SABCS 2015: Hormone receptor-positive breast cancer
GASCO Annual SABCS Review
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Topics to cover

- Early stage ER-positive breast cancer
  - Lack of chemotherapy benefit (Abstract 1-06)
  - Adjuvant denosumab (Abstract 2-02)
- Metastatic ER-positive breast cancer
  - PI3-kinase inhibition (Abstract 6-01)
  - ESR mutations in hormone-resistance (Abstracts 2-06, 6-02)
- Novel therapeutic approaches
  - Pembrolizumab (Abstract 5-07)
  - Pre-operative palbociclib (Abstract 6-05)

High risk premenopausal Luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: results from DBCG77B randomized trial

Presenter: Torsten O. Nielsen, MD/PhD, FRCPC
University of British Columbia, Canada

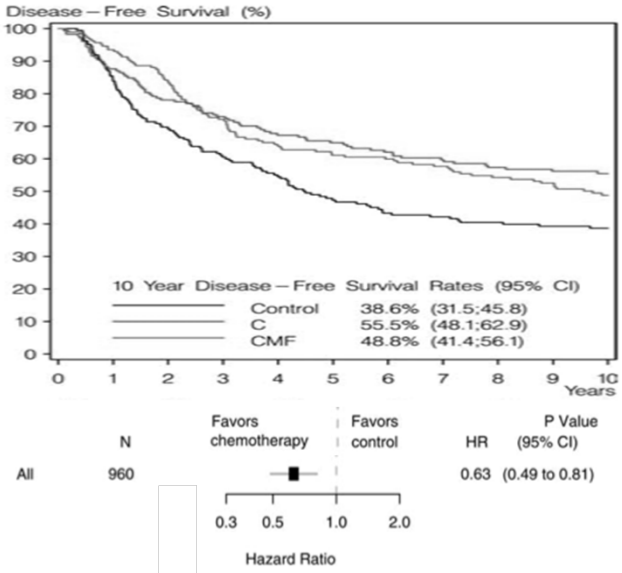
Abstract 1-06

Maj-Britt Jensen - *Statistical Office, Danish Breast Cancer Group*
Dongxia Gao, Samuel CY Leung, Samantha Burugu and Shuzhen Liu - *Genetic Pathology Evaluation Centre, Vancouver Coastal Health Research Institute*
Charlotte Levin Tykjaer Jorgensen and Eva Balslev - *Department of Pathology, Herlev University Hospital*
Bent Ejlertsen - *Medical Oncologist and Director, Danish Breast Cancer Group*

DBCG Danish Breast Cancer Cooperative Group

3

The DBCG77B Trial



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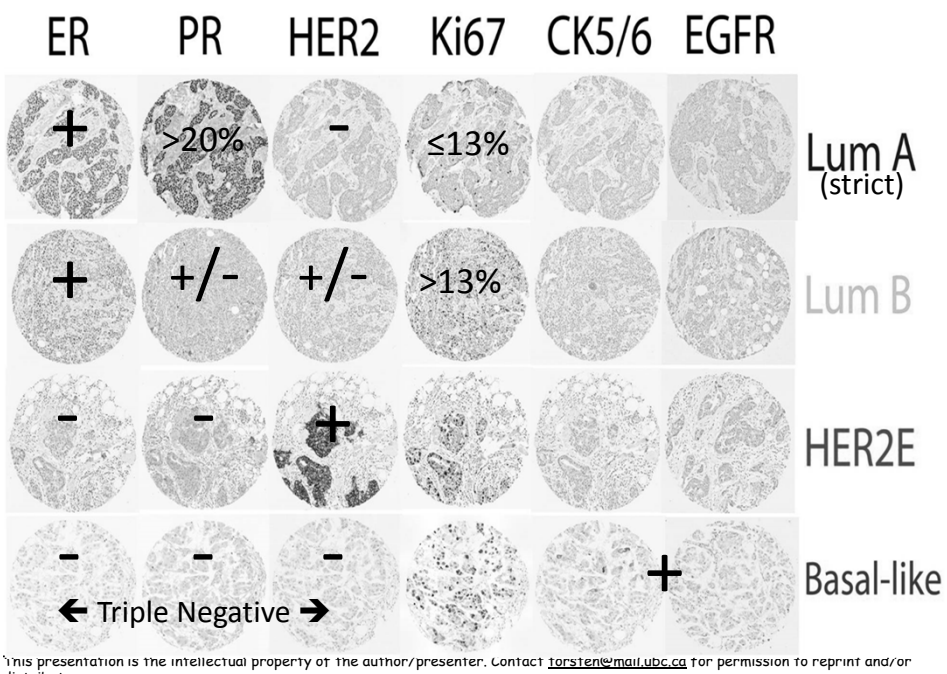
San Antonio Breast Cancer Symposium - December 8-12, 2015



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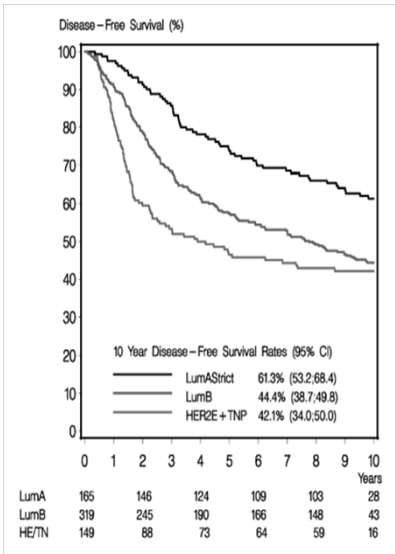
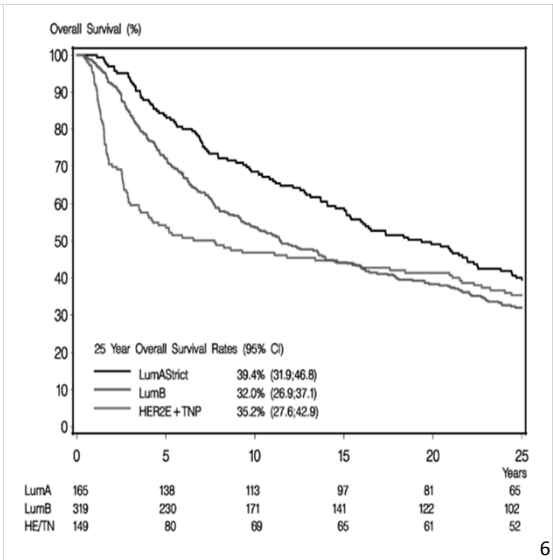
DBCG77B Trial: Prognosis by subtype





6

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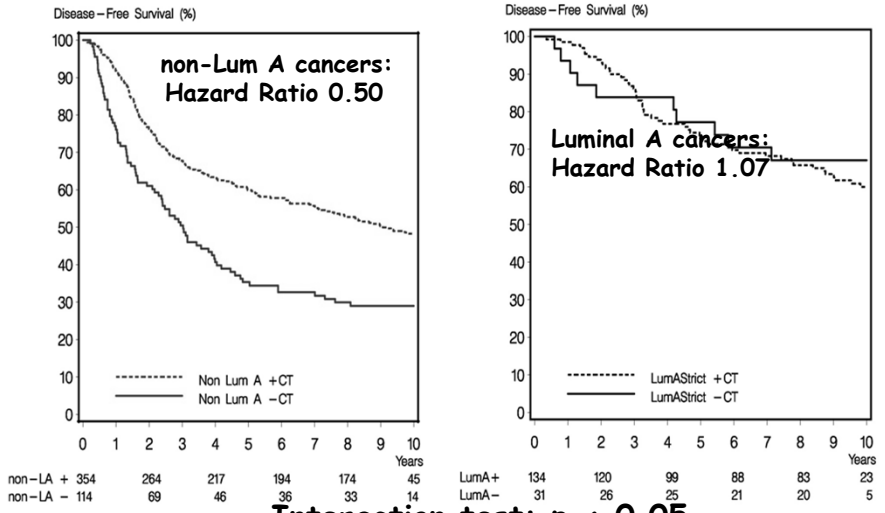
DBCG77B Trial: Prediction by subtype



Interaction test: p < 0.05

Methods: TAILORx Design & Rationale for RS Cutpoints

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Key Eligibility Criteria
- Node-negative
- ER-pos, HER2-neg
- T1c-T2 (high-risk T1b)
- Age 18-75 years
- No PBI planned

Preregister

Oncotype DX assay

Register
Specimen banking

Statistical Design
- RS 11-25: non-inferiority
  - 90% vs. ≤87% iDFS
  - 835 DFS events
- RS < 11
  - 95% vs. ≤93% DRFI at 10 years
  - 75 DRFI events

Secondary study group 1
RS < 11

ARM A
Hormonal therapy alone

Primary study group
RS 11-25

Randomly Assigned
Stratification factors:
Tumor size, menopausal status, planned chemo, planned radiation

ARM B
Hormonal therapy alone

ARM C
Chemotherapy + hormonal therapy

Secondary study group 2
RS > 25

ARM D
Chemotherapy + hormonal therapy

Recurrence Score = 11
- 7.3% distant recurrence rate at 10 years
- 95% CI 5%, 10%

Recurrence Score = 25
- 16.1% distant recurrence rate at 10 years
- 95% CI 13%, 20%

ECOG-ACRIN cancer research group | Reshaping the future of clinical trials

Sparano J A , and Paik S JCO 2008;26:721-728

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Patient Characteristics and Treatment

	RS < 11	RS 11-25	P Value
No. eligible patients	1626	6897	
Median age	58 years	55 years	P<0.001
Post-menopausal	70%	64%	P<0.001
Median tumor size	1.5 cm	1.5 cm	N.S
Histologic grade			
Low	34%	29%	P<0.001
Intermediate	59%	57%	
High	7%	14%	
ER Expression	> 99%	> 99%	N.S.
PgR Expression	98%	92%	P<0.001
Surgery			
Lumpectomy	68%	72%	P<0.001

- **Endocrine therapy in low RS group**: AI in 59%, tamoxifen in 34%, sequential tamoxifen-AI in 1%, OFS plus other therapy (3%), or other/unknown (3%)
- **Chemotherapy given to 6 patients in low RS group:** (1 of whom recurred)

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Results: Kaplan Meier Plots and 5 Year Event Rates

No. of events: 88 iDFS events and 30 deaths within 5 years of registration, including 18 recurrences (10 distant as first event), 15 second primary breast cancers, 43 other second primary cancers, 12 deaths without another event

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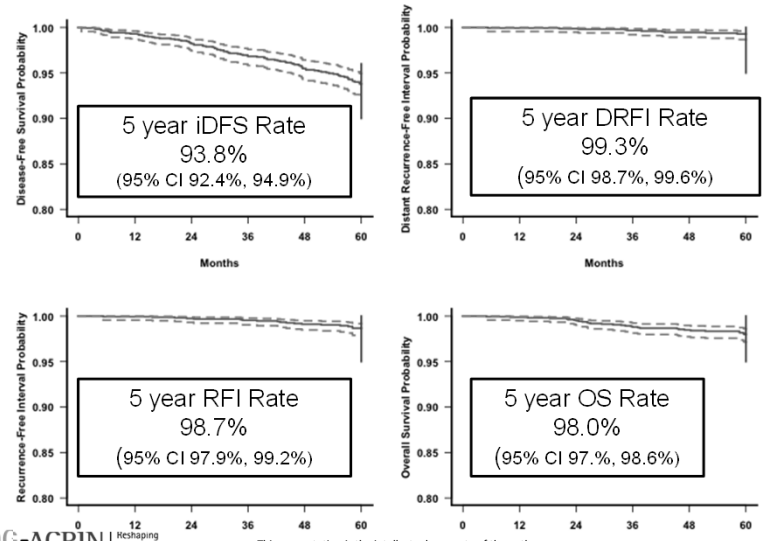
5-year event rate in cancers with recurrence scores 10 or less did not receive chemotherapy



