-36 role-function-physical subscale, but difference (3.2 pts) smaller than minimum difference for clinical significance (5 pts)

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MA.17R – Summary & Conclusions

- MA.17R is the first study to show benefit of extending AI beyond 5 years resulting in a 34% reduction in disease recurrences
- No worsening of QOL was observed on extended letrozole
- No new toxicities associated with long-term letrozole occurred
- Bone health remains important for risk/benefit consideration
- Importantly, unlike many anti-cancer therapies, AIs are readily accessible and therefore our results will further improve the outcome of many women with breast cancer around the world

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years

P.E. Goss, J.N. Ingle, K.I. Pritchard, N.J. Robert, H. Muss, J. Gralow, K. Gelmon, T. Whelan, K. Strasser-Weippl, S. Rubin, K. Sturtz, A.C. Wolff, E. Winer, C. Hudis, A. Stopeck, J.T. Beck, J.S. Kaur, K. Whelan, D. Tu, and W.R. Parulekar

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How has this changed my practice?

- For patients finishing 5 years of adjuvant AI therapy, we now have a better informed discussion about continuing AI – can quantify degree of benefit

- Decision based on benefit/side effect ratio: what is expected benefit of continuing AI based on present risk of relapse? What is expected side effect profile? What is patient's life expectancy?

- Currently not funded by BCCA (CAP requests denied x 2 since ASCO presentation) – private cost for 30 day supply of letrozole approx $100, anastrazole and exemestane approx $150

PALOMA-2: Primary Results From a Phase 3 Trial of Palbociclib Plus Letrozole Compared With Placebo Plus Letrozole in Postmenopausal Women With ER+/HER2– Advanced Breast Cancer

Richard S. Finn,[1] Miguel Martin,[2] Hope S. Rugo,[3] Stephen Jones,[4] Seock-Ah Im,[5] Karen Gelmon,[6] Nadia Harbeck,[7] Oleg N. Lipatov,[8] Janice M. Walshe,[9,10] Stacy Moulder,[11] Eric Gauthier,[12] Dongrui R. Lu,[12] Sophia Randolph,[12] Veronique Dieras,[13] Dennis J. Slamon[1]

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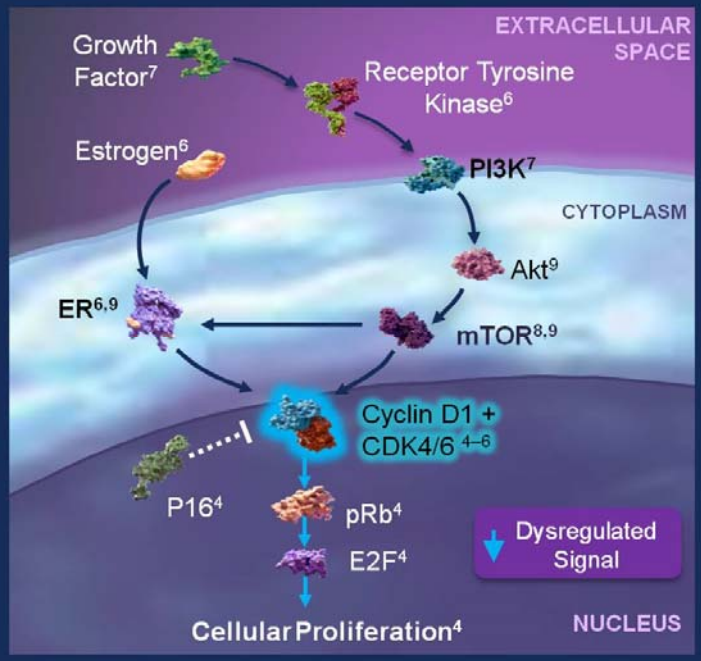
Presented by: Dennis J Slamon

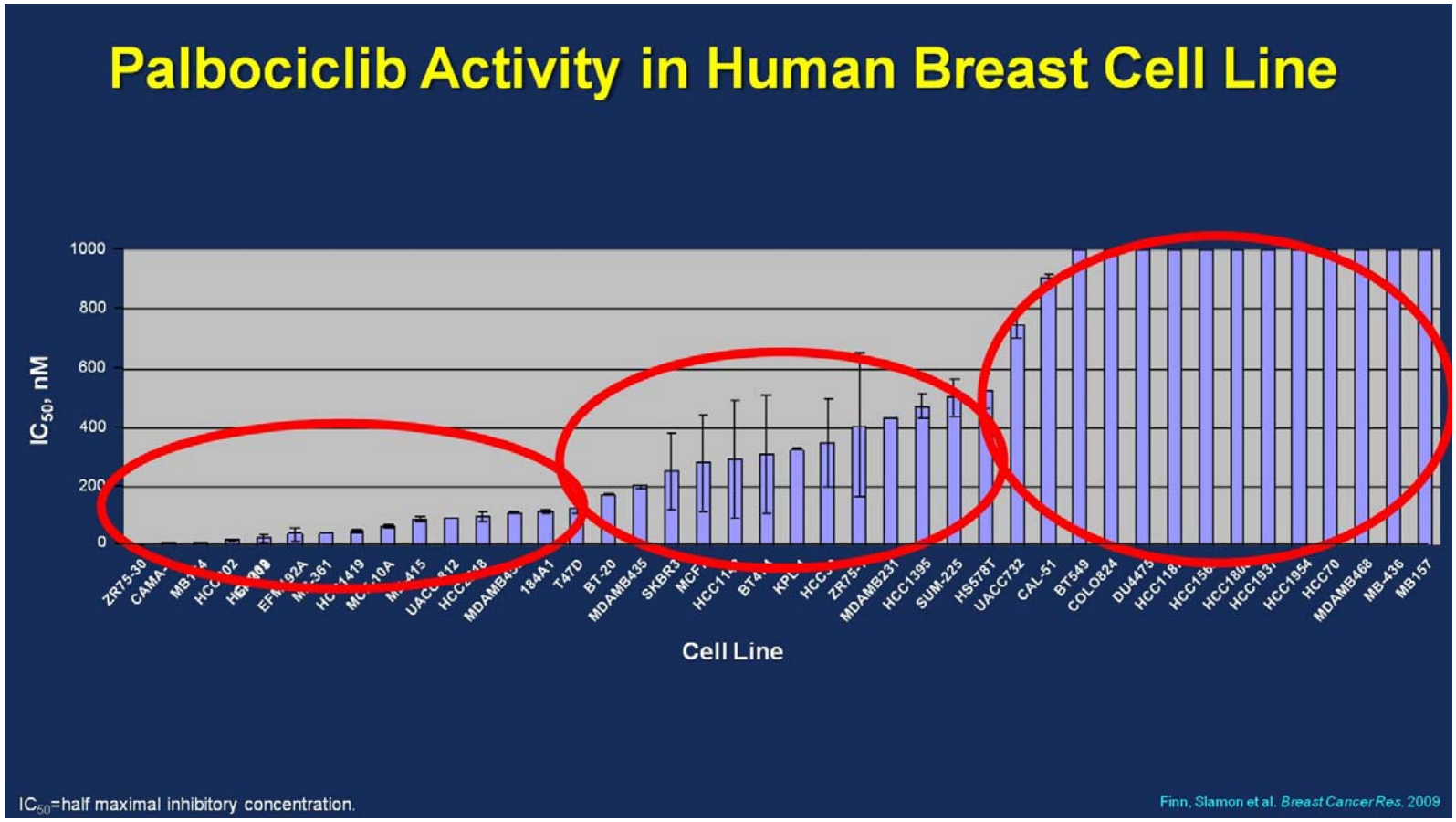
Presented By Richard Finn at 2016 ASCO Annual Meeting

Background: CDK-4/6

- Cyclin dependent kinases (CDKs) - family of serine-threonine kinases that partner with cyclins to regulate cell cycle progression[1]
- Altered expression and activation of various regulators of the cyclin D:CDK-4/6:Rb pathway have been implicated in numerous cancers
- Palbociclib is an oral, highly selective inhibitor of CDK-4/6 that inhibits cell proliferation by prohibiting cell cycle progression from G1 to S phase[2]
- Alterations in the cyclin D:CDK-4/6:Rb pathway have been associated with prognosis, endocrine sensitivity, and growth factor signaling in breast cancer.



1. Musgrove et al. *Nat Rev Cancer*. 2011. 2. Fry et al. *Mol Cancer Ther*. 2004. 3. Finn et al. *Breast Can Res* 2016. 4. Taneja et al. *Clin Med Insights*. 2010. 5. VanArsdale et al. *Clin Cancer Res*. 2015. 6. Osborne et al. *Annu Rev Med*. 2011. 7. Vicier et al. *Breast Cancer Res*. 2014. 8. Baselga. *Oncologist*. 2011. 9. Lange et al. *Endocr Relat Cancer*. 2011.



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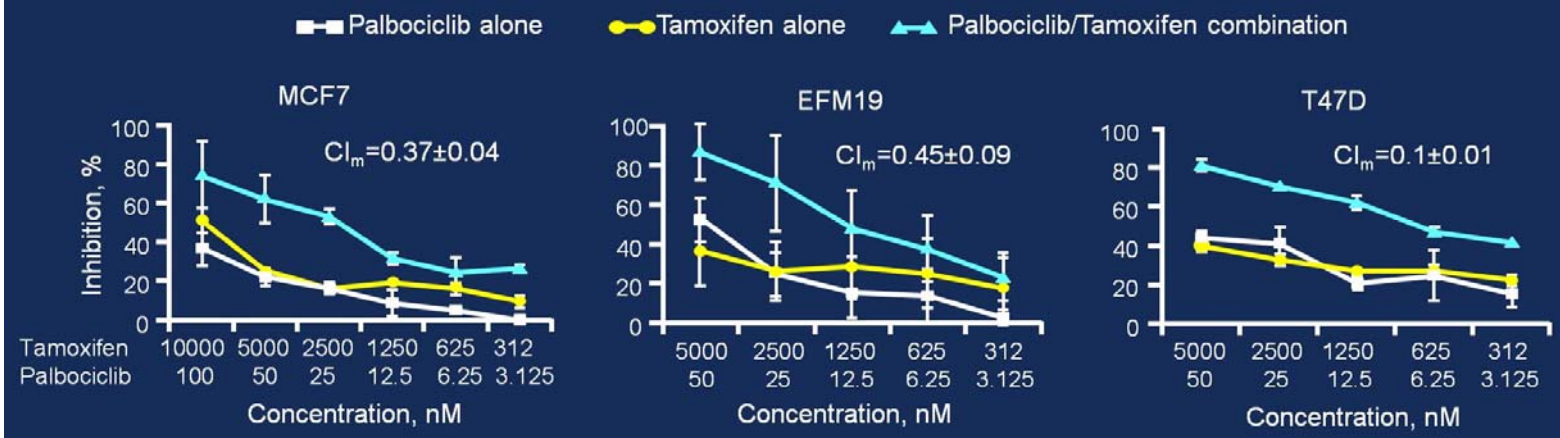
Palbociclib Acts Synergistically With Tamoxifen in ER+ Breast Cancer Cell Lines



- **Mean combination index (CI_m) <1 indicates synergy for the combinations**

Finn, Slamon et al. *Breast Cancer Res.* 2009.

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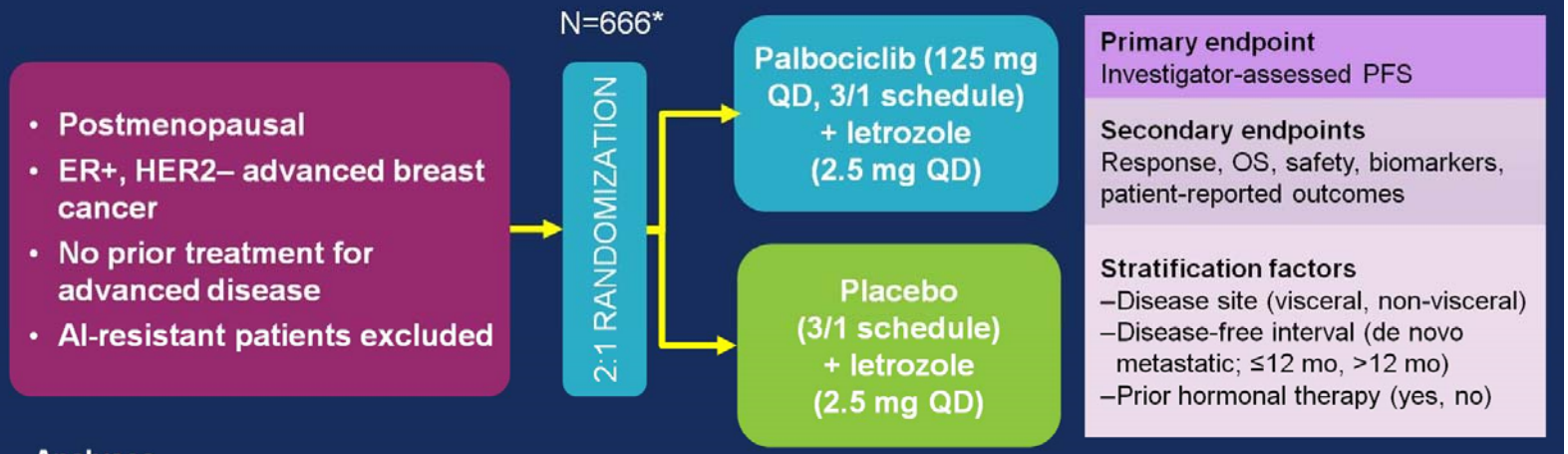
Palbociclib and Breast Cancer

- Preclinical studies identified the luminal estrogen receptor (ER) subtype as being palbociclib-sensitive, with synergy demonstrated between palbociclib and antiestrogens[1]
- These data supported a randomized, open-label, phase 2 study of palbociclib plus letrozole vs letrozole alone as first-line therapy for ER+ advanced breast cancer (PALOMA-1)[2]
  - Addition of palbociclib to letrozole demonstrated a 10-month improvement in progression-free survival (PFS) over letrozole alone (hazard ratio [HR] = 0.49; 95% CI, 0.319–0.748; 1-sided *P*=0.0004)[2] and an acceptable safety profile
  - This was the basis for the conditional US FDA approval for this indication
- PALOMA-3 evaluated palbociclib plus fulvestrant versus fulvestrant alone in patients with advanced breast cancer that had progressed on prior endocrine therapy[3]
  - Palbociclib plus fulvestrant demonstrated a significant improvement in PFS (HR = 0.42; 95% CI, 0.32–0.56, *P*<0.001) with a safety profile consistent with that observed in PALOMA-1
  - This served as the basis for the US FDA approval of palbociclib with fulvestrant[3]

1. Finn, Slamon et al. *Breast Cancer Res.* 2009. 2. Finn et al. *Lancet Oncol* 2015 3. Turner et al. *New Engl J Med* 2015.

PALOMA-2: Study Design (1008)[1]



Analyses

- Statistical analysis designed to detect an increase in PFS with a true HR of 0.69 (representing a 31% improvement) with 347 events
  - 90% power with 1-sided α=0.025

Statistical Assumptions

- Median PFS of placebo plus letrozole = 9 months
- Median PFS of palbociclib plus letrozole = 13 months

- Supportive blinded independent central review of efficacy endpoints performed

[a]Actual. AI=aromatase inhibitor; HER2=human epidermal growth factor receptor 2; OS=overall survival; PFS=progression-free survival; QD=once daily.

