Hormone receptor-positive breast cancers
GASCO Annual SABCS Review
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Ruth M. O'Regan, MD
Professor and Division Chief
Hematology and Medical Oncology,
Department of Medicine,
University of Wisconsin

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

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Topics to cover

- Extended adjuvant aromatase inhibitor therapy
  - Abstracts S1-03, S1-04, S1-05
- Metastatic hormone receptor-positive breast cancer
  - Fulvestrant plus everolimus (Abstract S1-02)
  - Fulvestrant plus buparsilib (Abstract S4-07)
  - BET inhibitor (Abstract S4-01)
- Adjuvant bisphosphonates (Abstract S6-01)

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A Randomized, Double-blinded, Placebo-controlled Clinical Trial of Extended Adjuvant Endocrine Therapy with Letrozole in Postmenopausal Women with Hormone-receptor (+) Breast Cancer who have Completed Previous Adjuvant Tx with an Aromatase Inhibitor: Results from NRG Oncology/ NSABP B-42

Eleftherios P. Mamounas, MD,[1,2] Hanna Bandos, PhD[1,3] Barry C. Lembersky, MD,[1,4] Charles E. Geyer, Jr., MD,[1,5] Louis Fehrenbacher, MD,[1,6] Mark L. Graham, MD,[1,7] Stephen L. Chia, MD, FRCPC[1,8] Adam M. Brufsky, MD, PhD,[1,4] Bryan T. Hennessy, MD,[1,9] Gamini S. Soori, MD,[1,10] Shaker R. Dakhil, MD,[1,11] Thomas E. Seay, MD,[1,12] James L. Wade, III, MD,[1,13] Edward C. McCarron,[1,14] Soonmyung Paik, MD,[1,15] Sandra M. Swain, MD,[1,16] D. Lawrence Wickerham, MD,[1,17] Norman Wolmark, MD[1,17]

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NSABP B-42: Schema

- Postmenopausal Pts with ER+ or PR+ Breast Cancer
- Stage I, II, or IIIa invasive BC at diagnosis
- Disease-free After 5 Years of Endocrine Therapy

AI X 5 yrs or **TAM X < 3 yrs** **AI to Complete 5 yrs**

Stratification:
Pathological nodal status (Negative, Positive)
Prior adjuvant TAM (Yes, No)
Lowest BMD T score: spine, hip, femur (>-2.0, ≤ -2.0 SD)

R

Letrozole X 5 yrs **Placebo X 5 yrs**

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NSABP B-42: Endpoints

- Primary endpoint:
  - Disease-free Survival (DFS):
    - Local, regional, distant recurrence, contralateral BC, 2nd non-breast primary Ca and death from any cause as first events
- Secondary endpoints:
  - Overall survival
  - Breast Cancer-Free Interval (BCFI):
    - Recurrence or contralateral BC as first event
  - Distant Recurrence (DR)
  - Osteoporotic fractures (OF)
  - Arterial thrombotic events (AT)

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NSABP B-42: Statistical Considerations

- Differences in primary and secondary endpoints between P and L groups were assessed by stratified log-rank tests, controlling for stratification variables
- Hazard ratios and corresponding 95% CIs were calculated based on stratified Cox proportional hazards model
- To account for alpha-spending during four pre-planned interim analyses, the adjusted two-sided significance level of 0.0418 was used for the primary endpoint analysis

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NSABP B-42: Statistical Considerations

- Two-sided p-values of < 0.05 were considered significant for secondary endpoint analyses
- Definitive analysis was based on the intent-to-treat principle
- All patients were analyzed as randomized, regardless of eligibility or protocol compliance
- Patients who had no follow-up and those not at risk for the primary endpoint were excluded:
  - Metastases at the time of random assignment
  - First event within 30 days from randomization

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NSABP B-42: Patient Population

- From SEP 2006 to JAN 2010, 3966 pts were randomized
- 43 patients excluded: 36 no follow-up ; 7 not at risk for the primary endpoint
- Median follow-up for 3923 pts included in efficacy analyses was 6.9 years
- Required 631 DFS events for definitive analysis occurred by August 2016

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NSABP B-42: Cohort Characteristics

- No significant differences in the distribution of patient, tumor and prior treatment characteristics between the two groups :
  - 34-35% < 60 years of age
  - 93% were white and 4% were black
  - 57-58% node-negative
  - 25% had lowest BMD score ≤ -2.0
  - 39% received prior tamoxifen
  - 61% breast conserving surgery
  - 78% HER-2 negative (8% unknown)

NSABP B-42: Treatment Compliance

- Median duration of treatment was 59.8 months in the P and 59.8 months in the L group
- Overall, 62.5% of P patients and 60.3% of L patients completed 5 years of therapy
- Main reasons for L treatment discontinuation:
  - Patient withdrawal/refusal: 13.8%
  - Adverse Event/Complications: 9.6%
  - Disease Progression: 4.1%
  - Other complicating disease/death: 2.7%
  - Declining Bone Density/Osteoporotic Fx: 1.4%

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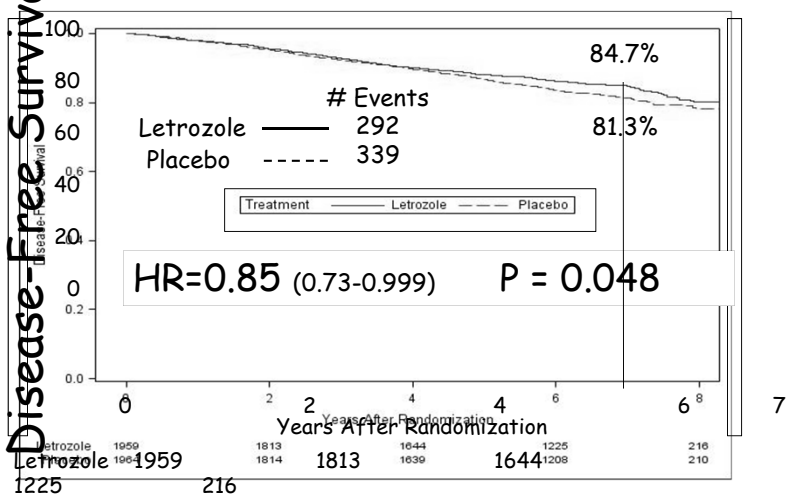
NSABP B-42: Disease-Free Survival



*P-value did not reach statistical significance level of 0.0418

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NSABP B-42: Multivariate Analysis for DFS

Characteristic		No. of pts (N=3,923)	% DFS events	HR (95%CI)	P
Treatment	Placebo	1964	17.3	0.86 (0.73,1.00)	0.05
	Letrozole	1959	14.9		
Age	< 60	1350	12.1	1.55 (1.29,1.86)	<0.01
	≥ 60	2573	18.2		
Path Nodal Status	Negative	2251	14.3	1.33 (1.13,1.56)	<0.01
	Positive	1672	18.5		
Prior Tamoxifen	No	2388	17.6	0.78 (0.66,0.92)	<0.01
	Yes	1535	13.7		
Surgery Type	Lumpectomy	2386	14.6	1.24 (1.05,1.45)	<0.01
	Mastectomy	1537	18.4		

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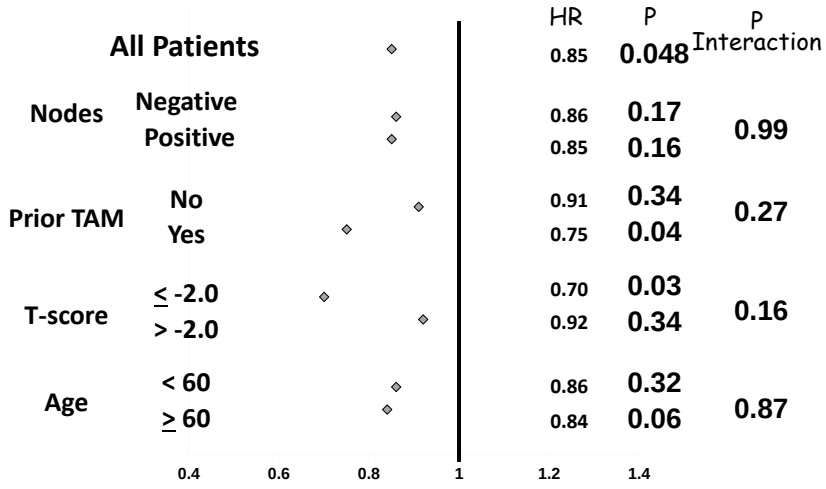
NSABP B-42: Letrozole Effect on DFS in Subgroups



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NSABP B-42: DFS First Events by Treatment

	Placebo (N=1964)		Letrozole (N=1959)	
First event	#	%	#	%
Distant Recurrence	87	4.4	61	3.1
Local Recurrence	33	1.7	36	1.8
Second Primary Ca	171	8.7	134	6.8
Breast	59	3.0	30	1.5
Non-Breast	112	5.7	104	5.3
Death	48	2.4	61	3.1
Total First Event	339	17.3	292	14.9

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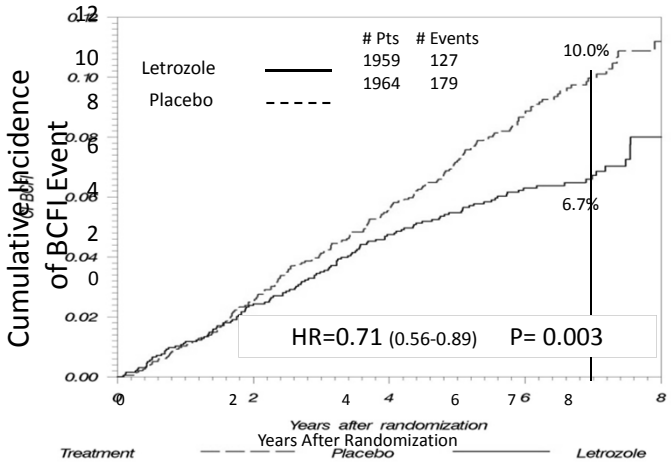
NSABP B-42: Cumulative Incidence of BCFI Event



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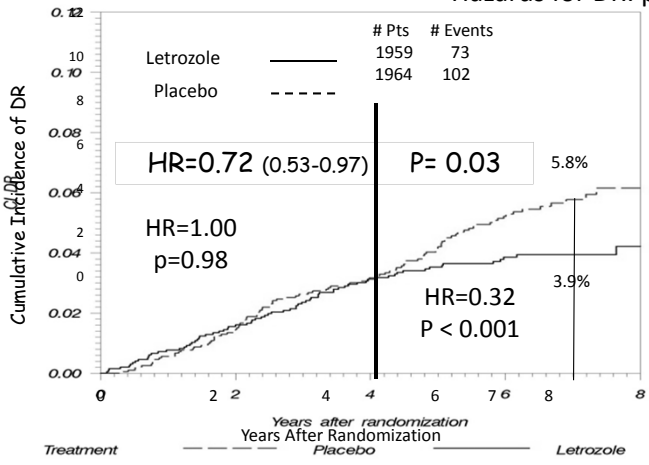
NSABP B-42: Cumulative Incidence of Distant Recurrence

