Penn Medicine
Abramson Cancer Center

Breast Cancer Highlights from 2020 International Oncology Meeting

ENDOCRINE THERAPY ABSTRACTS

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July 16, 2020

Disclosure

- Advisory board for Biotheranostics

- Note:
  - Please note that some of the studies reported in this presentation were published as abstracts only and/or presented at a conference. These data and conclusions are included because expert faculty found them to be important scientific contributions but should be considered to be preliminary until published in a peer-reviewed journal.

Endocrine Therapy Abstracts

- Adjuvant
  - MINDACT TRIAL UPDATE (#506)
  - BREAST CANCER INDEX IDEAL TRIAL (#512)
- Metastatic
  - BYLIEVE TRIAL (#1006)

Abstract 506:

MINDACT Trial Update

Does the 70-gene signature help discern which ER+ breast cancers with high clinical risk are associated with good prognosis without chemotherapy?

EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

MINDACT: Long-term results of the large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients

EORTC-10041/BIG3-04 (EudraCT Number2005-002625-31)

F. Cardoso, L. van 't Veer, C. Poncet, J. Lopes Cardozo, S. Delaloge, J. Pierga, P. Vuylsteke, E. Brain, G. Viale, S. Kümmel, I. Rubio, G. Zoppoli, A. Thompson, E. Matos, K. Zaman, F. Hilbers, A. Dudek-Perić, B. Meulemans, M.Piccart-Gebhart, E. Rutgers, on behalf of all MINDACT investigators

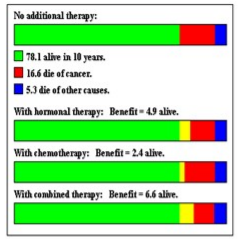
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Fatima Cardoso

BIG Breast International Group
TRANSBIG

Penn Medicine Abramson Cancer Center

MINDACT TRIAL DESIGN

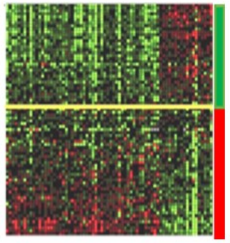


Registration & Screening
Surgery

N= 6693

Clinical-Pathological (C) risk
(Adjuvant! Online)

Genomic (G) risk
(70-gene signature)



C-low/G-low

C-high/G-high

No Chemotherapy

Chemotherapy

HR+

HR+

MINDACT population:
HR+/HER2- 81%
HER2+ 9.5%
TNBC 9.6%

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Fatima Cardoso

MINDACT is a DE-ESCALATION STUDY

- **Primary endpoint**

Distant metastasis free survival (DMFS) at 5 years for C-High / G-Low without chemotherapy

- **Primary statistical test**

Null hypothesis: 5-year DMFS rate C-High / G-Low no CT in Primary Test population = 92%

Power: 80% when true 5-year DMFS rate = 95%

Primary test 5-year DMFS rate significant if 2-sided 95% Confidence Interval exceeds 92%

F. Cardoso, NEJM 2016

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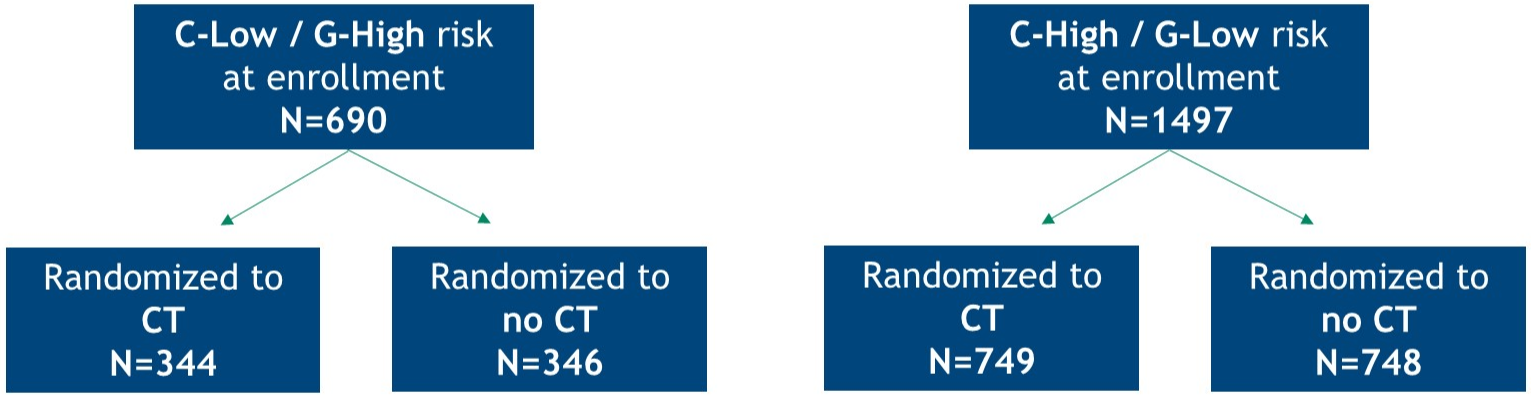
SECONDARY ENDPOINT