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Correlation between recurrence score and intrinsic subtype

Recurrence Score	Luminal A (n = 123)	Luminal B (n = 55)
Low	62	1
Intermediate	25	4
High	36	50

No benefit from chemotherapy

Fan et al NEJM 2006

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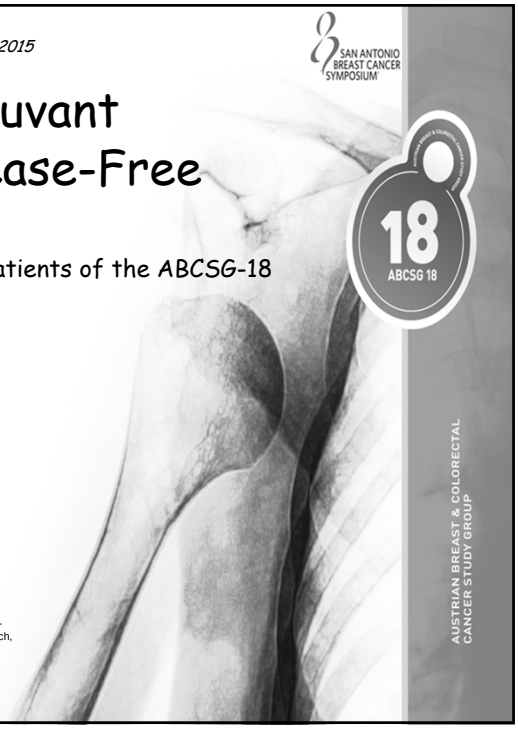
The Impact of Adjuvant Denosumab on Disease-Free Survival

Results from 3,425 Postmenopausal Patients of the ABCSG-18 Trial

Michael Gnant

Abstract 2-02



Abstract S2_02: M. Gnant, G. Pfeiler, P. Dubsky, M. Hubalek, R. Greil, R. Jakesz, V. Wette, M. Balic, F. Haslbauer, E. Melbinger-Zeinitzer, V. Bjelic-Radisic, S. Artner-Matuschek, F. Fitzal, C. Marth, P. Sevelda, B. Mlineritsch, G.Steger, D. Manfreda, R. Exner, D. Egle, J. Bergh, F. Kainberger, S. Talbot, D. Warner, C. Fesl, C. Singer, on behalf of the ABCSG

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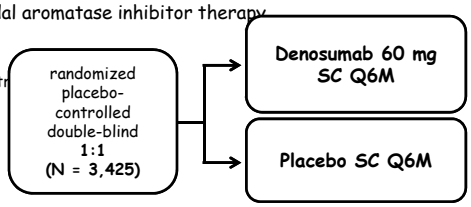
Trial Design ABCSG-18

- Prospective randomized placebo-controlled double-blind multicenter phase-3 trial
- Recruitment 2006 – 2013 (3,425 postmenopausal patients)
- Primary endpoint: Time to first clinical fracture (reached March 2014)
- Secondary endpoints:
  - Fracture related secondary endpoints (Primary Analysis March 2015)
  - **Disease outcome related endpoints**
    - **DFS – time driven analysis of disease free survival**
    - **OS, BMFS (will be analyzed at EoS)**
- Inclusion criteria:
  - Postmenopausal women with non-metastatic adenocarcinoma of the breast
  - ER+ and/ or PR+; adjuvant non-steroidal aromatase inhibitor therapy
- Exclusion criteria:
  - Prior or concurrent treatment with SERMs
  - Current or prior IV bisphosphonate administr
  - Known history of:
    - Paget's disease
    - Cushing's disease
    - hyperprolactinemia
    - hypercalcaemia or hypocalcaemia
    - other active metabolic bone disease



Gnant et al, Lancet 2015; 386: 433-43

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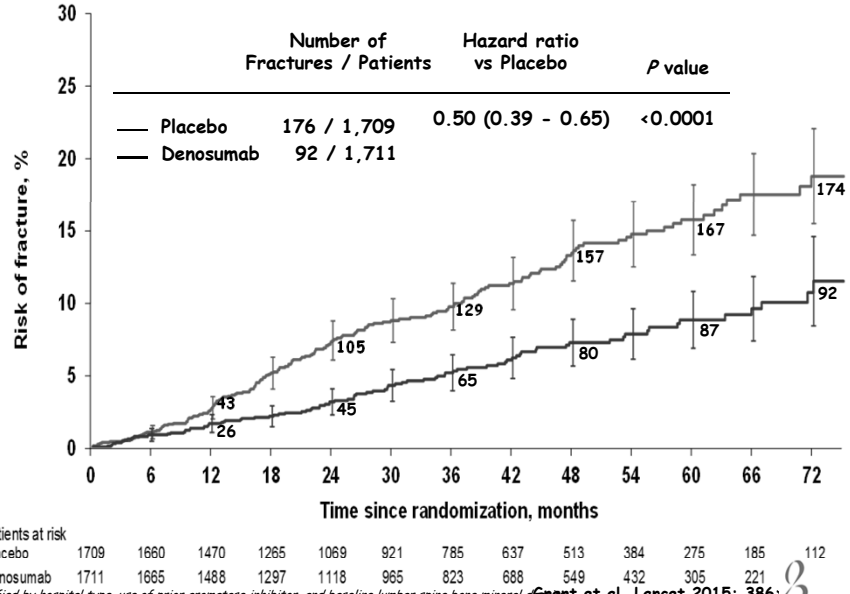
ABCSG-18 Primary Endpoint Results (ASCO 2015)



stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral d

Gnant et al, Lancet 2015; 386:

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ABCSG-18 Demographics and Safety

- 3,425 postmenopausal patients on adjuvant AI
  - Median age: 64 years (38-91)
  - Tumor size <2 cm: 72%
  - Node-negative disease: 71%
  - Grading: G3 19%
  - Ductal invasive histology: 74%
  - Both ER and PR positive: 83%
  - HER-2 overexpressing: 6%
  - (Neo)adjuvant Chemotherapy: 25%
- Adverse and serious adverse events
  - Mainly associated with known AI profile (Hot flushes, arthralgia, bone pain)
  - No measurable difference between denosumab and placebo in this double-blind trial
  - No case of ONJ despite proactive screening for this condition
  - No case of atypical fracture

Gnant et al, Lancet 2015; 386: 433-43

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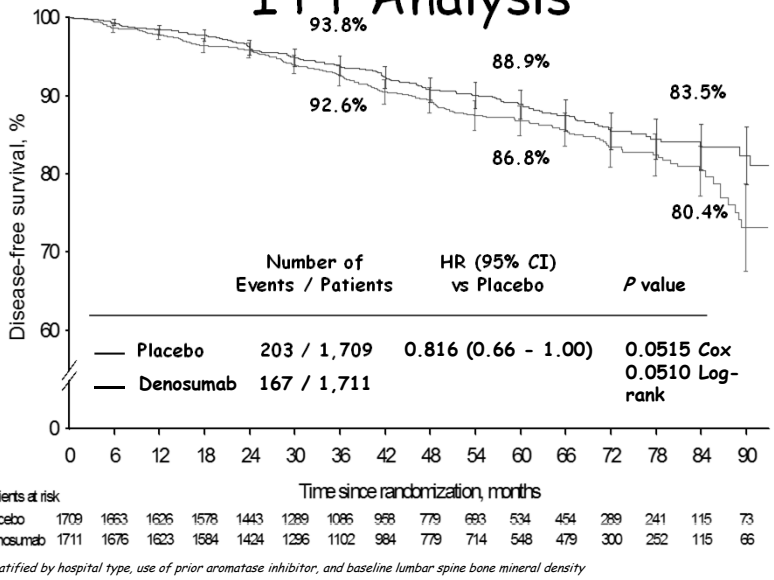
ABCSG-18 Results of the DFS ITT Analysis



stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral density

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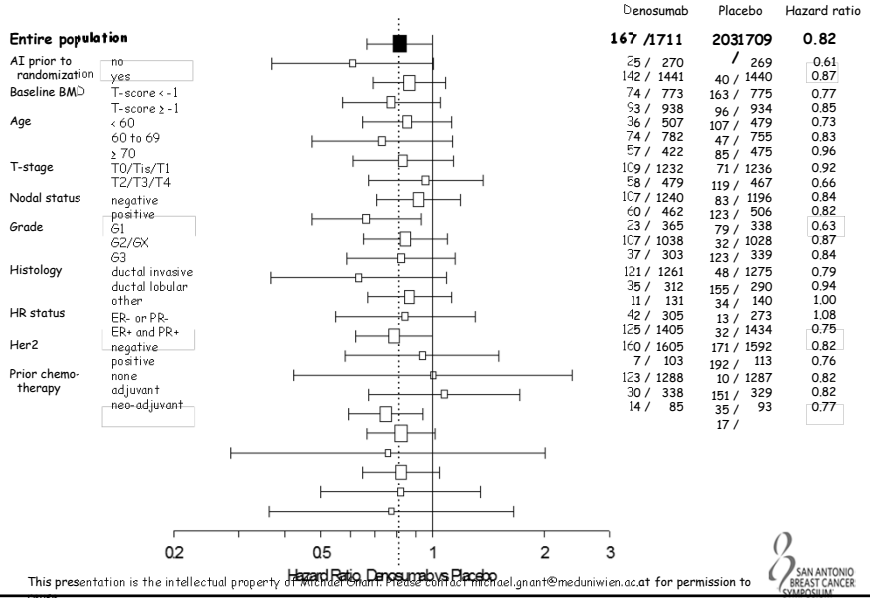
ABCSG-18 DFS ITT: Subgroups



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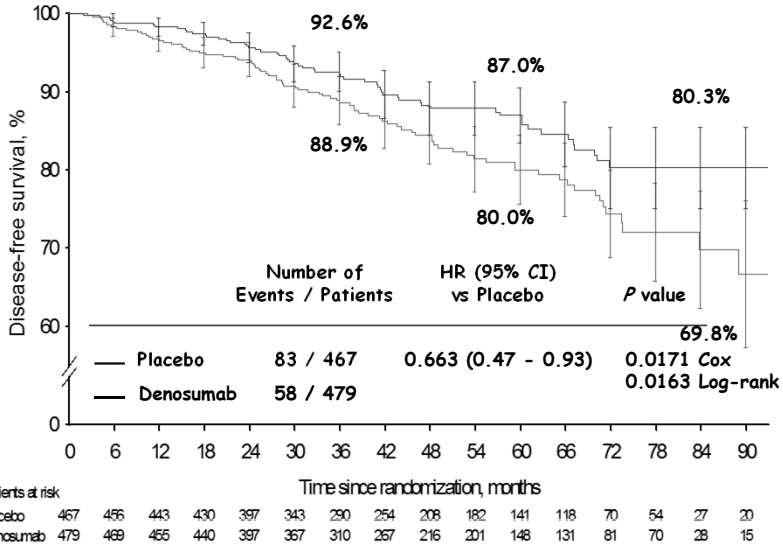
ABCSG 18- Subgroup Tumor Size >2 cm



stratified by hospital type, use of prior aromatase inhibitor, and baseline lumbar spine bone mineral density

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(Indirect) Comparison with Bisphosphonates

EBCTCG, Lancet 2015; 386: 1353-61

Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials

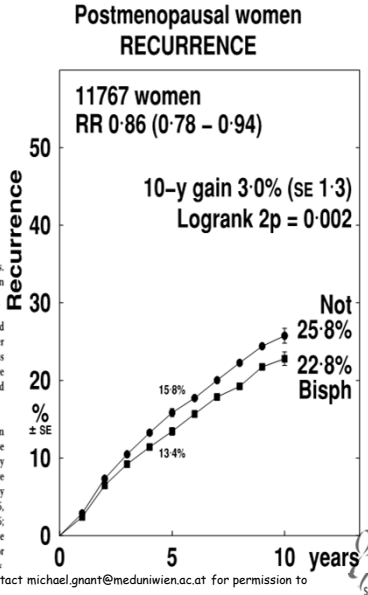
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Summary

Background Bisphosphonates have profound effects on bone physiology, and could modify the process of metastasis. We undertook collaborative meta-analyses to clarify the risks and benefits of adjuvant bisphosphonate treatment in breast cancer.