Non-proportionality of Hazards for DR: p = 0.012



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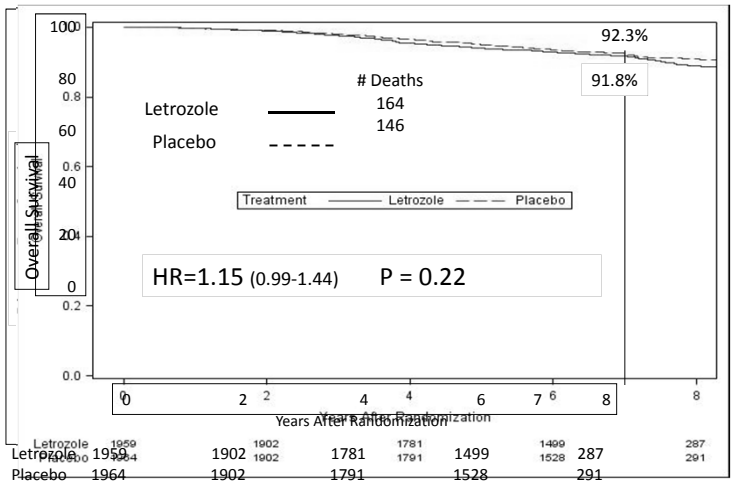
NSABP B-42: Overall Survival



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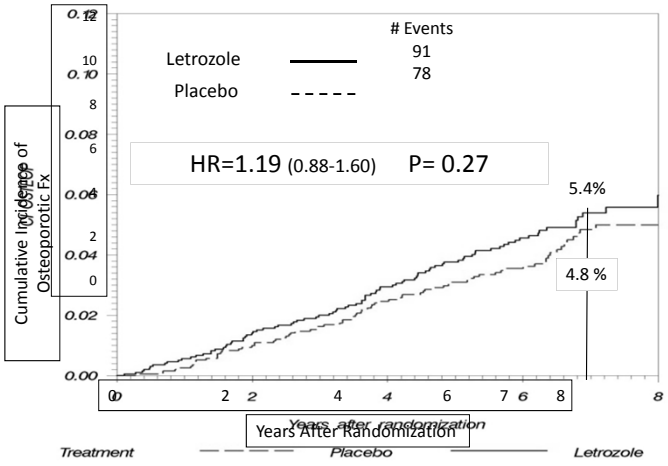
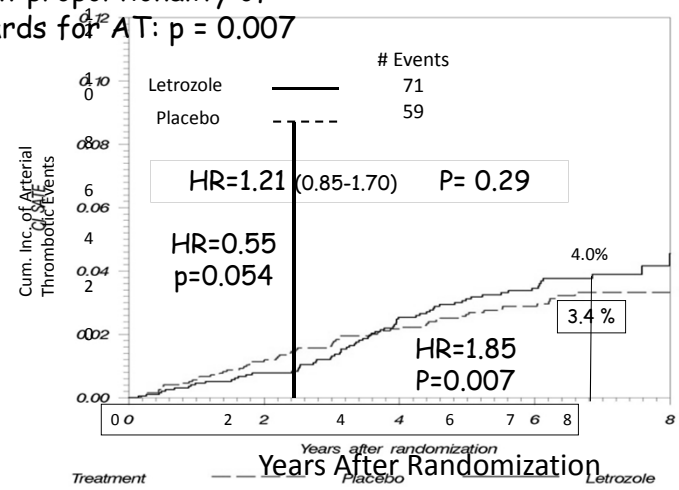
NSABP B-42: Cumulative Incidence of Osteoporotic Fx



NSABP B-42: Cum. Inc. of Arterial Thrombotic Events

Non-proportionality of Hazards for AT: p = 0.007



NSABP B-42: Summary

- The beneficial effect of extended L therapy on DFS did not reach statistical significance (15% reduction)
- No significant difference in overall survival with L vs. P
- Extended L provided:
  - Statistically significant improvement in BCFI (29% reduction in BCFI event)
  - Statistically significant reduction in the rate of DR (28% reduction in DR)
- L did not significantly increase risk of OF
- Risk of AT events was elevated for L after 2.5 years

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NSABP B-42 and NCIC MA.17R Comparison of HRs for Various Endpoints

Trial	Effect	Endpoint			
		DFS	BCFI	DR	OS
B-42 (n=3,923 631 events)	HR	0.85*	0.71	0.72	1.15
	P-value	0.048	0.003	0.03	0.22
MA.17R[1] (n=1,918 165 events)	HR	0.80***	0.66**	NR	0.97
	P-value	0.06	0.01	NR	0.83

* DFS (Recurrence + CBC + Non-breast CA + Deaths as first Events)
** Selected as DFS in MA.17R (Recurrence + CBC)
*** DFS (Recurrence + CBC + Deaths as first events)

[1]Goss P. et al: NEJM 2016

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NSABP B-42: Conclusions and Perspective

- Our findings suggest that careful assessment of potential risks and benefits is required before recommending extended L therapy in patients with early-stage BC, including:
  - Patient and tumor characteristics (age, nodal status)
  - Existing co-morbidities
  - Information on bone mineral density
  - Tolerance of the AI in the initial five years
- Genomic classifiers that predict risk of late recurrence and/or benefit from extended endocrine therapy may help to further individualize the recommendation for extended AI therapy

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S1-03: First results from the multicenter phase III DATA study comparing 3 versus 6 years of anastrozole after 2-3 years of tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer

Vivianne Tjan-Heijnen,[1] Irene van Hellemond,[1] Petronella Peer,[2] Astrid Swinkels,[3] Carolien Smorenburg,[4] Maurice van der Sangen,[5] Judith Kroep,[6] Hiltje De Graaf,[7] Aafke Honkoop,[8] Frans Erdkamp,[9] Franchette van den Berkmortel,[10] Jos Kitzen,[11] Maaike de Boer,[1] Wilfred de Roos,[12] Sabine Linn,[13] Alexander Imholz,[14] Caroline Seynaeve,[15] on behalf of the Dutch Breast Cancer Research Group (BOOG) for the DATA Investigators

[1]Maastricht University Medical Center, Maastricht; [2]Radboud University Medical Center, Nijmegen; [3]Netherlands Comprehensive Cancer Organization IKNL, Utrecht; [4]Medical Center Alkmaar, Alkmaar; [5]Catharina Hospital, Eindhoven; [6]Leiden University Medical Center, Leiden; [7]Medical Center Leeuwarden, Leeuwarden; [8]Isala Clinics, Zwolle; [9]Zuyderland Medical Center, Sittard; [10]Zuyderland Medical Center, Heerlen; [11]Albert Schweitzer Hospital, Dordrecht; [12]Gelderse Vallei Hospital, Ede; [13]Netherlands Cancer Institute, Amsterdam; [14]Deventer Hospital, Deventer; [15]Erasmus MC Cancer Institute, Rotterdam; all in The Netherlands

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DATA Study Design

- ✓ Postmenopausal at randomization
- ✓ ER+ and/or PR+
- ✓ M0 breast cancer
- ✓ After 2-3 years adjuvant tamoxifen

Stratification
- Nodal status
- ER/PR status
- HER2 status
- Tamoxifen duration

→ 6 years anastrozole, 1 mg daily

→ 3 years anastrozole, 1 mg daily

- 80% power to detect an increase in 3-year adapted Disease-Free Survival (aDFS) from 90% to 94%, i.e. a hazard ratio (HR) of 0.60 and a significance level of 0.05
- Accounting for 10% drop-out: 950 patients per group to be included (n=1912 patients actually included)
- Minimum follow-up: ≥6 years after randomization, i.e., ≥ 3 years of adapted follow-up

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DATA Study Endpoints

Primary endpoint:

Adapted Disease-Free Survival (aDFS), defined as the DFS starting as of 3 years after randomization, including as event:

- (Non-) invasive breast cancer recurrences (local, regional, distant);
- Second primary (non-) invasive (breast) cancers, incl. contralateral breast cancer, other than basal-cell or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix;
- Death of any cause.

Secondary endpoints:

Adapted Overall Survival (aOS) and adverse events.

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Patient and tumor characteristics well balanced

Characteristic		6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
Age at randomization – no. (%)			
	< 49 years	141 (17.0)	160 (19.2)
	50-59 years	342 (41.4)	328 (39.4)
	≥ 60 years	344 (41.6)	345 (41.4)
Tumor status – no. (%)			
	pT1	376 (45.5)	383 (46.0)
	pT2	392 (47.4)	382 (45.9)
	pT3/4	58 (7.0)	67 (8.0)
Nodal status – no. (%)			
	pN0 / pN0(i+)	266 (32.2)	282 (33.8)
	pN1	434 (52.5)	457 (54.9)
	pN2 / pN3	127 (15.3)	94 (11.3)
Histological grade – no. (%)			
	Grade I	139 (16.8)	158 (19.0)
	Grade II	430 (52.0)	415 (49.8)
	Grade III	229 (27.7)	238 (28.6)
Hormone-receptor status – no. (%)			
	ER- and PR-positive	627 (75.8)	633 (76.0)
	ER- or PR-positive	200 (24.2)	200 (24.0)
HER2 status – no. (%)			
	Positive	18 (2.2)	22 (2.6)
	Negative	745 (90.1)	748 (89.8)
	Unknown	64 (7.7)	63 (7.6)

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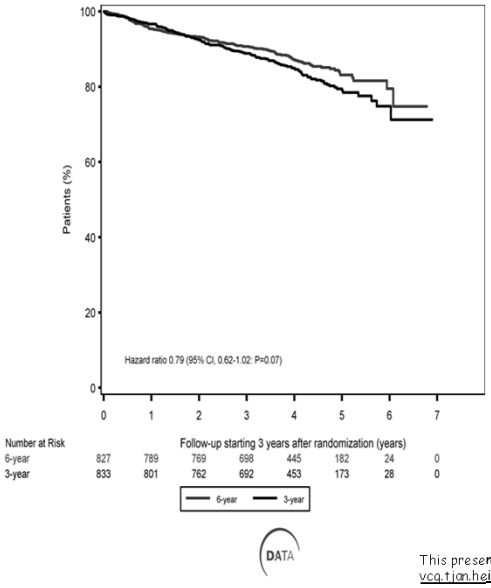
adapted Disease-Free Survival (aDFS)



