Faculty Biography

William J. Gradishar, MD, is the Betsy Bramsen Professor of Breast Oncology in the Division of Hematology and Medical Oncology, Department of Medicine at the Feinberg School of Medicine at Northwestern University and a member of Robert H. Lurie Comprehensive Cancer Center of Northwestern University. He serves as Director of the Maggie Daley Center for Women's Cancer Care. He also has served as Chair of the Annual Lynn Sage Comprehensive Breast Cancer Symposium since its inception.

Dr. Gradishar received his medical degree from the University of Illinois Abraham School of Medicine. He later completed a residency and chief residency in internal medicine at Michael Reese Hospital and Medical Center and a fellowship in medical oncology at the University of Chicago. He is board-certified in internal medicine and medical oncology.

Dr. Gradishar has published in the area of breast cancer therapeutics, with a focus on new endocrine therapy, chemotherapy, and biologic agents. A Fellow of the American College of Physicians, Dr. Gradishar also is a member of the American Association for Cancer Research, the American Federation for Clinical Research, and the Association of Subspecialty Professors. He is a Fellow of the American Society of Clinical Oncology (ASCO) and past-Chair of ASCO's Nominating Committee, Professional Development Committee, Oncology Training Program Committee, and Communications Committee.

Additionally, Dr. Gradishar serves as a consultant to the Oncology Drug Advisory Committee of the FDA. He has served on the Committee on Cancer for the American College of Surgeons. He also has served on numerous study sections including NIH, NCI, ACS, Komen, and Alberta Cancer Board. Dr. Gradishar was awarded the Betsy Bramsen Endowed Chair of Breast Oncology at Northwestern University.

Dr. Gradishar is an editorial board member for numerous journals, including the *Journal of Clinical Oncology, Oncology, Clinical Breast Cancer, Journal Watch,* the *European Journal of Clinical and Medical Oncology,* and *Clinical Cancer Research.*

Dr. Gradishar currently serves as Chair of the NCCN Breast Cancer Panel and as a member of the NCCN Breast Cancer Risk Reduction Panel.

2016
NCCN CONGRESS SERIES™
National Comprehensive Cancer Network

Late Stage Breast Cancer, Including SABCS Updates

Advances in Treatment of MBC: NCCN Update & SABCS 2015 Review

William J. Gradishar, MD

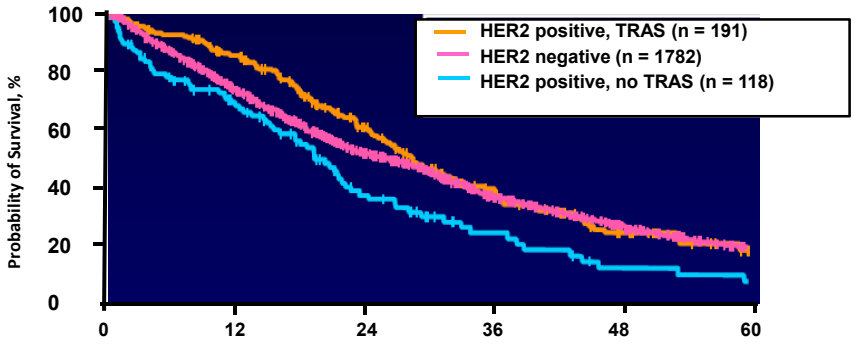
Betsy Bramsen Professor of Breast Oncology
Director, Maggie Daley Center for Womens' Cancer Care
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

OUTLINE

- The HER2 Algorithm
  - Theresa update
  - Marianne
- TNBC
  - No evidence based standard, still chemo
  - Emerging data with checkpoint inhibitors
- ER+
  - New partners?
  - Molecular clues for resistance providing insights to Precision Medicine

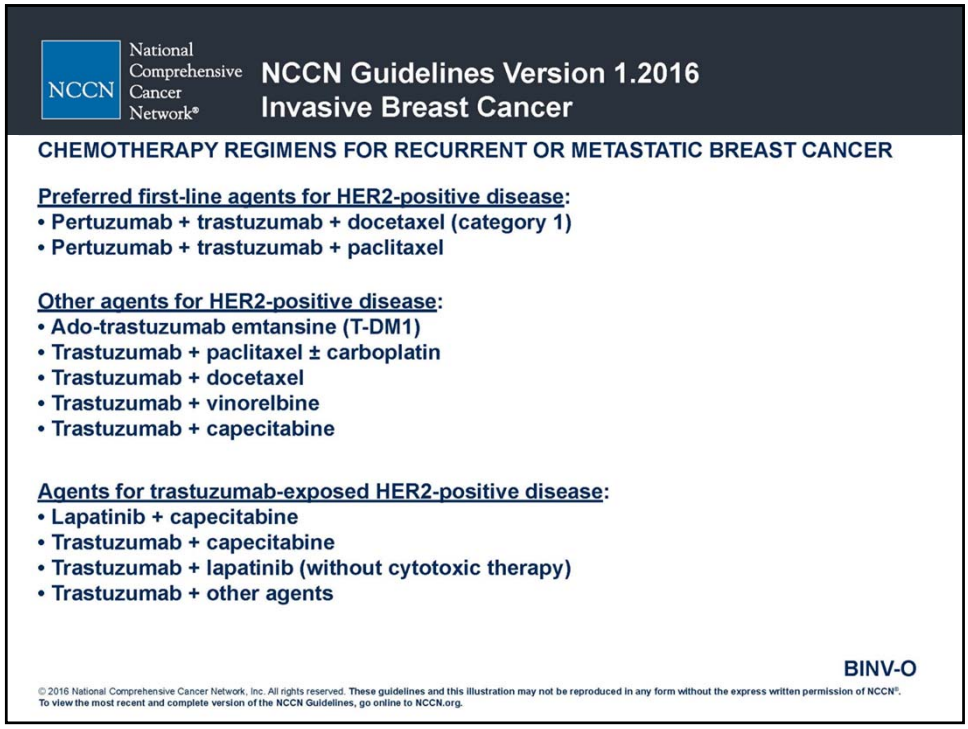
Trastuzumab Has Changed the Natural History of HER2-Positive Breast Cancer

- **Patients with HER2-positive metastatic breast cancer (MBC) now have comparable outcomes with HER2-negative MBC**



TRAS, trastuzumab

Dawood S, et al. *J Clin Oncol.* 2010;28(1):92-98.



First-Line Setting

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

CLEOPATRA: Study Design

- Primary endpoint: PFS (independently assessed)
- Secondary endpoints: PFS (investigator assessment), ORR, OS, Safety

Women with previously untreated, HER2-positive locally recurrent/metastatic breast cancer

(N = 808)

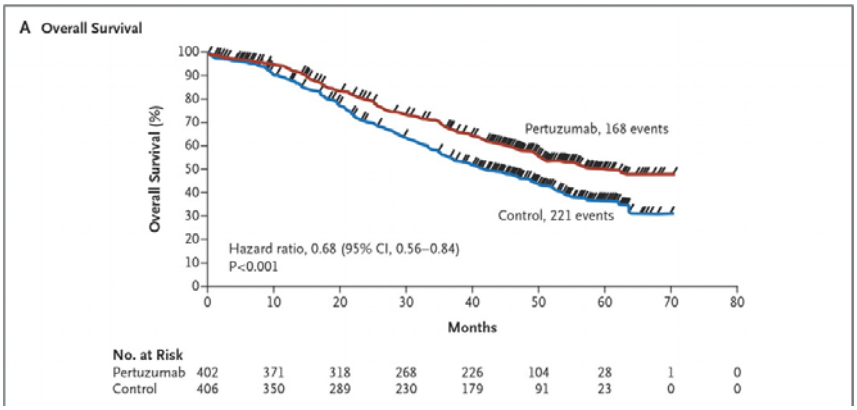
Trastuzumab 6 mg/kg q3w* + **Docetaxel** 75-100 mg/m^2 q3w† + **Pertuzumab (PTZ)** 420 mg q3w‡ (n = 402)

Trastuzumab 6 mg/kg q3w* + **Docetaxel** 75-100 mg/m^2 q3w† + **Placebo** q3w (n = 406)

Treatment until disease progression or unacceptable toxicity

Baselga J, et al. *N Engl J Med*. 2012;366(2):109-119. Swain S, et al. *Lancet Oncol.* 2013;14(6):461-471.

CLEOPATRA Overall Survival



PTZ + TRAS + DOC	Placebo + TRAS + DOC	
56.5 months	40.8 months	HR = 0.68, *P* = .0002

Swain SM et al. N Engl J Med 2015;372:724-734.

Hormonal Therapy in HER2-Positive Metastatic Breast Cancer

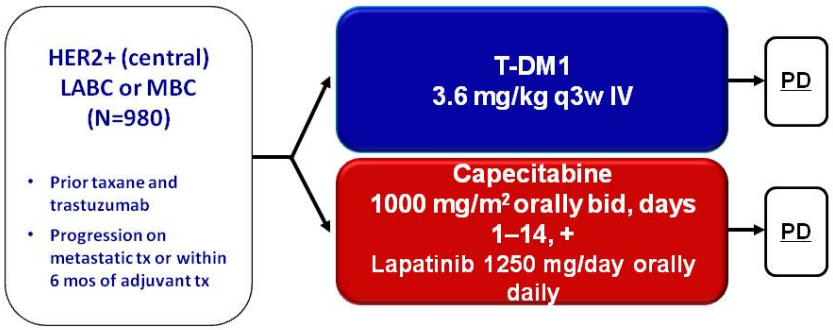
Regimen	ORR, %	Median PFS, months
Trastuzumab (N = 114; HER2 positive, n = 79)[1]	26	3.5-3.8
Anastrozole/trastuzumab (n = 103)[2]	20	4.8
Anastrozole (n = 104)[2]	7	2.4
Lapatinib/letrozole (n = 642)[3]	28	8.2
Letrozole (n = 644)[3]	15	3.0
Lapatinib (N = 138)[4]	24	NA

Summary: Optimal Choice First-Line Setting 2016

- **Clinicians should recommend combination of trastuzumab, pertuzumab and a taxane for first-line treatment, unless contraindication to taxane use**
- **If ER+, can consider endocrine therapy + trastuzumab or lapatinib in selected cases**

Giordano SH, et al. *J Clin Oncol.* 2014;32(19):2078-2099.

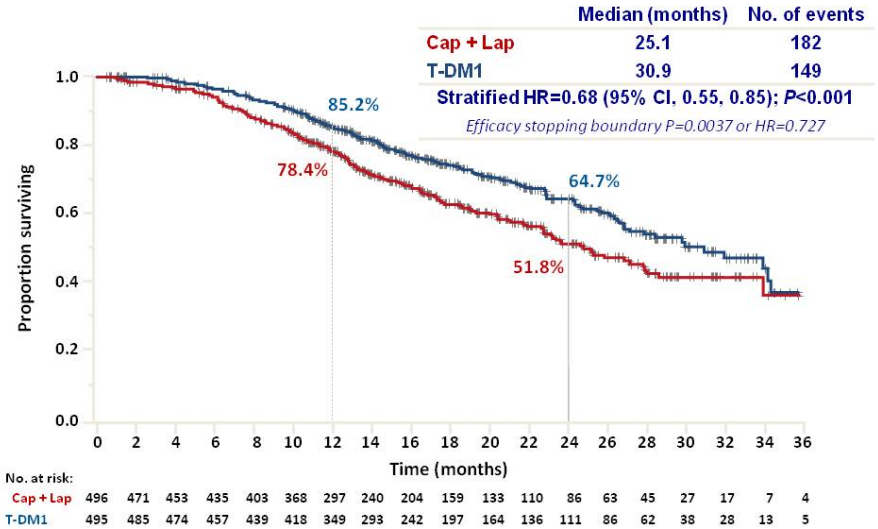
EMILIA Study Design



- **Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Blackwell et al, ASCO 2012
Verma et al, NEJM 2012

EMILIA: Overall Suvival



Verma et al. *NEJM*, 2012.