- **Efficacy:** CT vs no CT population of discordant risk groups (In ITT population)



Trial not powered for the comparisons of yes or no chemotherapy

F. Cardoso, NEJM 2016

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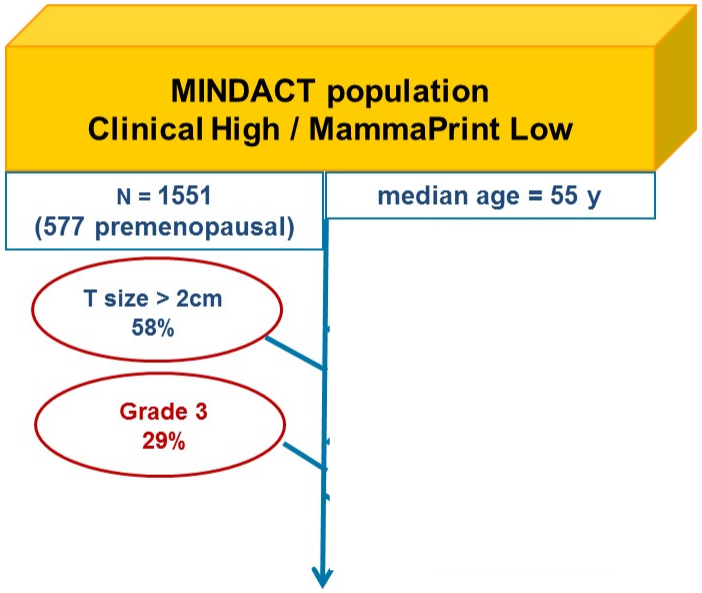
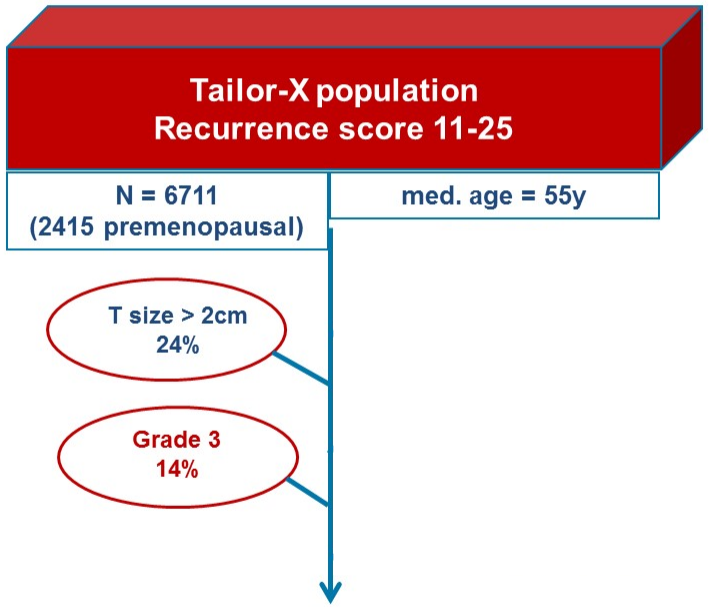
How high was CLINICAL HIGH risk population in MINDACT?

How MINDACT and TAILOR-X populations compare (for CT vs no CT question)