N=1660	6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
5-year aDFS (%)	83.1	79.4
HR (95% CI)	0.79 (0.62 – 1.02)	
P-value	0.07	

DATA

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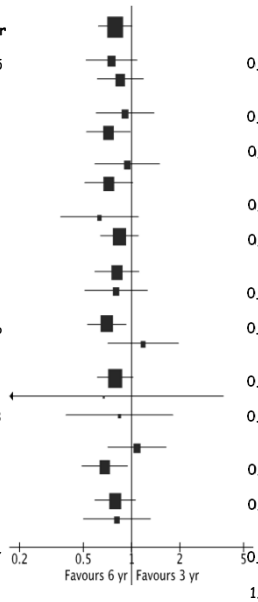
Subgroup analyses

Variable	No. of patients		No. of Events		Hazard ratio (95% CI)	5 yr adapted Disease-free Survival (%)	
	6-year	3-year	6-year	3-year		6-year	3-year
Adapted Disease-free Survival							
All	827	833	116	145	0.79 (0.62 - 1.02)	83.1	79.4
Age at randomization							
< 60 years	483	488	49	64	0.75 (0.52 - 1.10)	88.2	85.1
≥ 60 years	344	345	67	81	0.85 (0.61 - 1.19)	75.3	70.9
Tumor status							
pT1	376	383	45	50	0.91 (0.60 - 1.38)	85.0	84.4
pT2 and pT3/4	450	459	71	94	0.72 (0.51 - 0.98)	81.5	75.3
Nodal status							
pN negative	561	282	32	39	0.94 (0.59 - 1.50)	85.4	83.4
pN positive	266	551	84	106	0.72 (0.52 - 1.00)	82.2	77.4
Histology							
Lobular	154	140	24	32	0.63 (0.36 - 1.12)	83.0	72.4
Other	673	693	92	113	0.84 (0.64 - 1.11)	83.2	80.8
Histological grade							
Grade I and II	469	573	76	93	0.81 (0.59 - 1.10)	84.6	80.9
Grade III	229	238	36	49	0.80 (0.51 - 1.26)	80.3	75.4
Hormone receptor status							
			117		0.70 (0.53 - 0.92)	34.8	78.8
ER or PR positive	200	200	33	28	1.18 (0.71 - 1.96)	77.4	81.3



DATA

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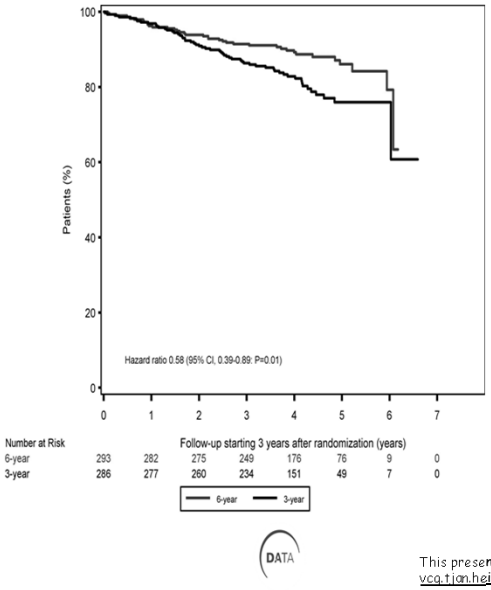
aDFS if ER+ *and* PR+, HER2-, Node+, Chemo+



N=1660	6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
5-year aDFS (%)	86.0	75.9
HR (95% CI)	0.58 (0.39 – 0.89)	
P-value	0.01	

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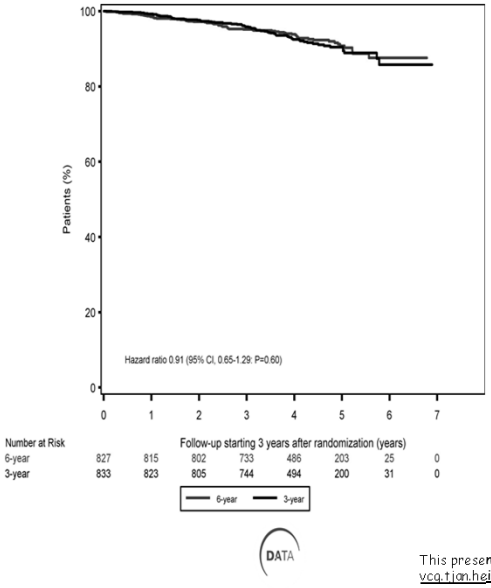
adapted Overall Survival (aOS)



N=1660	6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
5-year aOS (%)	92.4	91.7
HR (95% CI)	0.91 (0.65 – 1.29)	
P-value	0.60	

Median adapted follow-up of 4.1 years (P_5=2.9, P_{95}=5.8 years).

DATA

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Predefined Adverse Events

Grade, years 0-6	6-year Anastrozole (N=827)		3-year Anastrozole (N=833)	
	Any	Grade ≥ 3	Any	Grade ≥ 3
Arthralgia / myalgia	57.6%	8.0%	51.9%	5.5%
Bone fractures	9.8%	2.1%	7.4%	2.5%
Osteopenia / osteoporosis	20.9%	1.3%	16.5%	0.8%
Cardiovascular incl. arrhythmia	13.4%	3.5%	12.9%	3.4%
Other	25.6%	4.8%	20.8%	3.6%

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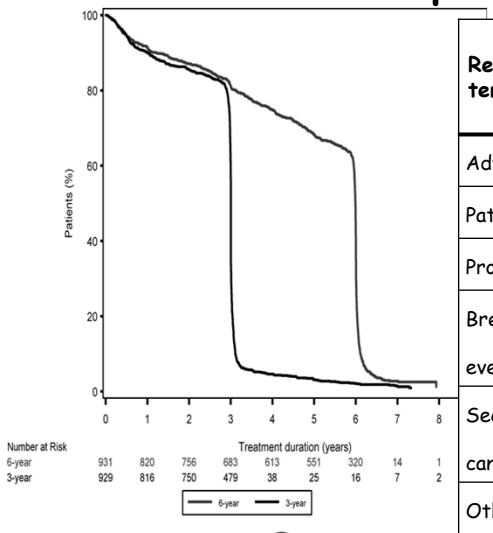
Compliance



Reasons early termination	6-year Anastrozole (%)	3-year Anastrozole (%)
Adverse events	23.0	14.4
Patient refusal	4.7	1.5
Protocol violation	2.2	3.6
Breast cancer event	10.4	5.2
Second non-breast cancer	1.9	1.3
Other	2.9	1.9

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Conclusions

- The findings do not support extended adjuvant AI use after 5 years of sequential endocrine therapy for all postmenopausal hormone receptor-positive breast cancer patients.
- It suggests benefit for a selected group of patients, i.e. node-positive, ER *and* PR positive, HER2 negative, and prior chemotherapy.
- Extended AI use is associated with increased toxicity (i.e. bone and muscle adverse events).
- We will perform a follow-up analysis when all patients have reached a minimum adapted follow-up of 9 years.

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Leiden University Medical Center

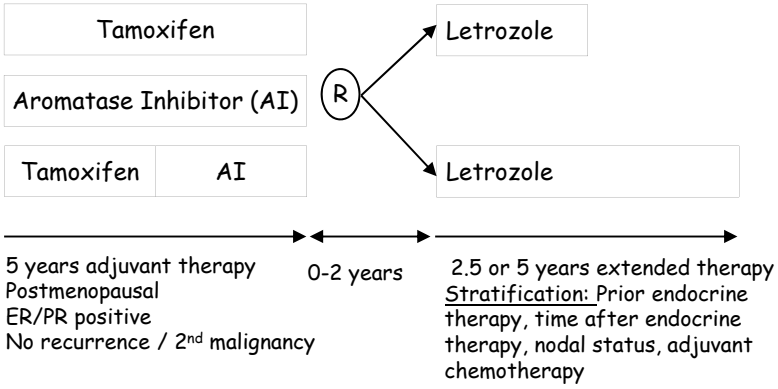
Optimal duration of extended letrozole treatment after 5 years of adjuvant endocrine therapy; results of the randomized phase III IDEAL trial (BOOG 2006-05)

C.J.H. van de Velde[1], **E.J. Blok[1,2],** E. Meershoek[1], H. Putter[3], J. van den Bosch[4], E. Maartense[5], A.E. van Leeuwen-Stok[6], G.J. Liefers[1], J.W.R. Nortier[2], E.J. Th. Rutgers[7], J.R. Kroep[2]

1. Department of Surgery, Leiden University Medical Center, Leiden, Netherlands;
2. Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands;
3. Department of Medical Statistics, Leiden University Medical Center, Leiden, Netherlands;
4. Department of Internal Medicine, Albert Schweitzer hospital, Dordrecht, Netherlands;
5. Department of Internal Medicine, Reinier de Graaff hospital, Delft, Netherlands;
6. Dutch Breast Cancer Research Group, Utrecht, Netherlands and
7. Department of Surgery, Netherlands Cancer Insitute, Amsterdam, Netherlands.

Trial design

- IDEAL trial
- Investigation on the Duration of Extended Adjuvant Letrozole treatment



Trial design (2)

- Primary endpoint
  - Disease free survival (DFS)
- Secondary endpoints
  - Overall survival (OS)
  - Distant metastasis free interval (DMFI)
  - 2nd primary breast cancer (DCIS or invasive)
  - Safety
- Competing risk model

Statistical analysis

- Two parallel analyses
  1. Starting at randomization: *"should we extend 2.5 or 5 years?"*
  2. Starting at 2.5 years: *"having extended to 2.5 years, continue up to 5 years?"*

Results – Baseline characteristics

Baseline characteristics		N	%
N-stage	pN0	472	25,9%
	pN1 mi/1-3 pos	1074	58,9%
	pN2: 4-9 pos	201	11,0%
	pN3: >=10 pos	59	3,2%
Prior endocrine treatment	5 years tamoxifen	222	12,2%
	5 years AI	524	28.8%
	2-3 years tam-> 3-2 years AI	1075	59.0%
Time after stop HT (months)	0 to <6	1614	88,6%
	6 to <12	95	5,2%
	12-27	112	6,2%