1.clinicaltrials.gov NCT01740427

Study Conduct

- **Accrual: February 2013 to July 2014**
- **666 patients randomized**
  - **186 centers in 17 countries**
- Data cutoff: **February 26, 2016**
- **331** progression or death events (by investigator assessment) occurred
- Median duration of follow-up:
  - 23.0 months (95% CI, 22.6–23.4) for the palbociclib plus letrozole arm
  - 22.3 months (95% CI, 21.9–22.9) for the placebo plus letrozole arm

Demographics and Baseline Characteristics (ITT)

	Palbociclib + Letrozole n=444	Placebo + Letrozole n=222
Age, y		
Median (min, max)	62 (30, 89)	61 (28, 88)
< 65	263 (59)	141 (64)
≥ 65	181 (41)	81 (36)
Race		
White	344 (77)	172 (77)
Black	8 (2)	3 (1)
Asian	65 (15)	30 (14)
Other	27 (6)	17 (8)
ECOG performance status		
0	257 (58)	102 (46)
1	178 (40)	117 (53)
2	9 (2)	3 (1)
Disease site[a]		
Visceral	217 (49)	111 (50)
Non-visceral	227 (51)	111 (50)
Bone-Only	103 (23)	48 (22)
Disease-free interval[a,b]		
>12 mo	207 (47)	104 (47)
≤12 mo	89 (20)	44 (20)
De novo advanced disease	148 (33)	74 (33)
Prior hormonal therapy use[a]		
No	191 (43)	95 (43)
Yes	253 (57)	127 (57)

ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat. Values presented as n (%) unless noted otherwise.
[a]Based on the randomization. [b]Time since completion of prior (neo) adjuvant therapy and onset of metastatic disease or recurrence.

Efficacy Results

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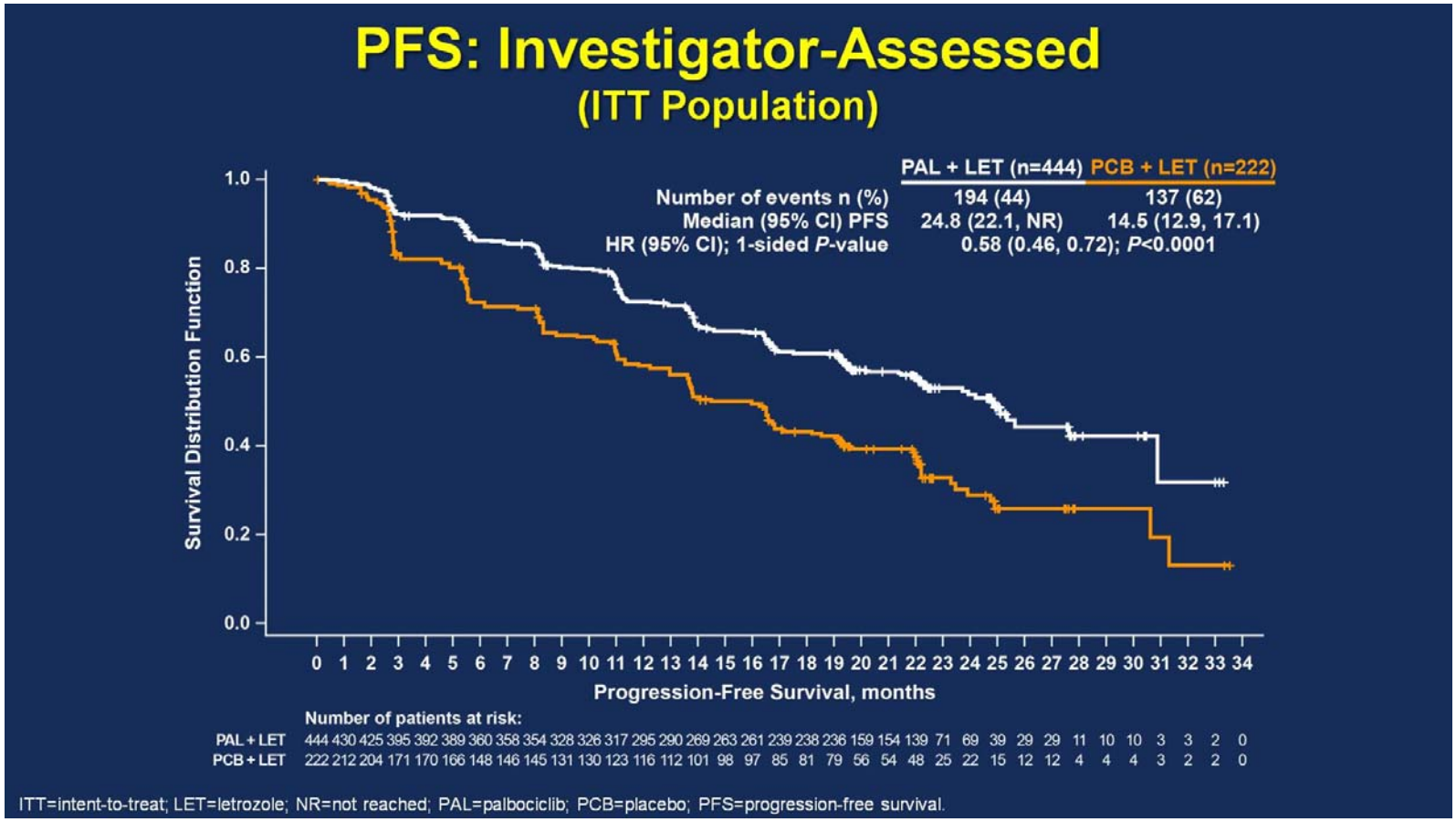

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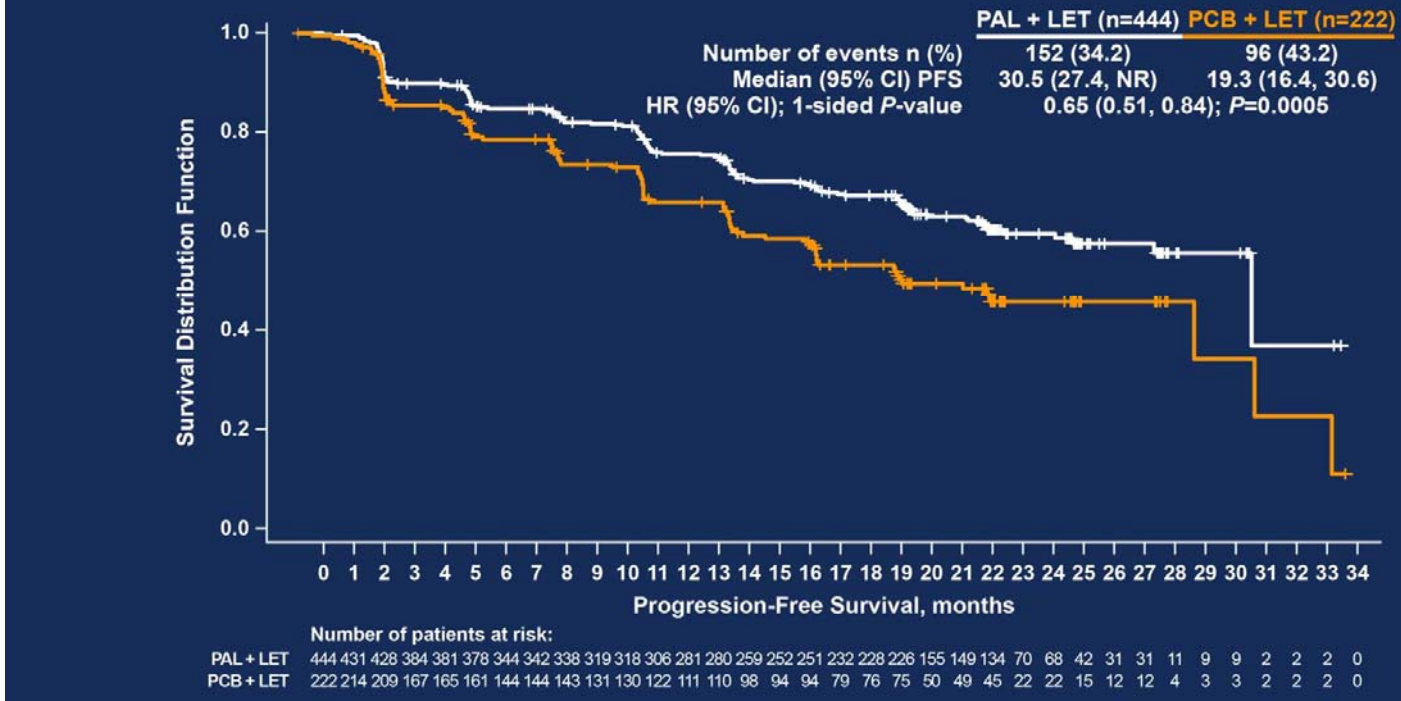
PFS: Blinded Independent Central Review

Confirms PFS Advantage Observed Using Investigator Assessment



ITT=intent-to-treat; LET=letrozole; NR=not reached; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

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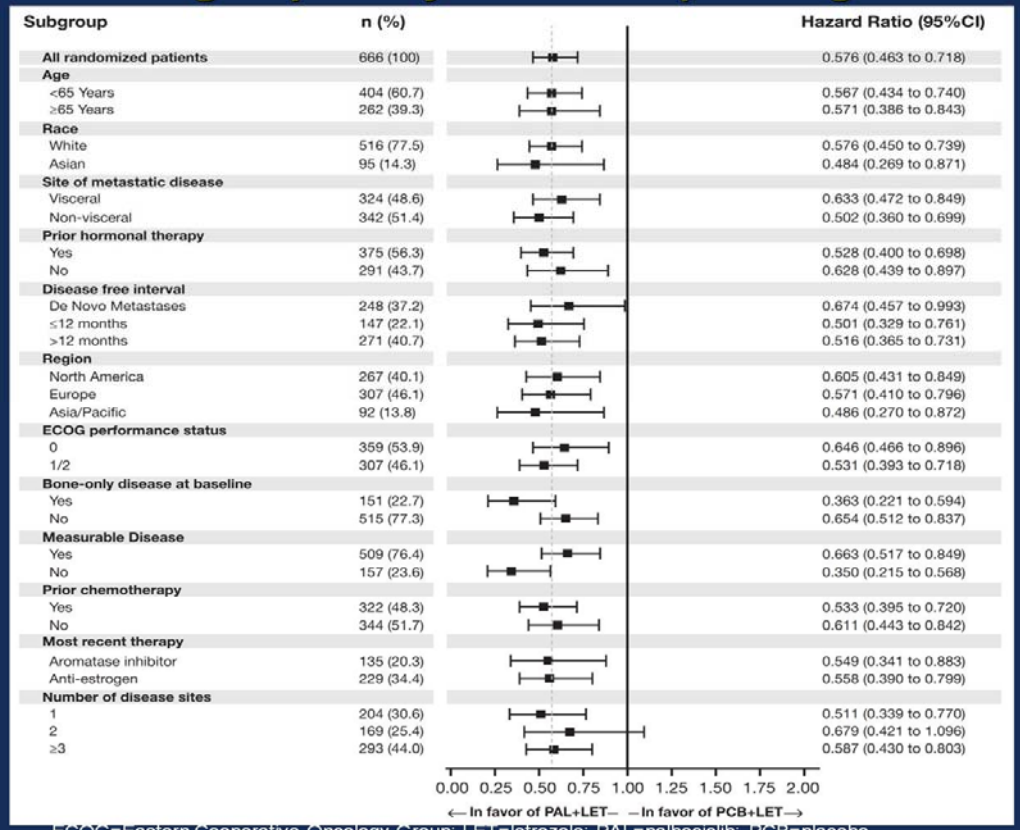
Forest Plot of Subgroup Analysis of PFS (Investigator Assessment)



ECOG=Eastern Cooperative Oncology Group; LET=letrozole; PAL=palbociclib; PCB=placebo.

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Key Secondary Efficacy Endpoints

	Palbociclib + Letrozole (n=444)	Placebo + Letrozole (n=222)	Odds Ratio [95% CI]	1-Sided *P* Value (Exact)
ITT population	**444**	**222**		
Objective response rate,[a] n (%) [95% CI]	187 (**42%**) [37.5, 46.9]	77 (**35%**) [28.4, 41.3]	1.40 [0.98, 2.01]	0.0310
Clinical benefit response rate,[b] n (%) [95% CI]	377 (**85%**) [81.2, 88.1]	156 (**70%**) [63.8, 76.2]	2.39 [1.58, 3.59]	<0.0001
Median Duration of Response, months [95% CI]	**23** [19.8, 28.0]	**17**[c] [14.2, 28.5]	NA	NA
Patients with measurable disease	**338**	**171**		
Objective response rate,[a] n (%) [95% CI]	187 (**55%**) [49.9, 60.7]	76 (**44%**) [36.9, 52.2]	1.55 [1.05, 2.28]	0.0132
Clinical benefit response rate,[b] n (%) [95% CI]	285 (**84%**) [80.0, 88.0]	121 (**71%**) [63.3, 77.5]	2.23 [1.39, 3.56]	0.0003
Median Duration of Response, months [95% CI]	**23** [19.8, 28.0]	**17** [15.4, 28.5]	NA	NA

ITT=intent-to-treat; NA=not applicable. Values presented as n (%) unless noted otherwise. [a]Confirmed complete response + partial response. [b]Confirmed complete response + partial response + stable disease ≥24 weeks. [c]1 patient with bone-only disease at baseline; all other patients had measurable disease at baseline.

Consistency of 1º and 2º Efficacy Endpoints Across PALOMA-1 and PALOMA-2 Studies

	1003[1] (PALOMA-1)	1008 (PALOMA-2)	1023[2] (PALOMA-3)
Design	Phase 2 Open label	Phase 3 Placebo control	Phase 3 Placebo control
Endocrine partner	Letrozole	Letrozole	Fulvestrant
Patients on study, n	165	666	521
Efficacy (palbociclib vs control arm)			
Primary endpoint: PFS			
HR	0.49	0.58	0.46
Median PFS, mo	20.2 vs 10.2 (↑ 10 mos)	24.8 vs 14.5 (↑ 10.3 mos)	9.6 vs 4.6
Secondary endpoints, %			
ORR (ITT, measurable disease)	43 vs 33, 55 vs 39	42 vs 35, 55 vs 44	19 vs 9, 25 vs 11
CBR (ITT)	81 vs 58	85 vs 70	67 vs 40

CBR=clinical benefit response; ITT=intent-to-treat; ORR=objective response rate.