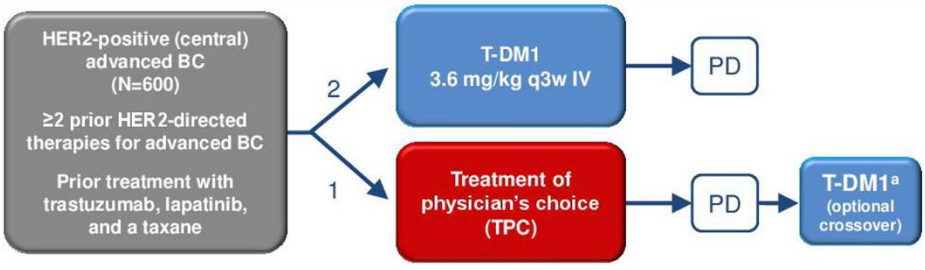
Trastuzumab emtansine (T-DM1) improves overall survival versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer: final overall survival results from the phase 3 TH3RESA study

Hans Wildiers,[1] Sung-Bae Kim,[2] Antonio Gonzalez Martin,[3] Patricia M. LoRusso,[4] Jean-Marc Ferrero,[5] Tanja Badovinac-Crnjevic,[6] Ron Yu,[7] Melanie Smitt,[7] Ian E. Krop[8]

[1]University Hospitals Leuven, Leuven, Belgium; [2]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [3]MD Anderson Cancer Center, Madrid, Spain; [4]Yale Cancer Center, Yale University Medical Center, New Haven, CT, USA; [5]Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France; [6]F. Hoffmann-La Roche, Ltd, Basel, Switzerland; [7]Genentech, Inc, South San Francisco, CA, USA; [8]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

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

TH3RESA Study Schema



Stratification factors: World region, number of prior regimens for advanced BC, presence of visceral disease

Co-primary endpoints: PFS by investigator and OS

Key secondary endpoints: ORR by investigator and safety

[a]First patient in: Sept, 2011. Study amended: Sept, 2012 following EMILIA 2nd interim OS results to allow patients in the TPC arm to receive T-DM1 after documented PD.

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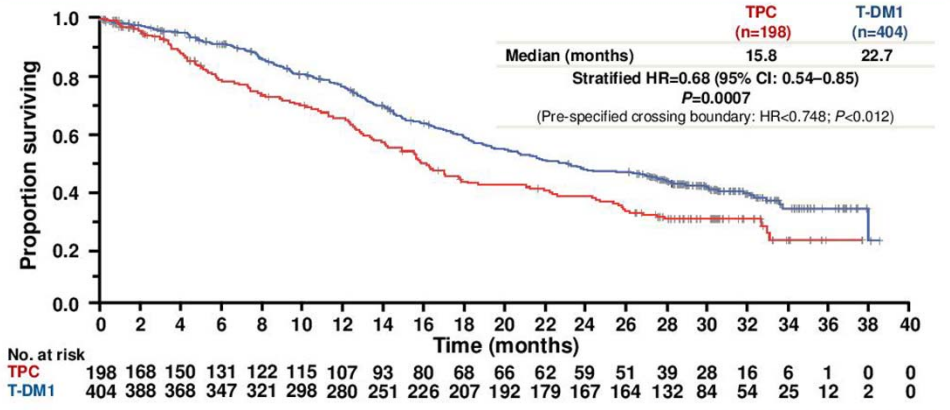
Treatment of Physician's Choice Regimen

TPC treatment regimen	TPC (n=184[a])	
Combination with HER2-directed agent, %	**83.2**	
Chemotherapy[b] + trastuzumab	68.5	**Trastuzumab-containing 80.4**
Lapatinib + trastuzumab	10.3	
Hormonal therapy + trastuzumab	1.6	
Chemotherapy[b] + lapatinib	2.7	
Single-agent chemotherapy,[b] %	**16.8**	

[a]Includes patients who received study treatment. Excludes one patient who was randomized to the TPC arm but received two cycles of T-DM1 by mistake.
[b]The most common chemotherapy agents used were vinorelbine, gemcitabine, eribulin, paclitaxel, and docetaxel.

Final OS Analysis



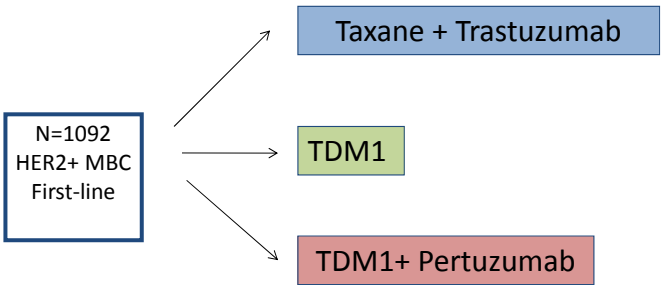
San Antonio Breast Cancer Symposium, December 8-12, 2015

Grade ≥3 AEs With Incidence ≥2% in Either Arm

	TPC (n=184)		T-DM1 (n=403)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Nonhematologic AEs, %				
Diarrhea	22.3	**4.3**	12.7	0.7
Dyspnea	13.0	3.8	11.7	2.5
Asthenia	17.9	3.3	19.1	1.0
Abdominal pain	12.5	2.7	7.4	1.2
AST increased	7.1	2.7	12.4	2.5
Fatigue	26.1	2.7	30.8	2.2
ALT increased	5.4	2.2	9.2	1.5
Cellulitis	3.8	2.2	1.7	0.5
Pulmonary embolism	2.2	2.2	0.5	0.5
Hematologic AEs, %				
Neutropenia	21.7	**15.8**	7.7	2.5
Febrile neutropenia	3.8	**3.8**	0.2	0.2
Anemia	11.4	3.3	11.4	3.5
Leukopenia	6.0	2.7	2.2	0.5
Thrombocytopenia[a]	3.8	2.7	20.6	**6.0**

Shading indicates grade ≥3 AEs with >3% difference between the TPC and T-DM1 arms.
[a]The incidence of grade ≥3 hemorrhage of any type (basket term) was 4.2% (T-DM1) and 0.5% (TPC).

MARIANNE Phase III

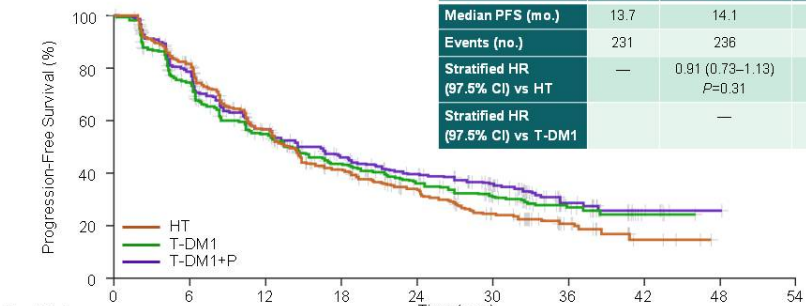


1° Endpoint: PFS
2° Endpoints: OS, TTF, DOR, ORR, CBR

T= paclitaxel 80 m/m weekly or docetaxel at 75-100 m/m q 3 w
H=trastuzumab 2 mg/kg q w or 6 mg/kg q 3 w
P=pertuzumab at 840 mg load → 420mg q 3 w
TDM= trastuzumab/DM1 at 3.6 mg/kg q 3 w

Progression-Free Survival by IRF

	HT	T-DM1	T-DM1+P
Median PFS (mo.)	13.7	14.1	15.2
Events (no.)	231	236	217
Stratified HR (97.5% CI) vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR (97.5% CI) vs T-DM1		—	0.91 (0.73–1.13)



No. at Risk								
HT	365	265	163	107	75	50	21	5
T-DM1	367	257	176	133	104	67	28	3
T-DM1+P	363	261	177	135	109	75	25	5	1

Non-inferiority: Established if the upper limit of the 97.5% CI for the HR is below 1.1765 (non-inferiority margin).

PRESENTED AT: ASCO Annual '15 Meeting

Key Differences Between CLEOPATRA and MARIANNE

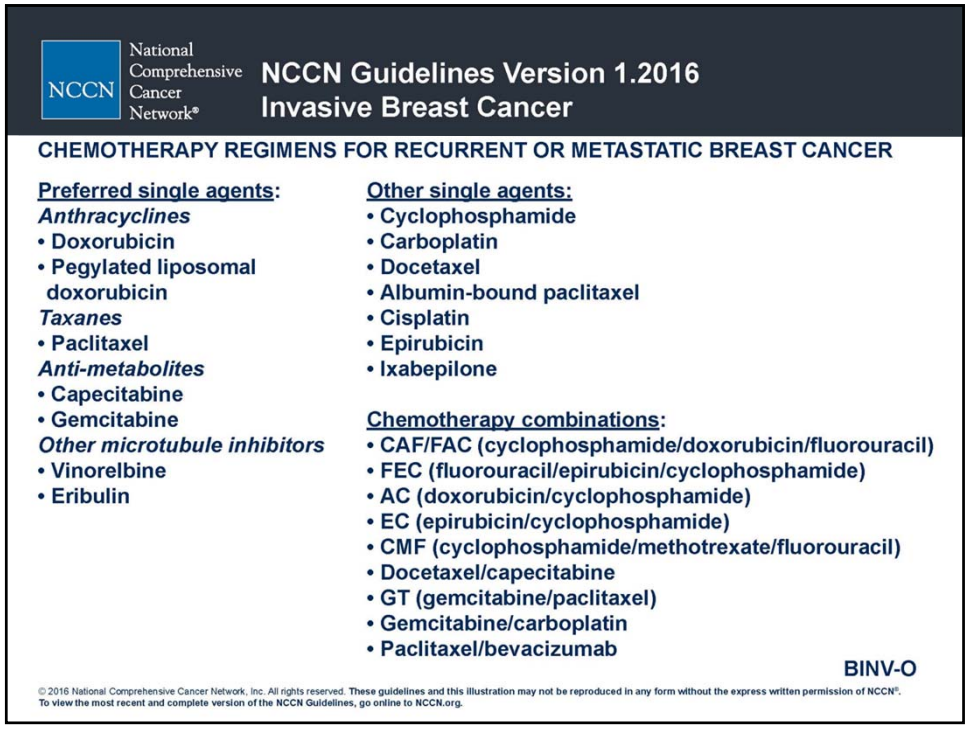
MARIANNE

- Poorer prognosis population
  - Shorter DFI required: > 6m
  - Less *de novo* MBC
  - More patients have prior taxane exposure
  - More patients have previous trastuzumab exposure

CLEOPATRA

- Better prognosis population
  - Longer DFI required: > 12m
  - More *de novo* MBC
  - Fewer patients have prior taxane exposure
  - Fewer patients have previous trastuzumab exposure

DFI = disease free interval from neoadjuvant or adjuvant setting

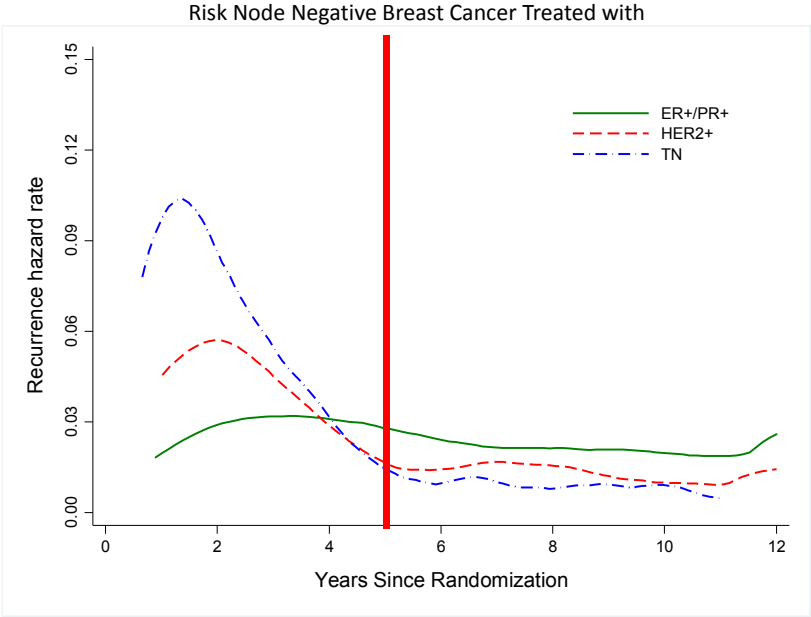


Triple-Negative Disease Compared with Other Phenotypes in the California Cancer Registry Study

Bauer et al. Cancer 2007: 109; 721
Parise et al. The Breast Journal 2009: 15: 593