F. Cardoso , NEJM 2016



J. Sparano , NEJM 2018



In HR+/HER2- C-high/G-low patients: *49% Node (1-3) positive and 27% grade 3*

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UPDATED ANALYSIS AT 8.7 YEARS MEDIAN FOLLOW-UP

RESULTS

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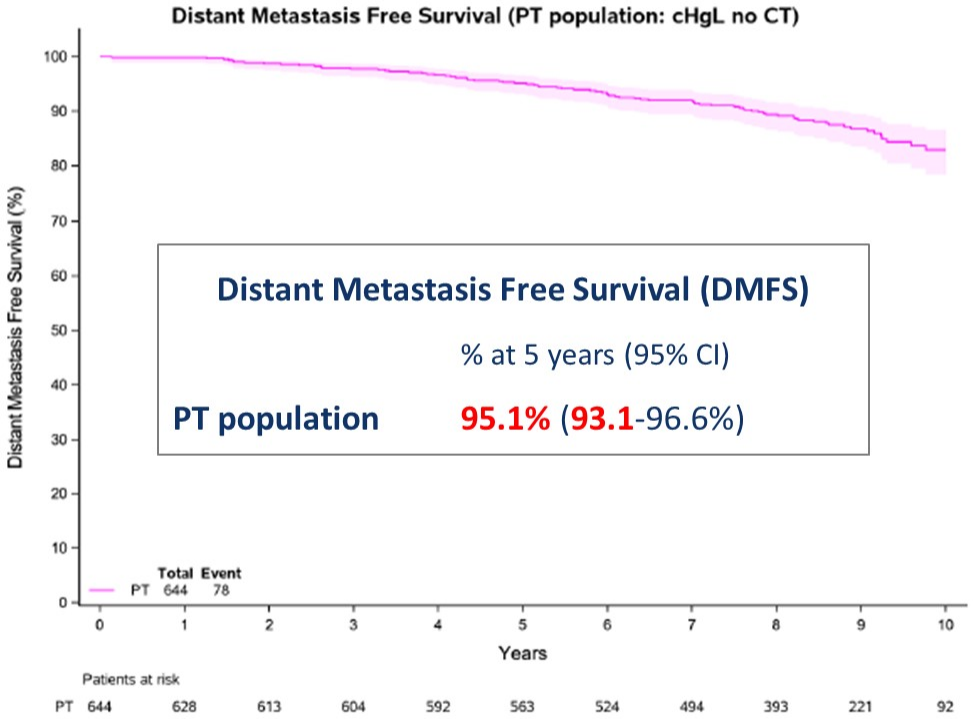
Update of PRIMARY ENDPOINT with more mature data at 5 years (>90% of pts with at least 5 years FU)



Distant Metastasis Free Survival (DMFS)	
	% at 5 years (95% CI)
PT population	**95.1%** (**93.1**-96.6%)

Clinical-High/Genomic-Low no chemotherapy

Null Hypothesis 5-year DMFS: set at 92%

Lower bound of 95%CI exceeds 92%!

Confirmation of primary results
Supported by sensitivity analyses

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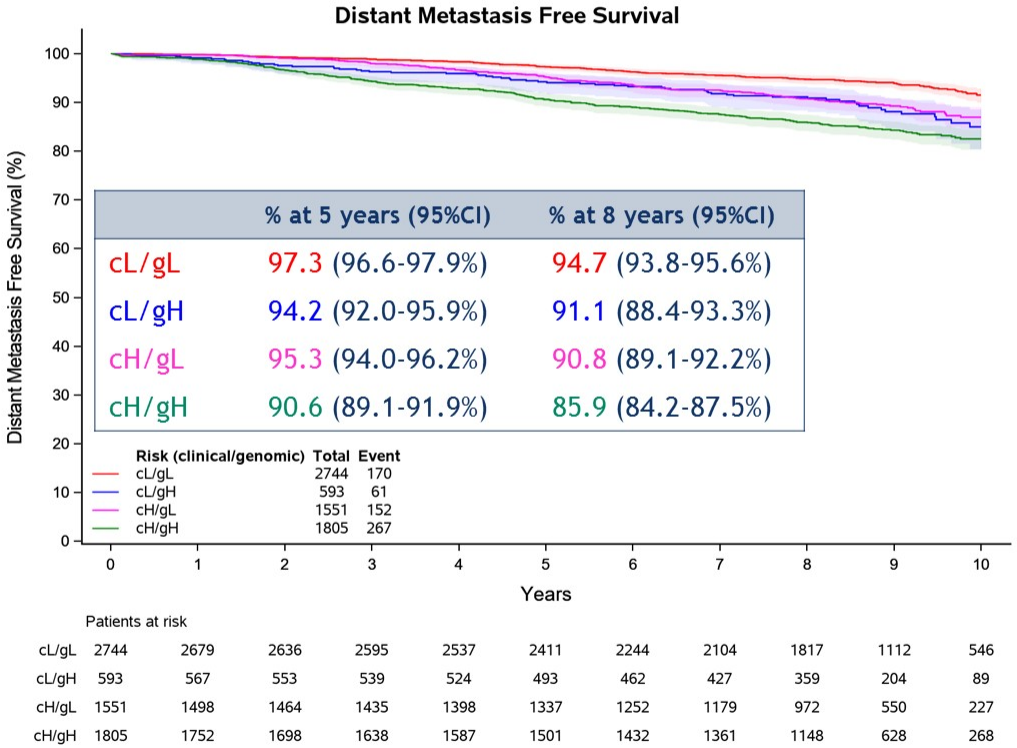
MINDACT proves the clinical utility of MammaPrint



	% at 5 years (95%CI)	% at 8 years (95%CI)
cL/gL	97.3 (96.6-97.9%)	94.7 (93.8-95.6%)
cL/gH	94.2 (92.0-95.9%)	91.1 (88.4-93.3%)
cH/gL	95.3 (94.0-96.2%)	90.8 (89.1-92.2%)
cH/gH	90.6 (89.1-91.9%)	85.9 (84.2-87.5%)