Methods We sought individual patient data from all unconfounded trials in early breast cancer that randomised between bisphosphonate and control. Primary outcomes were recurrence, distant recurrence, and breast cancer mortality. Primary subgroup investigations were site of first distant recurrence (bone or other), menopausal status (postmenopausal [combining natural and artificial] or not), and bisphosphonate class (aminobisphosphonate [eg, zoledronic acid, ibandronate, pamidronate] or other [ie, clodronate]). Intention-to-treat log-rank methods yielded bisphosphonate versus control first-event rate ratios (RRs).

Findings We received data on 18 766 women (18 206 [97%] in trials of 2–5 years of bisphosphonate) with median follow-up 5·6 woman-years, 3453 first recurrences, and 2106 subsequent deaths. Overall, the reductions in recurrence (RR 0·94, 95% CI 0·87–1·01; 2p=0·08), distant recurrence (0·92, 0·85–0·99; 2p=0·03), and breast cancer mortality (0·91, 0·83–0·99; 2p=0·04) were of only borderline significance, but the reduction in bone recurrence was more definite (0·83, 0·73–0·94; 2p=0·004). Among premenopausal women, treatment had no apparent effect on any outcome, but among 11 767 postmenopausal women it produced highly significant reductions in recurrence (RR 0·86, 95% CI 0·78–0·94; 2p=0·002), distant recurrence (0·82, 0·74–0·92; 2p=0·0003), bone recurrence (0·72, 0·60–0·86; 2p=0·0002), and breast cancer mortality (0·82, 0·73–0·93; 2p=0·002). Even for bone recurrence, however, the heterogeneity of benefit was barely significant by menopausal status (2p=0·06 for trend with menopausal status) or age (2p=0·03), and it was non-significant by bisphosphonate class, treatment schedule, oestrogen receptor status



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Summary of ABCSG-18

- These time-driven DFS analyses of ABCSG-18 indicate that adjuvant denosumab improves DFS
  - ITT analysis (Cox HR=0.816, p=0.0515, log rank p=0.0510)
  - Sensitivity analyses indicate that the estimate of the DFS difference in the ITT analysis is conservative
- Adjuvant denosumab is a safe treatment in ABCSG-18
  - No measurable differences between denosumab and placebo in terms of SAEs or AEs
  - No case of confirmed ONJ
  - No case of atypical fracture

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Clinical Conclusions ABCSG-18

- Adjuvant denosumab 60mg/Q6M s.c. reduces risk of disease recurrence or death in postmenopausal breast cancer patients
- The observed DFS benefit of adjuvant denosumab in ABCSG-18 is similar to the EBCTCG bisphosphonate meta-analysis
- This benefit comes in addition to significantly reducing clinical (and vertebral) fractures and improving BMD
- Adjuvant denosumab 60 mg/Q6M should be offered to postmenopausal breast cancer patients on adjuvant aromatase inhibitor therapy

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PIK3CA Status in Circulating Tumor DNA Predicts Efficacy of Buparlisib Plus Fulvestrant in Postmenopausal Women With Endocrine-resistant HR+/HER2– Advanced Breast Cancer: First Results From the Randomized, Phase III BELLE-2 Trial

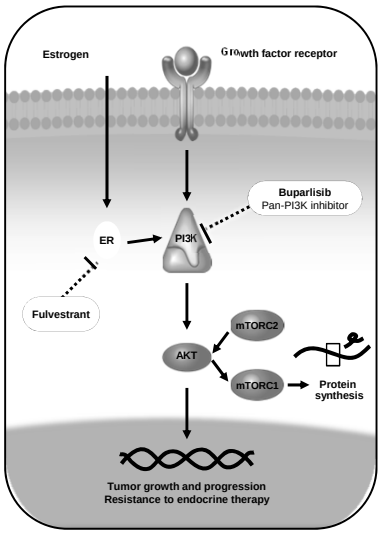
José Baselga,[1] Seock-Ah Im,[2] Hiroji Iwata,[3] Mark Clemons,[4] Yoshinori Ito,[5] Ahmad Awada,[6] Stephen Chia,[7] Agnieszka Jagiełło-Gruszfeld,[8] Barbara Pistilli,[9] Ling-Ming Tseng,[10] Sara Hurvitz,[11] Norikazu Masuda,[12] Javier Cortés,[13] Michele De Laurentiis,[14] Carlos L. Arteaga,[15] Zefei Jiang,[16] Walter Jonat,[17] Soulef Hachemi,[18] Sylvie Le Mouhaër,[18] Emmanuelle Di Tomaso,[19] Patrick Urban,[20] Cristian Massacesi,[18] Mario Campone[21]

Abstract 6-01

22

The PI3K Pathway is Activated in Breast Cancer

- PI3K/mTOR pathway activation is a hallmark of HR+/HER2– breast cancer cells that have developed resistance to endocrine therapy[1,2]
- The ER pathway is upregulated in tumors from patients treated with PI3K inhibitors[1]
- Dual blockade of the PI3K/mTOR and ER pathways may therefore restore sensitivity to endocrine therapy[1,3,4]



ER, estrogen receptor; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.

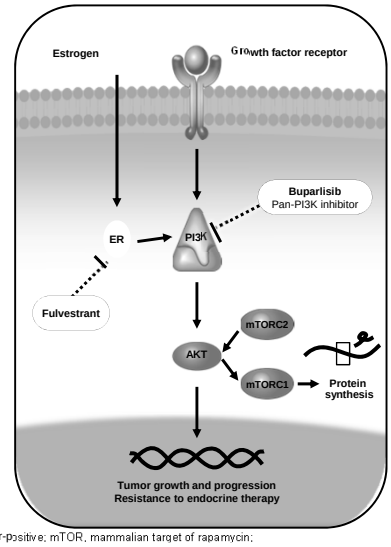
1. Bosch A, *et al. Sci Transl Med.* 2015;7:283ra51; 2. Miller TW, *et al. Cancer Discov.* 2011;1:338–351; 3. Fox EM, *et al. Front Oncol.* 2012;2:145; 4. Yardley D, *et al. Adv Ther.* 2013;30:870–884.

Clinical Rationale for BELLE-2

- Buparlisib (BKM120) is an oral pan-class I PI3K inhibitor that targets all four isoforms of PI3K (α, β, γ, δ)[1]

PI3K Isoform	α	β	γ	δ
IC_{50}, nM	52	166	262	116

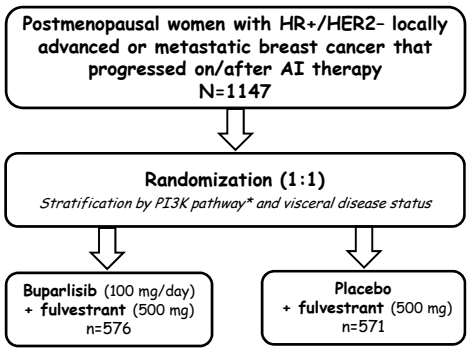
- Buparlisib has demonstrated preliminary clinical activity in combination with fulvestrant[2]
- BELLE-2 is the first randomized Phase III study to assess the safety and efficacy of a pan-PI3K inhibitor combined with fulvestrant in HR+/HER2– advanced breast cancer



ER, estrogen receptor; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase.

1. Maira SM, *et al. Mol Cancer Ther.* 2012;11:317–328; 2. Ma CX, *et al. Clin Cancer Res.* 2015;pii:1745 [ePub ahead of print].

BELLE-2 Study Design and Endpoints



Primary Endpoints

- **PFS** in the main population (PI3K activated and non-activated, excluding status unknown*)
- **PFS** in the PI3K activated group* (*PIK3CA* mutation and/or PTEN loss in archival tissue)
- **PFS** in the full population (local assessment)

Key Secondary Endpoint

- **Overall survival**

Other Secondary Endpoints

- **Overall response rate**
- **Clinical benefit rate**
- **Safety, pharmacokinetics, quality of life**

Exploratory Endpoint

- **PFS** by ctDNA *PIK3CA* mutation status†

BELLE-2: ClinicalTrials.gov NCT01610284.

AI, aromatase inhibitor; BEAMing, beads, emulsification, amplification, and magnetics; ctDNA, circulating tumor DNA; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor-positive; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

*PI3K pathway activation (activated, non-activated, unknown) was assessed in archival tumor tissue provided at screening, defined as PIK3CA mutation by Sanger sequencing (activating mutations in exons 1, 7, 9, or 20) and/or loss of PTEN expression by immunohistochemistry (1+ expression in <10% of cells); †ctDNA PIK3CA status was assessed by BEAMing technology.

25

BELLE-2 Key Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Postmenopausal women with ER+ and/or PgR+ and HER2– inoperable locally advanced or metastatic breast cancer
- Disease progression on/after AI therapy:
  - Recurrence during or ≤12 months from end of adjuvant AI therapy
  - Progression during or ≤1 month from end of AI therapy for locally advanced/metastatic breast cancer
- Measurable disease or non-measurable lytic or mixed bone lesions (RECIST v1.1)
- Adequate tumor tissue (archival/new) for analysis of PI3K-related biomarkers

Key Exclusion Criteria

- Prior therapy with a PI3K, AKT, or mTOR inhibitor, or fulvestrant
- >1 prior chemotherapy line for metastatic disease
- Anxiety (CTCAE Grade ≥3) or history/evidence of depression or other mood disorders
- GAD-7 mood scale score ≥15, PHQ-9 score ≥12, or positive response to PHQ-9 question 9 relating to suicidal ideation

AI, aromatase inhibitor; CTCAE, Common Terminology Criteria for Adverse Events; ER+, estrogen receptor-positive; GAD-7, 7-item Generalized Anxiety Disorder; HER2–, human epidermal growth factor receptor 2 negative; mTOR, mammalian target of rapamycin; PgR+, progesterone receptor-positive; PHQ-9, 9-item Patient Health Questionnaire; PI3K, phosphatidylinositol 3-kinase; RECIST, Response Evaluation Criteria in Solid Tumors.