1. Finn et al. *Lancet Oncol.* 2015. 2. Cristofinalli et al. *Lancet Oncol.* 2016.

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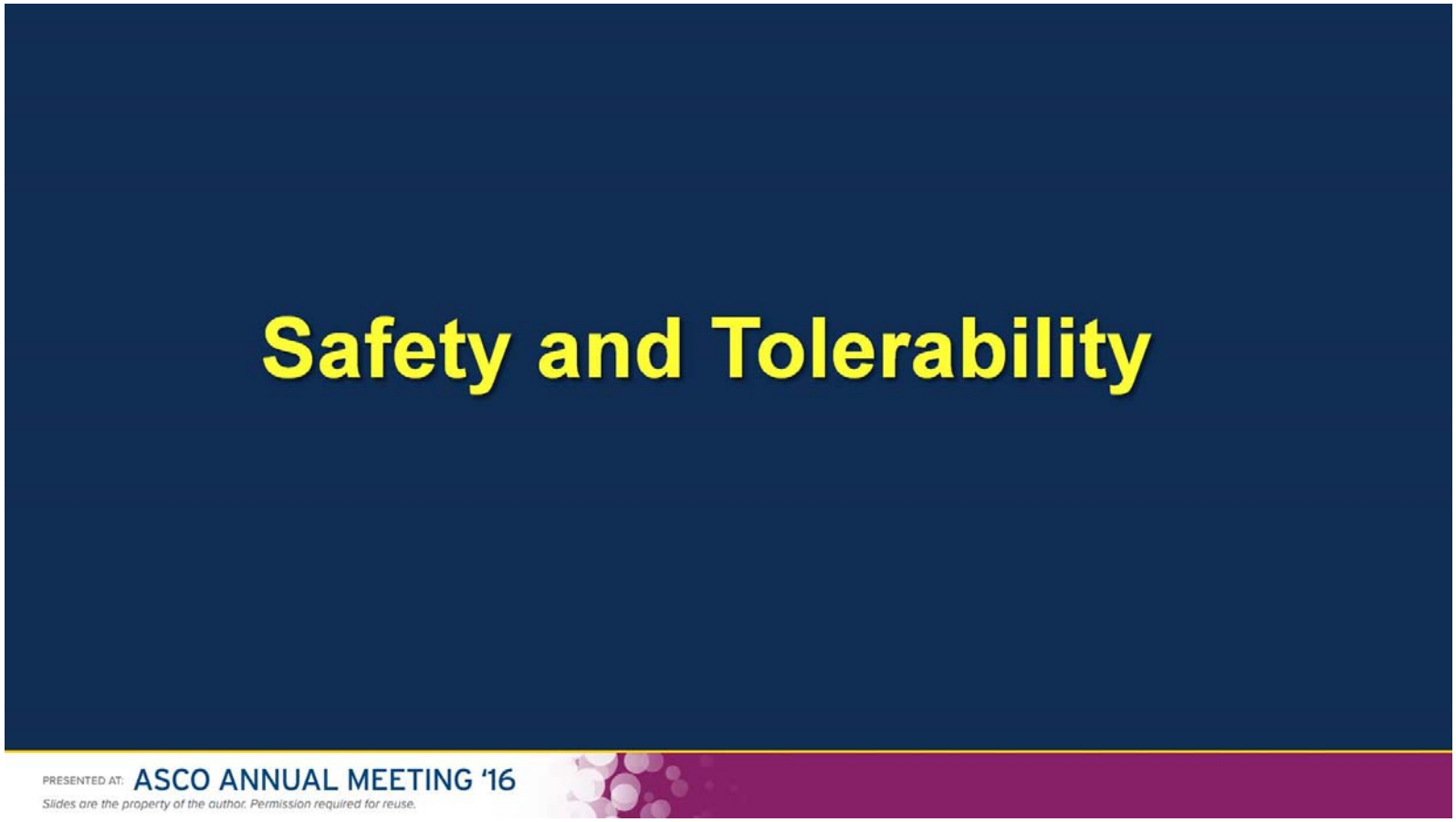

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Treatment Administration (As-Treated Population)

	Palbociclib + Letrozole (n=444)		Placebo + Letrozole (n=222)	
	Palbociclib	**Letrozole**	**Placebo**	**Letrozole**
Median (range) treatment duration, days	603 (1, 1037)	617 (1, 1037)	413 (10,1071)	420 (10, 1075)
Median (range) relative dose intensity, %	93.0 (40.3, 109.5)	99.9 (73.4, 100.2)	99.6 (56.1, 104.5)	100.0 (79.0, 100.0)
Patient with dose Interruptions, n (%)	310 (70)	237 (53)	94 (42)	99 (45)
Patients with cycle delays, n (%)	303 (68)	NA	60 (27)	NA
Patients with ≥1 dose reduction, n (%)	160 (36)	NA	3 (1)	NA

NA=not applicable.

TEAEs Occurring in ≥15% of Patients—All Causality

	Palbociclib + Letrozole (n=444)			Placebo + Letrozole (n=222)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any adverse event, n (%)	439 (99)	276 (62)	60 (14)	212 (95)	49 (22)	5 (2)
Neutropenia[a]	353 (80)	249 (56)	46 (10)	14 (6)	2 (1)	1 (<1)
Leukopenia[a]	173 (39)	107 (24)	3 (1)	5 (2)	0	0
Fatigue	166 (37)	8 (2)	0	61 (28)	1 (<1)	0
Nausea	156 (35)	1 (<1)	0	58 (26)	4 (2)	0
Arthralgia	148 (33)	3 (1)	0	75 (34)	0	0
Alopecia	146 (33)	0	0	35 (16)	0	0
Diarrhea	116 (26)	6 (1)	0	43 (19)	3 (1)	0
Cough	111 (25)	0	0	42 (19)	0	0
Anemia[a]	107 (24)	23 (5)	1 (<1)	20 (9)	4 (2)	0
Back pain	96 (22)	6 (1)	0	48 (22)	0	0
Headache	95 (21)	1 (<1)	0	58 (26)	4 (2)	0
Hot flush	93 (21)	0	0	68 (31)	0	0
Constipation	86 (19)	2 (<1)	0	34 (15)	1 (<1)	0
Rash[a]	79 (18)	4 (1)	0	26 (12)	1 (<1)	0
Asthenia	75 (17)	10 (2)	0	26 (12)	0	0
Thrombocytopenia[a]	69 (16)	6 (1)	1 (<1)	3 (1)	0	0
Vomiting	69 (16)	2 (<1)	0	37 (17)	3 (1)	0
Pain in extremity	68 (15)	1 (<1)	0	39 (18)	3 (1)	0
Stomatitis	68 (15)	1 (<1)	0	13 (6)	0	0
Decreased appetite	66 (15)	3 (1)	0	20 (9)	0	0
Dyspnea	66 (15)	5 (1)	0	30 (14)	3 (1)	0
Insomnia	66 (15)	0	0	26 (12)	0	0

TEAE=treatment-emergent adverse event. [a]Includes clustered Medical Dictionary for Regulatory Activity (MedDRA) preferred terms.

Summary of Adverse Events

Serious Adverse Events (SAEs)

- Overall incidence of SAEs was higher in patients receiving palbociclib + letrozole vs placebo + letrozole (19.6% vs 12.6%)
- SAEs were reported for <1% of patients in either treatment arm except febrile neutropenia (1.6% in the palbociclib arm) and pulmonary embolism (1.4% in the placebo arm)

Permanent Discontinuations Due to Adverse Events (AEs)

- 9.7% of patients in the palbociclib arm vs 5.9% in the placebo arm
- Most were reported as a single event

Deaths Due to AEs

- 2.3% of patients in the palbociclib arm vs 1.8% in the placebo arm
- None of the reported on-study deaths were due to treatment-related toxicity

Conclusions

- Palbociclib combined with letrozole significantly improved median PFS compared with placebo plus letrozole as first-line therapy in women with ER+/HER2– advanced breast cancer
  - A >10 month improvement in median PFS was observed (24.8 vs 14.5 mo)
  - HR = 0.58 (95% CI, 0.46–0.72; *P*<0.0001)
- Benefit from palbociclib was also demonstrated across prespecified subgroups and confirmed by blinded independent review
- Palbociclib was well tolerated with the most common AEs being neutropenia and leukopenia; however, the overall incidence of neutropenic fever was low (1.8%)
- These data confirm the results of the open label PALOMA-1 study and represent the longest significant improvement in median PFS in a front-line setting

How has this changed my practice?

- I have had discussions with the appropriate patient regarding first line NSAI + CDK 4/6 Inhibitor
- Meaningful improvement in clinical efficacy with negligible toxicities
- However, no public funding (yet) for this medication. Cost on a self-pay basis approximately $6200 per month – patient support program available

ESPAC-4: A multicenter, international, open label randomized controlled phase III trial of adjuvant combination chemotherapy of gemcitabine (GEM) and capecitabine (CAP), versus monotherapy gemcitabine in patients with resected pancreatic ductal adenocarcinoma

J. Neoptolemos , D. Palmer , P. Ghaneh , J. W. Valle , D. Cunningham , J. Wadsley , T. Meyer , A. Anthoney , B Glimelius , Pehr Lind, S. Falk , J. Izbicki , G. Middleton, P. Ross , H. Wasan, A. McDonald, T. Crosby, E. Psarelli, P. Hammel and M. Büchler for the European Study Group on Pancreatic Cancer (ESPAC)

NCRI Pancreatic Cancer Sub-Group

CRUK Liverpool Cancer Trials Unit

EudraCT#: 2007-004299-38

ISRCTN#: 43482138

CRUK#: C245/A8968/A20830

NCRN National Cancer Research Network

ASCO, Chicago 06/06/2016 8:00 AM - 11:00 AM LBA4006

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UKCRC Registered Clinical Trials Units

NHS National Institute for Health Research

CANCER RESEARCH UK

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John P. Neoptolemos, University of Liverpool, Liverpool/UK

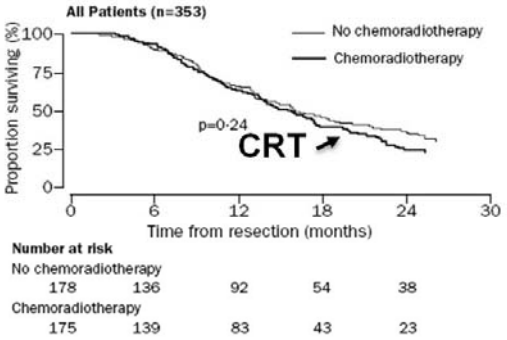
COI: Grants/research supports: Taiho Pharma, KAEL GemVax, AstraZeneca, Clovis Oncology and Ventana, Merck. Educational Travel Grants: NUCANA

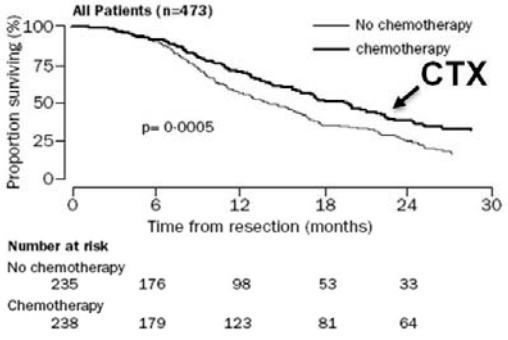
Background

ESPAC-1plus, N=541: Lancet, 2001

No benefit for Chemoradiation – Potential benefit for Chemotherapy

ALL, N=353





ALL, N=473

2x2 Factorial, N=285

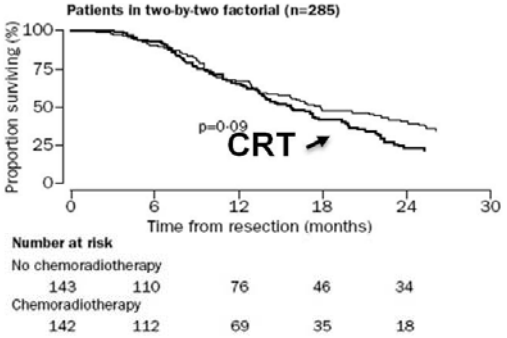


Figure 2: **Survival by chemoradiotherapy randomisation**
All patients (n=353) and for those randomised in the two-by-two factorial only (n=285).

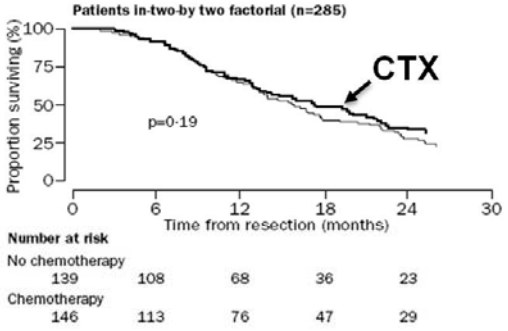


Figure 3: **Survival by chemotherapy randomisation**
All patients (n=473) and for those randomised in the two-by-two factorial only (n=285).

2x2 Factorial, N=285

Neoptolemos et al, Lancet, 2001;358(9293):1576-85

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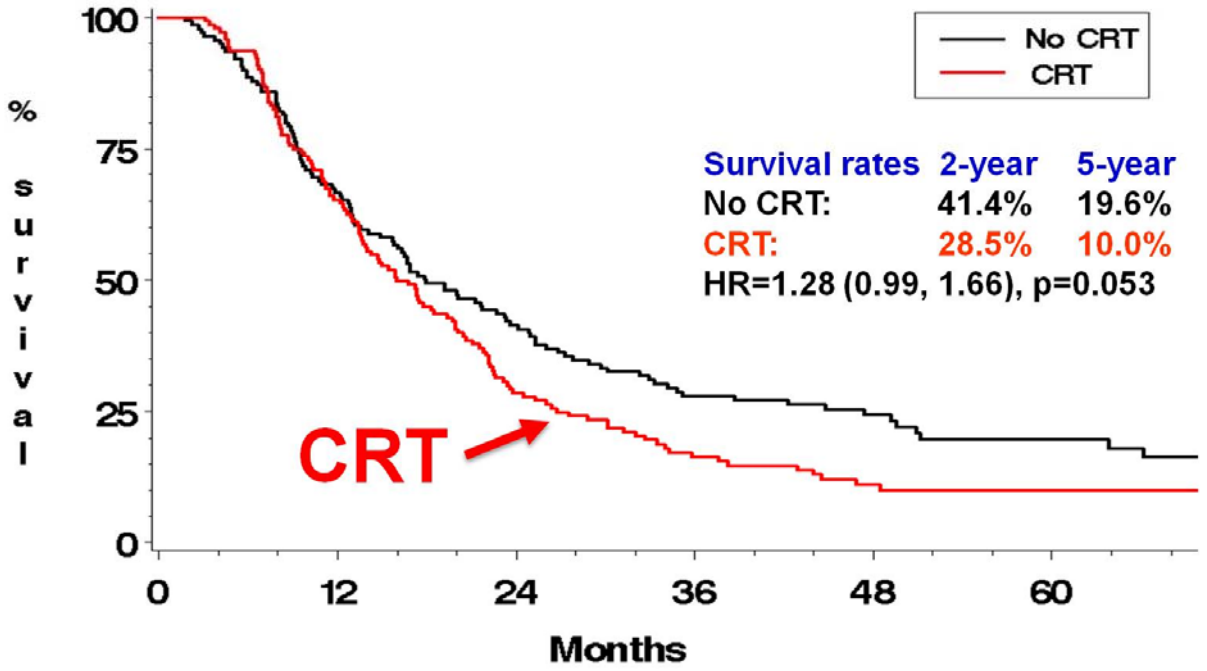
ESPAC-1, N=289, NEJM 2004: No benefit for Chemoradiation