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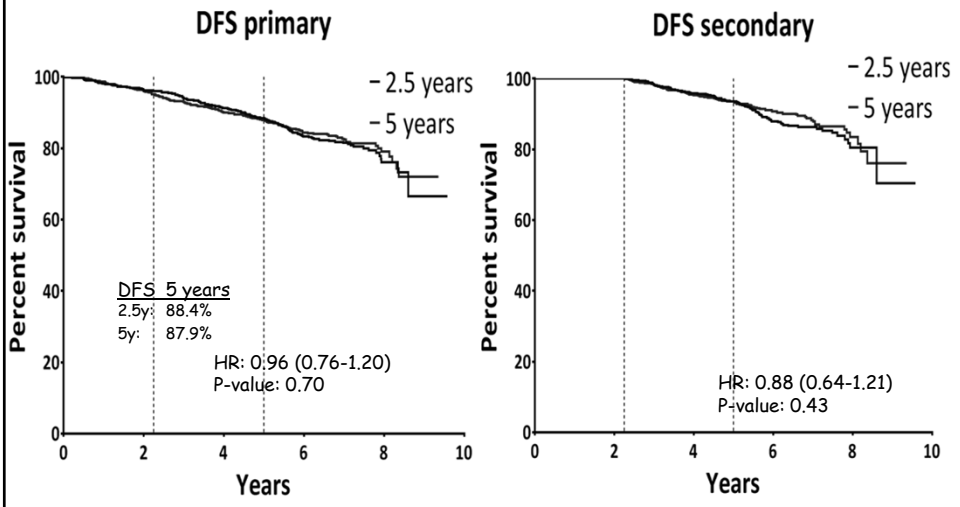
Results - DFS



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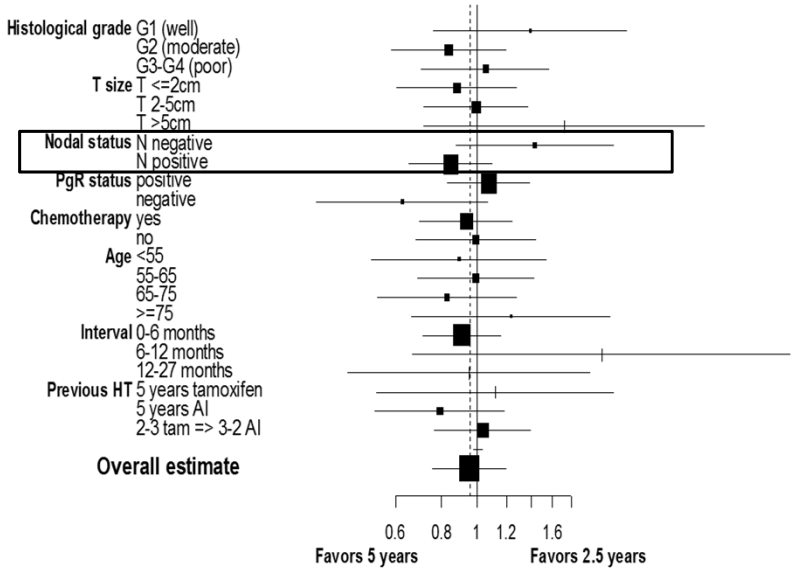
Results – subgroup analysis



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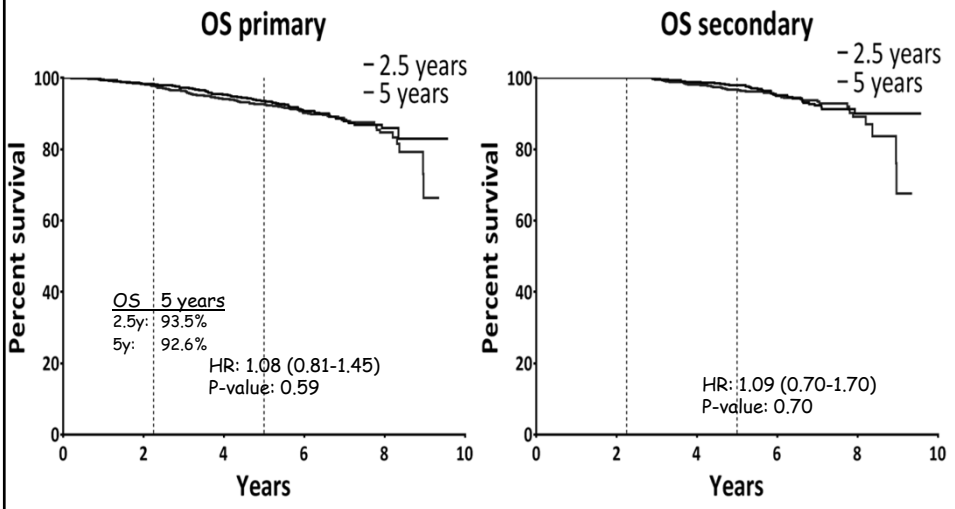
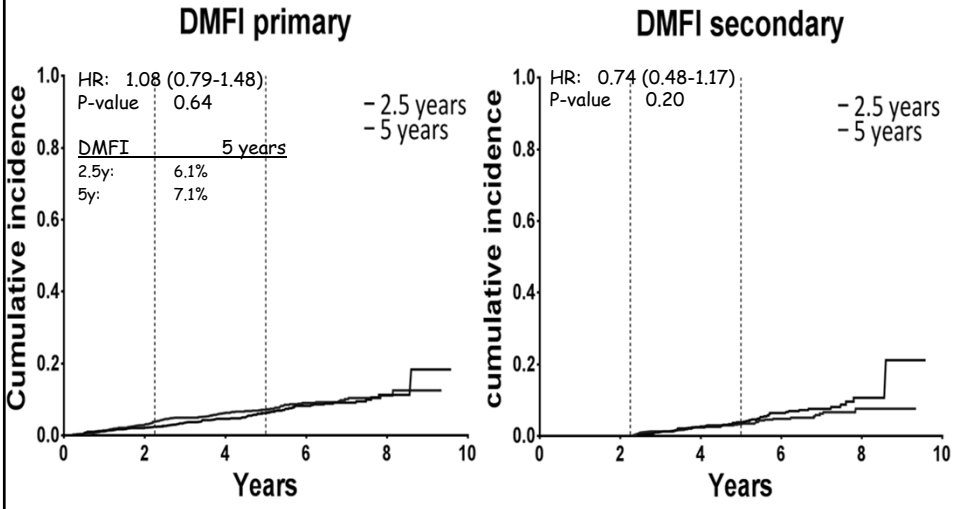
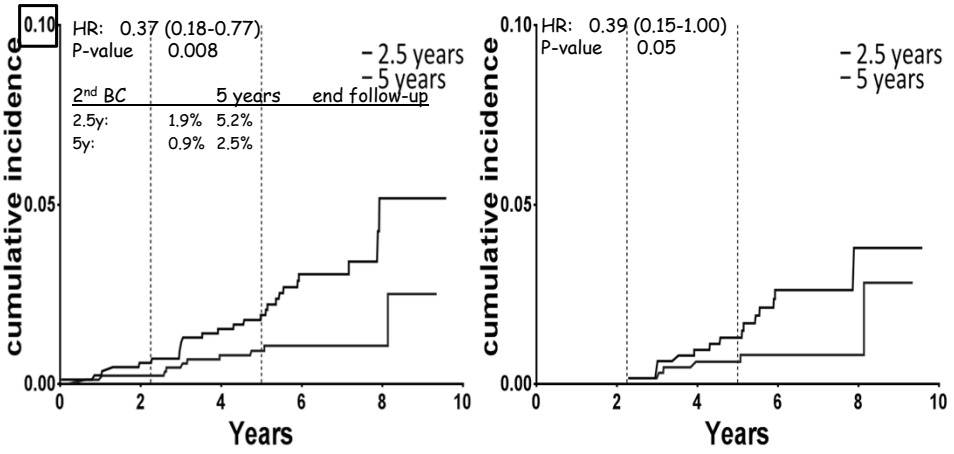
Results - OS



DMFI – competing risk model



2nd primary breast cancer – competing risk model

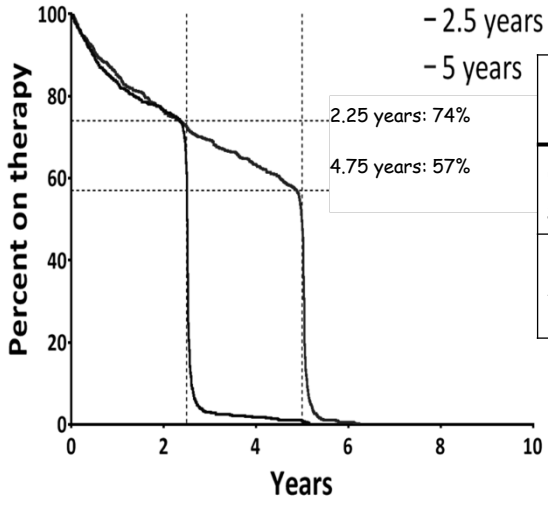


Toxicity – all grades

	2.5 years group	5 years group
N patients	640 (70%)	643 (70%)
N adverse events	1591	1843 (↑16%)
% CTC grade 3-4	9.8%	9.7%

- Arthralgia (13.8%)
- Hot flashes (12%)
- Osteoporosis (10%)

Compliance



	2.5 years	5 years
Early stop (n)	241	385
Symptoms /AE + refusal	*179 (74%)*	*254 (66%)*

Discussion & Conclusion

- No significant differences in disease-related outcomes
- Significant difference in prevention of 2nd primary breast cancer
  - HR 0.37, small absolute risk reduction of 2.5% at the end of follow-up
  - Similar to findings in healthy women (HR 0.35, MAP.3 trial, NEJM 2011)
  - Should prevention of new primary breast tumors be a therapy goal of adjuvant therapy?