26

Patient Demographics and Disease Characteristics Were Well Balanced Between Treatment Arms

Characteristic	Buparlisib + Fulvestrant (n=576)	Placebo + Fulvestrant (n=571)
Median age, years (range)	62 (29–90)	61 (31–90)
ECOG performance status, %		
0	57.8	60.2
1	40.1	37.0
2–3	2.1	2.8
Hormone receptor status, %		
ER+	99.1	98.6
PgR+	74.8	74.1
PI3K pathway activation status, %		
Activated	32.6	32.2
Non-activated	41.5	42.0
Unknown	25.9	25.7
Visceral disease present, %	59.2	59.0
Prior therapy in metastatic setting, %		
Any hormonal therapy	72.6	75.1
Any aromatase inhibitors	69.4	71.5
Any chemotherapy	24.5	31.0
Prior lines of hormonal therapy in metastatic setting, %		
0	27.4	24.9
1	53.1	52.7
≥2	19.4	22.4

ECOG, Eastern Cooperative Oncology Group; ER+, estrogen receptor-positive; PgR+, progesterone receptor-positive; PI3K, phosphatidylinositol 3-kinase.

27

BELLE-2 Safety Profile Was Characterized by Hyperglycemia, Transaminitis, Rash, and Mood Disorders

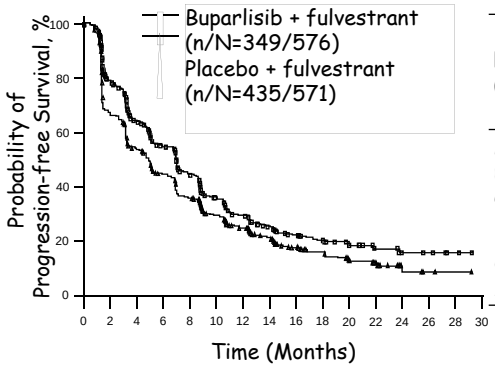
	Buparlisib + Fulvestrant n=573			Placebo + Fulvestrant n=570		
Adverse event, %	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Total	99.5	63.2	14.1	93.0	27.4	4.6
Increased ALT	40.1	18.7	6.8	6.8	1.1	0
Increased AST	37.3	15.0	3.0	9.3	2.8	0
Hyperglycemia	43.1	15.2	0.2	7.7	0.2	0
Rash	32.1	7.7	0.2	6.3	0	0
Anxiety	22.3	5.2	0.2	8.2	0.9	0
Fatigue	31.9	4.9	0	23.9	1.6	0
Depression	26.2	3.7	0.7	8.9	0.4	0
Diarrhea	34.2	3.7	0	14.6	1.1	0
Asthenia	20.1	2.8	0	10.5	1.1	0
Stomatitis	21.6	2.1	0	6.5	0.5	0
Nausea	38.7	1.7	0	23.2	1.4	0
Decreased appetite	29.8	1.6	0	11.1	0.2	0

- Serious adverse events occurred in 23.4% of patients in the buparlisib arm vs 15.8% in the placebo arm
- 12 on-treatment deaths (2.1%) were reported in each arm in the full population, the majority due to disease progression

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

28

BELLE-2 Met the Primary Endpoint for Statistically Significant PFS Improvement in the Full and Main Population



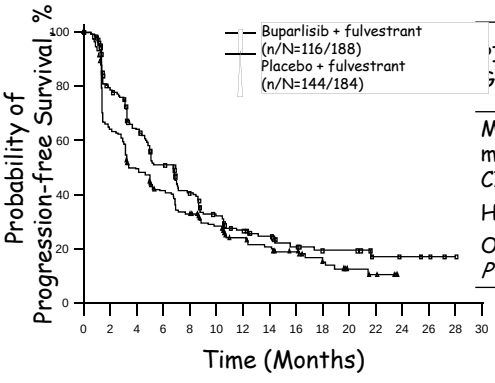
Full Population (N=1047)	Buparlisib + Fulvestrant n=576	Placebo + Fulvestrant n=571
Median PFS, months (95% CI)	6.9 (6.8–7.8)	5.0 (4.0–5.2)
HR (95% CI)	0.78 (0.67–0.89)	
One-sided *P* value	<0.001	

*Targeted improvement from 5.0 to 7.5 months, HR of 0.67

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI: 0.68–0.94]; one-sided *P* value 0.003)
- Follow-up for OS analysis is ongoing, with a pre-specified target of 588 deaths in the full population
  - At the time of primary PFS analysis, OS data were immature (281 deaths in the full population), with a trend in favor of the buparlisib arm

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

PFS Increase in the PI3K Activated Group was not Statistically Significant



PI3K Activated Group (N=372)	Buparlisib + Fulvestrant n=188	Placebo + Fulvestrant n=184
Median PFS, months (95% CI)	6.8 (4.9–7.1)	4.0 (3.1–5.2)
HR (95% CI)	0.76 (0.60–0.97)	
One-sided *P* value*	0.014	

*Targeted PFS improvement from 5.0 to 8.33 months, HR of 0.60

*PFS in the PI3K activated group was tested at a one-sided α=0.01 level of significance.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

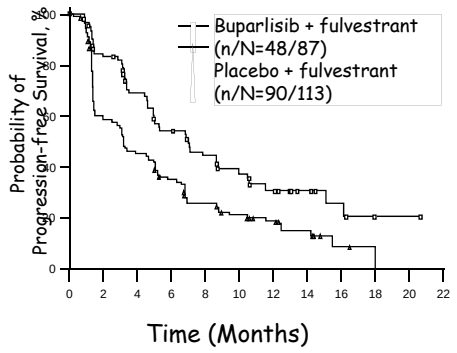
BELLE-2 Prospectively Evaluated *PIK3CA* Mutation Status in ctDNA

- In clinical trials, archival tumor biopsy samples typically represent the primary tumor at the time of initial diagnosis
  - Recent evidence suggests that tumor mutation status can change due to disease progression or exposure to prior treatments[1,2]
- ctDNA obtained from blood samples has emerged as a sensitive, reliable, and minimally invasive way to measure current *PIK3CA* mutation status[3–5]
- In BELLE-2, blood samples for ctDNA analysis were collected for 51.2% of enrolled patients
  - *PIK3CA* status in ctDNA was prospectively analyzed in 587 patients using BEAMing technology to detect mutations in exon 9 (E545K) or exon 20 (H1047R/L)[5]
  - Baseline patient characteristics were generally balanced in the full and ctDNA populations; based on sensitivity analyses, any imbalances did not influence the efficacy outcome

BEAMing, beads, emulsification, amplification, and magnetics; ctDNA, circulating tumor DNA.

1. McGranahan N, *et al. Sci Transl Med.* 2015;7:283ra54; 2. Arthur LM, *et al. Breast Cancer Res Treat.* 2014;147:211–219; 3. De Mattos-Arruda L, *et al. Ann Oncol.* 2014;25:1729–1735; 4. Board RE, *et al. Breast Cancer Res Treat.* 2010;120:461–467; 5. Higgins MJ, *et al. Clin Cancer Res.* 2012;18:3462–3469.

Buparlisib and Fulvestrant Produced a Clinically meaningful PFS Improvement in Patients With ctDNA *PIK3CA* Mutations



ctDNA *PIK3CA* Mutant n=200	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113
Median PFS, months (95% CI)	7.0 (5.0–10.0)	3.2 (2.0–5.1)
HR (95% CI)	0.56 (0.39–0.80)	
One-sided nominal *P* value	<0.001	

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival.

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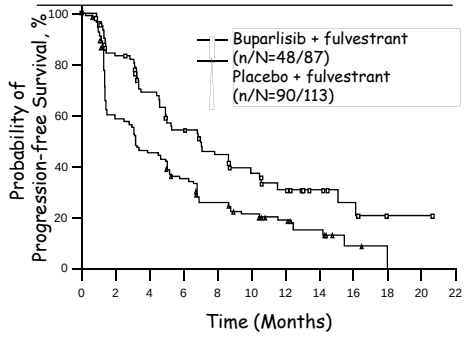
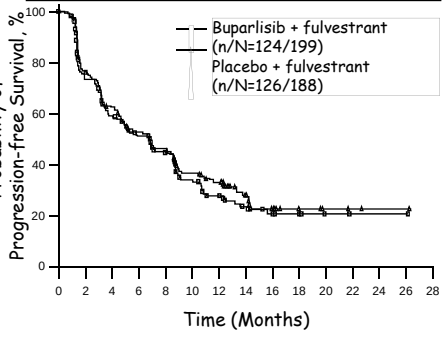


ctDNA *PIK3CA* Non-mutant n=387	Buparlisib + Fulvestrant n=199	Placebo + Fulvestrant n=188
Median PFS, months (95% CI)	6.8 (4.7–8.5)	6.8 (4.7–8.6)
HR (95% CI)	1.05 (0.82–1.34)	
One-sided nominal *P* value	0.642	



CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; PFS, progression-free survival.

Buparlisib and Fulvestrant Resulted in Higher Response Rates in the ctDNA *PIK3CA* Mutant Group

Efficacy Endpoint	*PIK3CA* Mutant (ctDNA)		*PIK3CA* Non-mutant (ctDNA)		PI3K Pathway Activated (Archival Tissue)	
	Buparlisib + Fulvestrant n=87	Placebo + Fulvestrant n=113	Buparlisib + Fulvestrant n=199	Placebo + Fulvestrant n=188	Buparlisib + Fulvestrant n=188	Placebo + Fulvestrant n=184
ORR,* % (95% CI)	**18.4 (10.9–28.1)**	**3.5 (1.0–8.8)**	11.6 (7.5–16.8)	10.6 (6.6–16.0)	10.6 (6.6–16.0)	8.2 (4.6–13.1)
CBR,† % (95% CI)	**47.1 (36.3–58.1)**	**31.9 (23.4–41.3)**	42.7 (35.7–49.9)	50.0 (42.6–57.4)	40.4 (33.3–47.8)	40.8 (33.6–48.2)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; ctDNA, circulating tumor DNA; ORR, objective response rate; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase; PR, partial response; SD, stable disease.
*ORR is defined as best overall response CR+PR; †CBR is defined as best overall response CR+PR, or overall response of SD or non-CR/non-PD lasting for at least 24 weeks.