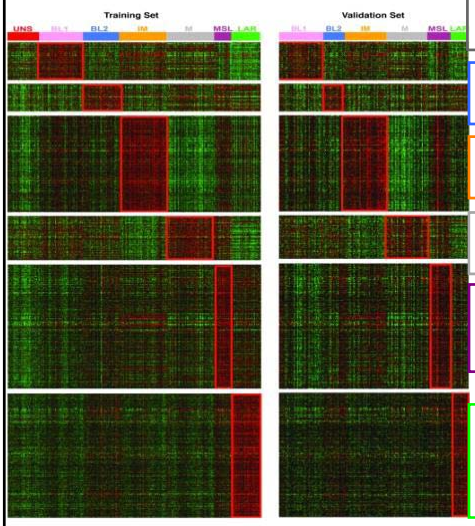
- Population-based study
  - 6370 with "triple-negative" disease compared with 44,704 "other" cases (12% of all cases)
- TNBC more likely to be associated with
  - Younger age (<40): OR 1.53
  - Non-Hispanic black race (OR 1.77) or Hispanic ethnicity (OR 1.23)
  - Higher grade (72% grade 3)
  - More advanced stage (66% >/= stage II vs. 50% ER+HER2-)
  - Poorer 5 year RFI irrespective of stage
    - TNBC: 76% (similar to 76% for HER2-Pos)
    - HR-Pos, HER2-Neg: 94%
  - Greater propensity for lung and brain mets

Annual Hazard Rate of Recurrence by Breast Cancer Subtype in E1199: Node-Positive & High-Risk Node Negative Breast Cancer Treated with



TNBC Subtypes

21 publicly available gene expression breast cancer datasets, 587 TNBCs



Basal-like 1 (BL1): Cell-cycle, proliferation and DNA damage response genes

Basal-like 2 (BL2): Growth factor signaling (EGF, MET, Wnt/β-catenin, IGF1R)

Immunomodulatory (IM): Immune cell & cytokine signaling (overlap with medullary signature

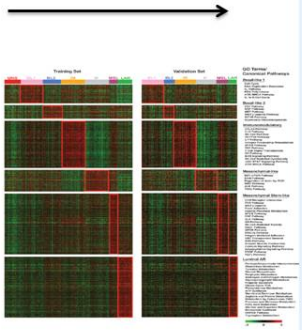
Mesenchymal (M): Cell motility and differentiation (Wnt, ALK, TGF-β)

Mesenchymal stem-like (MSL): Similar to M, but increased growth factors signaling, low proliferation, enrichment of stem cell genes

Luminal androgen receptor (LAR): Enriched in hormonally-regulated pathways, androgen receptor signaling. Displays luminal expression patterns (molecular apocrine carcinomas)

Lehmann BD, et al. Journal of Clinical Investigation, 2011

Exploitation of the Heterogeneity of TNBC:

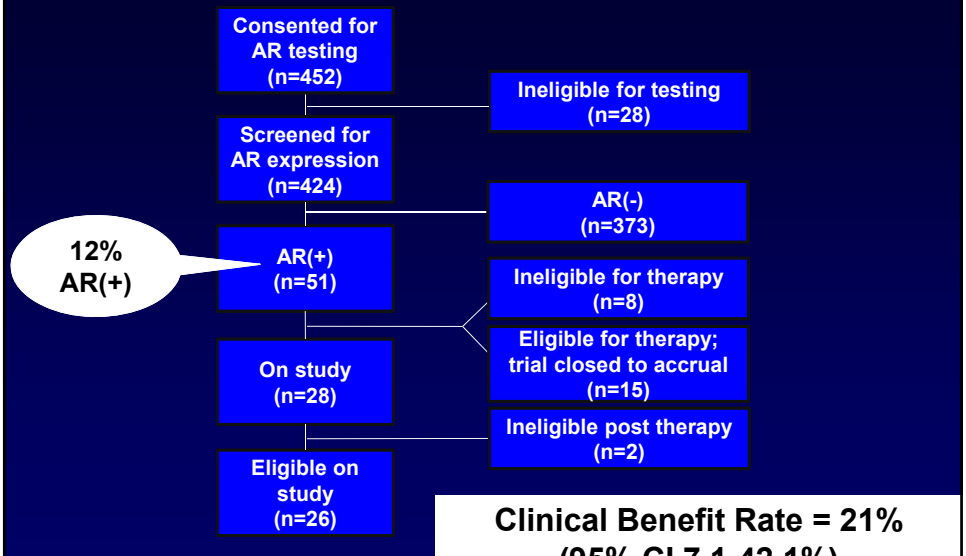


Therapeutic Strategies

- DNA damage and repair
- Hormone receptor modulation
- Immune modulation
- Signaling pathway inhibition
- ….

PRESENTED AT: ASCO Annual '15 Meeting

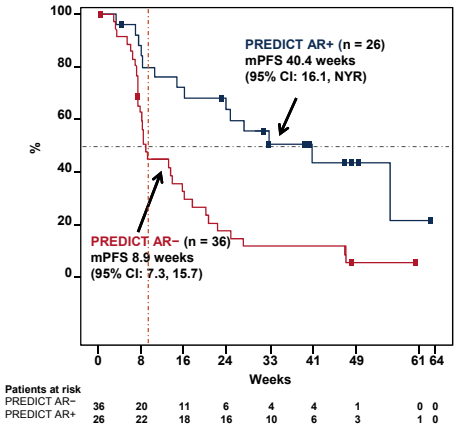
TBCRC 011: Bicalutamide in AR+ TNBC



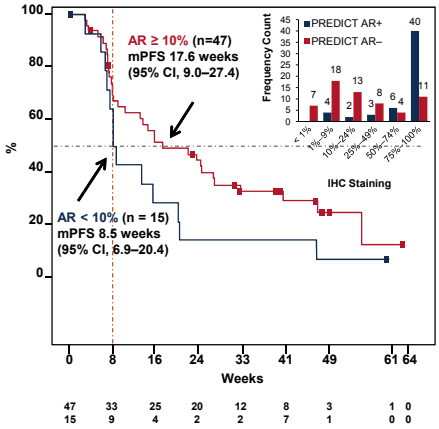
Gucalp et al, ASCO 2012

MDV3100-11: PFS Is Driven by AR Genomic Signature, Not IHC, in Patients with 0–1 Prior aTNBC Treatment

Enzalutamide in AR+ Metastatic TNBC Patients



AR by PREDICT AR



AR by IHC

39

Traina T. ASCO, 2015, abstr 1003

TNT Trial design

Tutt et al

ER-, PgR-/unknown & HER2- or known *BRCA1/2*
Metastatic or recurrent locally advanced

Exclusions include:
- Adjuvant taxane in ≤12 months
- Previous platinum treatment
- Non-anthracyclines for MBC

A Priori subgroup analyses:
- BRCA1/2 mutation
- Basal-like subgroups (PAM50 and IHC)
- Biomarkers of HRD

Carboplatin (C)
AUC 6 q3w, 6 cycles

On progression, crossover if appropriate

Docetaxel (D)
100mg/m^2 q3w, 6 cycles

n-376

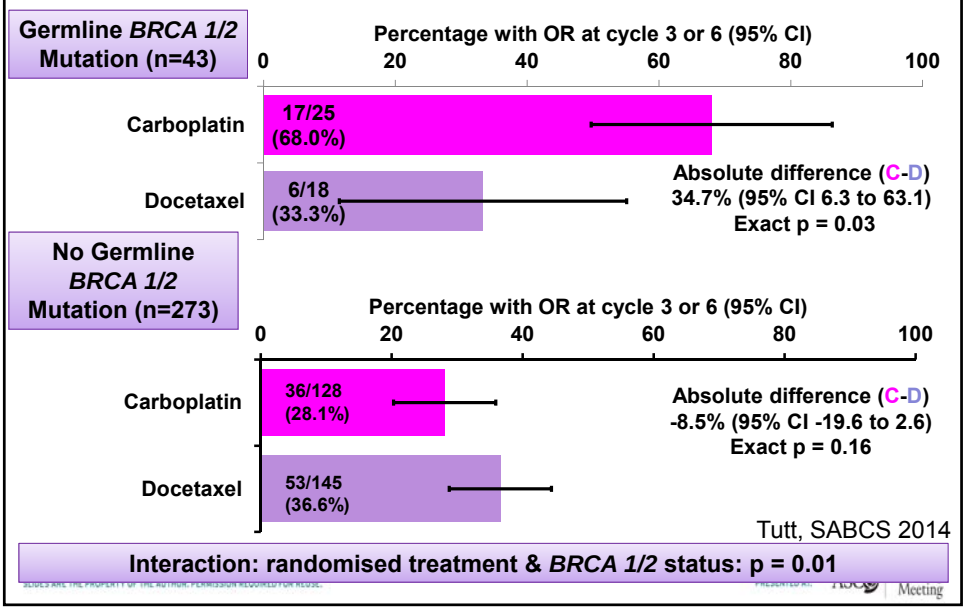
BRCA1/2 = 9%/12%

Docetaxel (D)
100mg/m^2 q3w, 6 cycles

On progression, crossover if appropriate

Carboplatin (C)
AUC 6 q3w, 6 cycles

Objective response – *BRCA 1/2* status



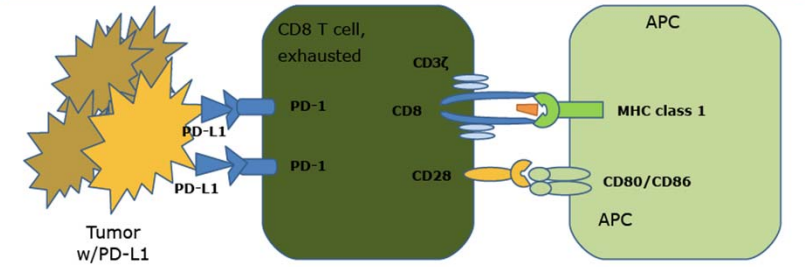
Tutt, SABCS 2014

Interaction: randomised treatment & *BRCA 1/2* status: p = 0.01

Checkpoint Inhibitors
The next frontier!

PD-1/PD-L1

PD-1-PD-L1 binding leads to peripheral CD8+ T cell "exhaustion" phenotype

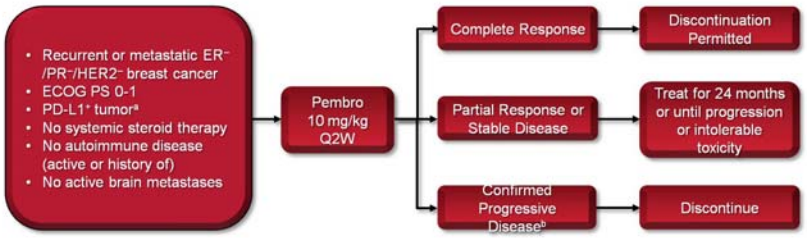


In a state of chronic antigen presentation, such as malignancy, the chronic presence of antigen or pro-inflammatory cytokines (IL-12, IFNgamma, etc) can upregulate PD-1 expression on the T cell; tumor clones can also select for PD-L1 expression. With PD-1-PD-L1 binding, even in the presence of the costimulatory molecule, "peripheral exhaustion" can occur.

PD-L1: programmed death-ligand 1; CD: cluster of differentiation; PD-1: programmed cell death-1; APC: antigen-presenting cells; MHC: major histocompatibility complex; IL: interleukin; IFNgamma: interferon gamma.

A Phase Ib Study of Pembrolizumab (MK-3475) in Patients With Advanced TNBC

KEYNOTE-012: Triple-Negative Breast Cancer Cohort



- **PD-L1 positivity: 58% of all patients screened had PD-L1-positive tumors**
- **Treatment: 10 mg/kg IV Q2W**
- **Response assessment: Performed every 8 weeks per RECIST v1.1**

[a]PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.