2x2 Factorial: Survival by Adjuvant Chemoradiation



Neoptolemos JP et al
NEJM 2004; 350:1200-10

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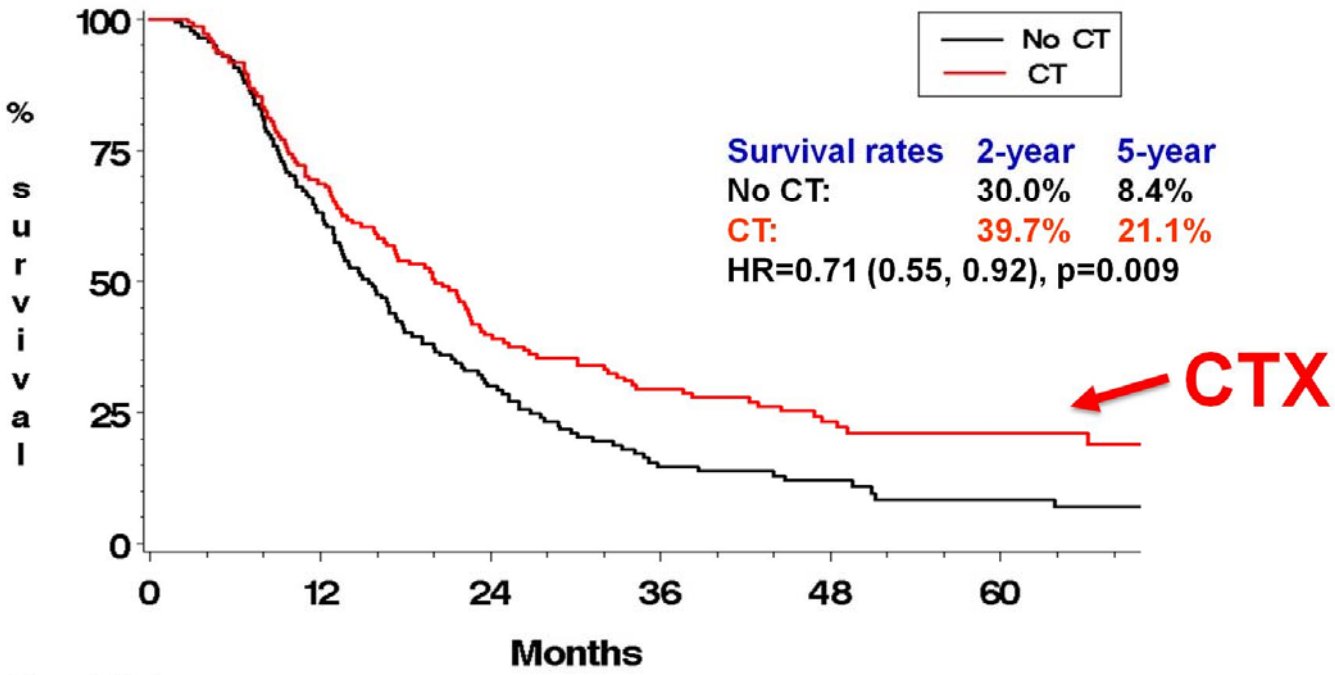
ESPAC-1, N=289, NEJM 2004: Benefit for Chemotherapy

2x2 Factorial: Survival by Adjuvant Chemotherapy



No. at Risk						
No CT	142	89	41	18	11	7
CT	147	99	56	38	22	11

Neoptolemos JP et al
NEJM 2004; 350:1200-10

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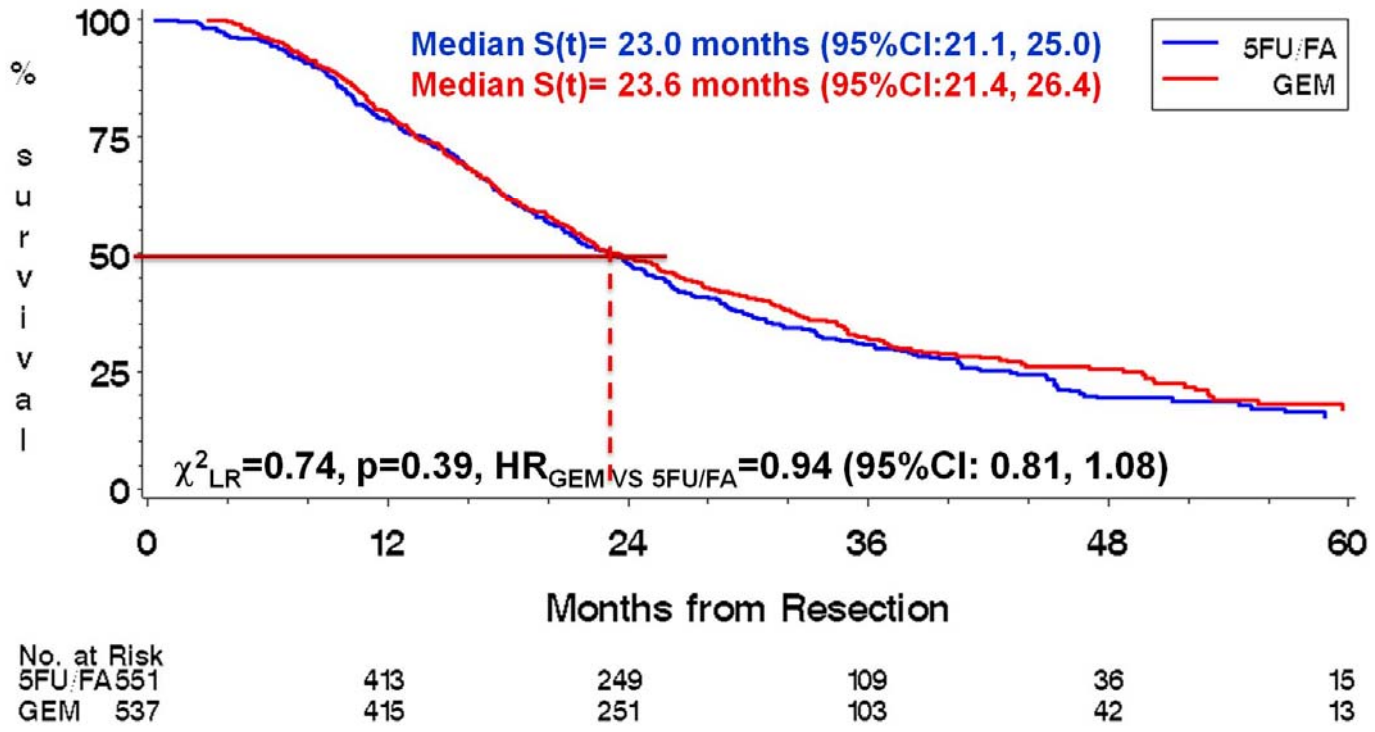
ESPAC-3, N=1,088: Gemcitabine not better than 5-FU/FA



No. at Risk					
5FU/FA	551	413	249	109	36	15
GEM	537	415	251	103	42	13

Neoptolemos et al JAMA 2010; 304: 1073-81

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ESPAC - 4

Stratified log-rank test with 5% 2-sided α, for a 10% difference in 2 year survival, 90% power = 480 events = 722 patients, 361 in @ arm

722 patients
pancreatic ductal adenocarcinoma
'curative' resection ≤12 wks

↓

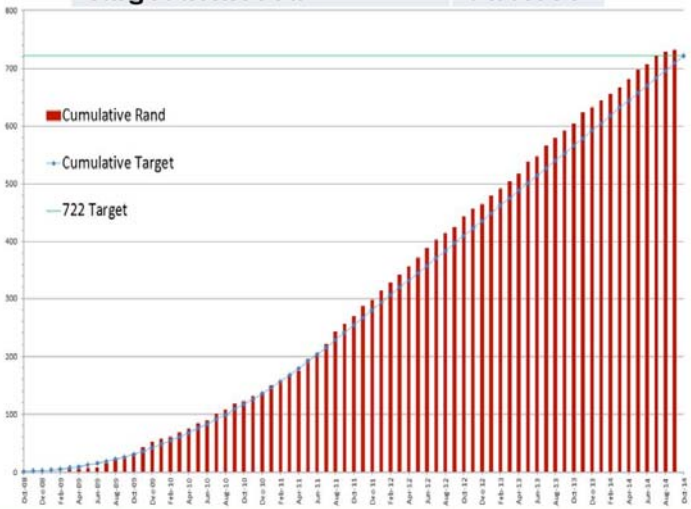
RANDOMISATION at Liverpool Cancer Trials Unit

GEMCITABINE
1000mg/m^2 -Days 1,8 and 15 for 6 cycles

GEMCITABINE
1000mg/m^2 -Days 1,8 and 15 for 6 cycles
CAPECITABINE
1660mg/m^2/day – 21/28d
i.e. 24 weeks

3-MONTHLY FOLLOW UP FROM RANDOMISATION TO DEATH

Target number of patients	722
Start date	13/01/08
Number of sites opened	106
Planned close date	01/11/14
Target achieved	31/07/14



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Eligibility

- Complete macroscopic resection for pancreatic ductal adenocarcinoma (WHO Classification)
- R0 or R1 resection (≤1mm any surface)
- No: ascites, liver or peritoneal metastasis, or any other distant abdominal or extra-abdominal organ spread
- No previous or concurrent malignancy diagnoses
- WHO performance status ≤ 2
- Life-expectancy of more than 3 months
- Fully informed written consent

Patient Demographics

		GEM n=366	GEMCAP n=364	TOTAL n=730
*Age (years)		65 (37-80)	65 (39-81)	65 (37-81)
Sex	Male	212 (58%)	202 (55%)	414 (57%)
	Female	154 (42%)	162 (45%)	316 (43%)
Baseline PS	0	158 (43%)	150 (41%)	308 (42%)
	1	199 (54%)	202 (56%)	401 (55%)
	2	9 (3%)	12 (3%)	21 (3%)
Smoking	Never	151 (41%)	146 (40%)	297 (41%)
	Past	136 (37%)	148 (41%)	284 (39%)
	Present	62 (17%)	61 (17%)	123 (17%)
	Unknown	17 (5%)	9 (2%)	26 (3%)
*Surgery to Rand (days)		65 (23-111)	64 (21-111)	64 (21-111)

** Median (Range)*

On-Study Data

		GEM n=366	GEMCAP n=364	TOTAL n=730
Diabetic	No	266 (73%)	272 (75%)	538 (74%)
	Non-insulin dep	52 (14%)	45 (12%)	97 (13%)
	Insulin dep	47 (13%)	46 (13%)	93 (13%)
	Unknown	1 (0%)	1 (0%)	2 (0%)
Surgery	Whipples	188 (51%)	182 (50%)	370 (51%)
	Pyl-Pres Whipples	122 (33%)	129 (35%)	251 (34%)
	Total Panctx	27 (8%)	22 (6%)	49 (7%)
	Distal Panctx	29 (8%)	31 (9%)	60 (8%)
Local Invasion	No	189 (52%)	189 (52%)	378 (52%)
	Yes	176 (48%)	173 (48%)	349 (48%)
	Unknown	1 (0%)	2 (0%)	3 (0%)
Post-op Comps	No	271 (74%)	250 (69%)	521 (72%)
	Yes	93 (25%)	113 (31%)	206 (28%)
	Unknown	2 (1%)	1 (0%)	3 (0%)
*Post-op CA19-9 (kU/L)		20.5 (0.1-2,448)	17.6 (0.6-8,112)	18.7 (0.1-8,112)
*Post-op CRP (mg/L)		5.0 (0.1-345)	5.0 (0.0-296)	5.0 (0.0-345)

** Median (Range)*

Tumour Pathology

		GEM n=366	GEMCAP n=364	TOTAL n=730
Stratification factors:				
R Status	R0	147 (40%)	143 (39%)	290 (40%)
	R1	219 (60%)	221 (61%)	440 (60%)
Country	UK	280 (77%)	276 (76%)	556 (76%)
	FR/GER/SWE	86 (23%)	88 (24%)	174 (24%)
*Max Tumour Size (mm)		30 (0-110)	30 (6-105)	30 (0-110)
Grade	Well	30 (8%)	32 (9%)	62 (9%)
	Moderate	192 (52%)	175 (48%)	367 (50%)
	Poor	140 (38%)	147 (40%)	287 (39%)
	Undifferentiated	2 (1%)	2 (1%)	4 (1%)
	Unknown	2 (1%)	8 (2%)	10 (1%)
Nodes	Negative	67 (18%)	76 (21%)	143 (20%)
	Positive	299 (82%)	288 (79%)	587 (80%)

** Median (Range)*

Follow-Up

	GEM n=366	GEMCAP n=364	Total n=730
Survival Status:			
Alive - number	127 (35%)	145 (40%)	272 (37%)
Dead - number	239 (65%)	219 (60%)	458 (63%) (target = 480)
Follow-up of alive patients:			
Number of patients	127	145	272
Median (95% CI) (months)*	40.5 (34.9-44.6)	44.4 (40.0-49.0)	43.2 (39.7-45.5)
Range (months)	0-78	0-81	0-81
Inter-quartile Range (months)	21-42	23-51	21-46
Number (%) with ≥24mth FU	80 (63%)	107 (74%)	187 (69%)

**Reverse Kaplan-Meier method*

Treatment Received

- GEM 1,000mg/m^2 d1 @wk for 3/4 wks for 6 cycles
- Total protocol GEM=3,000mg/m^2 per cycle, overall=18,000mg/m^2
- 1 (0.3%) of 366 patients received NO GEM
- 239 (65%) of 366 patients received 6 cycles GEM
- Median total GEM dose: 16,750mg/m^2 (Range: 1000-18,750)
- Median protocol GEM dose: 93% (Range: 5-104%)

- GEMCITABINE 1,000mg/m^2 d1 @wk for 3/4 wks for 6 cycles
- Total protocol GEM=3,000mg/m^2 per cycle, overall=18,000mg/m^2
- CAPECITABINE 1,660mg/m2/day – 21/28d
- Total protocol CAP=34,860mg/m^2 per cycle, overall=209,160mg/m^2
- 5 (1%) received no GEM and 6 (2%) of 364 patients received NO CAP
- 195 (54%) of 364 patients received 6 cycles GEMCAP
- Median total GEM dose: 15,000mg/m^2 (Range: 1,000-20,500)
- Median protocol GEM dose: 83% (Range: 5-114%)
- Median total CAP dose: 162,680mg/m^2 (Range: 1660-209,910)
- Median protocol CAP dose: 78% (Range: 0.8-100%)