  No benefit of extending AI-based adjuvant therapy longer than 2.5 years

- Toxicity
  - High frequency of adverse events (70% patients)
  - Effect on compliance
  - 2.5 vs 5 years: Low number of additional AEs
    → extending to 5 years well tolerated

PrECOG 0102: A Randomized, Double-Blind Phase II Trial of Fulvestrant plus Everolimus or Placebo in Post-Menopausal Women with Hormone-Receptor Positive, HER2-Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy
Abstract S1-02

Noah S Kornblum, MD[1], Judith Manola, MS[2], Paula Klein, MD[3], Bhuvaneswari Ramaswamy, MD[4], Adam Brufsky, MD PhD[5], Phillip J Stella, MD[6], Brian Burnette, MD[7], Melinda Telli, MD[8], Della F Makower, MD[1], Joseph Leach, MD[9], Cristina I Truica, MD[10], Antonio C Wolff, MD[11], Gamini S Soori, MD[12], Barbara Haley, MD[13], Arun Nagarajan, MD[14], Timothy R Wassenaar, MD[15], Lori Goldstein, MD[16], Kathy D Miller, MD[17], and Joseph A Sparano, MD[1]

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Methods: Key Eligibility Criteria

- Post-menopausal women
- HR-positive, HER2-negative (ASCO-CAP)
- Inoperable locally advanced *or* metastatic breast cancer
- AI resistant disease:
  - Relapse while receiving adjuvant AI therapy
  - Progression after one or more AIs for metastatic disease
- ECOG PS 0-1
- Normal organ function
- ≤ 1 prior chemotherapy regimen for metastasis
- Measurable and/or non-measurable disease (RECIST 1.1)
- 2 doses of fulvestrant permitted within 28d prior to randomization

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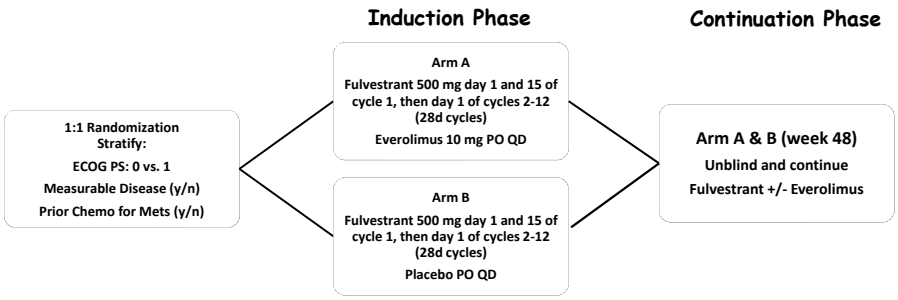
Methods: Study Schema



- **Induction Phase**: Treat until evidence of progressive disease or unacceptable toxicity for a maximum of 12 cycles (48 weeks)
- **Continuation Phase**: If no disease progression or unacceptable toxicity after 12 cycles, unblind and continue fulvestrant +/- everolimus

- **Treatment Plan:** Tumor measurements every 12 weeks (+/- 1 week) by local treating physician
- **Supportive Care:** Corticosteroid mouthwash prophylaxis was not used

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Results: Patient Characteristics

Characteristic	Fulvestrant + Everolimus	Fulvestrant + Placebo
Number of Randomized Patients (treated)	66 (64)	65 (65)
Age (Median/Range)	64 (39-92)	59 (35-85)
ECOG Performance Status: 0 1	40 (61%) 26 (39%)	38 (58%) 27 (41%)
Measurable Disease	44 (67%)	42 (65%)
Metastatic Disease Site		
Bone	43 (65%)	46 (71%)
Lung	28 (42%)	22 (34%)
Liver	18 (27%)	17 (26%)
Lymph Nodes	27 (41%)	28 (43%)
Prior Therapy		
Prior Chemo for Metastatic Disease	11 (17%)	12 (18%)
Fulvestrant prior to C1D1	6 (9%)	5 (8%)
Prior CDK4/6 Inhibitor	0	2 (3%)

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Results: Grade 1-4 Adverse Events

(Possible/Probable/Definitely Related to Therapy)

CTCAE 4.0	Fulvestrant + Everolimus (N=64)				Fulvestrant + Placebo (N=65)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Worst Grade Toxicity	4 (6%)	24 (37%)	31 (48%)	0	21 (32%)	11 (17%)	8 (12%)	1 (2%)
Mucositis/Stomatitis	13 (20%)	15(23%)	6 (9%)	0	6 (9%)	2 (3%)	0	0
Pneumonitis	2 (3%)	3 (5%)	4 (6%)	0	0	0	0	0
Fatigue	12 (19%)	11 (17%)	4 (6%)	0	9 (14%)	3 (5%)	3 (5%)	0
Hyperglycemia	8 (13%)	2 (3%)	3 (5%)	0	3 (5%)	0	0	0
Anemia	10 (16%)	6 (9%)	2 (3%)	0	3	0	1	0
Hypertriglyceridemia	10 (16%)	2 (3%)	2 (3%)	0	2 (3%)	0	0	0

- **3 deaths occurred during or within 30 days of last protocol treatment**
- **2 in the F/E arm (1sepsis/1 cardiac arrest), 1 in the F/P arm (sepsis)**
- **None attributed to study treatment by local Tx physician**

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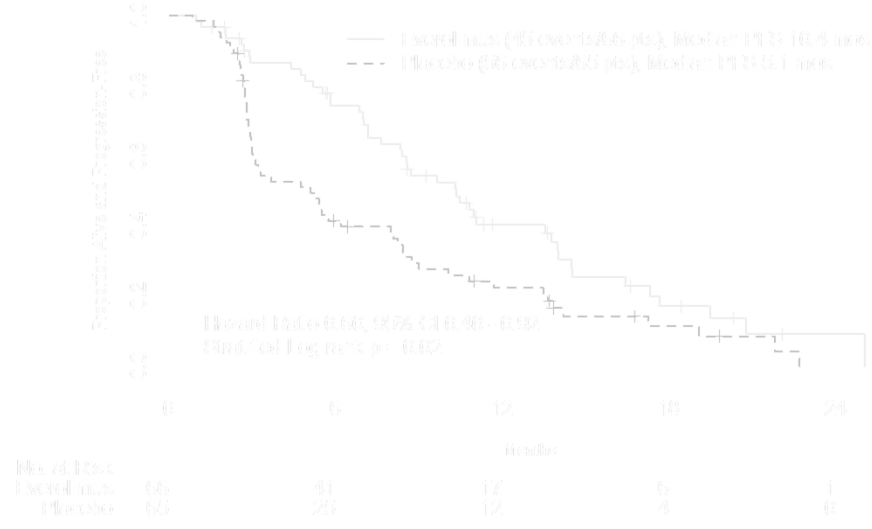
Progression Free Survival

(by investigator assessment – primary study endpoint)



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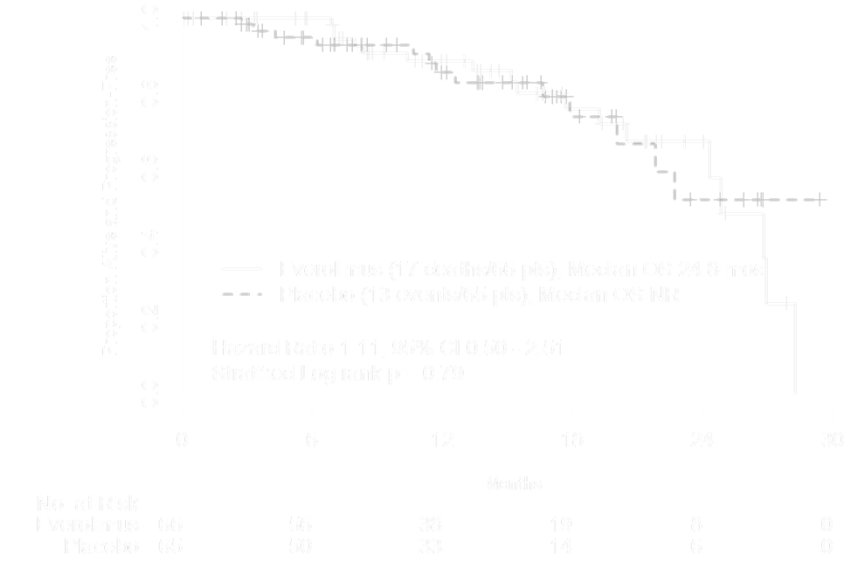
Overall Survival



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Conclusions

- Addition of everolimus to fulvestrant improved PFS
  - median PFS 5.1 vs. 10.4 months
  - HR 0.60, p=0.02
- Associated with more toxicity, including
  - Grade 3 adverse events: 48% (F/E) vs. 14% (F/P)
  - Most common grade 3 A.E.s occurring in > 5% included stomatitis (9%), pneumonitis (6%), fatigue (5%), & hyperglycemia (6%)
  - Saftey profile consistent with everolimus in BOLERO-2[1]
  - Prophylactic corticosteroid mouthwash was not used, which has been shown to reduce risk of grade 1-2 stomatitis from about 65% to 20%[2]
- Provides additional evidence that adding everolimus to anti-estrogen therapy in AI resistant disease improves clinical outcomes

1 Baselga, J. et al, New Engl. J. Med. 366, 520–529 (2012)
2 Rugo, H, et al. J Clin Oncol 34, 2016 (suppl; abstr 525)

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Discussion

- The improvement in PFS observed in this study (median PFS 5.1 vs. 10.4 mo., HR 0.60, p=0.02) is comparable that observed in the PALOMA3 trial (3.8 vs. 9.2 mo. HR 0.42, p<0.001) with the CDK4/6 inhibitor palbociclib
- Study completed prior to availability to CDK 4/6 inhibitors, which are effective when added to first-line AI therapy or second line fulvestrant in AI-resistant disease (PALOMA-1[1], MONALEESA-2[2], PALOMA-3[3])
- mTOR inhibitors are effective as second line therapy in AI resistant disease (BOLERO2[4],TAMRAD[5]), but not as first line (HORIZON)[6]
- Most patients in this study did not receive prior CDK4/6 therapy, and further work is required to define prior CDK 4/6i would impact response to mTORi/SERD therapy
- Optimal sequencing of available agents/combinations in AI resistant disease requires additional study

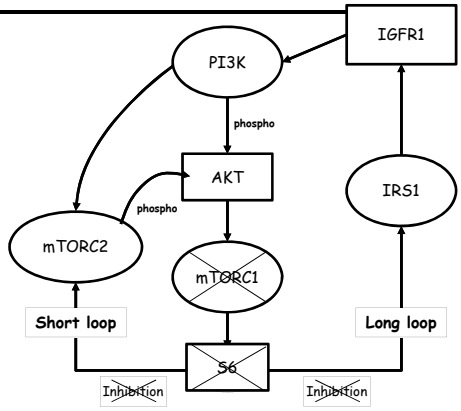
[1]Cristofanilli, M. et a. Lancet Oncol,17, 425–439 (2016); [2]Hortobagyi,, G.N. et al. N Engl J Med. 375,1738-1748 (2016); [3]Finn, RS et al. Lancet Oncol, 16, 25–35 (2015); [4]Baselga, J. et al, New Engl. J. Med. 366, 520–529 (2012) ; [5]Bachelot, T. et al. J Clin Oncol. 30, 2718-2724 (2012); [6]Wolff, A.C. et al. J Clin Oncol 31, 195-202 (2012)

BELLE-3: A Phase III Study of Buparlisib and Fulvestrant in Postmenopausal Women With HR+, HER2–, AI-treated, Locally Advanced or Metastatic Breast Cancer, Who Progressed On or After mTOR Inhibitor-based Treatment

Angelo Di Leo,[1] Keun Seok Lee,[2] Eva Ciruelos,[3] Per Lønning,[4] Wolfgang Janni,[5] Ruth O'Regan,[6] Marie-Ange Mouret Reynier,[7] Dimitar Kalev,[8] Daniel Egle,[9] Tibor Csőszi,[10] Roberto Bordonaro,[11] Thomas Decker,[12] Vivianne CG Tjan-Heijnen,[13] Sibel Blau,[14] Alessio Schirone,[15] Denis Weber,[16] Mona El-Hashimy,[17] Bharani Dharan,[17] Dalila Sellami,[17] Thomas Bachelot[18]

Preclinical Rationale for PI3K Inhibition After progression on mTORC1 Inhibitors

- mTORC1 inhibition elicits AKT phosphorylation via feedback activation
- PI3K inhibitors abrogate or attenuate AKT phosphorylation elicited by mTORC1 inhibition
- Is there a role for PI3K inhibition after progression on an mTORC1 inhibitor-based regimen?