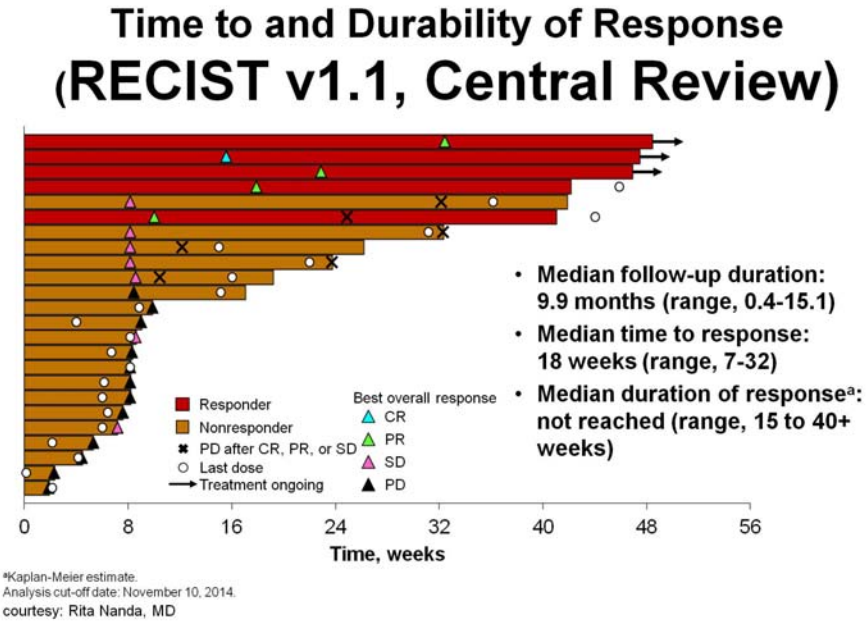
[b]If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed ≥4 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

courtesy: Rita Nanda, MD

SABCS 2014 Abstract S1-09

PD-1 & Breast Cancer

- SABCS 2014 presentation[7]
  - Phase IB study
  - 27 patients with heavily pretreated metastatic TNBC treated with the humanized IgG4κ isotype mAb against PD-1, pembrolizumab
    - 18.5% response rate (1 CR, 4 PR)
    - 7 patients had stable disease
    - Median PFS "just under 2 months"
    - 3 pts remained on treatment for at least 11 months
    - 1 pt died of treatment-related DIC



Inhibition of PD-L1 by MPDL3280A leads to clinical activity in TNBC
Emens et al. AACR 2015 Abst. 2859

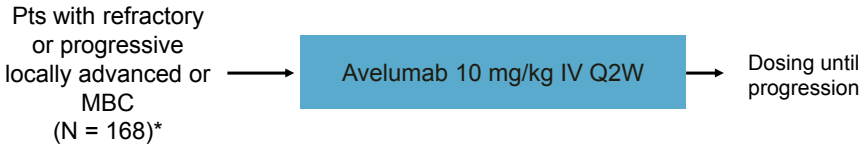
- Metastatic TNBC expansion cohort as part of Phase Ia study
- N =27
- ORR =24% (3 PR; 2 CR)
- 24 week PFS = 33%
- Toxicity tolerable
- 0.1-41.6 week duration; median duration not reached

Avelumab (MSB0010718C), an anti-PD-L1 Antibody, in Patients with Locally Advanced or Metastatic Breast Cancer: a Phase IB JAVELIN Solid Tumor Trial

Dirix LY, Takacs I, Nikolinakos P, Jerusalem G, Arkenau H-T, Hamilton EP, von Heydebreck A, Grote H-J, Chin K, Lippman ME

Courtesy of Dirix et al. SABCS 2015 abs S1-04

JAVELIN: Phase Ib Study Design



- Primary endpoint: DLT
- Secondary endpoints: clinical activity, immune response, safety
- PD-L1 expression assessed by IHC

*Pts eligible if ≤ 3 previous cytotoxic regimens, previous treatment with taxane + anthracycline, biopsy/tissue sample taken within 90 days of avelumab initial dose, ECOG PS 1 or 2, ≥ 1 quantifiable lesion, life expectancy ≥ 3 mos.
Pts unselected for PD-L1 expression, HER2/ER/PR subtype.

Courtesy of Dirix et al. SABCS 2015 abs S1-04

JAVELIN: Baseline Characteristics

Characteristic	All Pts (N = 168)	Pts With TNBC (n = 58)
Median age, yrs (range)	55 (31-81)	52.5 (31-80)
Female, %	99.4	100
ECOG PS, % ▪ 0 ▪ 1	 49.4 50.6	 56.9 43.1
Molecular subtype, % ▪ TNBC ▪ HER2-/ER+ or HER2-/PgR+ ▪ HER2+ ▪ Unknown	 34.5 42.9 15.5 7.1	 100 -- -- --
Previous regimens,* % ▪ ≥ 3 ▪ 2 ▪ ≤ 1	 52.4 20.8 26.8	 22.4 27.6 50.0
Median time since Dx of MBC, mos (range)†	21.6 (0.7-176.8)	13.2 (0.7-176.8)

*Excluding neoadjuvants. †Missing data in 8 pts.

Dirix LY, et al. SABCS 2015. Abstract S1-04.

Courtesy of Dirix et al. SABCS 2015 abs S1-04

Grade 5 treatment-related TEAEs and discontinuation

- Discontinuation related to treatment with avelumab occurred in 8 patients (4.8%)
  - Treatment-related TEAEs that were potentially immune-related led to permanent discontinuation in 3 patients: autoimmune hepatitis (2) and pemphigoid (1)
  - Other events leading to discontinuation were GGT increase (2), AST increase (1), CPK increase (1), and respiratory distress (1)
- Treatment-related death occurred in 2 patients (1.2%)
  - Acute liver failure in patient with liver metastases
  - Respiratory distress in patient with metastatic lesions of liver, lung, and soft tissues; prior/ongoing history of respiratory disorder (cough, dyspnea, pneumonia)
- At the time of data cut-off, 9 patients remained on treatment with avelumab

JAVELIN: Antitumor Activity

Best Overall Response, %	All Pts (N = 168)	Pts With TNBC (n = 58)
CR	0.6	0
PR	4.2	8.6
SD*	23.2	22.4
PD	63.1	65.5
Not evaluable	8.9	3.4
ORR	4.8 (95% CI: 2.1-9.2)	8.6 (95% CI: 2.9-19.0)
DCR†	28.0	31.0

*Defined as SD at first assessment after 6 wks.
†Defined as response plus SD.

Dirix LY, et al. SABCS 2015. Abstract S1-04.

Courtesy of Dirix et al. SABCS 2015 abs S1-04

JAVELIN: ORR According to PD-L1 Expression

- ORR increased in pts with PD-L1–positive tumors
  - Pts with PD-L1 expression by immune cells showed greater response than pts with PD-L1–negative immune cells (33.3% [4/12] vs 2.4% [3/124])
  - PD-L1 expression also appeared associated with ORR in subgroup with TNBC (4 of 9 PD-L1 positive vs 1/39 PD-L1 negative)

Dirix LY, et al. SABCS 2015. Abstract S1-04.

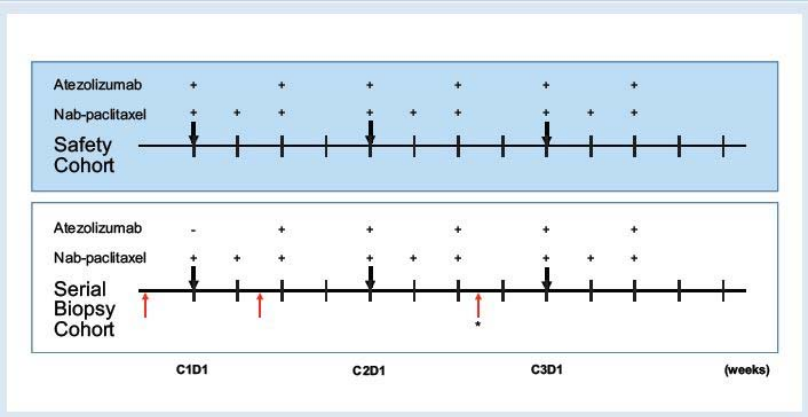
Courtesy of Dirix et al. SABCS 2015 abs S1-04

Safety and Clinical Activity pf Atezolizumab (anti-PDL1) in Combination with nab-Paclitaxel in Patients with Metastatic Triple-Negative Breast Cancer

Adams S, Diamond J, Hamilton E, Pohlmann P, Tolaney S, Molinero L, Zou W, Liu B, Waterkamp D, Funke R, Powderly J

Courtesy of Adams et al. SABCS 2015 P2-11-06

Treatment & Biopsy Schedule



Red arrow indicates biopsy.
*A second post-dose biopsy was taken in serial biopsy cohort ≈ 4 wk after first dose of atezolizumab.

Courtesy of Adams et al. SABCS 2015 P2-11-06

Table 3. Summary of Best Overall Responses by RECIST v1.1

Best Overall Response	1L (n = 9)	2L (n = 8)	3L+ (n = 7)	All Patients N = 24
Confirmed ORR (95% CI)[a]	66.7% (29.9, 92.5)	25% (3.2, 65.1)	28.6% (3.7, 71.0)	41.7% (22.1, 63.4)
ORR (95% CI)[b]	88.9% (51.7, 99.7)	75.0% (34.9, 96.8)	42.9% (9.9, 81.6)	70.8% (48.9, 87.4)
CR	11.1%	0	0	4.2%
PR	77.8%	75.0%	42.9%	66.7%
SD	11.1%	25.0%	28.6%	20.8%
PD	0	0	28.6%	8.3%

[a] Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.
[b] Including investigator-assessed unconfirmed responses.

Courtesy of Adams et al. SABCS 2015 P2-11-06

Table 5. Objective Response Rate by PD-L1 Expression Level[a]

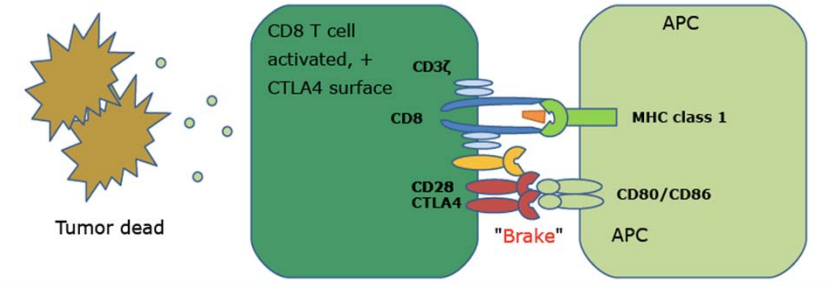
	IC0 (n = 7)	IC1/2/3 (n = 9)	Unknown (n = 8)
ORR (95% CI)	57.1% (18.4, 90.1)	77.8% (40.0, 97.2)	75% (34.9, 96.8)
CR	0	0	12.5%
PR	57.1%	77.8%	62.5%
SD	42.9%	22.2%	0
PD	0	0	25%

[a] Including investigator-assessed unconfirmed responses.

Courtesy of Adams et al. SABCS 2015 P2-11-06

CTLA-4

CTLA-4 acting as physiologic "brake" on costimulation of CD8+ T cell



CTLA4 outcompetes CD28 for CD80 and CD86, and the costimulatory signal ceases as the target is eliminated, reducing the release of pro-effector cytokines such as IL-12 and cytotoxic enzymes such as perforin and granzyme B. Homeostasis is restored.

CD: cluster of differentiation; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; APC: antigen-presenting cells; MHC: major histocompatibility complex; IL: interleukin.