34

Conclusions

- The BELLE-2 study met its primary endpoint, demonstrating prolonged PFS for combined buparlisib and fulvestrant in postmenopausal women with HR+/HER2– advanced breast cancer that had progressed after prior AI therapy
- Patients with tumors harboring *PIK3CA* mutations in ctDNA performed poorly on fulvestrant monotherapy, achieving a clinically meaningful PFS improvement with combined buparlisib and fulvestrant
  - 3.8 month PFS improvement was supported by higher response rates in this patient population
- Frequent discontinuations due to AEs reduced treatment duration in the buparlisib arm, potentially limiting the efficacy of combination therapy
- Further studies of PI3K inhibitor and endocrine therapy combinations this setting are ongoing
  - Alpelisib (SOLAR-1), taselisib (SANDPIPER)

AEs, adverse events; CBR, clinical benefit rate; CI, confidence interval; ctDNA, circulating tumor DNA; HER2–, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor-positive; ORR, objective response rate; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

35

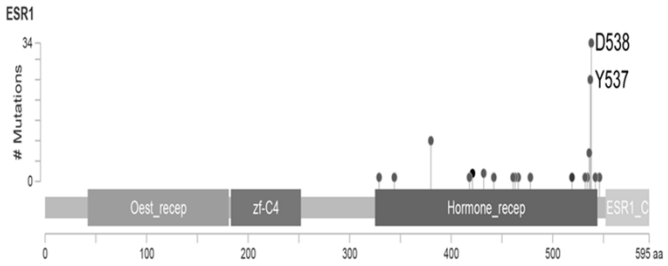
cfDNA Analysis From BOLERO-2 Plasma Samples Identifies a High Rate of *ESR1* Mutations: Exploratory Analysis For Prognostic And Predictive Correlation of Mutations Reveals Different Efficacy Outcomes of Endocrine Therapy–based Regimens

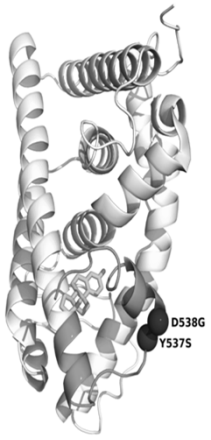
Sarat Chandarlapaty[1], Patricia Sung[1], David Chen[2], Wei He[2], Aliaksandra Samoila[1], Daoqi You[1], Trusha Bhatt[1], Parul Patel[2], Maurizio Voi[2], Michael Gnant[3], Gabriel Hortobagyi[4], Jose Baselga[1], and Mary Ellen Moynahan[1]

[1]Memorial Sloan Kettering Cancer Center, New York, United States; [2]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States;
[3]Dept. Of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [4]The University of Texas MD Anderson Cancer Center, Houston, United States

36

Introduction And Rationale



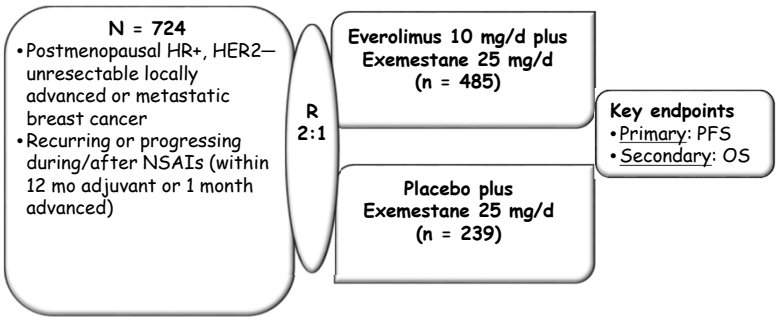


- Y537S and D538G mutations in Estrogen Receptor *(ESR1)* are observed in metastatic breast cancer (MBC) and promote ligand-independent receptor activation
- *ESR1* mutation could be a predictive marker for early patient selection for endocrine based therapies

mTOR, mammalian target of rapamycin.

37

BOLERO-2: Study Design and Primary Results



Assessment	Arms	Events/N	PFS (mo)	HR (95% CI)	P-value
Local	EVE + EXE	310/485	7.8	0.45 (0.38-0.54)	P < 0.0001
	PBO + EXE	200/239	3.2		

HR+
surv
Yard

Methodology and Statistical Analysis

Patients with HR+, HER2− MBC whose disease recurred or progressed on/after prior NSAIs were enrolled in BOLERO-2
N = 724

Consent for genomic testing

cfDNA* extraction from archival plasma samples
Evaluable samples N = 541

cfDNA analysis for *ESR1* D538G and Y537S mutations by ddPCR

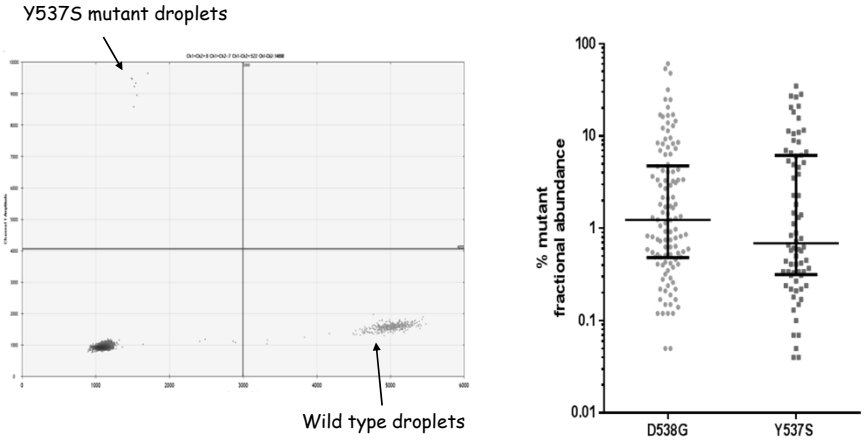
Statistical Analysis:

- Cox-proportional hazards model was used to assess
  - Prognostic effect on OS in patient subgroups defined by *ESR1* mutation or specific mutations
  - Predictive effect on PFS in patient subgroups defined by *ESR1* mutation or specific mutations

cfDNA, cell free DNA; ddPCR, droplet digital PCR; HR+, hormone receptor-positive; HER2−, human epidermal growth factor receptor-negative; MBC, metastatic breast cancer; NSAIs, non-steroidal aromatase inhibitors; OS, overall survival; PFS, progression free survival.

39

Detection and Quantification of ESR1 Mutations by ddPCR



ddPCR, droplet digital PCR.

40

Frequency of *ESR1* Mutations

- High *ESR1* mutation frequency in cfDNA samples
  - Some double mutations were detected

	D538G and/or Y537S mutation	D538G mutation	Y537S mutation	Double mutation
Overall, N = 541 (74.7% of ITT)	156 (28.8%)	83 (15.3%)	42 (7.8%)	30 (5.5%)

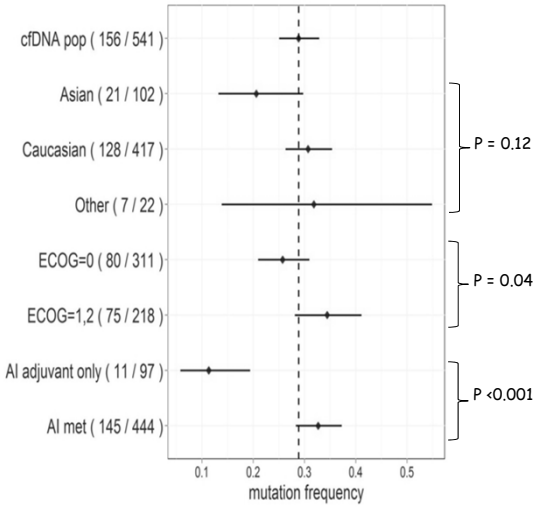
cfDNA, cell free DNA; ITT, intention to treat.

ddPCR on cfDNA vs NGS on Archival Tumor DNA

- 541 cfDNA were analyzed by ddPCR and 302 archival tumor DNA by next generation sequencing (NGS)
- 236 paired samples with assessment of Y537S and D538G mutations in *ESR1*
  - 3 (1.3%) archival tumor samples had one of the two mutations
  - 67 (28.4%) cfDNA samples had one of the two mutations
- 247 paired samples with assessment of H1047R, E545K, E542K mutations in *PIK3CA*
  - 85 (34.4%) tumor samples had at least one of the three mutations
  - 114 (46.2%) cfDNA samples had at least one of the three mutations

cfDNA, cell free DNA; ddPCR, droplet digital PCR.

ESR1 Mutation Frequency by Clinical Covariates

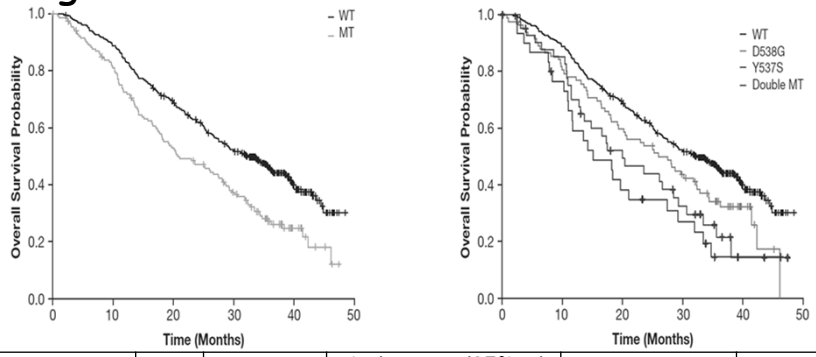


- *ESR1* mutation frequency is not significantly different based on race or patient age or site of disease (visceral vs soft tissue/bone-only)

AI, aromatase inhibitor; cfDNA, cell free DNA; ECOG, Eastern Cooperative Oncology Group.

43

Prognostic Effect of *ESR1* Mutation on OS



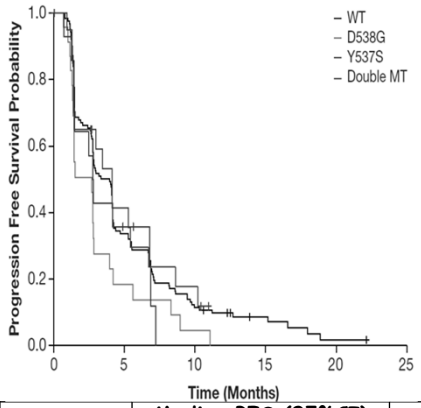
Mutations	N	Events	Median OS (95%CI) (months)	HR (95%CI)	P-value*
WT	385	217	32.1 (28.1-36.4)		
MT	156	112	20.7 (17.7 - 28.1)	1.40 (1.2 - 1.65)	0.000037
D538G	83	57	26.0 (19.2-32.4)	1.25 (1.02-1.54)	0.033
Y537S	42	30	20.0 (13.0-29.3)	2.31 (1.34-3.97)	0.0024
Double MT	30	24	15.2 (10.9-27.4)	1.77 (1.31-2.39)	0.00018

- Both D538G and Y537S mutations were poor prognostic factors associated with shorter OS
- In a multivariate analysis adjusting for sensitivity to prior hormonal therapy, visceral disease and ECOG status, the effect of ESR1 mutation (compared to wild-type) on OS remained significant

CI, confidence interval; HR, hazard ratio; MT, mutation; OS, overall survival; WT, wild-type.