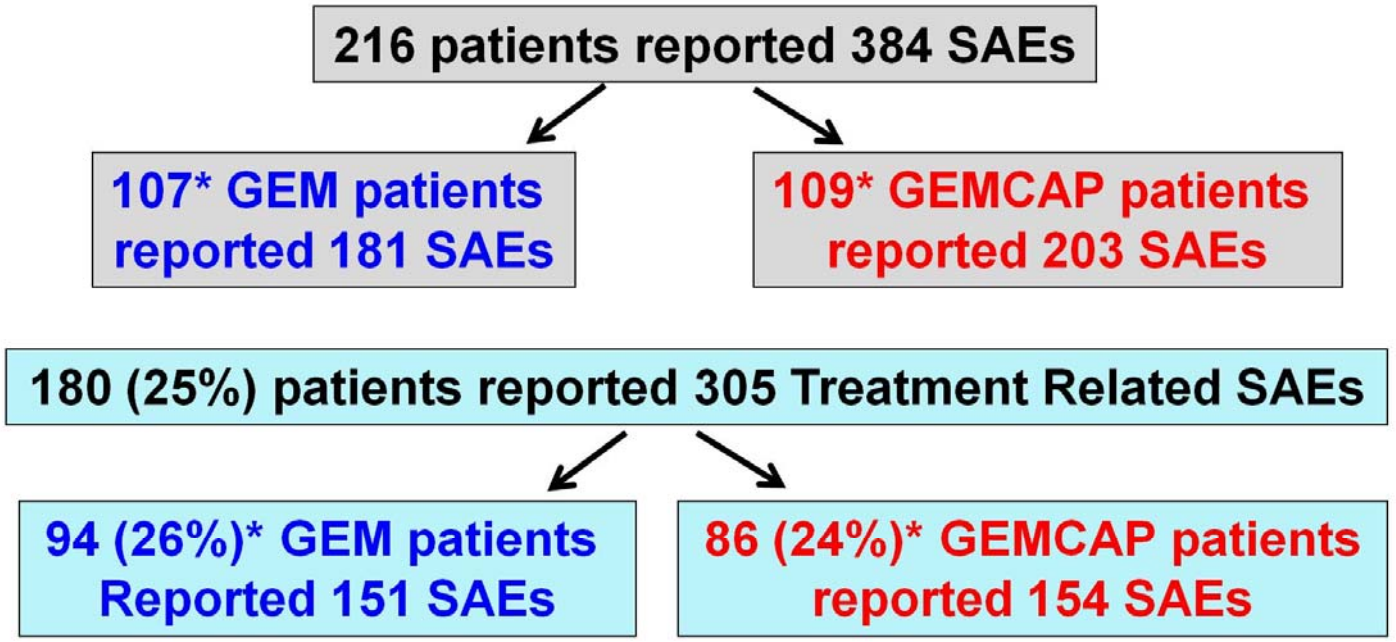
Reported Toxicity

Number of patients in Safety Set with at least one NCI CTC v4 grade 3/4 event

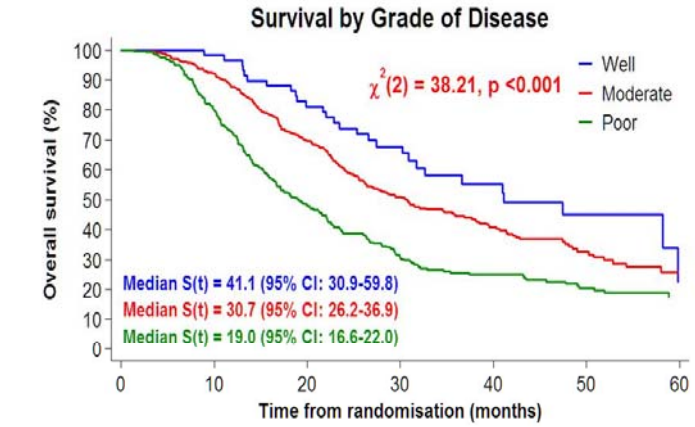
CTC 3/4 event	GEM Number of patients (% of 366)	P-value*	GEMCAP Number of patients (% of 359)
Anaemia	14 (4%)	0.279	8 (2%)
Diarrhoea	6 (2%)	0.008	19 (5%)
Fatigue	19 (5%)	0.870	20 (6%)
Fever	6 (2%)	1.000	6 (2%)
Infection and infestations, Other	24 (7%)	0.012	9 (3%)
Lymphocytes	11 (3%)	0.821	9 (3%)
Neutrophils	89 (24%)	<0.001	137 (38%)
Hand-Foot syndrome	0 (0%)	<0.001	26 (7%)
Platelets	7 (2%)	0.800	8 (2%)
Thromboembolic event	9 (2%)	1.000	8 (2%)
WBC	28 (8%)	0.242	37 (10%)

* Exploratory analysis: Fisher's exact test

Serious Adverse Events

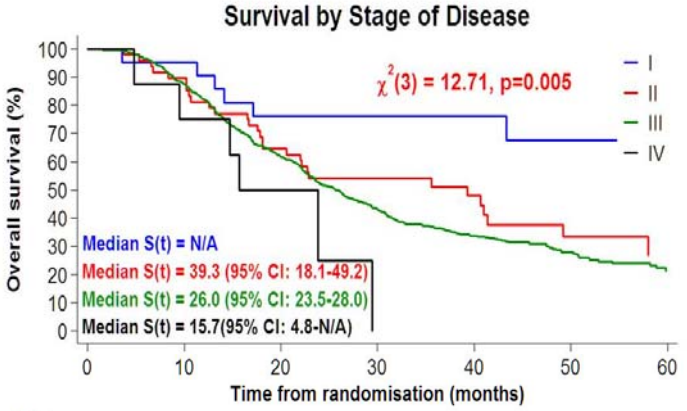


*Exploratory analysis: χ^2_{df1} test p>0.05



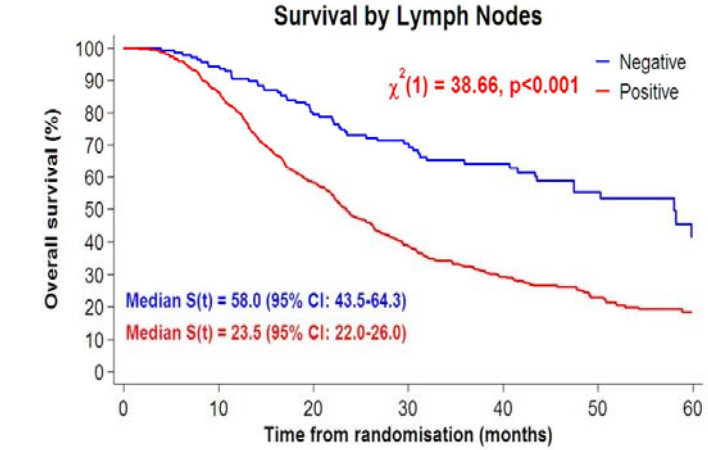
No. at Risk

Well	62	59	46	30	18	10	2
Moderate	367	332	238	138	80	35	15
Poor	287	227	132	72	43	29	11



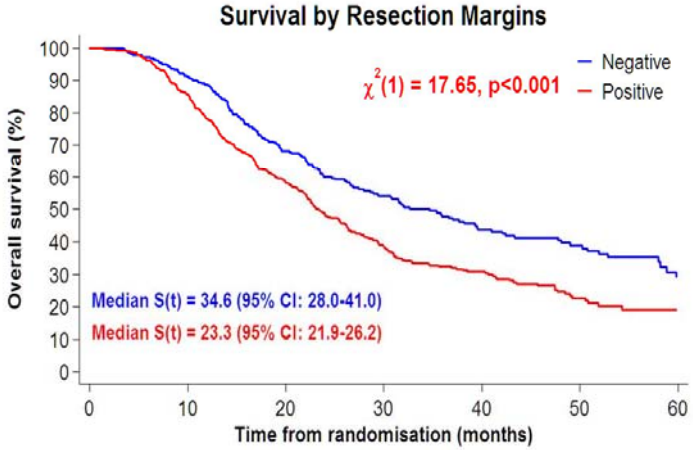
No. at Risk

I	22	20	16	14	9	4	1
II	49	43	31	21	15	8	4
III	651	561	377	213	120	65	23
IV	8	6	2	0	0	0	0



No. at Risk

Negative	143	130	104	71	49	30	10
Positive	587	500	322	177	95	47	18



No. at Risk

Negative	290	259	184	119	71	45	19
Positive	440	371	242	129	73	32	9

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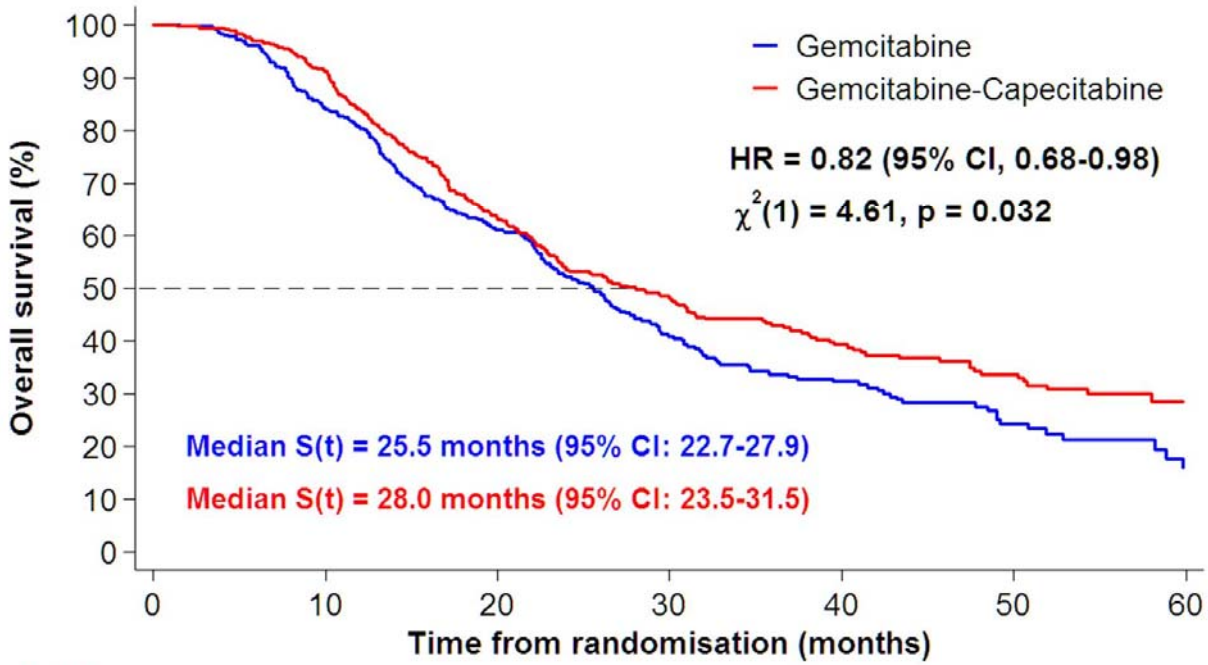
Survival by Treatment



No. at Risk

Gem	366	302	207	109	61	27	9
GemCap	364	328	219	139	83	50	19

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Univariate Survival Analysis:
Cox PH model

Factor		Unadjusted HR (95% CI)	Log-Rank χ^2	P-value
Smoking status				
	Never	1		
	Past	1.05 (0.85 - 1.29)	0.20	0.654
	Present	1.38 (1.07 - 1.78)	5.97	0.015
Post-op CA19-9 (kU/L)[a]		1.36 (1.28 - 1.45)	91.6	<0.001*
Tumour grade				
	Well	1		
	Moderately	1.41 (0.96 - 2.08)	3.01	0.082
	Poorly	2.35 (1.59 - 3.46)	18.6	<0.001*
Local invasion				
	No	1		
	Yes	1.32 (1.10 - 1.58)	8.62	0.003
Lymph nodes				
	Negative	1		
	Positive	2.36 (1.78 - 3.11)	36.4	<0.001*
Resection margin				
	Negative	1		
	Positive	1.51 (1.24 - 1.83)	17.4	<0.001*
Max. tumour size (mm)[b]		1.12 (1.06 – 1.18)	16.4	<0.001*
Tumour stage				
	I+II	1		
	III+IV	1.60 (1.13 - 2.25)	7.02	0.008
Venous resection				
	No	1		
	Yes	1.30 (1.01 - 1.67)	4.11	0.043

[a] Log transformation
[b] Square root transformation
* Significant in multivariate

ESPAC Trials: 5 Year Overall Survival

Trial	Treatment	No. of pts (N=2092)	5-Year OS (95% CI)	Stratified Log-Rank χ^2	p-value
ESPAC-1	5FU/FA	149	21 (14.6 – 28.5) %		
	No chemotherapy	143	8.0 (3.8 – 14.1) %	7.03	0.030*
	Chemoradiotherapy (5FU/Rad)	145	10.8 (6.1 – 17.0) %		
ESPAC-3	GEM	539	17.5 (14.0 – 21.2) %	0.74	0.390*
	5FU/FA	551	15.9 (12.7 – 19.4) %		
ESPAC-4	GEM	366	16.3 (10.2 – 23.7) %	4.61	0.032†
	GEMCAP	364	28.8 (22.9 – 35.2) %		

*Stratification factor: resection margin status; †stratification factors: resection margin status and country

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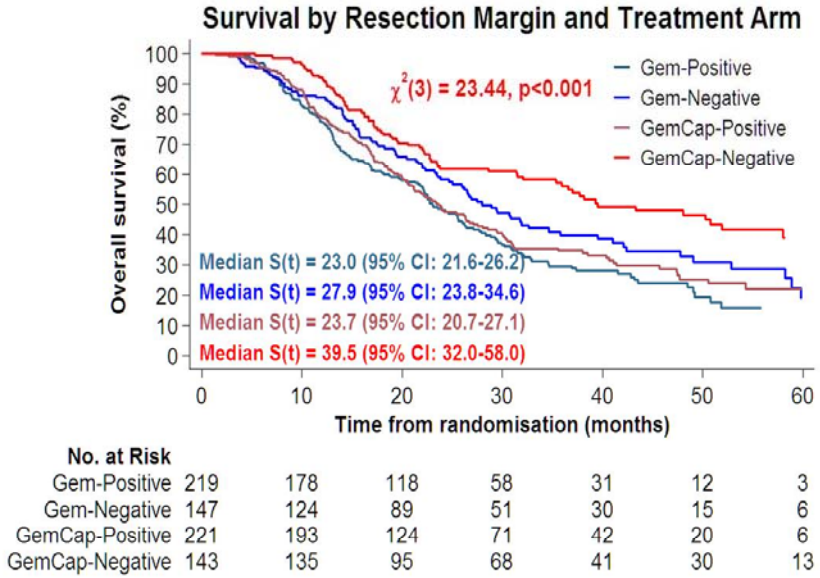
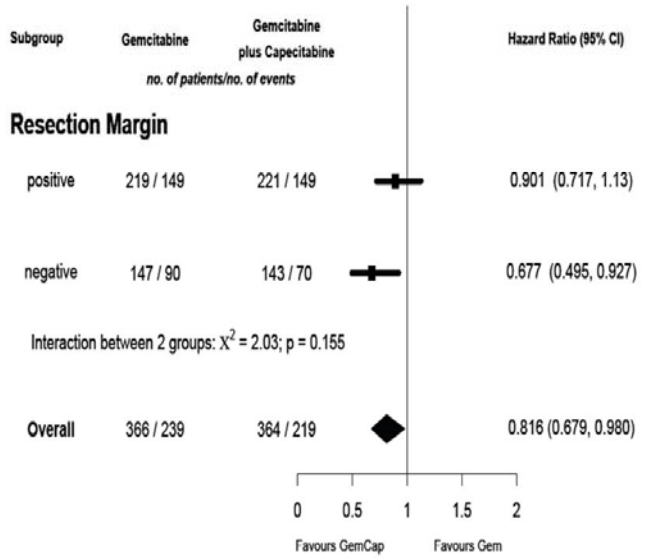
Treatment Effect by R-Status





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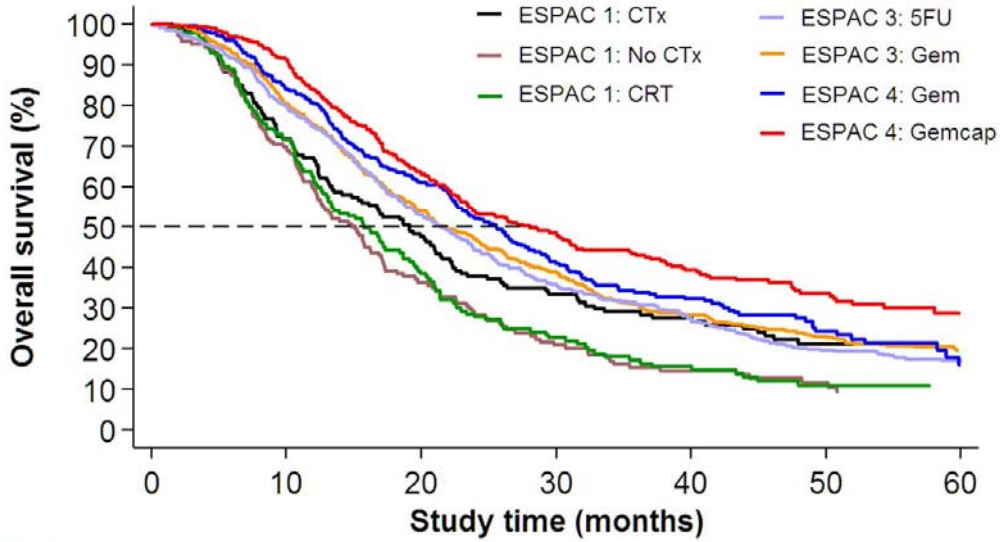
ESPAC Trials Overall Survival