Type of first event (n = 650)
- distant recurrences: 68.8%
- death of any cause: 31.2%

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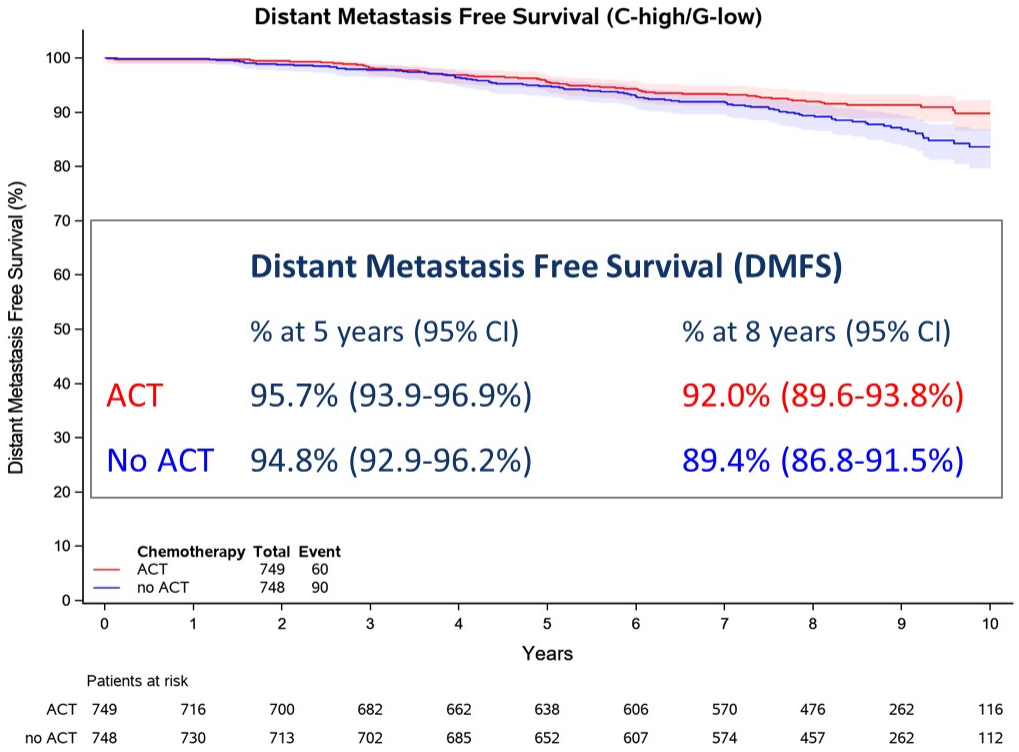
SECONDARY ENDPOINT
DMFS C-High/G-Low risk (ITT population) CT vs no CT



Absolute difference in DMFS between CT and no CT groups:

- at 5 years: **0.9 ± 1.1** % points
- at 8 years: **2.6 ± 1.6** % points

Type of first event (n = 150)

- distant recurrences: 74.7%
- death of any cause: 25.3%

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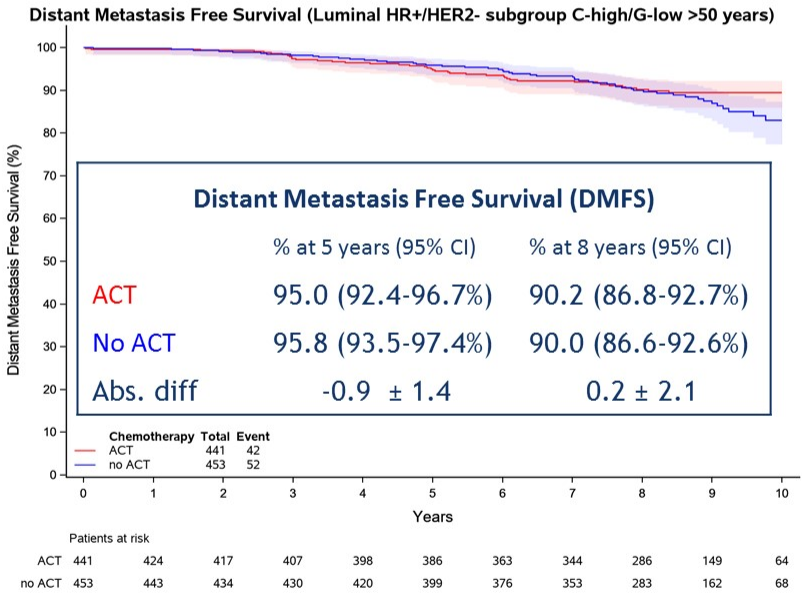
Effect of chemotherapy by age in HR+/HER2- subgroup C-High/G-Low group

DMFS in C-High / G-Low risk patients with luminal cancers (HR+/HER2-) stratified by age ITT population