*All p-values were unadjusted for multiple testing

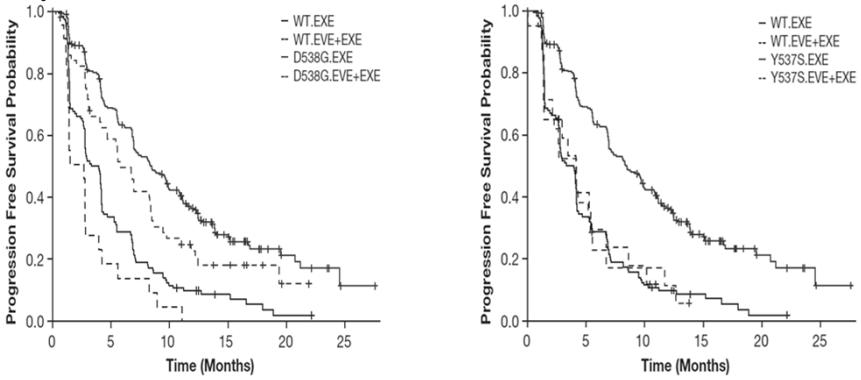
Impact of *ESR1* Mutations on EXE Treatment



Alteration	N	Events	Median PFS (95%CI) (months)	HR (95%CI)	P-value*
WT	128	116	3.94 (2.76-4.17)		
MT	61	51	2.76 (1.41-4.14)	1.18 (0.94-1.5)	0.16
D538G	24	22	2.69 (1.35-2.83)	1.44 (1.04-1.99)	**0.029**
Y537S	21	16	4.14 (1.38-6.7)	0.92 (0.44-1.93)	0.83
Double MT	15	12	2.78 (1.41-6.87)	1.15 (0.75-1.75)	0.82

CI, [illegible]; *All p-values were adjusted for multiple testing

Impact of *ESR1* Mutations on EVE treatment



Alteration	Group	N	Events	Median PFS (95%CI) (months)	HR (95%CI)	P-value*
WT	EXE	128	116	3.9 (2.8-4.2)	0.4 (0.31-0.51)	<0.00001
	EVE + EXE	257	172	8.5 (6.9-9.9)		
D538G	EXE	24	22	2.7 (1.4-2.8)	0.34 (0.2-0.57)	0.00006
	EVE + EXE	59	45	5.8 (4.2-8.4)		
Y537S	EXE	21	16	4.1 (1.4-6.7)	0.98 (0.49-1.94)	0.95
	EVE + EXE	21	19	4.2 (1.4-5.4)		
Double MT	EXE	15	12	2.78 (1.41-6.87)	0.53 (0.23-1.25)	0.15
	EVE + EXE	15	14	5.42 (2.46-7.82)		

CI, [illegible]; *All p-values were adjusted for multiple testing

Conclusions

- cfDNA analysis of archival plasma samples is feasible for mutation detection
- *ESR1* mutation frequency in cfDNA samples is higher than identified with tumor sequencing
  - The 28% mutation frequency for D538G and Y537S ESR1 mutations assayed likely underestimates the frequency for all activating *ESR1* mutations
  - The occurrence of multiple *ESR1* mutations is not uncommon
- *ESR1* mutations are identified in HR+ MBC prior to first-line therapy; frequency markedly increases in patients treated with AIs in the metastatic setting
- D538G and Y537S mutations appear to be associated with a more aggressive disease biology as demonstrated by a shorter OS
- Differential effects of the Y537S and D538G mutations on treatment
  - In the EXE only arm, patients with D538G mutation had a shorter PFS as compared to wild-type
  - Patients with D538G mutation demonstrate PFS benefit with the addition of EVE, whereas those with Y537S mutation did not

AIs, aromatase inhibitors; cfDNA, cell free DNA; EVE, everolimus; HR+, hormone receptor-positive; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival. 47

San Antonio Breast Cancer Symposium, December 8-12, 2015

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Occurrence of natural *ESR1* mutations during acquisition of endocrine resistance in breast cancers and widely used ER+ cell lines

Pascal Gellert[1,2], Ricardo Ribas[1], Sunil Pancholi[1], Elena Lopez-Knowles[1,2], Belinda Yeo[2], Isaac Garcia-Murillas[1], Charlotte Fribbens[1], Alex Pearson[1], Ian Smith[2], Nicholas Turner[1,2], Mitch Dowsett[1,2], Lesley-Ann Martin[1]

[1]Breast Cancer Now at The Institute of Cancer Research, London, UK
[2]Royal Marsden Hospital, London, UK

Abstract 6-02

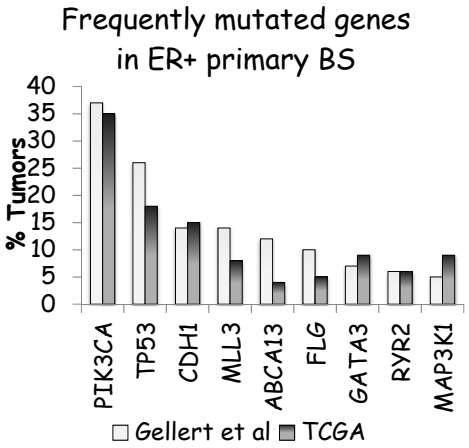
Aims

- To identify changes in the mutational profile of ER+ breast cancers at progression on Aromatase Inhibitor treatment
- To identify concomitant mutations occurring in cell line models of resistance to E-deprivation

49

ER+ Breast Cancer

- Mutational landscape of ER+ primary BC well described
- Few studies on mutational landscape of metastatic BC
- Landscape changes between primary and metastatic BC likely to determine the integration of diagnostic and treatment

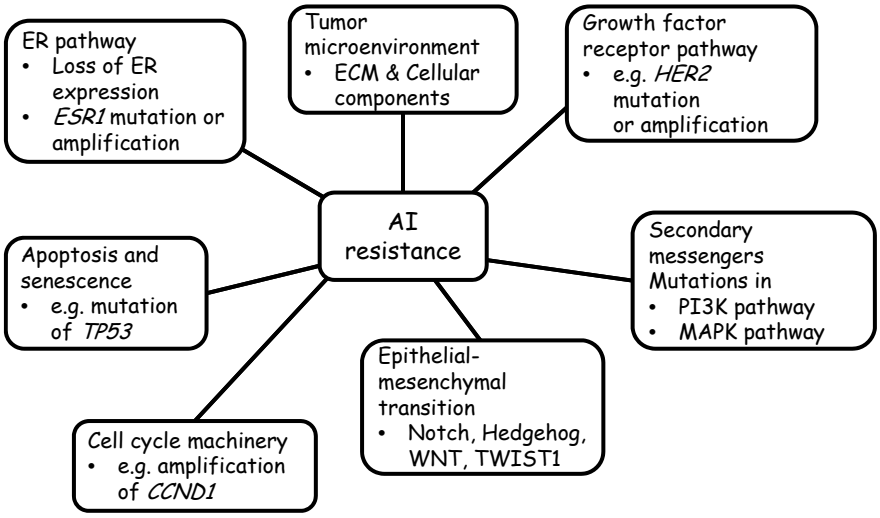


Gellert *et al*, SABCS 2014
TCGA, Nature 2012

50

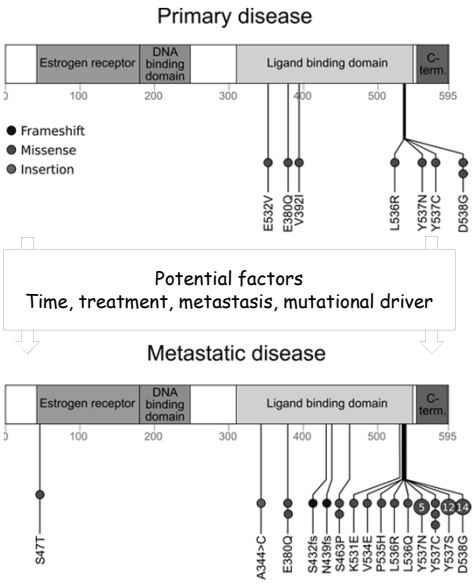
The Hallmarks of AI resistance

51



modified from Ma *et al*, Nature 2015

ESR1 mutations in metastases



Samples	% ESR1 mutated samples	Pairs
261 primary 195 mets	3.3% primary 13.3% mets	47 pairs

Li *et al*, Cell Rep 2013
Merenbach-Lamin *et al*, Cancer Res 2013
Toy *et al*, Nature Genet 2013
Robinson *et al*, Nature Genet 2013
Jeselsohn *et al*, Clin Cancer Res 2014

- Small number of pairs
- Great treatment heterogeneity

Modified from Segal and Dowsett, CCR 2014

52

Patients and Methods

Arnedos M *et al*, Annals Oncology 2014:

- 55 patients selected retrospectively (2004-2009, Royal Marsden Hospital)
- Paired primary and recurrences available
- ER+
- Locally advanced or metastatic setting
- Relapsed or progression during AI treatment

Immunohistochemical analysis:

- 7% ER- in metastases
- Decrease of PgR
- Higher Ki67
- 5% gained HER2 amplification

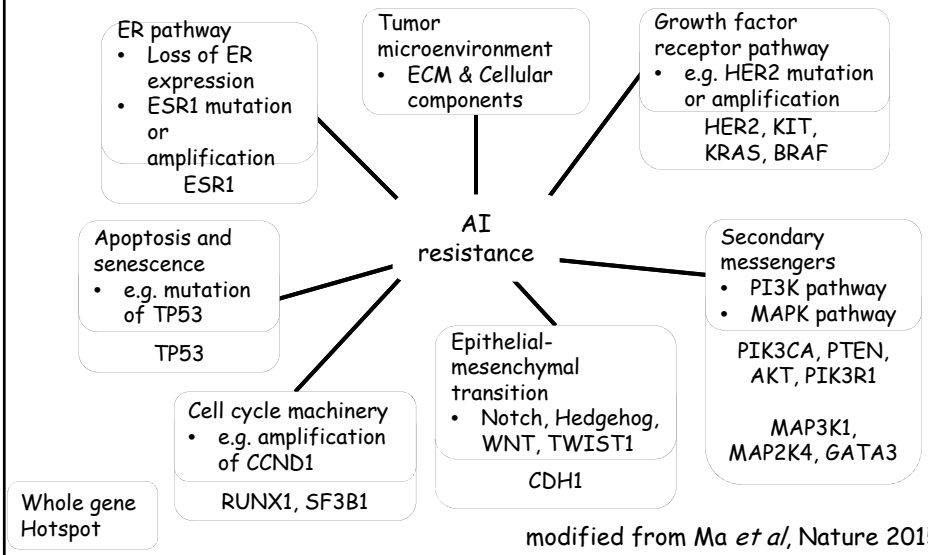
↳ 51 FFPE blocks pre and post AI

↳ 48 pairs for targeted sequencing

53

Genes of Interest

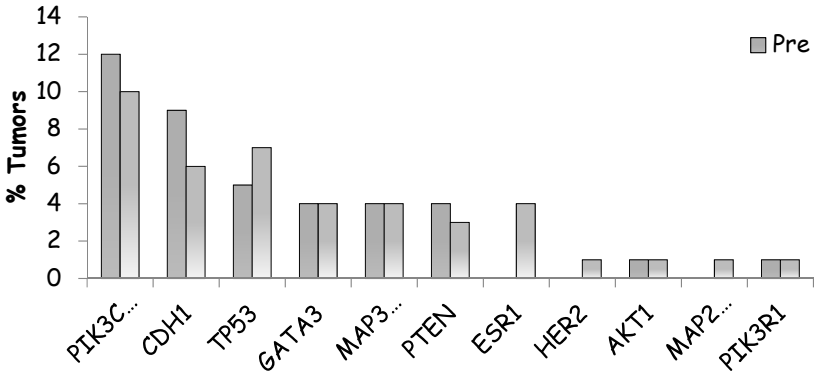
54



modified from Ma *et al*, Nature 2015

Results

- Good quality data was available on 41 pairs
- Median depth was 782-fold
- A total of 87 tier 1 mutations were identified
- No significant difference in the number of mutations between the pre and post AI lesions