No. at Risk							
E1 - CTx	149	105	68	46	34	19	16
E1 - No CTx	143	99	50	28	17	10	8
E1 - CRT	145	103	54	30	19	10	8
E3 - Gem	539	422	283	187	126	93	64
E3 - 5FU	551	430	283	180	131	81	56
E4 - Gem	366	302	207	109	61	27	9
E4 - GemCap	364	328	219	139	83	50	19

**Study time = time from surgery for ESPAC 1/3, study time = time from randomisation for ESPAC 4*

LCTU Liverpool Clinical Trials Unit | NCRI National Cancer Research Institute | UKCRC Registered Clinical Trials Units | NWSTC | NHS National Institute for Health Research | CANCER RESEARCH UK

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Conclusions

- Median survival for patients treated with GEMCAP was significantly better than GEM: 28.0 (95% CI, 23.5 -31.5) vs 25.5 (22.7-27.9) months
- The estimated 5 years survival rate was superior with GEMCAP than GEM: 28.8 (22.9-35.2)% vs 16.3 (10.2-23.7)%
- As expected there was slightly more toxicity in the GEMCAP arm but overall this was manageable and not significant: 154 SAEs in 86 (24%) GEMCAP patients vs 151 SAEs in 94 (26%) GEM patients
- The 5 year survival rate with GEMCAP=28.8 (22.9-35.2)%, was superior to previous ESPAC trial arms including no chemotherapy=8.0 (3.8-14.1)%, chemoradiotherapy=10.8 (6.1-17.0)%, 5FU/FA=15.9 (12.7-19.4)%
- Marginal benefit of active agents in advanced pancreatic cancer can translate into a much bigger effect in the adjuvant setting
- All patients with pancreatic cancer should be offered entry into randomised trials: biomarkers must be evaluated (hENT1, etc)
- Adjuvant GEMCAP is the new standard of care for resected pancreatic cancer

How has this changed my practice?

- Adjuvant capecitabine/gemcitabine should become standard of care for resected pancreatic adenocarcinoma
- I have not yet seen had this discussion with any patients
- ? Covered by BCCA CAP – If not, capecitabine at 1500mg BID 21/28 costs approximately $600 per cycle

A Multicenter Randomized Phase III Trial of Neo-adjuvant Chemotherapy Followed by Surgery and Chemotherapy or by Surgery and Chemoradiotherapy in Resectable Gastric Cancer

First results from the CRITICS study

Marcel Verheij[1], EPM Jansen[1], A Cats[1], NCT van Grieken[2], H Boot[1], PA Lind[3], E Meershoek-Klein Kranenbarg[4], M Nordsmark[5], HH Hartgrink[4], H Putter[4], AK Trip[1], JW van Sandick[1], K Sikorska[1], H van Tinteren[1], YHM Claassen[4], CJH van de Velde[4], on behalf of the CRITICS Investigators

[1]Netherlands Cancer Institute, [2]VU University Medical Center, [3]Karolinska University Hospital, [4]Leiden University Medical Center, [5]Århus University Hospital

PRESENTED AT: ASCO ANNUAL MEETING '16

Disclosures

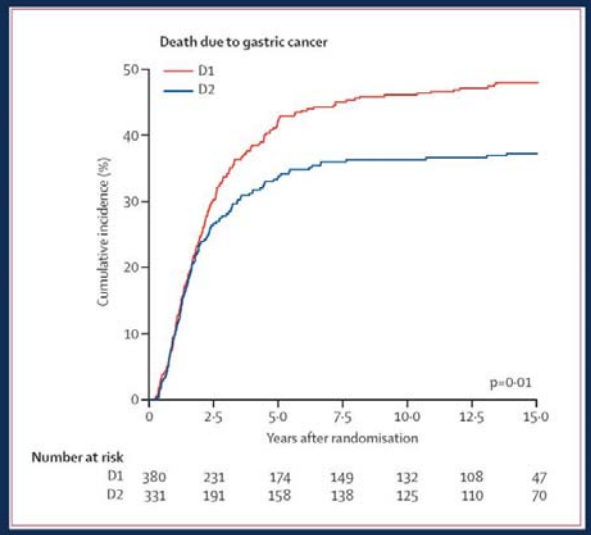
Research funding provided by:

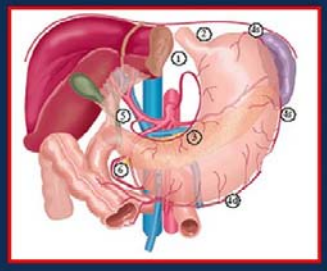
- Roche
- Dutch Cancer Society

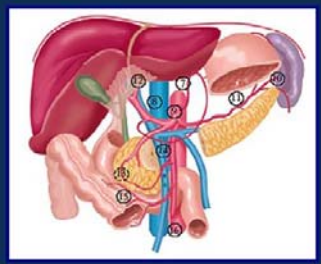
Background (1)

- Gastric cancer has a poor outcome
- Evidence-based strategies to improve treatment results include:

  - adequate surgery







Songun et al. Lancet Oncol 2010

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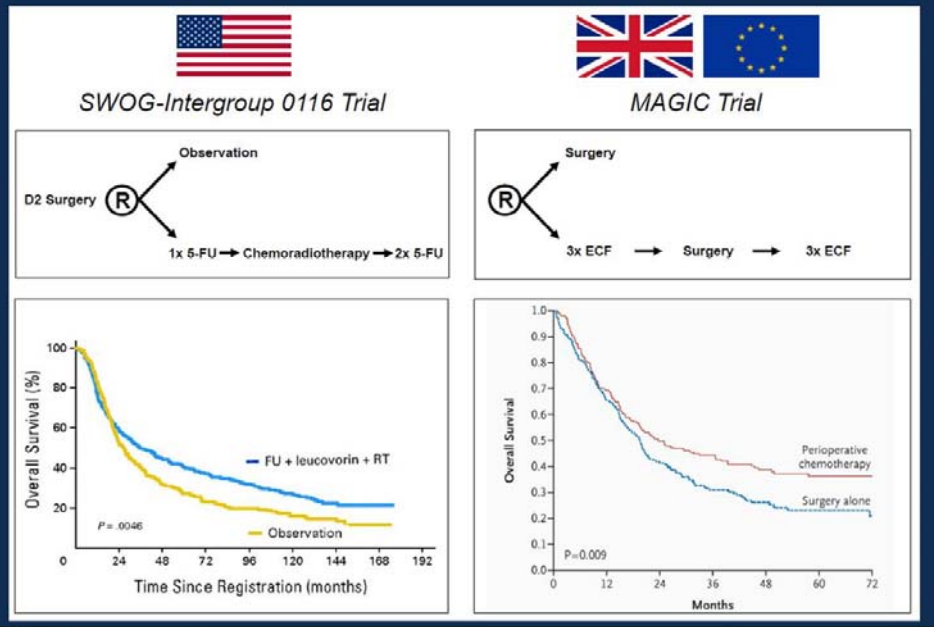
Background (2)

- Evidence-based strategies to improve treatment results include:

- post-operative chemoradiotherapy
- peri-operative chemotherapy

Macdonald et al. NEJM 2001; Smalley et al. JCO 2012
Cunningham et al. NEJM 2006



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Aim

To improve survival by optimal local and systemic therapy

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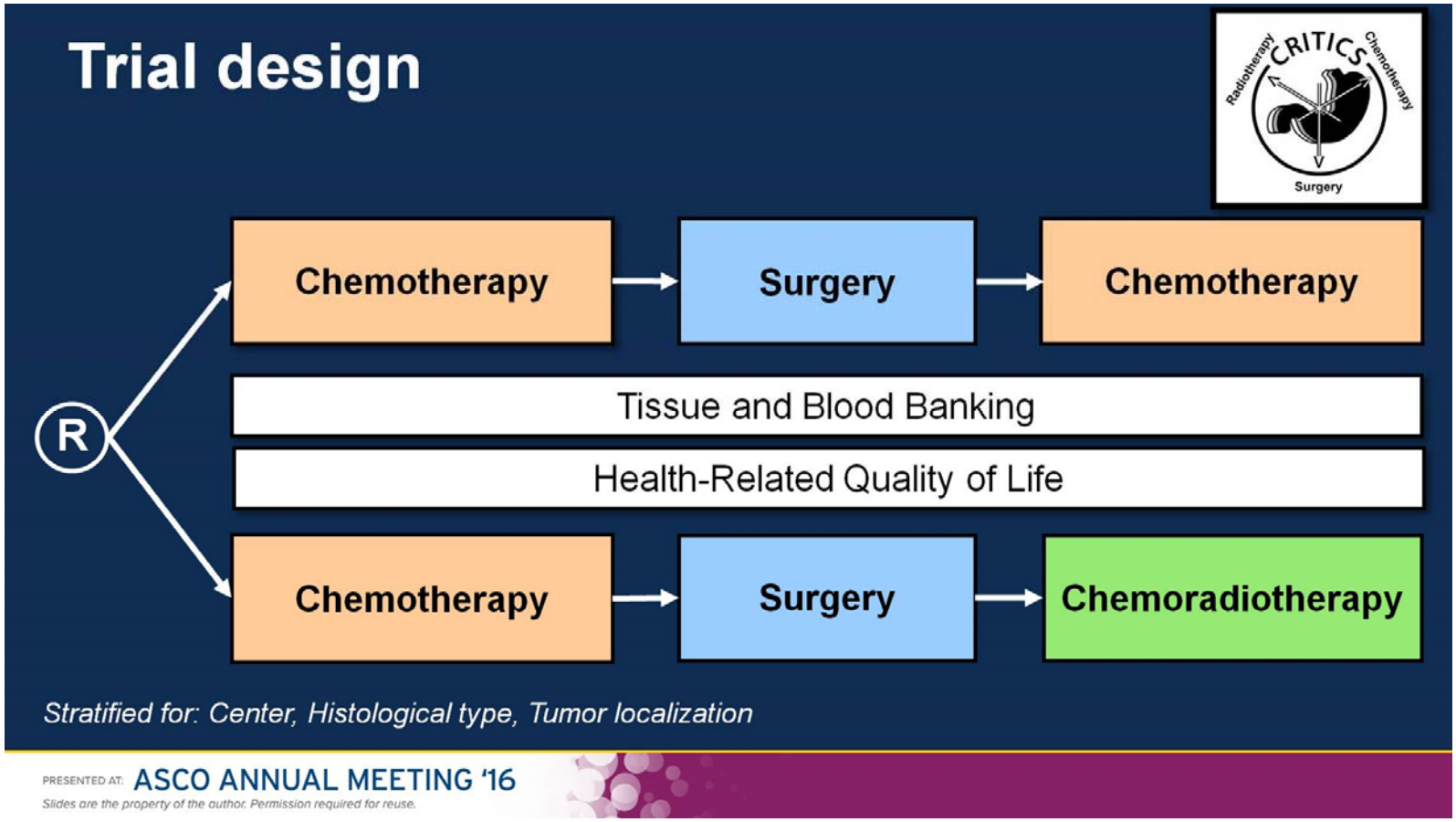

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Treatment Details

Chemotherapy: Pre-operative and post-operative: 3x ECC or EOC q3 wks

Epirubicin 50 mg/m^2 day 1; Cisplatin 60 mg/m^2 day 1; Capecitabine 1000 mg/m^2 b.i.d. 1-14
Epirubicin 50 mg/m^2 day 1; Oxaliplatin 130 mg/m^2 day 1; Capecitabine 625 mg/m^2 b.i.d. 1-21

Surgery: Total / partial gastrectomy + *en bloc* N1 and N2 lymph nodes

D1$^+$ resection: lymph node stations 1-9 and 11; no splenectomy or pancreatectomy
Removal of ≥15 lymph nodes
Quality assurance: Maruyama Index

Chemoradiotherapy: Post-operative: 45 Gy in 25 fractions combined with CC

3D-CRT or IMRT; CTV includes tumor bed, anastomoses, draining lymph node stations
Concurrent during RT: Cisplatin 20 mg/m^2 weekly; Capecitabine 575 mg/m^2 b.i.d./d.d.w.d.
Quality assurance: central review of RT plans

Patient Eligibility

Main Inclusion Criteria

- Stage Ib-IVa resectable gastric adenocarcinoma (TNM 6th ed.)
- No distant metastases
- Localization: stomach or GEJ (tumor bulk in stomach)
- Performance status WHO 0-1
- Age ≥ 18 years

Trial Overview

Primary endpoint: Overall Survival

Secondary endpoints:

- Progression-free Survival
- Toxicity
- Health-Related Quality of Life
- Translational Research

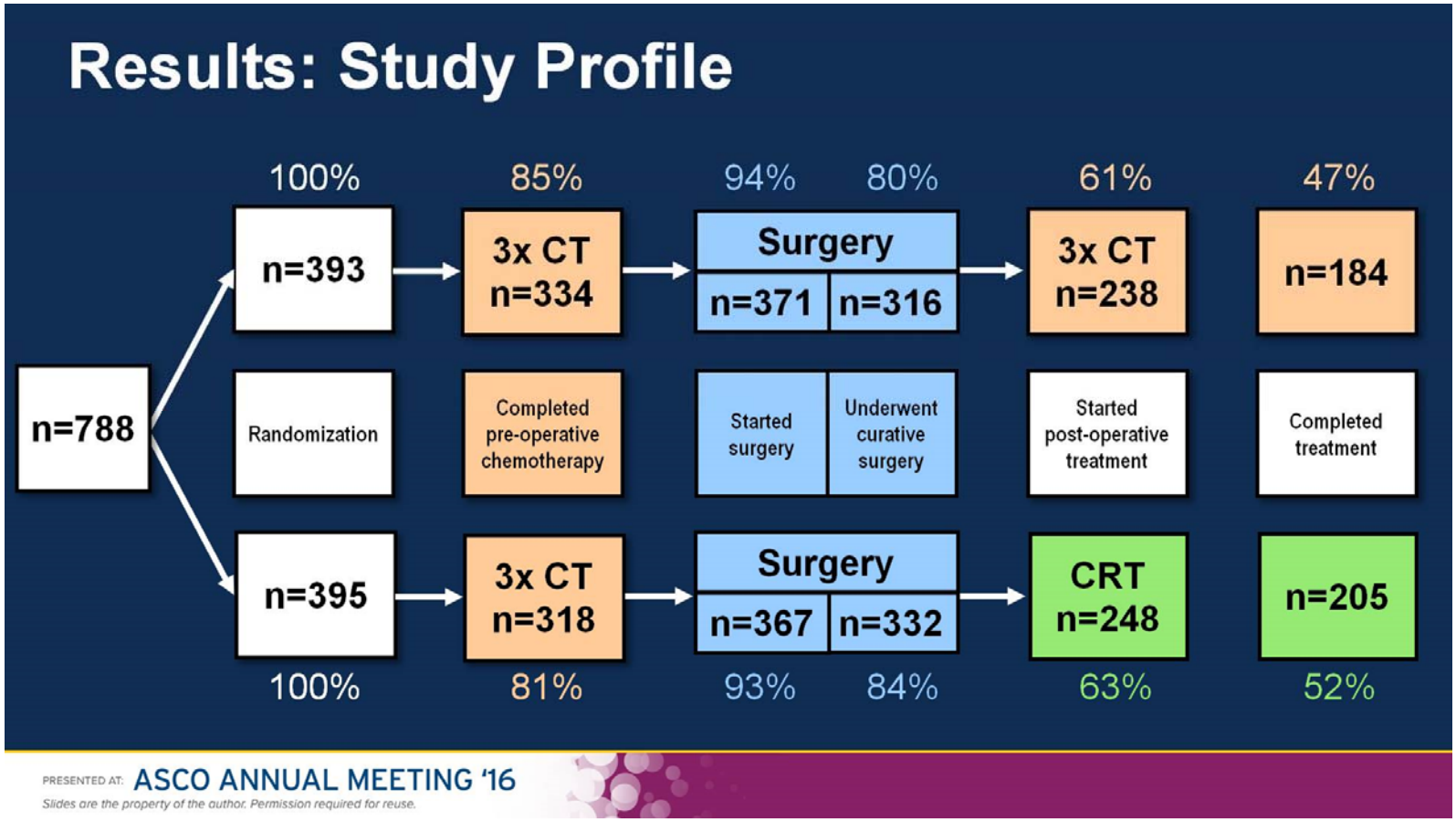
Enrollment period: 2007 - 2015 (The Netherlands, Sweden, Denmark)