Age >50 years



NO difference

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CONCLUSIONS

- **At 8.7 years** medium FU, **the primary endpoint continues to be met in CT untreated C-High/G-Low risk women, confirming MINDACT as a positive de-escalation study**

DISCUSSION

	MINDACT TRIAL	TAILORx TRIAL
Clinical Population		
T>2cm	58%	24%
Grade 3	29%	14%
LN+ (1-3)	48%	0%

DISCUSSION

- **70-gene signature is able to identify subsets of patients who have a low likelihood of distant recurrence despite high-risk clinical features.**
  - Must decide whether the 5-year DMFS endpoint is adequate for ER+ patients with high risk disease
  - Study is not powered to predict a benefit from chemotherapy

- Both MINDACT and TAILORx trials highlight that chemotherapy discussion will need to be modified by age
  - some of the postulated benefit of chemotherapy may be due to ovarian function suppression in women <50 years old, but this has not yet been proven
- RxPonder trial results are still pending to evaluate the 21-gene RS in LN+ patients

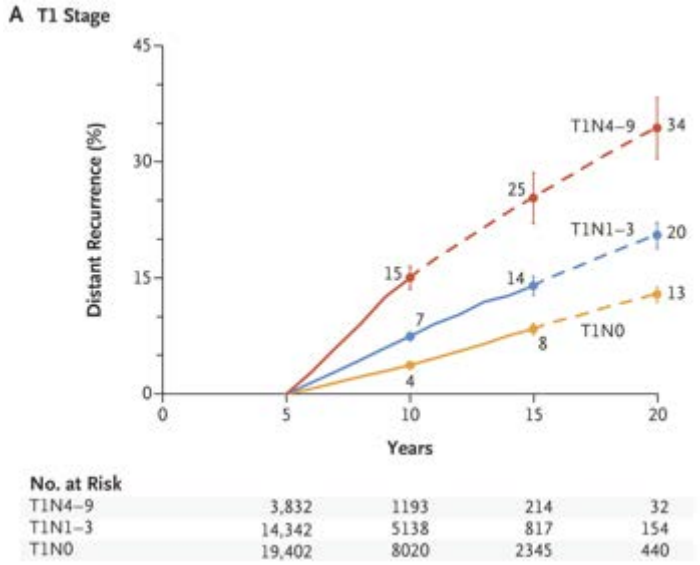
Abstract 512:

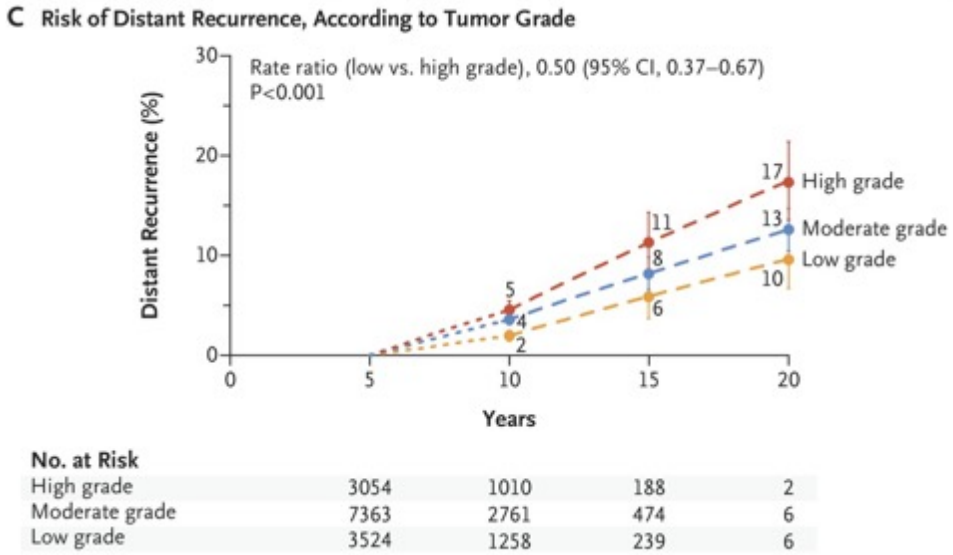
Breast Cancer Index
IDEAL TRIAL

In patients treated with an AI during the first 5 years of endocrine therapy, does BCI predict benefit of extending treatment with an AI for an additional 2.5 v. 5 years?