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NU 15B01
PI: Cesar Santa-Maria

- Non-randomized, open-label, pilot phase II clinical trial of the PD-L1 inhibitor, durvalumab (MEDI4736), in combination with the CTLA-4 inhibitor, tremelimumab, in patients with stage IV HER2-negative breast cancer (hormone-refractory & TNBC)

NU 15B01

- Durvalumab (MEDI4736)
  - Human IgG1κ monoclonal antibody directed against human PD-L1
  - Currently being evaluated in three phase I clinical trials
- Tremelimumab
  - IgG2κ isotype mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) aka CD152
  - 10 clinical studies
  - Response rates generally low (~10%)
  - Responses are durable, lasting months to years even in subjects with aggressive tumors, such as refractory metastatic melanoma

Key Inclusion Criteria

- Stage IV HER2-negative breast cancer
- TNBC: must have progressed through at least 1 prior chemotherapy regimen in the metastatic setting or within 12 months of last adjuvant systemic tx
- ER positive disease: must have received prior therapy with palbociclib (in addition to 1 line of chemotherapy and standard hormone therapy options) prior to enrollment in the study
- ECOG PS 0-2
- Willing to provide fresh biopsies prior to enrollment & after 2 cycles of treatment

Big Questions in ER+ MBC

- Overcoming endocrine resistance
- Role for endocrine monotherapy
- New partners for endocrine therapy
- Challenges is certain subsets (ER+/HER+)

Estimated Cancer Deaths From ER+ Breast Cancer

ER+ Breast Cancer Is Responsible For Approximately 30,000 Deaths Each Year

26%	Lung & bronchus
10-11%	Breast Luminal
9%	Colon & rectum
7%	Pancreas
5%	Ovary
4-5%	Breast TNBC
4%	Non-Hodgkin lymphoma
3%	Leukemia
3%	Uterine corpus
2%	Liver & intrahepatic bile duct
2%	Brain/Other nervous system
24%	All other sites

O'Brien et al. CCR. 2010

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENT OR STAGE IV DISEASE

BINV-23

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

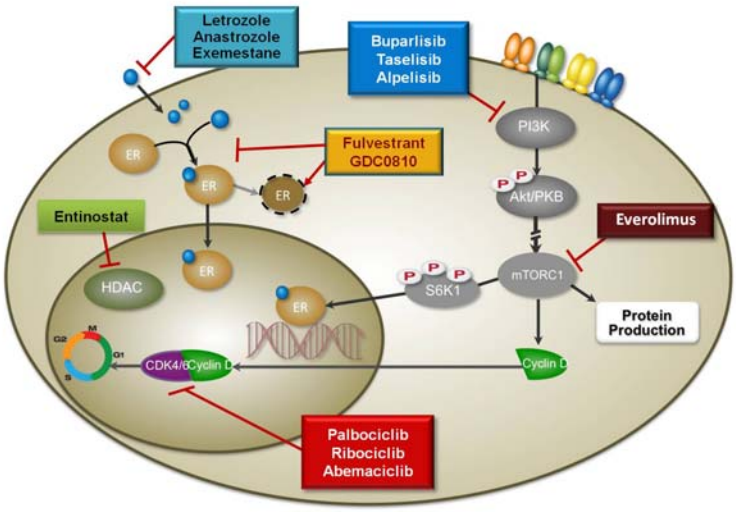
ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal patients with hormone-receptor positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines

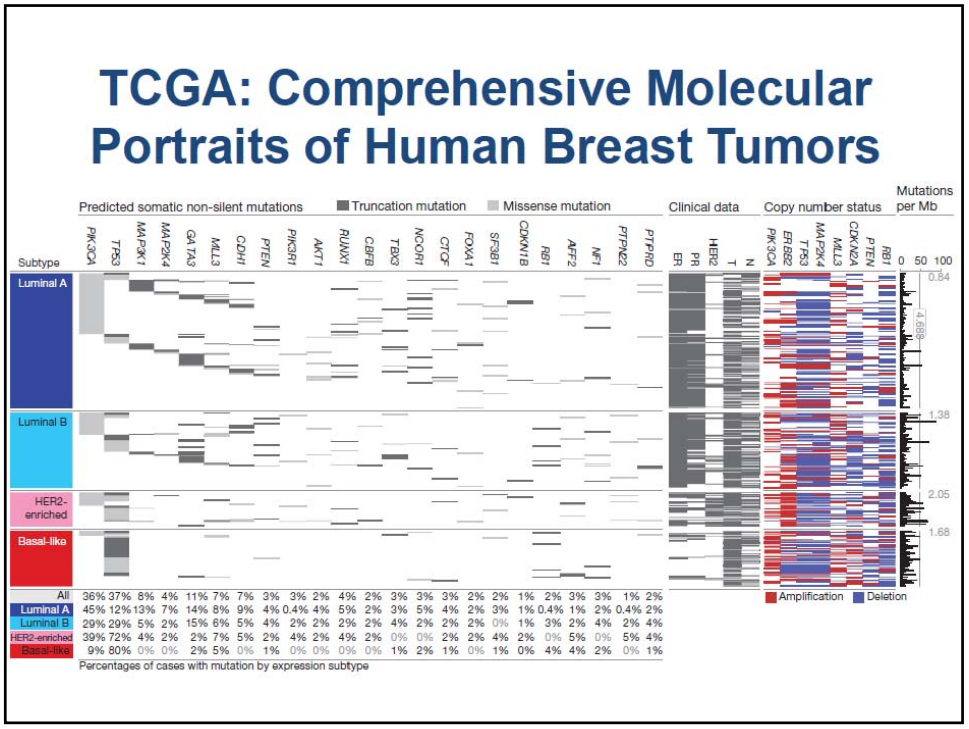
Postmenopausal Patients
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Exemestane + everolimus
- Palbociclib + letrozole
- Palbociclib + fulvestrant (category 1)
- Fulvestrant
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

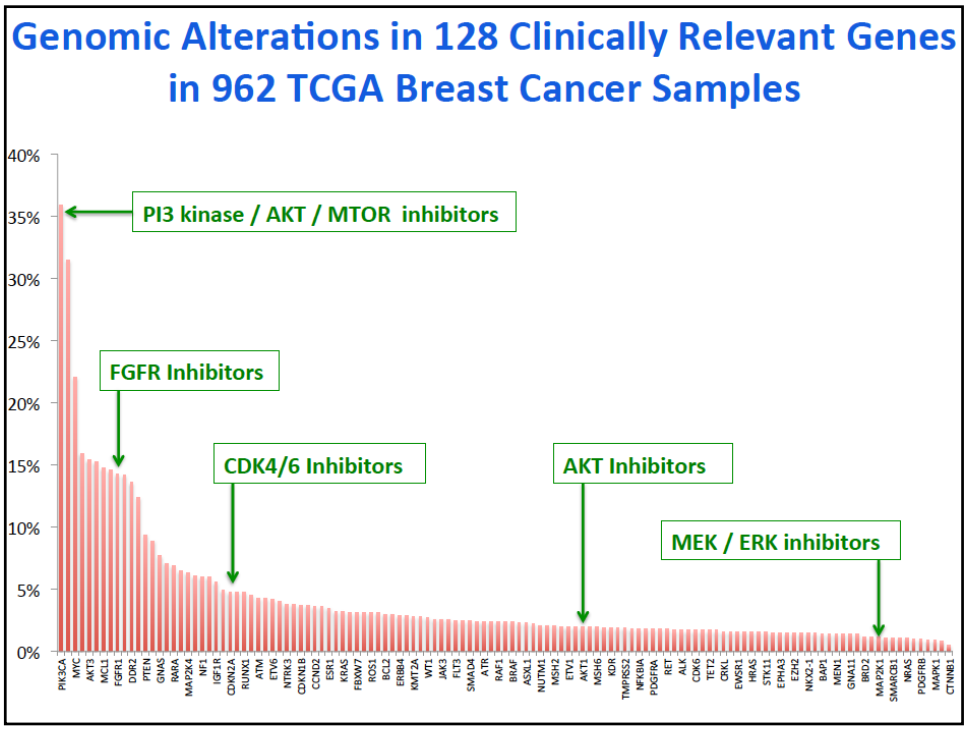
BINV-N

The Future (and Present!) Treatment In ER+ MBC

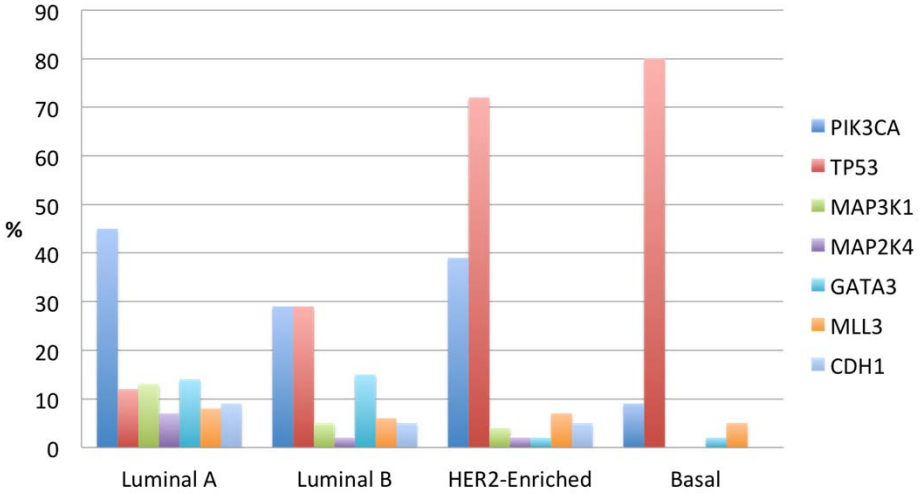


Yamamoto-Ibrusuki, M, et al. BMC Medicine. 2015;12:137.

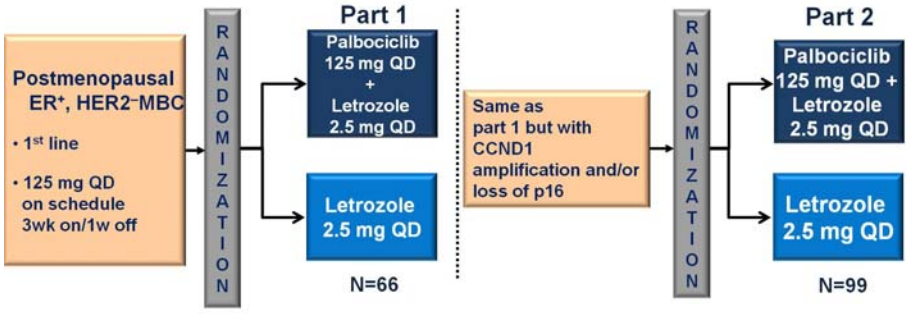




Distribution of Mutations in TCGA by Breast Cancer Subtype

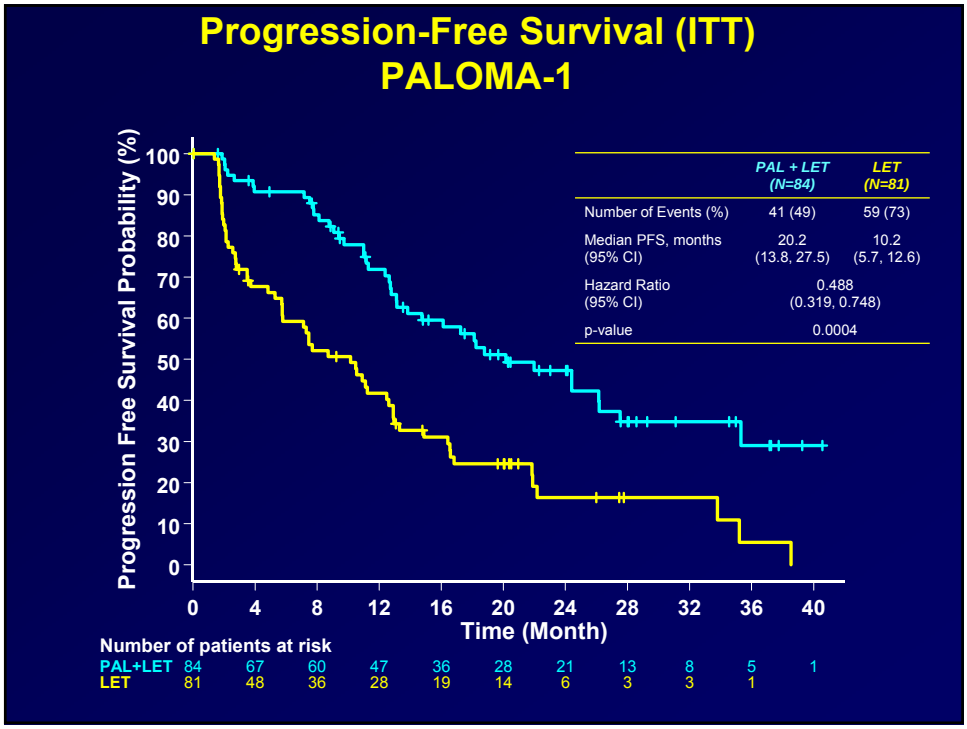


Phase II PALOMA-1/TRIO-18: Let +/- Palbociclib 1st line ER+ MBC



Stratification Factors
•Disease site (visceral vs bone only vs other)
•Disease-free interval (>12 vs ≤12 mo from and of adjuvant to recurrence or *de novo* advanced disease)

Finn et al. The Lancet Oncology, Volume 16, Issue 1, 2015, 25 - 35



PALOMA3: A Double-Blind, Phase III Trial of Fulvestrant with or without Palbociclib in Pre- and Post-Menopausal Women with Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer that Progressed on Prior Endocrine Therapy

Turner NC et al. *Proc ASCO* 2015;Abstract LBA502.