AKT, protein kinase B; IGFR1, insulin-like growth factor receptor 1; IRS1, insulin receptor substrate 1; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.
Sun S-Y, *et al. Cancer Res* 2005;65:7052–7058; O'Reilly KE, *et al. Cancer Res* 2006;66:1500–1508; Breuleux M, *et al. Mol Cancer Ther* 2009;8:742–753; O'Brien NA, *et al. Clin Cancer Res* 2014;20:3507–3520; Wander SA, *et al. J Clin Invest* 2011;121:1231–1241; Mayer IA & Arteaga C. *Annu Rev Med* 2016;67:11–28.

BELLE-3 Study Design and Endpoints

- Postmenopausal women with HR+/HER2–, AI-pretreated, locally advanced or metastatic breast cancer
- Progression on or after an mTOR inhibitor as last line of treatment
- N=432

Randomization (2:1)
Stratified by visceral disease status

Buparlisib (100 mg/day) + fulvestrant (500 mg) n=289

Placebo + fulvestrant (500 mg) n=143

Primary endpoint
- PFS (locally assessed per RECIST v1.1)

Key secondary endpoint
- OS

Other secondary endpoints
- PFS by *PIK3CA* status (ctDNA)
- OS by *PIK3CA* status (ctDNA)
- ORR and CBR in the full population and by *PIK3CA* status (ctDNA)
- Safety, pharmacokinetics, quality of life

- Tumor assessments were performed every 6 weeks
- 90% power to detect a 33% risk reduction in PFS (disease progression or death) at one-sided a=0.025, based on the observation of 313 PFS events
- Prior fulvestrant was not allowed

AI, aromatase inhibitor; CBR, clinical benefit rate; ctDNA, circulating tumor DNA; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors.
BELLE-3: ClinicalTrials.gov NCT01633060.

Prior mTOR Inhibitor Treatment

Characteristic	Buparlisib + Fulvestrant (n=289)	Placebo + Fulvestrant (n=143)
Prior mTOR inhibitor treatment, %	100	100
Disease progression during mTOR inhibitor treatment or within 30 days of completion, %	91	84
Median duration of mTOR inhibitor treatment, months	8.0	8.6

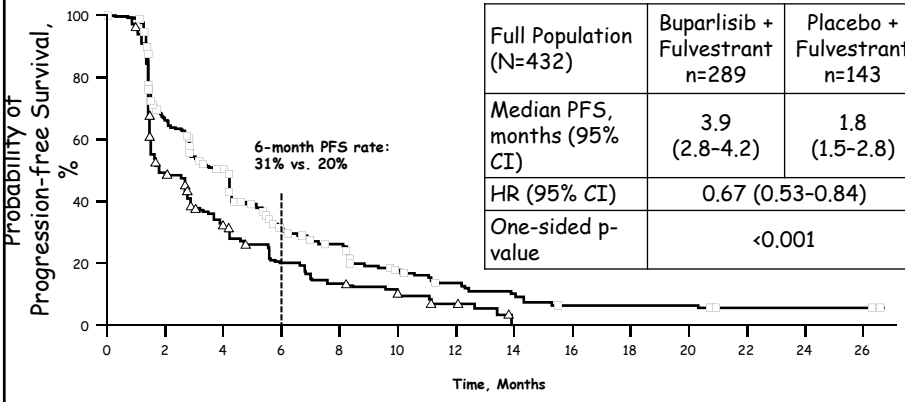
- Prior mTOR inhibitor treatment included everolimus (99%) and ridaforolimus (1%)
- 69% of patients had received ≥ 2 lines of endocrine therapy in the metastatic setting.

Patient Disposition and Treatment Exposure

	Buparlisib + Fulvestrant (n=289)	Placebo + Fulvestrant (n=143)
Number of patients treated	288	140
Treatment ongoing, %*	13	8
Median duration of study treatment, months (range)	3.3 (0.3–27.1)	2.3 (0.4–14.7)
Buparlisib/placebo dose interruptions due to AEs, %	36	9
Buparlisib/placebo dose reductions due to AEs, %	31	8
Treatment discontinuation due to AE / physician or patient decision, %	8 / 13	2 / 6
On-treatment deaths suspected to be study treatment-related, n (%)	2 (1)	2 (1)

AE, adverse event.
*Treatment ongoing as of data cut-off (May 23, 2016).

Progression-free Survival per Investigator Assessment (Primary Endpoint)



Full Population (N=432)	Buparlisib + Fulvestrant n=289	Placebo + Fulvestrant n=143
Median PFS, months (95% CI)	3.9 (2.8–4.2)	1.8 (1.5–2.8)
HR (95% CI)	0.67 (0.53–0.84)	
One-sided p-value	<0.001	

- PFS results by independent central review were consistent with local assessment:
  - HR 0.57 (95% CI: 0.44–0.74; one-sided p<0.001)

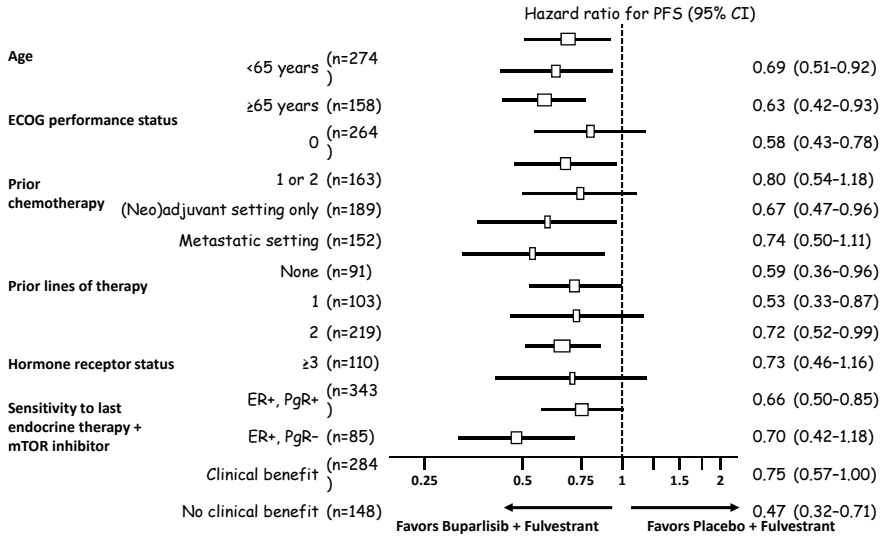
CI, confidence interval; HR, hazard ratio.

Objective Response Rate and Clinical Benefit Rate

	Buparlisib + Fulvestrant (n=289)	Placebo + Fulvestrant (n=143)
ORR, % (95% CI)	7.6 (4.8–11.3)	2.1 (0.4–6.0)
CR, %	0.3	0
PR, %	7.3	2.1
CBR, % (95% CI)	24.6 (19.7–29.9)	15.4 (9.9–22.4)

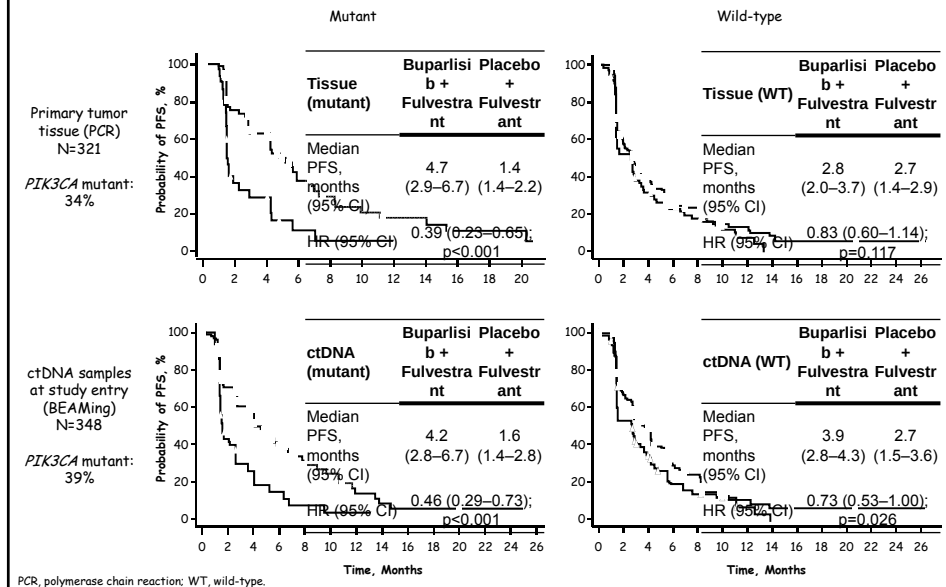
CR, complete response; PR, partial response; SD, stable disease.
ORR defined as CR + PR; CBR defined as CR + PR + SD ≥24 weeks.

Subgroup Analyses of PFS



ECOG, Eastern Cooperative Oncology Group; ER+, estrogen receptor-positive; PgR–, progesterone receptor-negative; PgR+, progesterone receptor-positive.

Progression-free Survival by *PIK3CA* Status



PCR, polymerase chain reaction; WT, wild-type.
p-values are one-sided.