Persistent Long-Term Risk of Distant Recurrence

- Patients with early-stage (I/II), HR+ have good overall prognosis
  - >50% of recurrences occur after Year 5[1,2]
  - Risk is persistent
  - Risk of late distant recurrence after 5 years of adjuvant endocrine therapy persists across all clinical stages[3]





1. EBCTCG. Lancet 2005;365:1687-71. **2.** Saphner T, et al. J Clin Oncol 1996;14:2738-4 3 Pan et al. N Engl J Med. 2017 Nov 9;377(19):1836-1846

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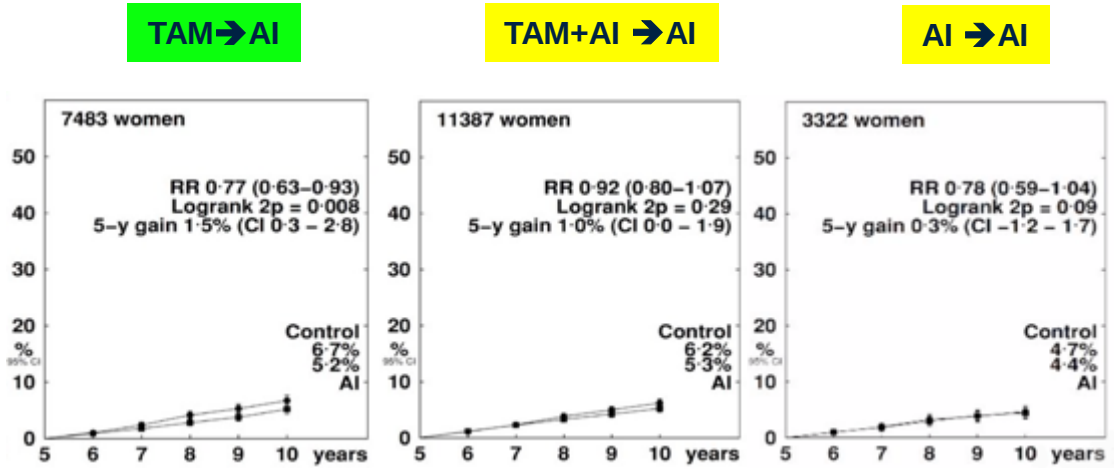
Extension of Adjuvant Endocrine Therapy: 5 vs 10 Years

	Trial	Duration of Therapy (y)		N	Median Follow-up (y)	Disease-free Survival[1]	Absolute Benefit	Hazard Ratio or Rate Ratio (95% CI)
TAM → AI	MA.17	TAM x 5y	→ Placebo x 5y → AI x 5y	2587 2583	2.5	89.8% 94.4%	4.6%	HR 0.58 (0.45-0.76) P<0.001
TAM → AI	NSABP B-33	TAM x 5y	→ Placebo x 5y → AI x 5y	779 783	2.5	89% 91%	2%	RR: 0.68 P=0.07
TAM → AI	ABCSG 6A	TAM x 5y	→ Placebo x 3y → AI x 3y	469 387	5.2	88.2% 92.9%	4.7%	HR 0.62 (0.40-0.96) P=0.031
TAM → AI	aTTom	TAM x 5y	→ No treatment → TAM x 5y	3485 3468	10	68% 72%	4%	RR 0.85 (0.76-0.95) P=0.003
TAM → TAM	ATLAS	TAM x 5y	→ No treatment → TAM x 5y	3418 3428	7.6	74.9% 78.6%	3.7%	RR 0.84 (0.76-0.94) p=0.002
TAM → TAM	MA.17R	TAM x 0-5y → AI x 5y	→ Placebo → AI x 5y	959 959	6.3	91% 95%	4%	HR 0.66 (0.48-0.91) P=0.01
AI → AI	NSABP B-42	AI x 5y	→ Placebo x 5y → AI x 5y	1983 1983	9.3	72.1% 76.1%	4%	HR 0.84 (0.74-0.96) P=0.011
AI → AI	AERAS (N-SAS BC 05)*	AI x 5y	→ No treatment → AI x 5y	843 840	4.9	84.4% 91.9%	7.5%	HR 0.548 P=0.0004

1. Based on disease-free survival or cumulative risk of recurrence rates as reported in the primary publications (note that the definitions of disease-free were not identical across trials)

1. Goss PE et al, J Natl Cancer Inst 2005;97:1262–71. 2. Mamounas EP et al., J Clin Oncol 2008;26:1965-1971. 3. Jakesz et al., J Natl Cancer Inst. 2007 Dec 19;99(24):1845-53. 4. Davies C et al., Lancet. 2013 ;381(9869):805-16. 5. Gray et al., J Clin Oncol 31, 2013 (suppl; abstr 5). 6. Goss PE et al., N Engl J Med. 2016 Jun 5 (Online) 7. Mamounas et al Lancet 2018 November 30 (online)