Current analysis: Intention-to-treat at median follow-up of 4.2 years

Statistical consideration: To achieve 80% power to detect a 10% increase in 5 year OS from 40% (CT) to 50% (CRT) at $p<0.05$, **405 events** are needed in **788 patients**

Baseline Patient Characteristics

	CT n=393	CRT n=395	Total (%) n=788 (100)
Gender			
male	264	265	529 (67)
female	129	130	259 (33)
Age: median (IQR)	62 (54;69)	63 (56;68)	62 (55;69)
WHO			
0	260	273	533 (68)
1	103	106	209 (26)
unknown	30	16	46 (6)
Localization			
GE-junction	68	67	135 (17)
proximal	79	84	163 (21)
middle	120	117	237 (30)
distal	126	127	253 (32)
Lauren classification			
intestinal	127	126	253 (32)
diffuse	116	117	233 (30)
mixed	20	22	42 (5)
unknown	130	130	260 (33)



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Results: Pre-operative Toxicity

Adverse Events (both arms; ≥ 5%)	Grade 3	Grade 4	Sum (%)
Neutropenia	171	76	247 (31)
Febrile neutropenia	53	10	63 (8)
Diarrhea	94	5	99 (13)
Nausea	83	1	84 (11)
Anorexia	71	2	73 (9)
Vomiting	58	3	61 (8)
Fatigue	57	8	65 (8)
Thromboembolic	39	19	58 (7)
Dehydration	37	2	39 (5)

Grade 5 (all)	Sum (%)
Cardiovascular	7
Gastrointestinal	3
Infectious	2
Total	12 (2)

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Results: Surgery

Curative resection	CT n=316	CRT n=332	Total (%) n=648 (100)
Type of gastrectomy			
total	163	164	327 (51)
distal/subtotal	141	159	300 (46)
esophageal-cardia	12	9	21 (3)
Type of lymph node dissection			
D1+	149	167	316 (49)
D2	123	116	239 (37)
D3	5	4	9 (1)
none	6	5	11 (2)
unknown	33	40	73 (11)
Splenectomy			
yes	22	17	39 (6)
Pancreatectomy			
yes	7	11	18 (3)

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Results: Surgery Related Complications

Surgery related complication (after curative resection; both arms)	Sum (%)
Anastomotic leakage	47 (7)
Bleeding	20 (3)
Ileus	18 (3)
Abdominal wound dehiscence	10 (2)
Fistula	6 (1)
Intestinal necrosis	3 (<1)
Other	73 (11)
Any	**145 (22)**

Complication	Sum (%)
In-hospital deaths	**15 (2)**

Results: Pathology

	CT n=316	CRT n=332	Total (%) n=648 (100)
Pathological T-stage			
pT0	18	21	39 (6)
pTis	0	5	5 (1)
pT1	41	45	86 (13)
pT2	111	112	223 (34)
pT3	113	108	221 (34)
pT4	30	35	65 (10)
unknown	3	6	9 (1)
Pathological N-stage			
pN0	149	158	307 (47)
pN1	111	108	219 (34)
pN2	37	43	80 (12)
pN3	15	19	34 (5)
unknown	4	4	8 (1)
Number of lymph nodes (median, range)	21 (0 - 72)	19 (0 - 71)	20 (0 - 72)

Central review in progress

Results: Post-operative Noncompliance

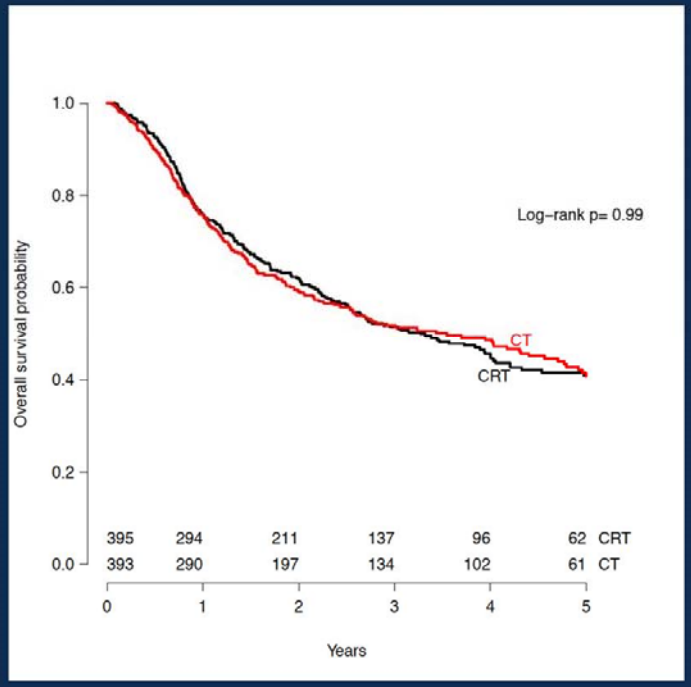
Reasons for not starting post-operative treatment after curative resection	CT n=316 (%)	CRT n=332 (%)
Refusal patient	16 (8)	19 (6)
Progressive disease	16 (8)	14 (4)
Toxicity pre-operative chemotherapy	14 (4)	13 (4)
Post-operative complications	5 (2)	18 (5)
Died	12 (4)	6 (2)
Poor condition	3 (1)	4 (1)
Other	13 (4)	7 (2)
Total	**79 (25)**	**81 (24)**

Results: Post-operative Toxicity

	CT n=238			CRT n=248		
Adverse Events (for patients who started post-operative treatment)	Grade 3	Grade 4	Sum (%)	Grade 3	Grade 4	Sum (%)
Neutropenia	63	18	81 (34)*	7	3	10 (4)*
Febrile neutropenia	4	1	5 (2)	6	0	6 (2)
Anorexia	20	0	20 (8)	30	0	30 (12)
Nausea	27	0	27 (11)	22	0	22 (9)
Fatigue	20	0	20 (8)	25	0	25 (10)
Diarrhea	14	0	14 (6)	10	0	10 (4)
Vomiting	12	0	12 (5)	13	0	13 (5)

*$p<0.001$

Results: Overall Survival



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

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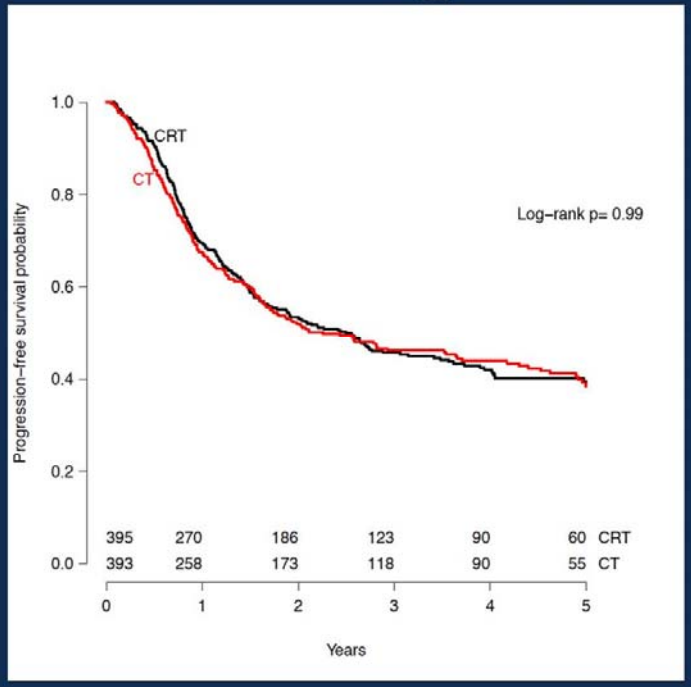
Results: Progression-Free Survival



	CT	CRT
5-year PFS (%)	38.5	39.5
Median PFS (yrs)	2.3	2.5

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Summary (1)

- CRITICS-study compared peri-operative chemotherapy with pre-operative chemotherapy and post-operative chemoradiotherapy and randomized patients upfront to reflect daily practice and avoid patient selection
- Toxicity associated with pre-operative chemotherapy was mainly neutropenia
- Surgical quality was excellent with 87% undergoing ≥ D1^{+} dissection without splenectomy / pancreatectomy and removal of a median of 20 lymph nodes
- Surgery related complications (22%) and in-hospital mortality (2%) were acceptable

Summary (2)

- Main reasons for not starting post-operative treatment were patient refusal, progressive disease, pre-operative toxicity and surgical complications
- Post-operative toxicity was mainly neutropenia and gastrointestinal
- Approximately 60% started post-operative therapy, and 50% completed the entire treatment
- After a median follow-up of 4.2 years, no significant differences in 5-yr OS and 5-yr PFS were found

Conclusions

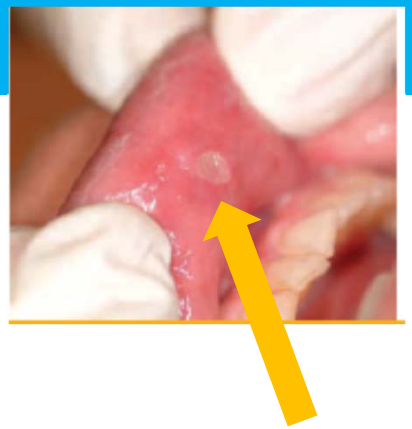
- The expected treatment difference in overall survival has not been observed
- 5-year overall and median survival are comparable with other studies in Western countries
- Based on the currently available data, no advise can be given on the preferred adjuvant strategy
- Ongoing analyses may identify treatment benefits in specific subgroups
- As less than 50% of patients could complete full treatment, more emphasis on pre-operative strategies should be considered

How has this changed my practice?

- Makes me glad not to be a radiation oncologist…
- Confirms previous studies that perioperative chemotherapy is standard of care, as it is in many parts of the world (especially Asia)
- ARTIST study from S. Korea also showed no benefit in adding radiation therapy to post-op chemotherapy for resected early stomach cancer (ARTIST II study only including node+ patients pending)

Steroid-based Magic Mouth Washes as Prophylaxis for Everolimus-Associated Stomatitis.

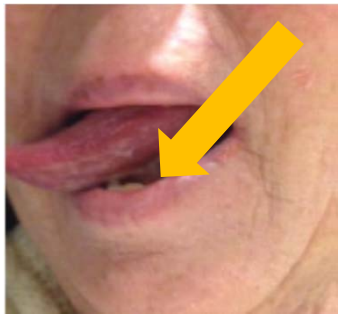
BACKGROUND



Stomatitis is a the most frequent adverse event associated with mTOR inhibition and can impact adherence and patient quality of life

BOLERO-2

- Among patients receiving EVE plus EXE, all-grade stomatitis was **67%**; 30% had grade ≥2 [1,2]
- More than a third of grade ≥ 2 stomatitis and related events occurred in the **first 2 weeks** of initiating everolimus +exemestane (median time to onset was 15 days): the incidence of new stomatitis (grade ≥2) plateaued at 6 weeks[1]
- In a recent meta-analysis of phase 3 trials of solid tumors (BC, RCC, pNET) and TSC, **89% of first stomatitis events occurred within 8 weeks of initiating EVE**[3]



1. Yardley DA, et al. *Adv Ther.* 2013;30(10):870-884. 2. Rugo HS, et al. *Ann Oncol.* 2014;25(4):808-815. 3. Rugo HS, et al. *Ann Oncol.* 2016;00:1-7.

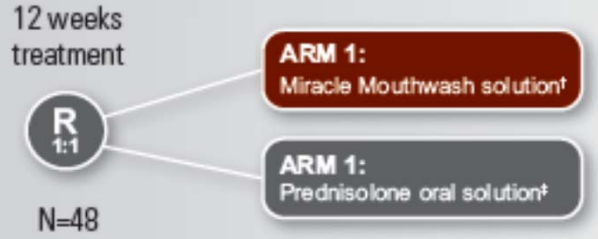
Evaluation of a "Miracle Mouthwash" (MMW) Plus Hydrocortisone versus Prednisolone Mouth Rinses as Prophylaxis for Everolimus-Associated Stomatitis[1]

Jones = O'Shaughnessy

PRESENTED AT SABCS 2015

Evaluating a Prophylactic Approach to Oral Stomatitis

Phase 2 Prospective Study Design and Inclusion Criteria



47 patients received treatment

Two steroid-based mouth rinses for the prevention or amelioration of oral stomatitis and related events* were evaluated in postmenopausal women with HR+ metastatic breast cancer undergoing planned treatment with an aromatase inhibitor and everolimus.

Self-Administration Schedule and Duration

Self-administered rinse

4X Per day swish/expectorate 10 mL of assigned rinse

Self-administered rinse began on Day 1 and continued through the first 12 weeks of treatment with everolimus

†Miracle mouthwash solution contained 320 mL oral Benadryl, 2 g tetracycline, 80 mg hydrocortisone, 40 mL nystatin solution, in water
‡Prednisolone oral solution contained 15 mg prednisolone/5 mL oral solution

*Includes preferred terms: stomatitis, canker sores oral, mouth ulceration, mucositis oral, and oral mucosal eruption.

1. Jones VE et al, Evaluation of Miracle Mouthwash (MMW) Plus Hydrocortisone versus Prednisolone Mouth Wash as Prophylacxis for Everolimus-associated stomatitis: Preliminary results of a randomized phase II study: poster presented at SanAntonio Breast Cancer Symposium, December 2015; San Antonio Tx.