Adverse Events (≥10% of Patients) Regardless of Relationship to Study Treatment

	Buparlisib + Fulvestrant n=288		Placebo + Fulvestrant n=140	
Adverse event, %	All Grades	Grade 3/4	All Grades	Grade 3/4
Total	98	62	91	34
ALT increased	39	22	7	3
AST increased	37	18	10	3
Hyperglycemia	36	12	3	0
Nausea	34	1	18	2
Diarrhea	26	3	9	1
Fatigue	23	4	19	1
Depression	21	1	8	0
Anxiety	18	1	10	0
Asthenia	17	2	10	0
Decreased appetite	16	1	6	1
Dizziness	12	1	7	0
Hypertension	12	6	6	4
Rash	12	2	2	0
Stomatitis	10	1	4	0
Headache	9	0	11	0

- One confirmed case of Hy's Law was observed in the buparlisib + fulvestrant arm

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Conclusions

- The BELLE-3 trial met its primary endpoint: buparlisib + fulvestrant prolonged PFS compared with placebo + fulvestrant in postmenopausal women with HR+/HER2– ABC who had received prior AI and mTOR inhibitor treatment
  - Approximately 90% of patients enrolled had progressed on or after treatment with an mTOR inhibitor
- Overall survival data are still immature
- The higher rate of toxicity in patients receiving buparlisib + fulvestrant (including transaminase elevations and mood disorders) may represent a clinically relevant challenge

Conclusions

- Exploratory subgroup analyses suggest that treatment benefit with combined buparlisib + fulvestrant is confined to:
  - Patients with *PIK3CA*-mutant tumors, assessed either at the primary site or in ctDNA collected at baseline
  - Patients with visceral disease
- Perspective: investigation of p110a-selective PI3K inhibitors in patients with *PIK3CA*-mutant tumors, whose disease has progressed before or after treatment with an mTOR inhibitor

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A novel BRD4 inhibitor enhances endocrine therapy efficacy and circumvents endocrine resistance in estrogen receptor positive breast cancer models

Carmine De Angelis, Agostina Nardone, Maria Letizia Cataldo, Xiaoyong Fu, Meghana Trivedi, Saili Yi, David Breckenridge, Gary C. Chamness, Phil Vitorino, C. Kent Osborne and Rachel Schiff

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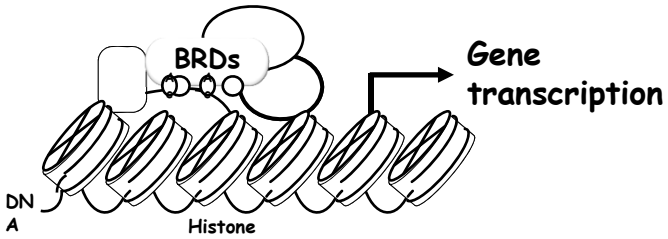
The BET (bromodomain and extraterminal domain) protein family

- BRD2, BRD3, BRD4 and BRDT
- Epigenetic readers that bind acetylated lysines on histones
- Facilitate the recruitment of additional epigenetic and transcription factors required in gene transcription



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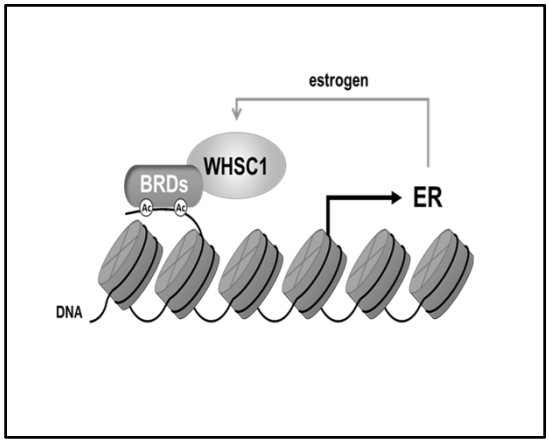
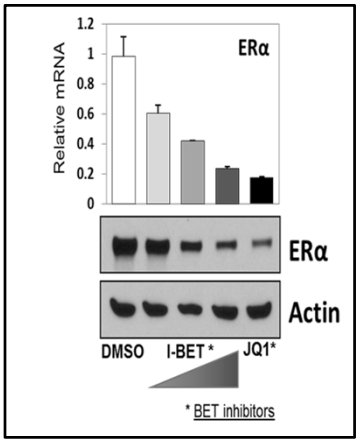
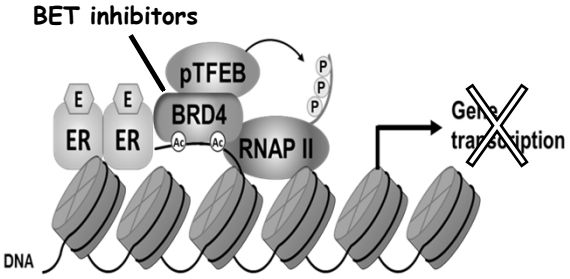
BRD4 inhibition reduces ESR1 gene expression





Qin F, et al. Cell Research 2014

BRD4 inhibition impacts ER transcriptional activity



Qin et al. Cell Research 2014
Nagarajan et al. Cell Reports 2014
Sengupta et al. BCRT 2015

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Aim of the study

- To assess the activity of the new BRD4 inhibitor **GS-6510** in ER+ endocrine sensitive and resistant breast cancer models as monotherapy or in combination with fulvestrant

ER+ Cell lines

- **MCF7**
- **T47D**
- **ZR75-I**

Parental (P)
Estrogen-deprivation resistant (EDR)
Tamoxifen resistant (TAMR)
Fulvestrant resistant (FULR)

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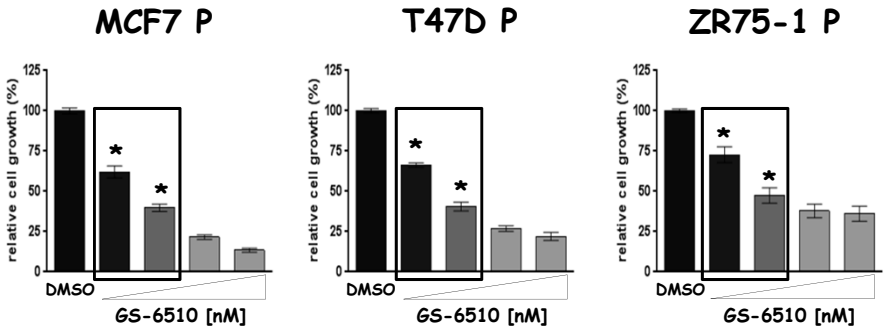
GS-6510 reduces E2-stimulated cell growth



* p <0.05 relative to DMSO

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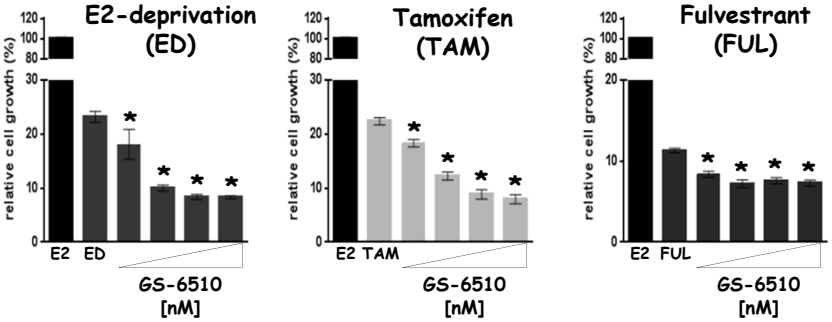
GS-6510 enhances the efficacy of endocrine therapies

MCF7 P



* p <0.05 relative to ED

* p <0.05 relative to TAM

* p <0.05 relative to FUL

E2=1nM; Ful=100nM; Tam=100nM

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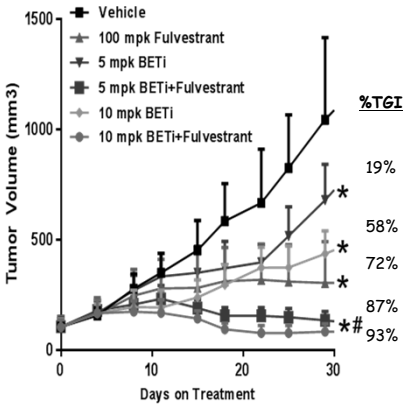
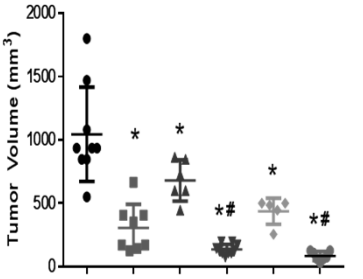
GS-6510 reduces tumor growth and in combination with Ful induces tumor regression in HBCx34 PDX model





* p<0.01 relative to Vehicle

\# p<0.01 relative to Fulvestrant

%TGI, percentage of tumor growth inhibition

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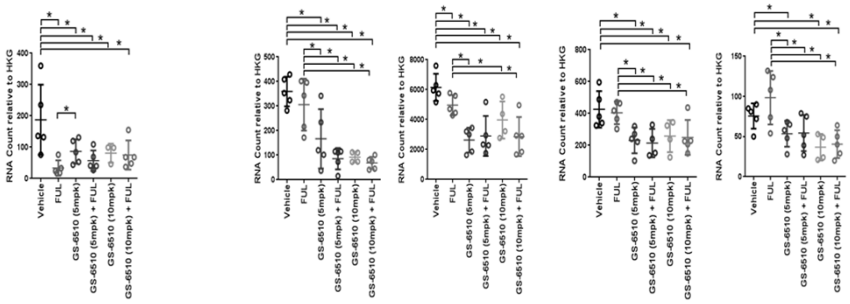
GS-6510 alone or in combination with Ful reduces the expression of ER-dependent and cell cycle related genes *in vivo*

Highly Fulvestrant Sensitive | **Moderately Fulvestrant Sensitive** | **Fulvestrant insensitive**

PGR | **MYC** | **CCND1** | **BCL2** | **CDK6**



Vehicle GS-6510 (5mpk) GS-6510 (5mpk) + FUL

FUL GS-6510 (10mpk) GS-6510 (10mpk) + FUL

* p<0.05

This presentation is the intellectual property of Carmine De Angelis, Rachel Schiff, and Phil Vitorino. Contact them at carmine.deangelis@bcm.edu, rschiff@bcm.edu, phil.vitorino@gilead.com

Aim of the study

- To assess the activity of the new BRD4 inhibitor GS-6510 in ER+ endocrine sensitive and resistant breast cancer models as monotherapy or in combination with fulvestrant

ER+ Cell lines

- MCF7
- T47D
- ZR75 -I

Parental (P)

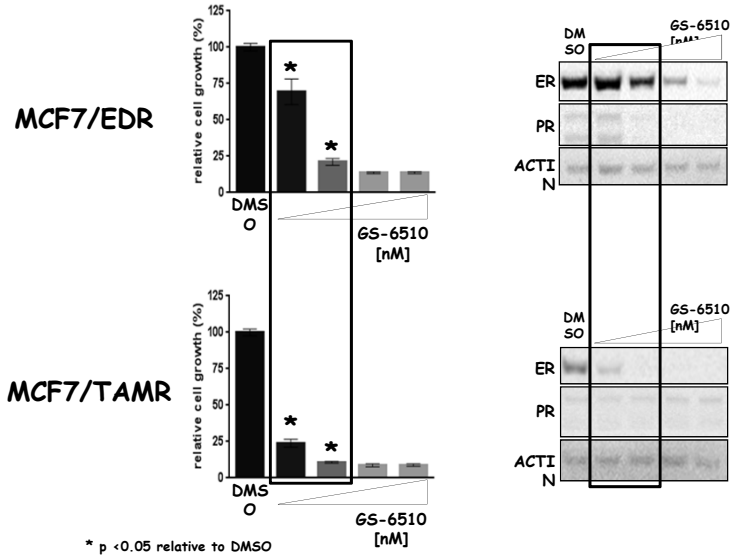
Estrogen-deprivation resistant (EDR)