Sequencing of ET Agents and Nodal Status are Important

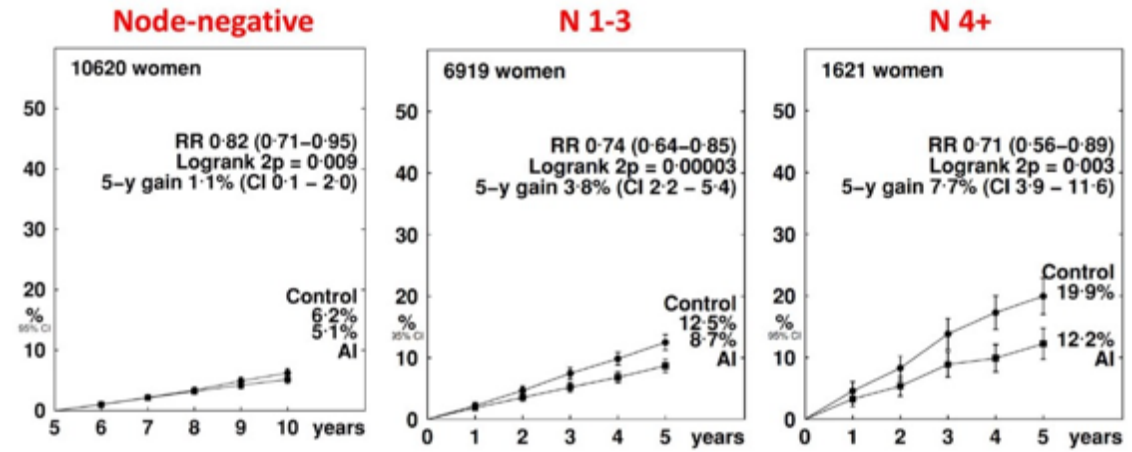


TAM➔AI } **~35% proportional risk reduction**

TAM+AI ➔AI

AI ➔AI

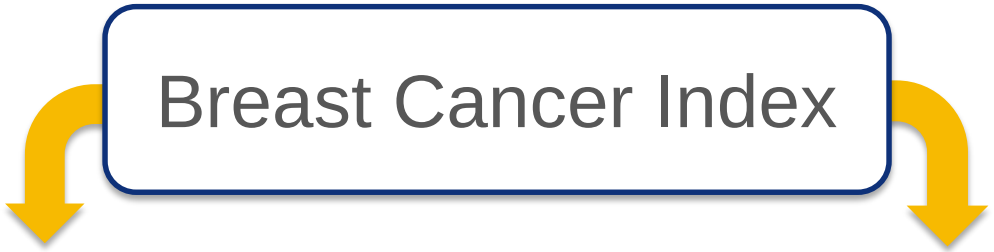
} **~20% proportional risk reduction**



Greater benefit from extended AIs seen with more positive nodes in an unselected population

Gray et al EBCTCG. SABCS 2018

Breast Cancer Index (BCI) Clinical Assay Reports Results from Two Biomarkers



BCI Prognostic

Individualized Risk of Cumulative Overall (0-10 yr) and **Late** Recurrence (5-10 yrs)

BUB1B, CENPA, NEK2, RACGAP1, RRM2 + **HOXB13/IL17BR**

- Algorithmic combination of proliferation-related gene signature (Molecular Grade Index, MGI) and an estrogen signaling pathway signature (HoxB13/IL17BR, a.k.a. H/I)

BCI Predictive

Individualized Prediction of Likelihood of Benefit from **Extended** Endocrine Therapy

HOXB13/IL17BR

- A separate algorithm based exclusively on H/I to provide a quantitative molecular assessment of estrogen signaling pathways

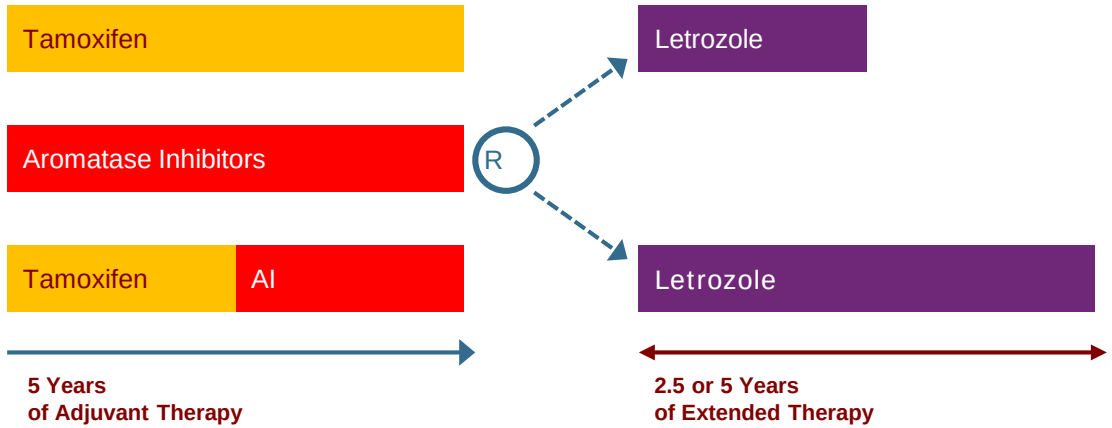
BCI Predictive Assay Summary

- BCI (H/I) has demonstrated consistent predictive ability in patients with LN- and LN+ disease, treated with an initial 5 years of tamoxifen, followed by an additional 5 years tamoxifen (trans-aTTOM) or AI (MA-17)
- Previous BCI predictive data had not evaluated the benefit of EET with 5 years of AI after initial treatment with AI during the first 5 years
- The BCI IDEAL study sought to determine whether BCI (H/I) (High vs Low) is predictive of extended endocrine benefit in patients treated in the IDEAL trial[5]