Evaluation of a "Miracle Mouthwash" (MMW) Plus Hydrocortisone versus Prednisolone Mouth Rinses as Prophylaxis for Everolimus-Associated Stomatitis[1]

Preliminary Results: Incidence and Resolution

Incidence of stomatitis and related events*

There was a 26% incidence of stomatitis and related events* of any grade. Most of the stomatitis and related events were Grade 1, and there was no reported incidence of Grade ≥3 stomatitis and related events*

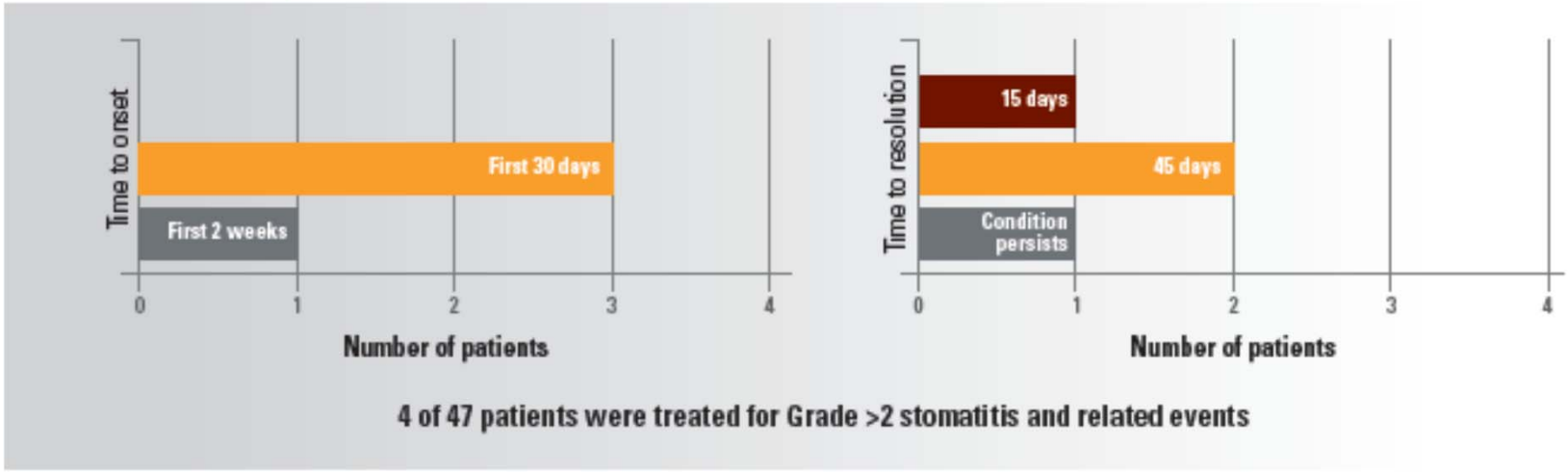
Incidence When Using Prophylactic Management		**Incidence in BOLERO-2 (No prophylactic Management)**
N patients (%)		**% patients (n =485)**
12/47 (26%)	All grades	67%
8/47 (17%)	Grade 1	34%
4/47 (9%)	Grade 2	25%
0/47 (0%)	Grade 3	8%
0/47 (0%)	Grade 4	0%

*Includes preferred terms: stomatitis, canker sores oral, mouth ulceration, mucositis oral, and oral mucosal eruption.

1. Jones VE et al, Evaluation of Miracle Mouthwash (MMW) Plus Hydrocortisone versus Prednisolone Mouth Wash as Prophylacxis for Everolimus-associated stomatitis: Preliminary results of a randomized phase II study: poster presented at SanAntonio Breast Cancer Symposium, December 2015; San Antonio Tx.

Evaluation of a "Miracle Mouthwash" (MMW) Plus Hydrocortisone versus Prednisolone Mouth Rinses as Prophylaxis for Everolimus-Associated Stomatitis[1]

Onset of Grade ≥2 stomatitis and related events* occurred with in the first 30 days and resolved within 45 days



Only one patient required a dose delay action for Grade ≥2 stomatitis and related events*

Action taken for Grade ≥ 2 stomatitis and related events	N patients (%)
No action	3/47 (6%)
Dose delay	1/47 (2%)
Dose reduction	0/47 (0%)

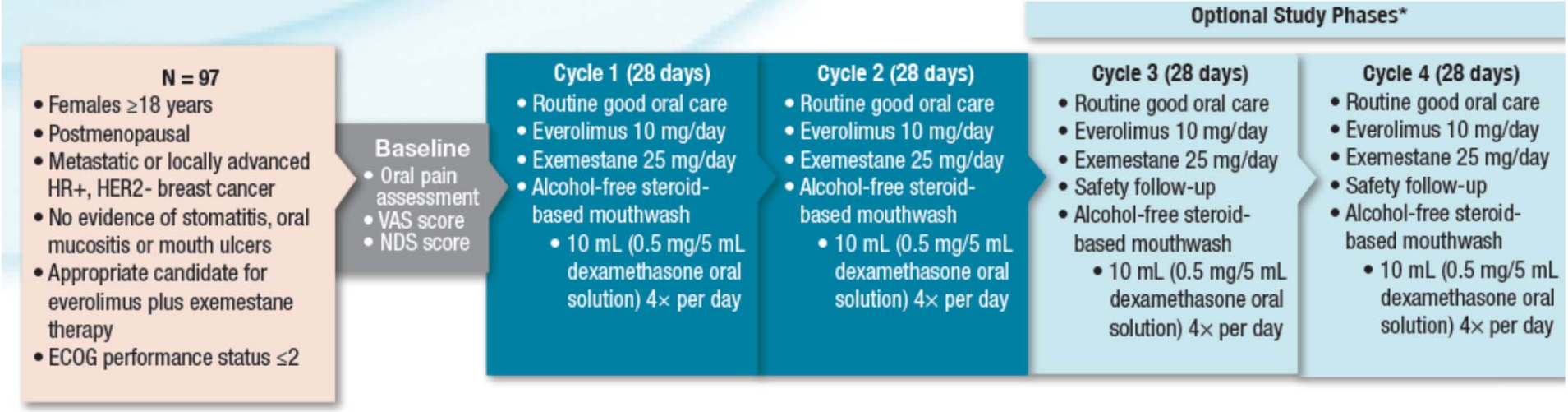
*Includes preferred terms: stomatitis, canker sores oral, mouth ulceration, mucositis oral, and oral mucosal eruption.

1. Jones VE et al, Evaluation of Miracle Mouthwash (MMW) Plus Hydrocortisone versus Prednisolone Mouth Wash as Prophylacxis for Everolimus-associated stomatitis: Preliminary results of a randomized phase II study: poster presented at SanAntonio Breast Cancer Symposium, December 2015; San Antonio Tx.

Dr. Rugo: Stomatitis Prevention study: SWISH

PRESENTED AT
ASCO 2016
June 5th

- A phase 2, single-arm study [1]



- **Median age was 61 years (range 34-87); 61.6% were Caucasian; 93% were classified with ECOG performance status of 0-1**
- **20 (23%) patients received optional antifungal oral prophylaxis against oral thrush**

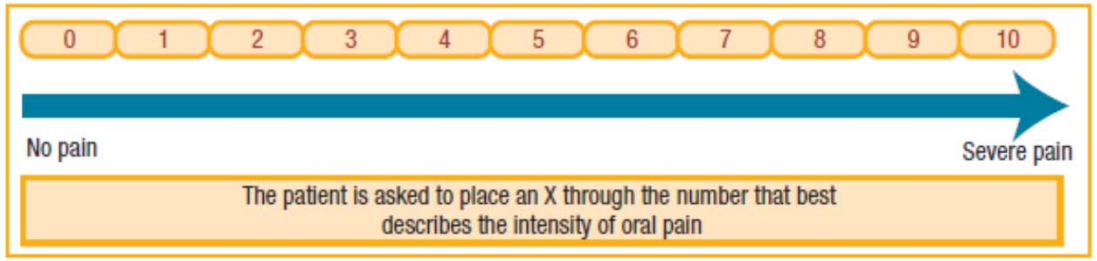
1. 2014 ASCO, Rugo et al. TPS661 Poster, NCT # NCT02069093 ; 2. Donahue SR et al. 2015 Oncology Nurse Advisor Navigation Summit; June 26-28, 2015; Hyatt Regency, Denver, Colorado.

Stomatitis Evaluation: Evaluation done by investigator via physical exam or phone call: Evidence of changes to oral mucosa consistent with stomatitis.

Figure 3. Normalcy of Diet Scale[11]

Normal diet was reported in 88% of patients at 8 weeks

Figure 4. Visual Analog Scale[12]



The mean oral pain score was <1 at all visits (range 0.1-0.6)

Sarah R Donohue

Presented at the 2015 Oncology Nurse Advisor Navigation Summit; June 26-28, 2015; Hyatt Regency, Denver, Colorado.

Treatment of Stomatitis

- Patients will self-report an oral pain score using the VAS and their diet using the Normalcy of Diet Scale daily throughout the duration of the study
- Patients will be instructed to contact the study site at the first sign of oral pain or changes to the oral mucosa

- Following diagnosis of grade 1 stomatitis, patients will be instructed to begin using a saltwater (0.9%) mouth rinse 4 times a day, in addition to their study-assigned mouthwash
  - Patients will be instructed to perform the saltwater mouth rinse regimen first, followed by the steroid mouthwash 10 to 15 minutes later
- Upon confirmation of stomatitis grade 2 or 3, everolimus will be held until recovery to grade ≤1
  - Steroid-based mouthwash will be continued for stomatitis grade 2, and either continued or stopped at investigator's discretion for grade 3
  - Additional treatment(s) will be initiated if needed

Sarah R Donohue

Presented at the 2015 Oncology Nurse Advisor Navigation Summit; June 26-28, 2015; Hyatt Regency, Denver, Colorado.

Patient Education and Instructions

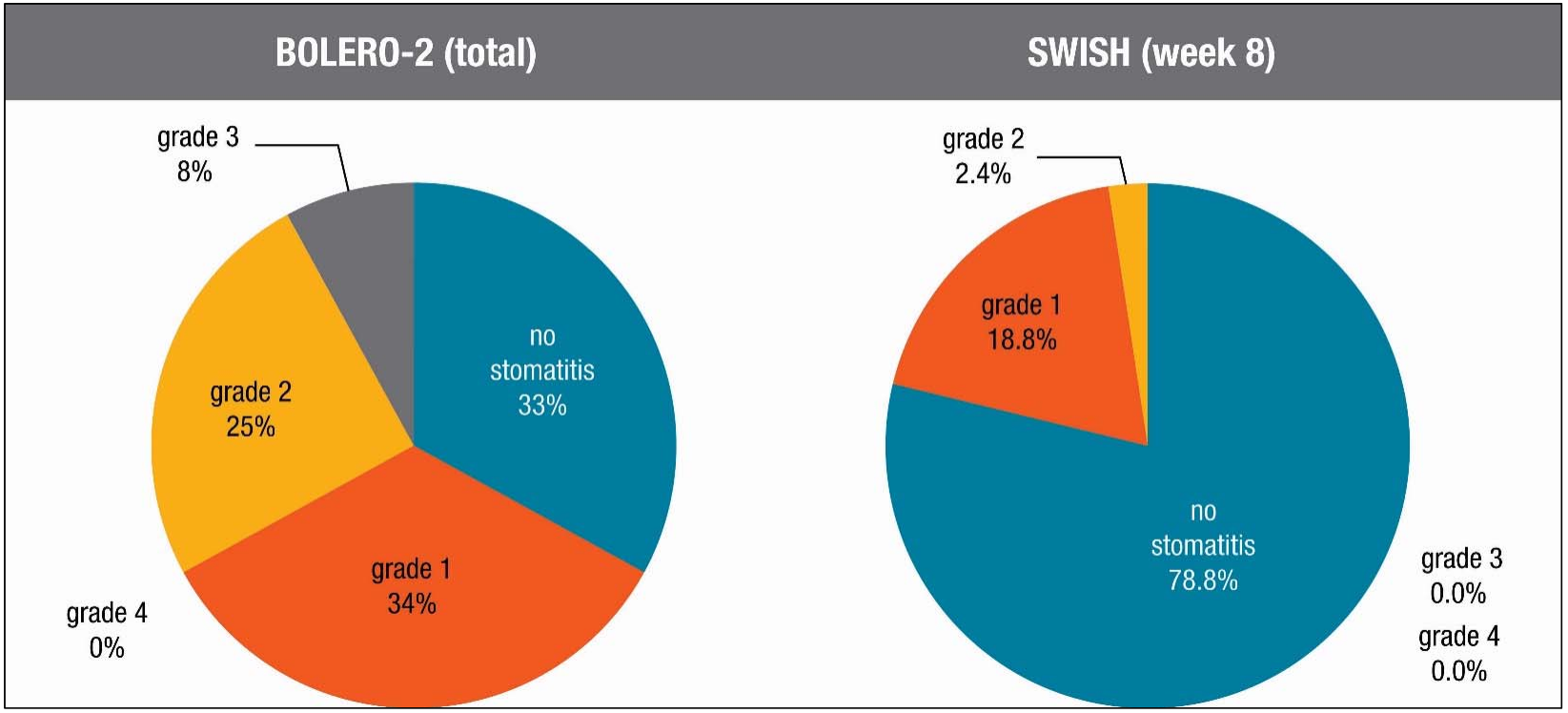
- Swish and spit 10 mL of mouthwash 4 times each day
- Hold mouthwash in mouth for a minimum of 2 minutes
- Swish it around in the mouth, so it comes in contact with every surface of the mouth
- Spit it out (do not swallow mouthwash)
- Abstain from eating or drinking for at least 1 hour after performing mouthwash regimen
- Continue with assigned oral care regimen for the first 2 months (56 days) of everolimus + exemestane therapy, after which mouthwash will be stopped: [a,b]
- a Patients will continue to be followed up for safety for an additional 2 months (56 days).
- b An additional 2 months (56 days) of mouthwash may be administered as per the physician's discretion.
- A baseline oral assessment was conducted, and patients were provided instructions on how to self-monitor for stomatitis, along with instructions to contact the study site at the first sign of oral pain or changes to the oral mucosa

NDS: Normalcy of Diet Scale; VAS: visual analog scale

Results

- The incidence of grade ≥2 stomatitis at 8 weeks was 2.4% (n=2, 95% CI 0.29-8.24, *P*<0.001) compared with a total of 33% in BOLERO-2

Incidence of Stomatitis



In the 2 patients who developed grade ≥2 stomatitis, resolution to grade ≤1 occurred after a duration of 11 days for 1 patient and 15 days for the other patient

BOLERO-2, The Breast Cancer Trials of Oral Everolimus-2
BOLER-2 stomatitis grading based on CTCAE v3.0

Secondary Outcomes

- 95% of patients used dexamethasone mouthwash 3-4 times/day (median 3.95 [range 1.9-4])
- >70% of patients remained on all 3 drugs at ≥8 weeks (eve, exe and dexamethasone)
- The median dose intensities of EVE and EXE were 10 mg and 25 mg, respectively

Secondary Outcomes

Outcomes		
Number of mouthwash applications/day, median (range)	**3.95 (1.9-4.0)**	
Actual dose intensity, mg, (range)	**SWISH**	**BOLERO-2**
Everolimus	**10 (3-10)**	**8.6**

EVE: everolimus; EXE: exemestane

Safety Outcomes

- No new safety signal
- The incidence of treatment-related SAEs was 6.5%
- 2 patients developed oral candidiasis; both used antifungal prophylaxis
- Among 75 patients with complete ECOG scores, 88% maintained or improved ECOG status

AE: adverse event; BOLERO-2, The Breast Cancer Trials of Oral Everolimus-2; ECOG: Eastern Cooperative Oncology Group; EVE: everolimus; EXE: exemestane; SAE: serious adverse event

1. Yardley DA, et al. *Adv Ther.* 2013;30(10):870-884.

How has this changed my practice?

- Single arm phase 2 studies can still be practice changing
- I now prescribe prophylactic alcohol free steroid mouthwash for any patients starting everolimus/exemestane combination
- Should this apply to patients taking everolimus for RCC or PNET?