Phase III PALOMA-3: Fulvestrant +/- Palbociclib 2nd line ER+ MBC

- HR+, HER2– ABC
- Pre-/peri-* or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

*All received goserelin

2:1 Randomization
N=521

Stratification:
- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-/peri- vs Post-menopausal

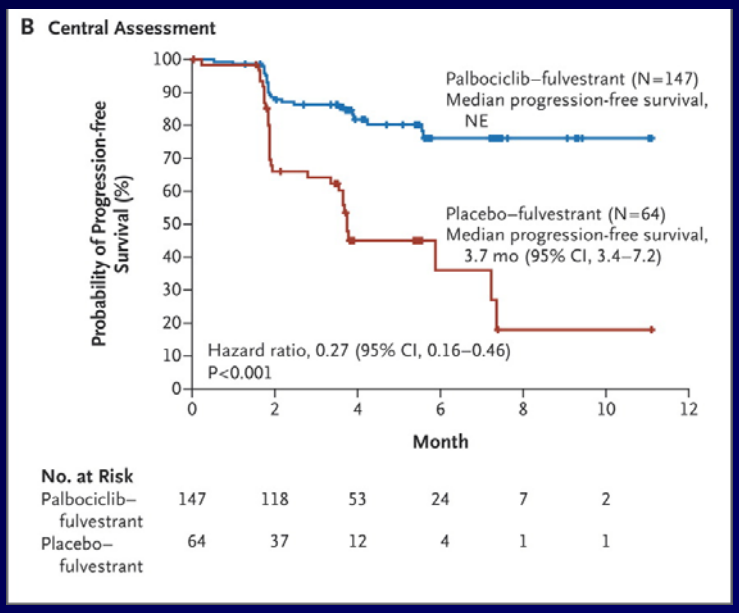
n=347 → Palbociclib (125 mg QD; 3 wks on/1 wk off) + Fulvestrant† (500 mg IM q4w)

n=174 → Placebo (3 wks on/ 1wk off) + Fulvestrant† (500 mg IM q4w)

- ***Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.***

Nicholas Turner at 2015 ASCO Annual Meeting

Progression-free Survival.



Turner NC et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1505270

The NEW ENGLAND JOURNAL of MEDICINE

Summary of Key Secondary Efficacy Endpoints

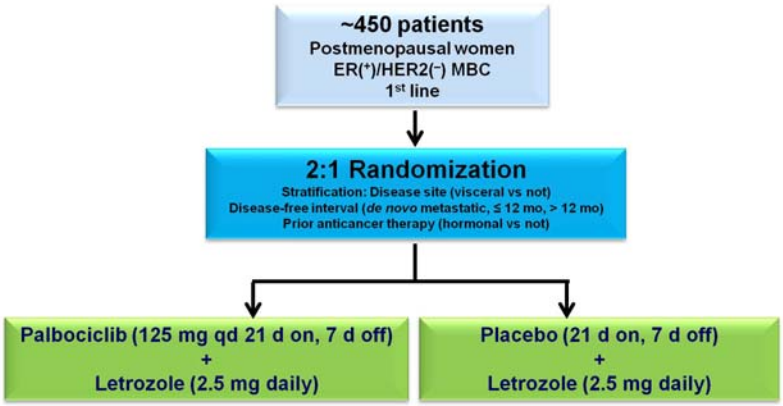
	Palbociclib + Fulvestrant (n=347), % of patients	Placebo + Fulvestrant (n=174), % of patients	*P* value
ORR	10.4	6.3	0.1582
CBR*	34.0	19.0	0.0004

* CBR is underestimated.
36% of palbociclib and 24% of placebo pts remain on study treatment with <24 weeks of follow up.

At the time of the interim analysis, OS data was immature with 28 deaths.

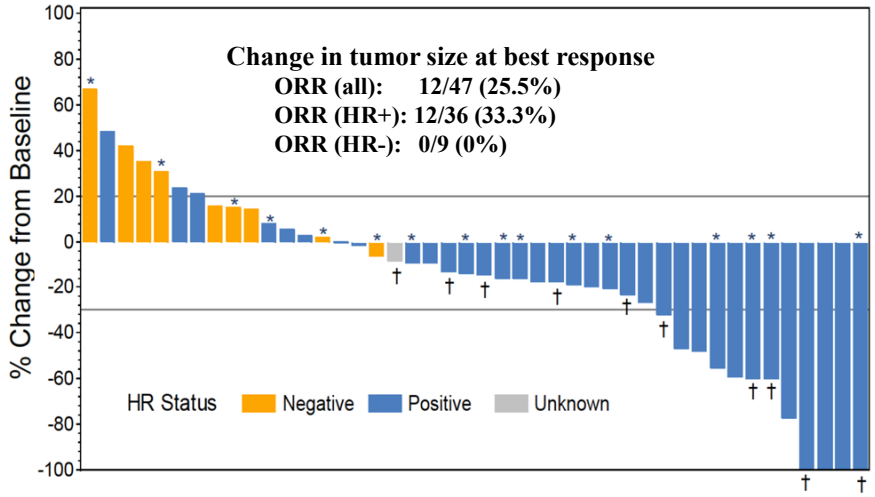
CBR=clinical benefit rate (CR+PR+SD ≥24 wk); CR=complete response; ORR=objective response (CR+PR); OS=overall survival; PR=partial response; SD=stable disease.

Phase III PALOMA-2: Letrozole +/- Palbociclib 1st Line ER+ MBC



NCT01740427

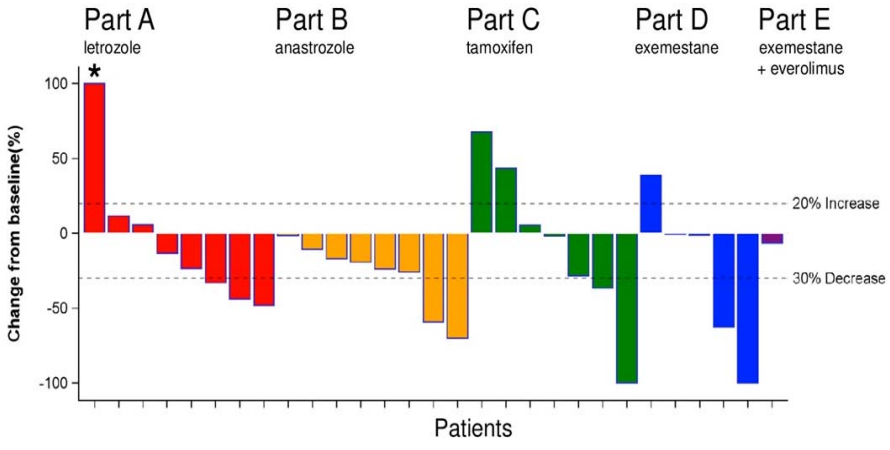
Abemaciclib Monotherapy in Advanced or Metastatic Breast Cancer



[a]3 non-evaluable patients are not shown. All patients were required to have measurable disease.
† Patient progressing on endocrine therapy before study entry and continued on that specific therapy
* Indicates HER2+

Tolaney SM et al. SABCS 2014; Abstract 763.

Best Change in Tumor Size from Baseline with Abemaciclib Combined with Other Therapies



Tolaney SM et al. *Proc ASCO* 2015;Abstract 522.

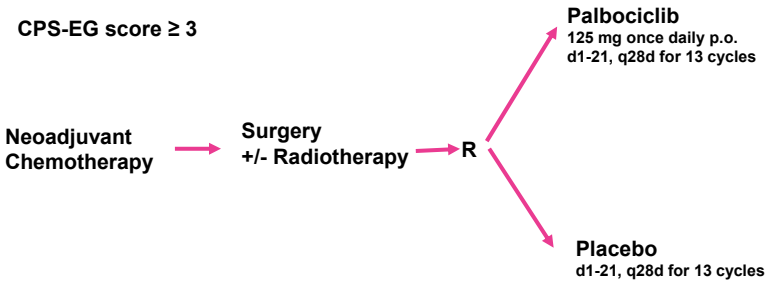
PENELOPE-B Phase III Trial

N = 800 pts. with

HR+/HER2- breast cancer

no PCR and

CPS-EG score ≥ 3

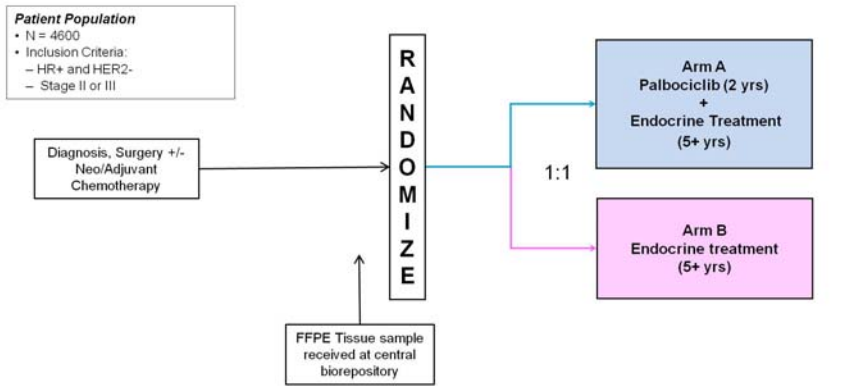


All patients will receive concomitantly endocrine therapy according to local standards