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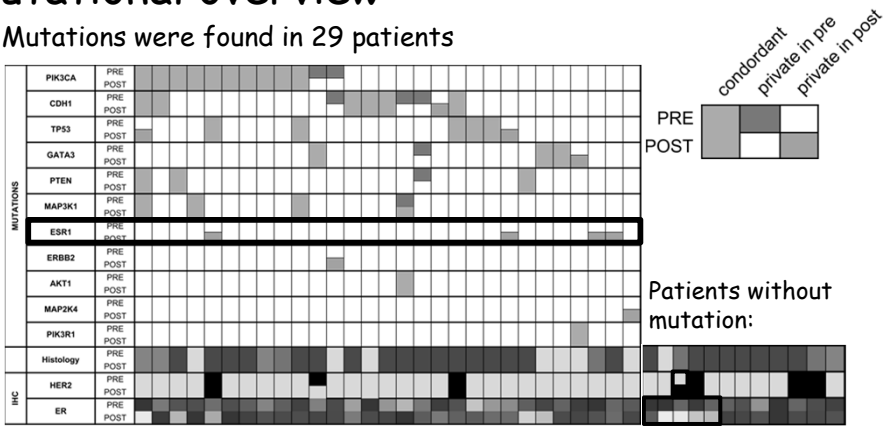
Mutational overview

Mutations were found in 29 patients



- 12 patients with private mutations
- Mutations found in post only for *HER2*, *MAP2K4* and *ESR1*
- No mutations found in 12 patients, loss/reduction of ER and gain of *HER2* amplification in these

56

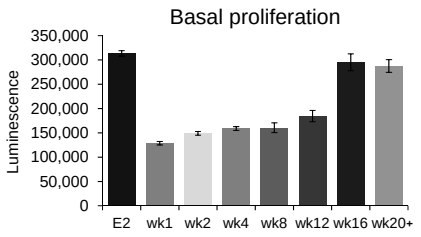
In vitro model for AI resistance

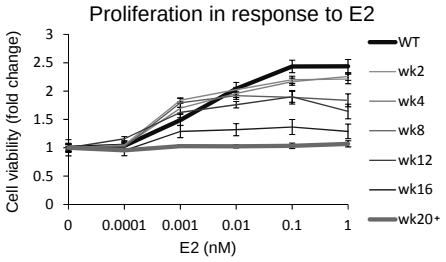
- Long term estrogen deprivation (LTED) to model relapse on an AI
- Study mutational changes of *ESR1* between wild type and resistant breast cancer cell lines

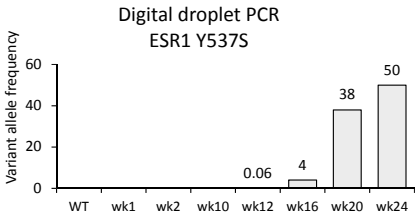
57

Acquisition of *ESR1* mutations *in vitro* SUM44

58





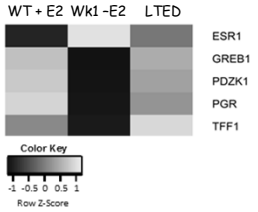


1.3x10^6 WT-SUM44 were WT for *ESR1*, suggesting the mutation is absent or at extremely low VAF

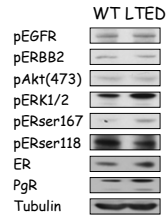
Acquisition of *ESR1* mutations *in vitro* SUM44

59

Expression of endogenous E-regulated genes

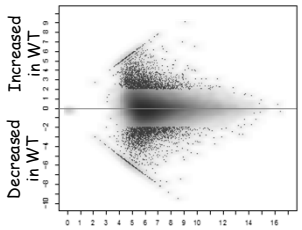


Phenotypic analysis

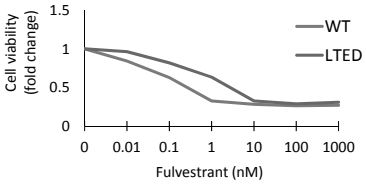


RIME shows altered ER-proteome

ChIP-seq WT versus LTED



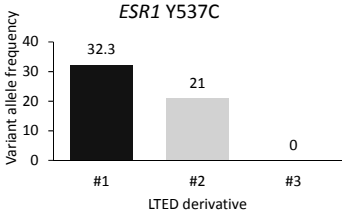
Anti-proliferative effect of fulvestrant



Acquisition of *ESR1* mutations *in vitro* MCF7

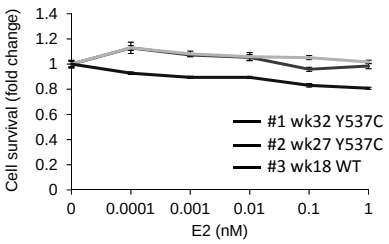
60

ESR1 Y537C

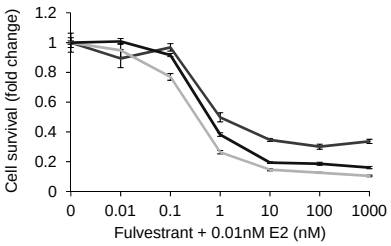


1.34x10^6 WT-MCF7 were WT for *ESR1*, suggesting the mutation is absent or at extremely low VAF

Proliferative in response to E2



Anti-proliferative effect of fulvestrant



Conclusions

- Recurrences after AI but not primary ER+ tumors may contain *ESR1* mutations that could influence clinical decision making.
- Other than *ESR1* there are no consistent acquisition of mutations.
- High variability of genotype and phenotype requires individual interpretation for personalised treatment.
- *In vitro ESR1* mutations can be acquired under estrogen deprivation resulting in a ligand independent phenotype
- Anti-proliferative effect of SERDs remains effective

61

S5-07

Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD- L1-positive, estrogen receptor-positive (ER+)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028

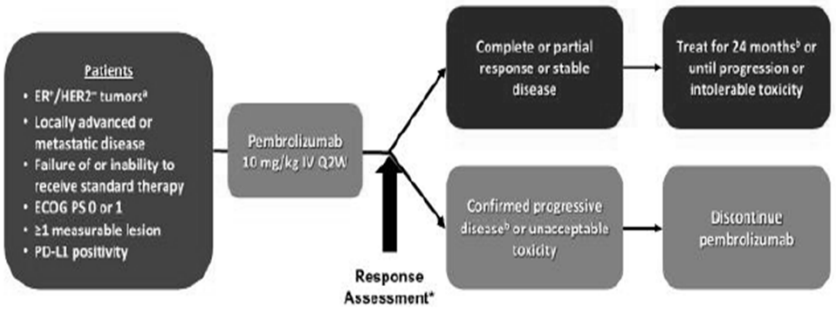
Hope S. Rugo: Research funding to the institution from Merck & Co., Inc., and Genentech

Study supported by Merck & Co., Inc., Kenilworth, NJ, USA

Editorial assistance by the ApotheCom Merck oncology team (Yardley, PA, USA) and supported by Merck & Co., Inc.

December 8-12, 2015
SAN ANTONIO BREAST CANCER SYMPOSIUM

KEYNOTE-028: ER+/HER2- Breast Cancer Cohort



***Response assessment:** Every 8 weeks for the first 6 months; every 12 weeks thereafter

Primary end points: ORR per RECIST v1.1 by investigator and safety

Secondary end points: PFS, OS, duration of response

[a]Defined by institutional standards. [b]If clinically stable, patients were to remain on pembrolizumab until progressive disease was confirmed on a second scan performed ≥4 weeks later. Only patients who discontinued pembrolizumab for complete response or after 24 months of continuous treatment without evidence of disease progression were eligible for up to 1 year of additional pembrolizumab.

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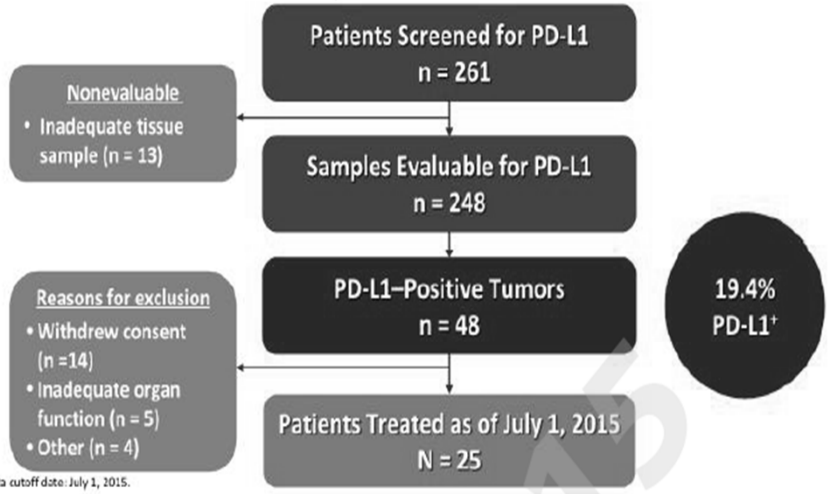
Patients Screened for Tumor PD-L1 Expression in the ER+/HER2- Breast Cancer Cohort



Data cutoff date: July 1, 2015.

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Antitumor Activity (N =25)
(RECIST v1.1, Investigator Review)

	n (%)	95 % CI
Overall response rate	3 (12.0)	2.5-31.2
Complete response	0 (0.0)	0.0-13.7
Partial response[a]	3 (12.0)	2.5-31.2
Stable disease	4 (16.0)	4.5-36.1
Clinical benefit rate[b]	5 (20.0)	6.8-40.7
Progressive disease	15 (60.0)	38.7-78.9
No assessment[c]	3 (12.0)	2.5-31.2

In the 22 patients with at least one scan after baseline, ORR was 14% and CBR was 23%

Includes confirmed responses only.
[a]All patients with a partial response received ≥3 lines of therapy in the metastatic setting. [b]Complete response + partial response + stable disease for ≥24 weeks. [c]"No assessment" signifies patients who discontinued therapy before the first post-baseline scan. Data cutoff date: July 1, 2015.

SAN ANTONIO BREAST CANCER SYMPOSIUM 2015

UT Mays Cancer Center CTRC | AACR American Association for Cancer Research | Baylor College of Medicine

S6-04

A phase II trial of neoadjuvant palbociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with anastrozole for clinical stage 2 or 3 estrogen receptor positive HER2 negative (ER+HER2-) breast cancer (BC)

Dr. Ma has disclosed that she receives clinical trial research support from Pfizer related to palbociclib.

Statistical Design

- **Fleming's single-stage phase II design**
  - To test the hypothesis that adding palbociclib would result in at least 50% improvement in the complete cell cycle arrest (CCCA) rate over AI alone, with 80% power and at 1-sided 0.05 significance.
  - Estimates were 44% with AI alone* versus 66% with the combination.
  - The study was initially only open to the *PIK3CA* WT cohort.
    - A sample size of 33 patients was required.
    - The primary endpoint is met if at least 20 of 33 had CCCA.
  - A subsequent protocol amendment allowed patients with mutant or non-diagnostic *PIK3CA* status to enroll to the study in separate cohorts.