Tamoxifen resistant (TAMR)

Fulvestrant resistant (FULR)

This presentation is the intellectual property of Carmine De Angelis, Rachel Schiff, and Phil Vitorino. Contact them at carmine.deangelis@bcm.edu, rschiff@bcm.edu, phil.vitorino@gilead.com

GS-6510 inhibits the growth of MCF7/EDR and TAMR cells



* p <0.05 relative to DMSO

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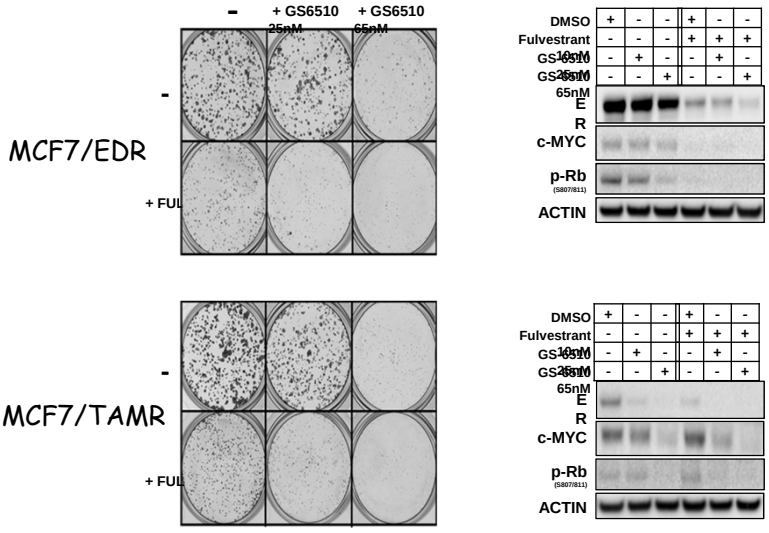
San Antonio Breast Cancer Symposium, December 6-10, 2016

GS-6510 enhances Ful efficacy in MCF7/EDR and MCF7/TAMR cells



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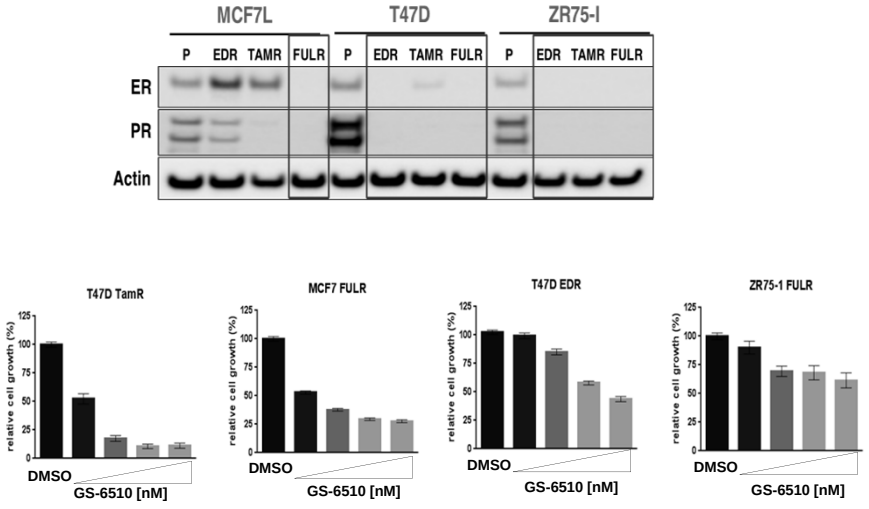
GS-6510 efficacy in ER-independent Endo-Res models



Conclusion

- The epigenetic regulator BRD4 is a suitable target for therapeutic intervention in ER+ BC.
- The antitumor efficacy of GS-6510 in endocrine sensitive and especially in ER-dependent EndoR models is worthy of further clinical investigation.
- The growth inhibitory effects observed in some of the ER-independent EndoR models suggests that additional genes/pathways involved in endocrine resistance could be affected by GS-6510.
- Identifying these pathways and determining their predictive role are needed to guide patient selection for future clinical trials.

Adjuvant Ibandronate in postmenopausal women with early breast cancer

First results of the TEAM Iib trial

S.B. Vliek[1]; E. Meershoek-Klein Kranenbarg[2] ; A.G.J. van Rossum[1]; B.C. Tanis[3]; H. Putter[2]; A.W.G. van der Velden[4]; M.P. Hendriks[5] ; A. van Bochove[6]; Y. van Riet[7]; A.E. van Leeuwen-Stok[8]; J.R. Kroep[2]; J.W.R. Nortier[2]; V.C.G. Tjan-Heijnen[9]; C.J.H. van de Velde[2]; S.C. Linn[1]

BOOG TEAM II

LUMC Leiden University Medical Center

NETHERLANDS CANCER INSTITUTE ANTONI VAN LEEUWENHOEK

Team Iib trial

who did we enroll

INCLUSION

Postmenopausal
- amenorrhoea >1 year (<55y laboratory confirmation)
- oophorectomy

Stage I-III breast cancer (BC)
- ER and/or PgR receptor positive (≥10%) adenocarcinoma

Completed adequate surgical treatment
Adequate renal and hepatic function

EXCLUSION

Chemotherapy induced menopause
Bilateral invasive BC / BC in last 15 years / previous other malignancy
History of disease with influence on bone metabolism (e.g. Paget)

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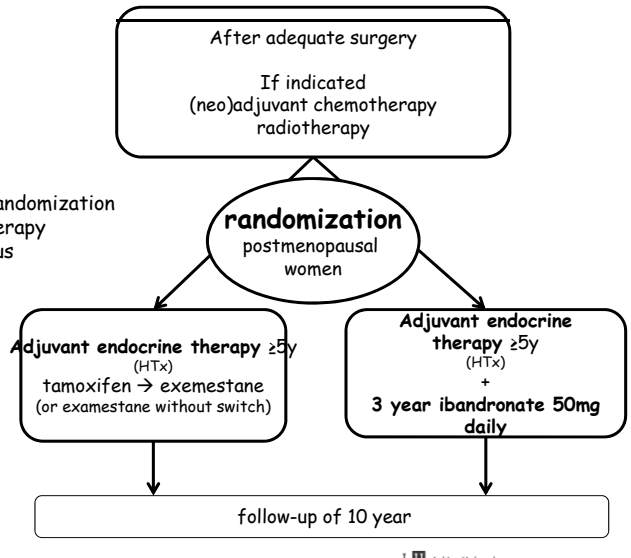
Team Iib trial: Study design

Stratification by:
- age
- time from surgery to randomization
- (neo)adjuvant chemotherapy
- hormone receptor status
- HER2 overexpression
- grade
- T-stage
- N-stage
- center



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First results

not all patients completed 3 year ibandronate yet

CURRENTLY

- Median follow-up of 4.6 years
  - 21 patients never started ibandronate
  - 73 patients are still on ibandronate
  - adherance to ibandronate → 67% at 3 years

- Total DFS events: 149

		Adjuvant HTx	Adjuvant HTx + 3 year ibandronate
Mortality	all causes	47	48
	breast cancer	29 (61.7%)	17 (35.4%)
	secondary malignancy	9 (19.1%)	14 (29.2%)

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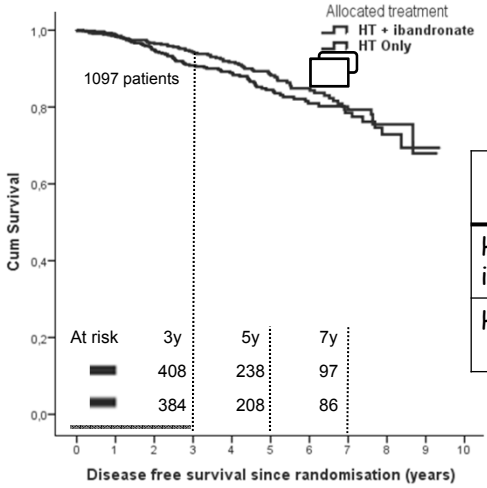
First results

primary endpoint: Disease free survival at 3 years



	Events	DFS	HR (CI)
HTx+ ibandronate	29	94.3 %	0.80 (0.58-1.10)
HTx only	46	90.8 %	

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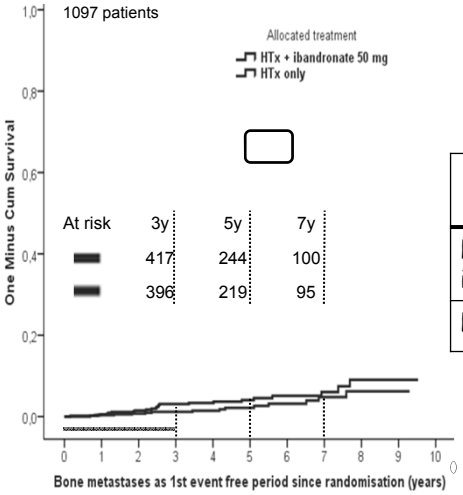
FIRST RESULTS

TIME TO BONE METASTASES AS FIRST EVENT



	Events	BM1[s] [t]E	HR (CI)
HTx+ ibandronate	6	1.2%	0.59 (0.30-1.14)
HTx only	15	3.1%	

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First results

Safety and Toxicity

- Gastro-intestinal adverse events reported (CTCAE v3.0)

Adverse Event	HTx only		HTx + ibandronate	
	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Stomach pain / esophagitis / heartburn	12 (2.2%)	0	46 (8.3%)	2
Nausea / vomiting	34 (6.3%)	3	52 (9.4%)	1

- 4 patients (0.7%) developed osteonecrosis of the jaw

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Team IIb trial

conclusions

Adjuvant ibandronate:

- Increase of DFS at 3 year: 90.8% → 94.3% (HR 0.80; CI 0.58-1.10)
- Less bone metastases as first event at 3 year: 3.1% → 1.2% (HR 0.59; CI 0.30-1.14)
- Safe
  - < 1% developed osteonecrosis
  - < 1% stopped ibandronate because of decreased renal function
- Side-effect(s)
  - upper gastro-intestinal tract symptoms 2.2% vs. 8.3%
  - stopped for side effect(s) adjuvant therapy 20%

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Practice changing?

- Maybe:
  - Extending AI therapy beyond 5-years
    - Consider in patients who have previously received tamoxifen
    - Molecular profiling
- Confirmatory:
  - Fulvestrant efficacy with everolimus
  - Adjuvant ibandronate (maybe)
- Disappointing:
  - Pan PI3K inhibitor in hormone-resistant MBC
- Potentially interesting
  - BET inhibitor in ER-positive breast cancer