GBG GERMAN BREAST GROUP

NCT01864746

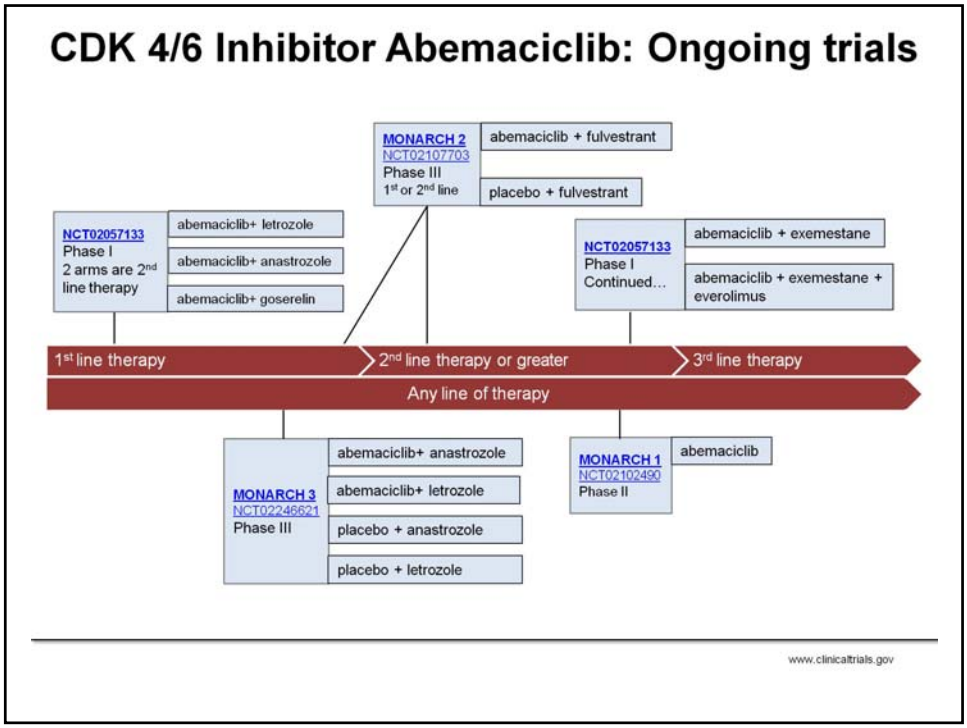
PALLAS Phase III Trial

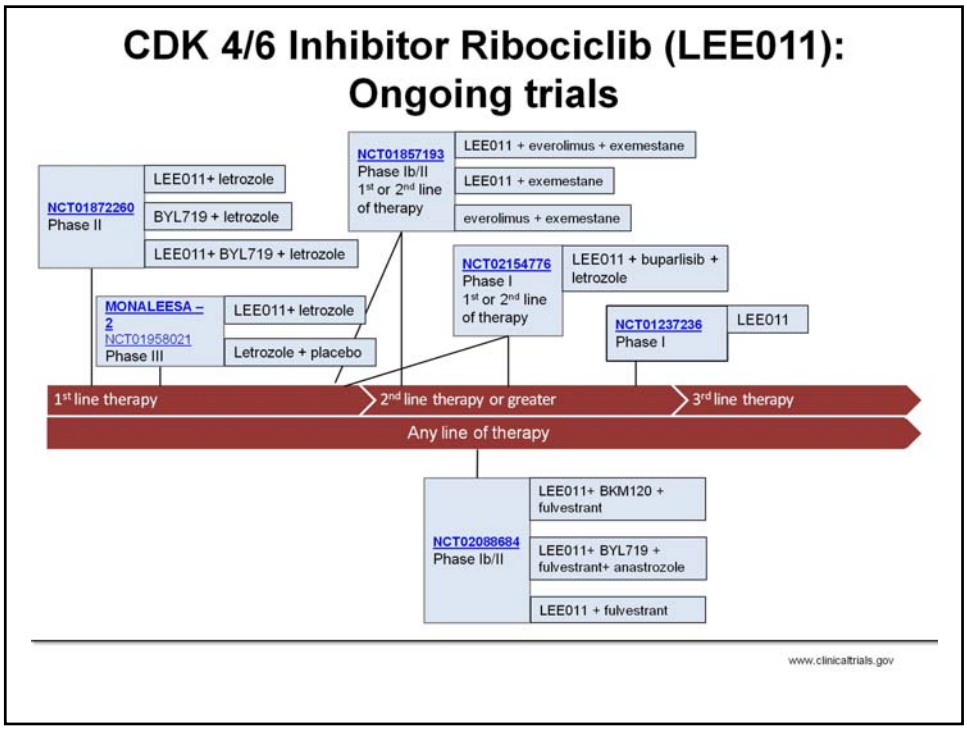


Arm A: palbociclib at a dose of 125 mg once daily, Day 1-21 in a 28-day cycle for total duration of 2 years, in addition to standard adjuvant endocrine therapy
Arm B: standard adjuvant endocrine therapy (AI, tamoxifen, LHRH agonist)

Stratification Factors:
•Pathologic stage (IIA vs IIB/III)
•Neo/adjuvant chemotherapy (yes vs no),
•Age (< 50 vs > 50 years),
•Geographic region (North America vs Europe vs Asia)

NCT02513394



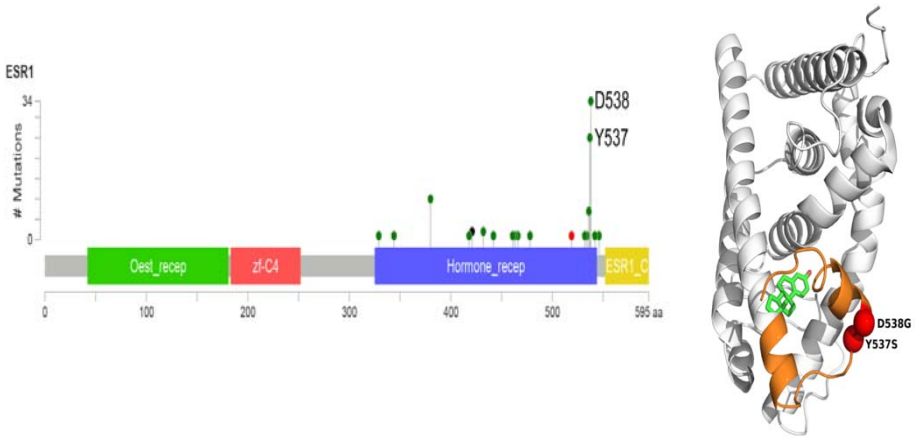


cfDNA Analysis From BOLERO-2 Plasma Samples Identifies a High Rate of *ESR1* Mutations: Exploratory Analysis For Prognostic And Predictive Correlation of Mutations Reveals Different Efficacy Outcomes of Endocrine Therapy–based Regimens

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

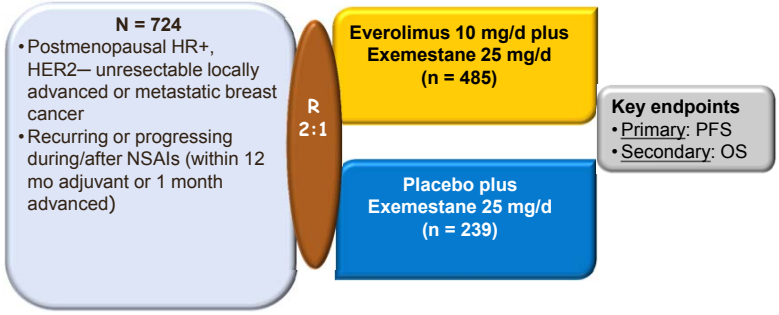
Introduction And Rationale



- 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.

BOLERO-2: Study Design and Primary Results

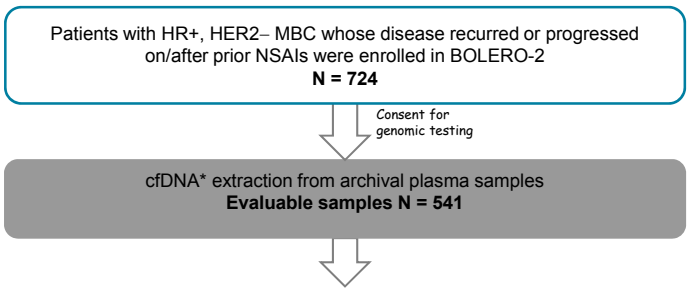


HR+, hormone receptor-positive; HER2–, human epidermal growth factor receptor-negative; NSAIs, non-steroidal aromatase inhibitors; OS, overall survival; PFS, progression-free survival.

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		

Yardley et al. Adv Ther. 2013;30(10):870-84.

Methodology and Statistical Analysis



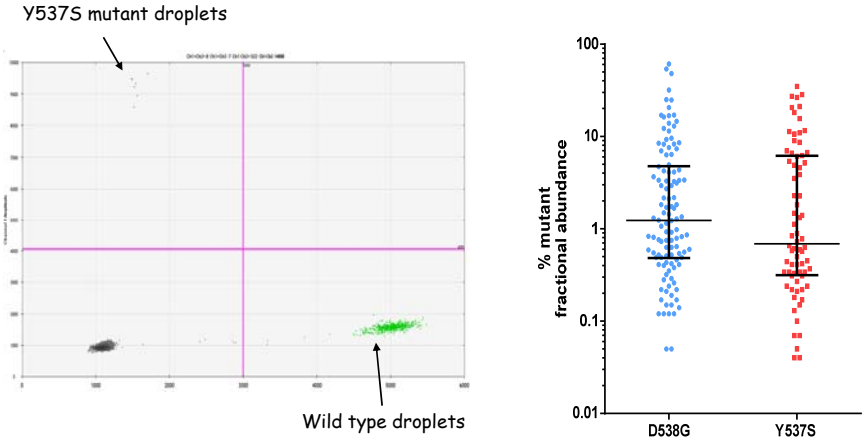
cfDNA analysis for *ESR1* D538G and Y537S mutations by ddPCR

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.

Detection and Quantification of ESR1 Mutations by ddPCR



ddPCR, droplet digital PCR.

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%)

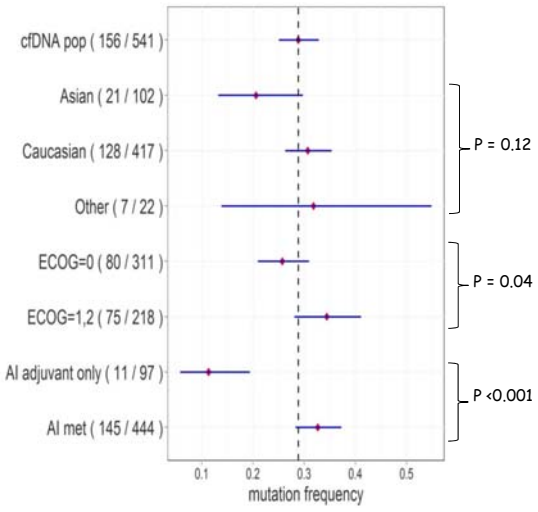
cfDNA, cell free DNA; ITT, intention to treat.

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.

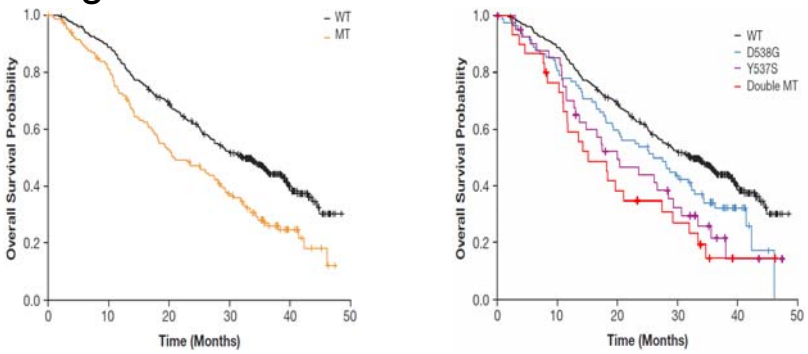
ESR1 Mutation Frequency by Clinical Covariates



- *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.

Prognostic Effect of *ESR1* Mutation on OS



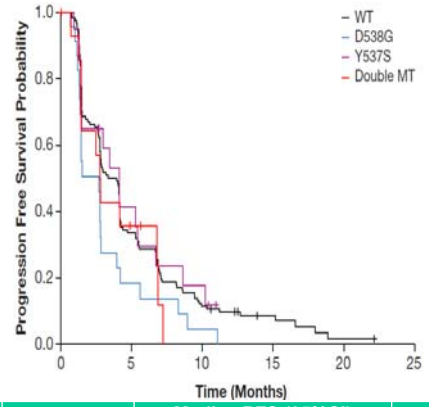
Mutations	N	Events	Median OS (95%CI) (months)	HR (95%CI)	P-value*
WT	385	217	32.1 (28.1-36.4)		
MT	156	112	20.7 (17.7 - 28.1)	1.40 (1.2 - 1.65)	0.000037
D538G	83	57	26.0 (19.2-32.4)	1.25 (1.02-1.54)	0.033
Y537S	42	30	20.0 (13.0-29.3)	2.31 (1.34-3.97)	0.0024
Double MT	30	24	15.2 (10.9-27.4)	1.77 (1.31-2.39)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

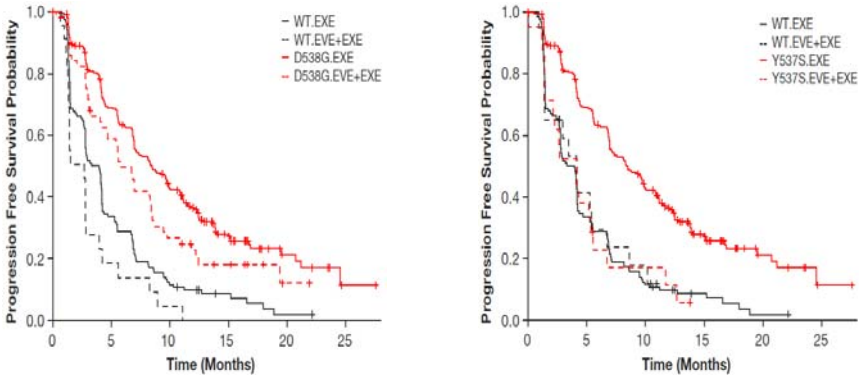


*All p-values were unadjusted for multiple testing

Alteration	N	Events	Median PFS (95%CI) (months)	HR (95%CI)	P-value*
WT	128	116	3.94 (2.76-4.17)		0.16
MT	61	51	2.76 (1.41-4.14)	1.18 (0.94-1.5)	
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, confidence interval; EXE, exemestane; HR, hazard ratio; MT, mutation; PFS, progression free survival; WT, wild-type.