**Ellis, MJ, et al JCO 2011*

Primary Endpoint:

Complete Cell Cycle Arrest (CCCA: Ki67≤2.7%) Rate at C1D15

Study Population	C1D15 CCCA, N (%, 90% CIs)
Total (n=45)	39 (87%, 75-94%)
PIK3CA WT (n=28)	22 (79%, 62-90%)
PIK3CA Mut (n=15)	15 (100%, 82-100%)
PIK3CA Undetermined (n=2)	2 (100%, NE)

Study objective: Demonstrate a CCCA rate of 66%.
If at least 20 of 33-patient cohort achieved CCCA on C1D15 biopsy, the primary endpoint of the study is met.

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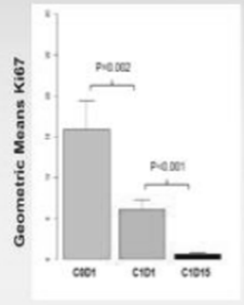
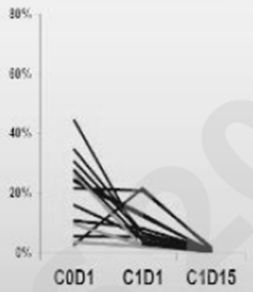
Ki67 Response by *PIK3CA* Status

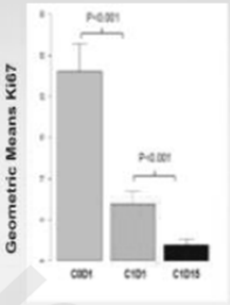
- H1047L/R
- E545K or E542K or Q546K
- C420R
- Insufficient tumor

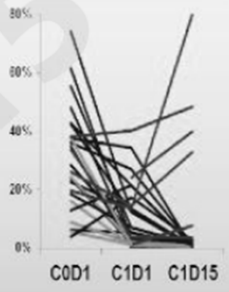
PIK3CA Mut. (n=15)





PIK3CA WT (n=28)





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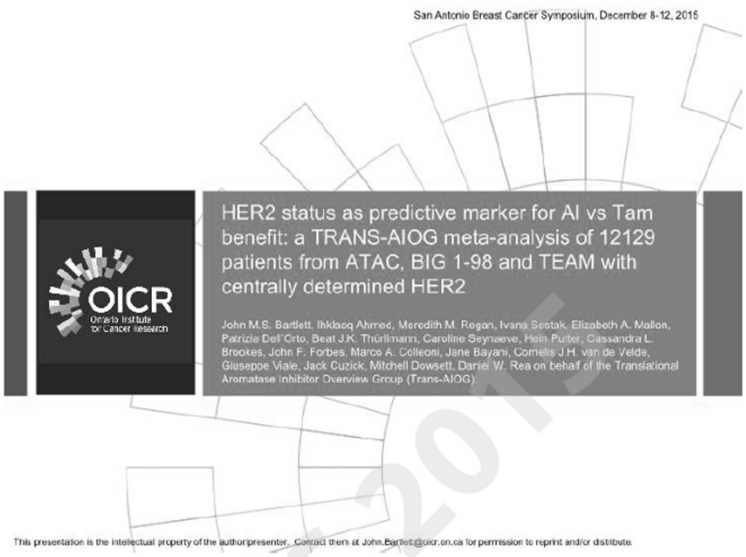
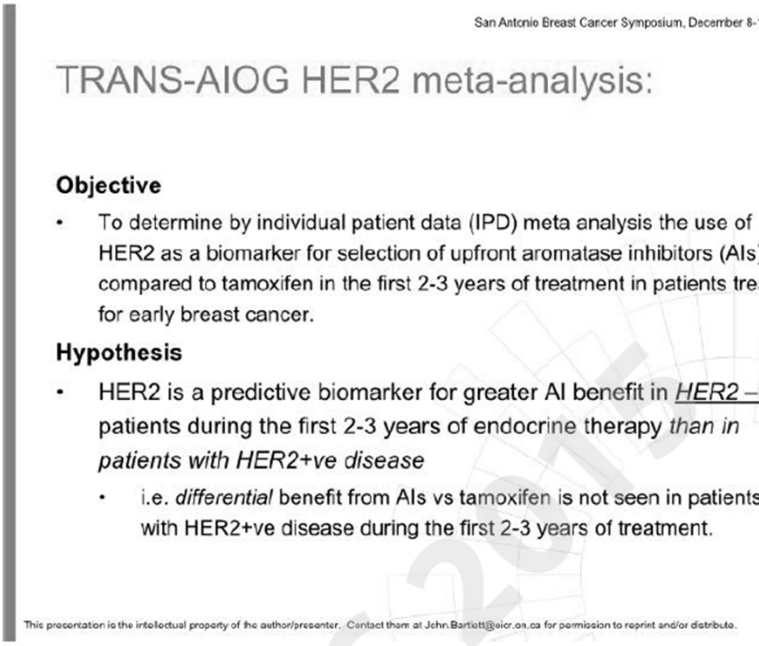
Conclusions

- Palbociclib provides enhanced cell cycle control over that achieved by anastrozole alone.
- Palbociclib enhanced cell cycle control regardless of PIK3CA mutation status or luminal A or B status.
- The combination was ineffective in the two patients with non-luminal breast cancers and a subset of luminal B cancers.
- The combination of palbociclib and anastrozole was well tolerated.
- These results support the evaluation of this combination in the adjuvant setting for ER+ HER2- BC.
- Rebound Ki67 values at surgery after an average of 4 weeks of palbociclib washout indicates that palbociclib is, like endocrine therapy, a maintenance treatment.



Abstract 4-06



TRANS-AIOG HER2 meta-analysis:

Objective

- To determine by individual patient data (IPD) meta analysis the use of HER2 as a biomarker for selection of upfront aromatase inhibitors (AIs) compared to tamoxifen in the first 2-3 years of treatment in patients treated for early breast cancer.

Hypothesis

- HER2 is a predictive biomarker for greater AI benefit in *HER2 –ve* patients during the first 2-3 years of endocrine therapy *than in patients with HER2+ve disease*
  - i.e. *differential* benefit from AIs vs tamoxifen is not seen in patients with HER2+ve disease during the first 2-3 years of treatment.

Patient characteristics:

	TEAM	ATAC	BIG 1-98	Overall
	N %	N %	N %	N %
	(N=4263)	(N=1684)	(N=6182)	(N=12129
Randomized treatment				
Tamoxifen	49.8%	48.9%	49.9%	49.8%
Aromatase Inhibitor	50.2%	51.1%	50.1%	50.2%
Tumour Size				
≤20mm	48.3%	66.9%	62.3%	58.0%
>20mm	48.9%	32.7%	37.0%	40.65
Unknown	2.8%	0.4%	0.7%	1.4%
Nodal Status				
Negative	25.7%	65.6%	57.2%	47.3%
Positive	57.6%	30.2%	41.8%	45.7%
Unknown	16.7%	4.2%	1.0%	7.0%
Grade				
Well	11.3%	26.9%	20.8%	18.3%
Moderate	51.2%	51.0%	56.6%	54.0%
Poor	31.4%	16.3%	22.3%	24.6%
Unknown	6.2%	5.8%	0.2%	3.1%
Central Her2 status				
HER2 Negative	87.7%	89.4%	93.7%	91.0%
HER2 Positive	12.3%	10.6%	6.3%	9.0%

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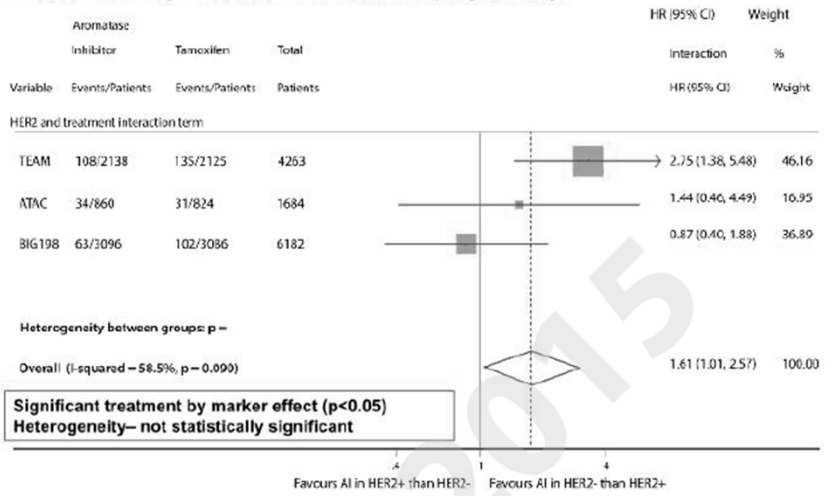
Primary endpoint Distant recurrence free interval: Treatment by marker interaction (adjusted):



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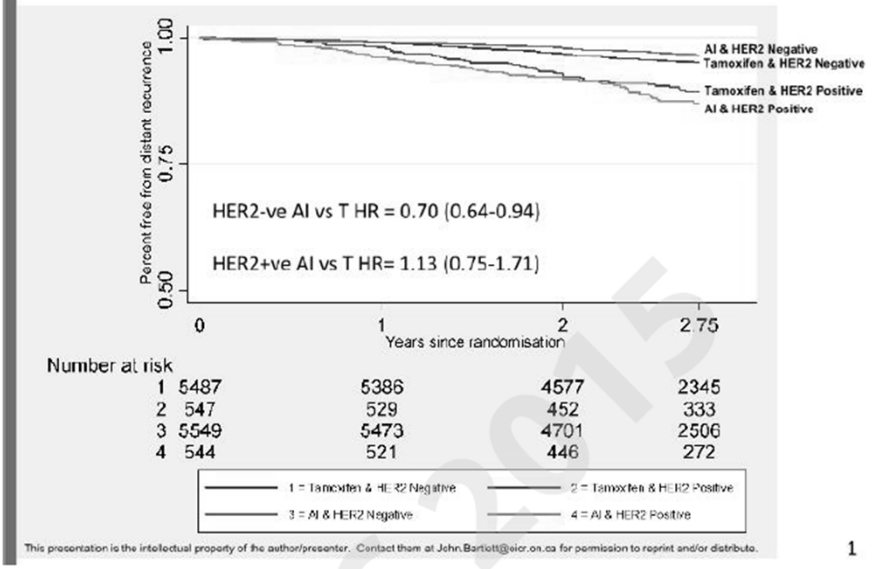
Distant recurrence free interval



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Conclusion

- A patient level meta-analysis demonstrated a significant interaction between HER2 status and treatment with AIs versus Tamoxifen
  - Prior to "switching" between tamoxifen and AIs.
- Satisfies the required criteria for level 1B evidence according to Simon et al
  - Simon RM, et al JNCI 2009;101(21):1446-1452.
  - Heterogeneity observed in the HER2 positive subgroup,
    - Heterogeneity did not reach statistical significance within the primary endpoint population.

Practice changing?

- Perhaps?
  - Denosumab in patients receiving Ais
- Confirmatory
  - Lack of chemotherapy benefit in luminal A cancers
- Requires further evaluation
  - Palbociclib in adjuvant setting
  - Buparlisib in AI-resistant ER-positive MBC
  - Pembrolizumab (maybe – disappointing results)
- Interesting
  - Acquired ESR mutations in cfDNA