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, confidence interval; EXE, exemestane; HR, hazard ratio; MT, mutation; PFS, progression free survival; WT, wild-type.

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.

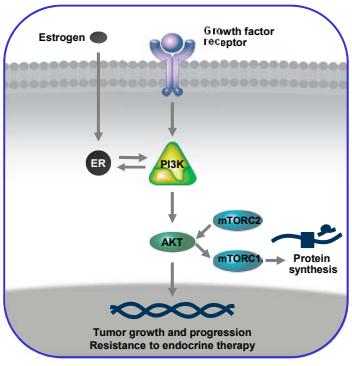
PIK3CA Status in Circulating Tumor DNA Predicts Efficacy of Buparlisib Plus Fulvestrant in Postmenopausal Women With Endocrine-Resistant HR+/HER2– Advanced Breast Cancer: First Results From the Randomized, Phase III BELLE-2 Trial

Abstract #S6-01

Baselga J, Im S-A, Iwata H, Clemons M, Ito Y, Awada A, Chia S, Jagiełło-Gruszfeld A, Pistilli B, Tseng L-M, Hurvitz S, Masuda N, Cortés J, De Laurentiis M, Arteaga CL, Jiang Z, Jonat W, Hachemi S, Le Mouhaër S, Di Tomaso E, Urban P, Massacesi C, Campone M

Rationale for Combination of Fulvestrant With Buparlisib

- The PI3K/mTOR pathway is the most frequently altered oncogenic pathway in ER+ breast cancer. PIK3CA mutations present in approximately 35% of ER+ breast cancer[1]
- PI3K/mTOR pathway activation is a hallmark of HR+/HER2- breast cancer cells that have developed resistance to endocrine therapy[2,3]
- PI3K inhibitors upregulate ER expression and transcriptional activity[3]
- Therefore, dual blockade of the PI3K/mTOR and ER pathways may act synergistically and help overcome resistance to endocrine therapies[2,4,5]



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. Cancer Genome Atlas Network. *Nature.* 2012;490(7418):61-70; 2. Bosch A, et al. *Sci Transl Med.* 2015;7(283):283ra51; 3. Miller TW, et al. *Cancer Discov.* 2011;1(4):338–351; 4. Fox EM, et al. *Front Oncol.* 2012;2:145; 5. Yardley D, *et al. Adv Ther.* 2013;30(10):870-884.

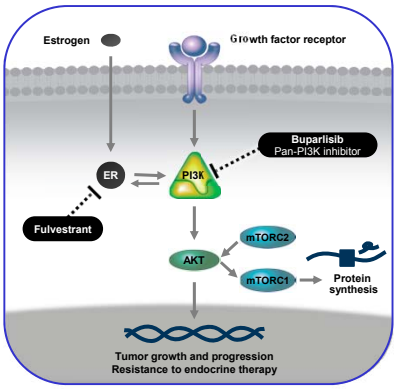
Baselga J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-01.

Rationale for Combination of Fulvestrant With Buparlisib

- 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(2):317–328; 2. Ma CX, *et al. Clin Cancer Res.* 2015;pii:1745 [ePub ahead of print].

Baselga J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-01.

BELLE-2 Study Design and Endpoints

Postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer that progressed on/after AI therapy
N = 1147

Randomization (1:1)
Stratification by PI3K pathway and visceral disease status*

Buparlisib (100 mg/day) **+ fulvestrant** (500 mg)
n = 576

Placebo + fulvestrant (500 mg)
n = 571

BELLE-2: ClinicalTrials.gov NCT01610284.

*PI3K pathway activation (activated, non-activated, unknown) was assessed in archival tumor tissue provided at screening, defined as *PIK3CA* mutation by Sanger sequencing (any 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.

Primary Endpoints
- **PFS** in the full population
- **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)

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†

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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 on AI therapy for advanced/metastatic disease
- Measurable disease or non-measurable lytic or mixed bone lesions (RECIST v1.1)
- Tumor tissue for analysis of PI3K-related biomarkers

Key Exclusion Criteria

- Prior therapy with a PI3K, AKT, or mTOR inhibitor, or fulvestrant
- More than one prior chemotherapy line for metastatic disease
- History of, or active, anxiety, depression, or other major psychiatric disorders (measured using validated questionnaires)

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BELLE-2 Statistical Assumptions

Population	Assumed median PFS improvement, months	One-sided alpha*	Power
Full population	7.5 vs 5.0	0.014	99.9%
Main population	7.5 vs 5.0	0.02	91.8%
PI3K activated group	8.33 vs 5.0	0.01	93.6%

Statistical significance would be achieved if hazard ratio is <0.86 in the full population

***Alpha allocation was split using a graphical gate-keeping approach to test the multiple primary endpoints, conserving the overall type-1 error at one-sided α = 0.025**

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Patient Demographics and Disease Characteristics

Characteristic	Buparlisib + fulvestrant (n = 576)	Placebo + fulvestrant (n =5 71)
Median age, years (range)	62 (29–90)	61 (31–90)
ECOG performance status, %		
0	57.8	60.2
1	40.1	37.0
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

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BELLE-2 Patient Disposition and Exposure to Study Treatment

Patient disposition, %	Buparlisib + fulvestrant (n = 576)	Placebo + fulvestrant (n = 571)
Treatment phase ongoing	16.1	16.5
Treatment discontinued	83.5	83.2
Primary reason for treatment discontinuation		
Progressive disease	54.3	73.0
Adverse event	13.2	1.8
Patient decision	8.9	3.2
Physician decision	4.0	3.7
Death	1.2	0.9
Other	1.9	0.7

Exposure to study treatment	Buparlisib + fulvestrant (n = 573)	Placebo + fulvestrant (n = 570)
Median duration of treatment exposure, months	4.2	5.0
Buparlisib/placebo median relative dose intensity, %	93.2	100
Buparlisib/placebo dose adjustments, %		
Dose reduction	46.4	7.0
Dose interruption	55.8	31.4

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BELLE-2 Safety Profile Was Characterized by Transaminitis, Hyperglycemia, 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

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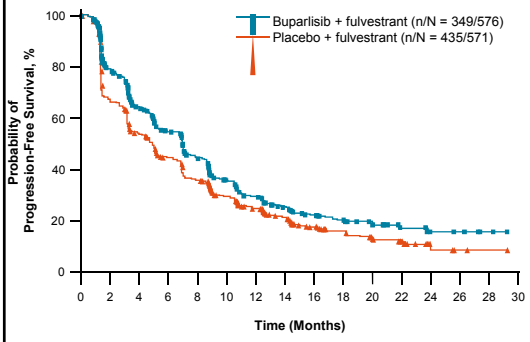
BELLE-2 Met the Primary Endpoint for PFS Improvement in the Full Population



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	<.001	

- A similar PFS improvement was observed in the main population (HR 0.80 [95% CI: 0.68–0.94]; one-sided *P* value .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

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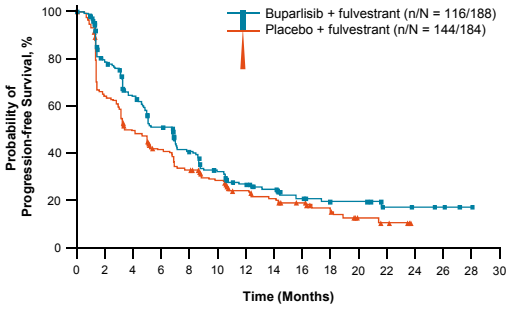
PFS Improvement in the PI3K Activated Group Was Not Statistically Significant



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*	.014	

*PFS in the PI3K activated group was tested at a one-sided α = 0.01 level of significance.

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

- There are substantial limitations in utilizing archival tumor tissue for PI3K testing in patients with metastatic disease, including tumor evolution under selective pressure, sample bias, and tumor heterogeneity
  - Approximately 80% of archival tissue biopsy samples were obtained from the primary tumor
- ctDNA obtained from blood samples has emerged as a sensitive, reliable, and minimally invasive way to measure current *PIK3CA* mutation status[1-4]
- In BELLE-2, ctDNA from 587 patients was analyzed for *PIK3CA* mutations by BEAMing technology[4]
  - 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.

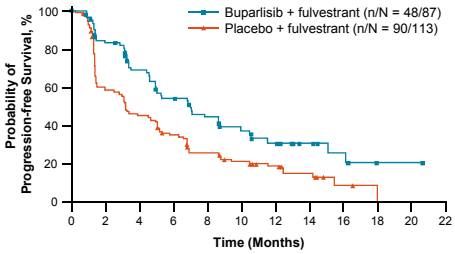
1. Garcia-Murillas I, *et al. Sci Transl Med.* 2015; 7:302ra133; 2 Bettegowda C, *et al. Sci Transl Med.* 2014;6:224ra24.
3. Rothé F, *et al. Ann Oncol.* 2014;25:1959–1965; 4. Higgins MJ, *et al. Clin Cancer Res.* 2012;18:3462–3469.

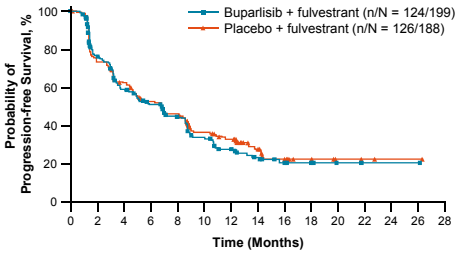
Baselga J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-01.

Buparlisib Plus 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	<.001	

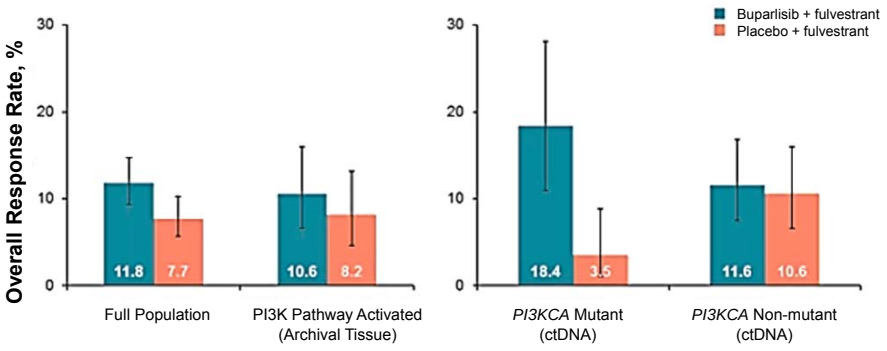
ctDNA *PIK3CA* Non-mutant n = 387	Buparlisib + Fulvestrant n = 199	Placebo + Fulvestrant n = 188
Median PFS, months (95% CI)	6.8 (4.7–8.5)	6.8 (4.7–8.6)
HR (95% CI)	1.05 (0.82–1.34)	
One-sided nominal *P* value	.642	





Baselga J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-01.

Buparlisib Plus Fulvestrant Resulted in Higher Response Rates in Patients With ctDNA *PIK3CA* Mutations



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Conclusions

- The BELLE-2 study met its primary endpoint, demonstrating a modest PFS improvement for combined buparlisib and fulvestrant in postmenopausal women with HR+/HER2– advanced breast cancer that had progressed after prior AI therapy
- Frequent discontinuations due to adverse events reduced treatment duration in the buparlisib arm, potentially limiting the efficacy of combination therapy
- Patients with tumors harboring *PIK3CA* mutations in ctDNA performed poorly on fulvestrant monotherapy, achieving a clinically meaningful PFS improvement with the combination
  - 3.8 month PFS improvement was supported by higher response rates (18.4% vs 3.5%) in this patient population
- The BELLE-2 study suggests that assessment of *PIK3CA* mutations in ctDNA may help select patients who would benefit from adding a PI3K inhibitor to endocrine therapy
- Phase III studies with PI3Kα-selective inhibitors are underway to confirm the predictive value of *PIK3CA* mutations detected in ctDNA and tumor tissue

Baselga J, et al. Presented at: 2015 San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, Texas. Abstract S6-01.

Conclusions: SABCS 2015/NCCN 2016

- Significant progress in HER2 + disease with new agents under evaluation
- TNBC remains a huge challenge, molecular interogation of the tumor may lead to better options; Immunologic strategies in their infancy
- Monotherapy for ER+ disease is now losing to a strategy of combining with novel agents