1. Zhang Y et al. CCR 2013; 19(15):4196-205 **2.** Sgroi DC et al JNCI 2013; 105(14):1036-42 **3.** Bartlett JMS et al. Annals of Oncol 2019: 30(11):1776-1783 4. Liefers et al J Clin Oncol 38: 2020 (suppl; abstr 512)
5. Blok et al. 2018 *J Natl Cancer Inst*; 110(1); 40-48. 6. Liefers et al J Clin Oncol 38: 2020 (suppl; abstr 512)

Investigation on the Duration of Extended Letrozole (IDEAL)

STUDY DESIGN

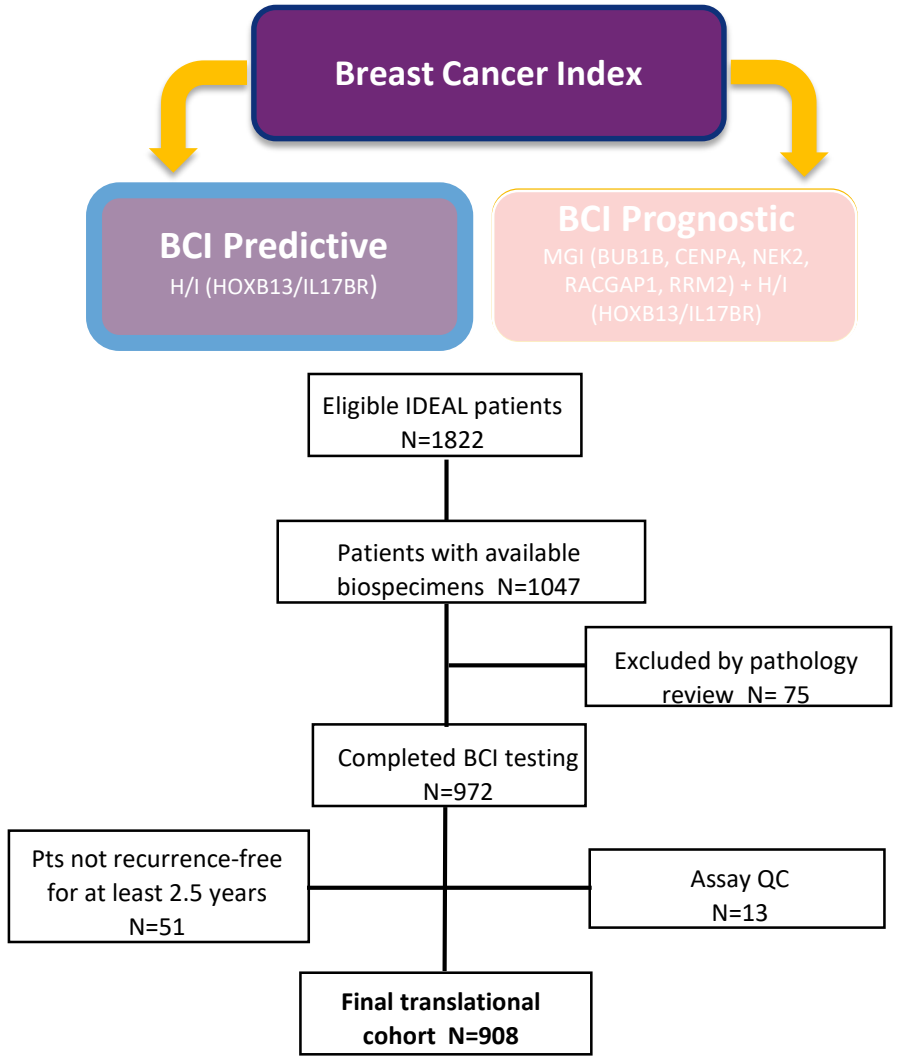


- Study explored whether a shorter extension of AI therapy is sufficient vs a full additional 5 years
- 88% of patients received either AI only (29%) or sequence of tamoxifen + AI (59%) in the first 5 years
- 73% of patients had LN+ disease
- HR 0.92 (0.74-1.16) for 5 vs 2.5 years
- Similar to studies such as ABCSG16, results suggested that shorter duration of AI therapy might be as effective as full 10 years

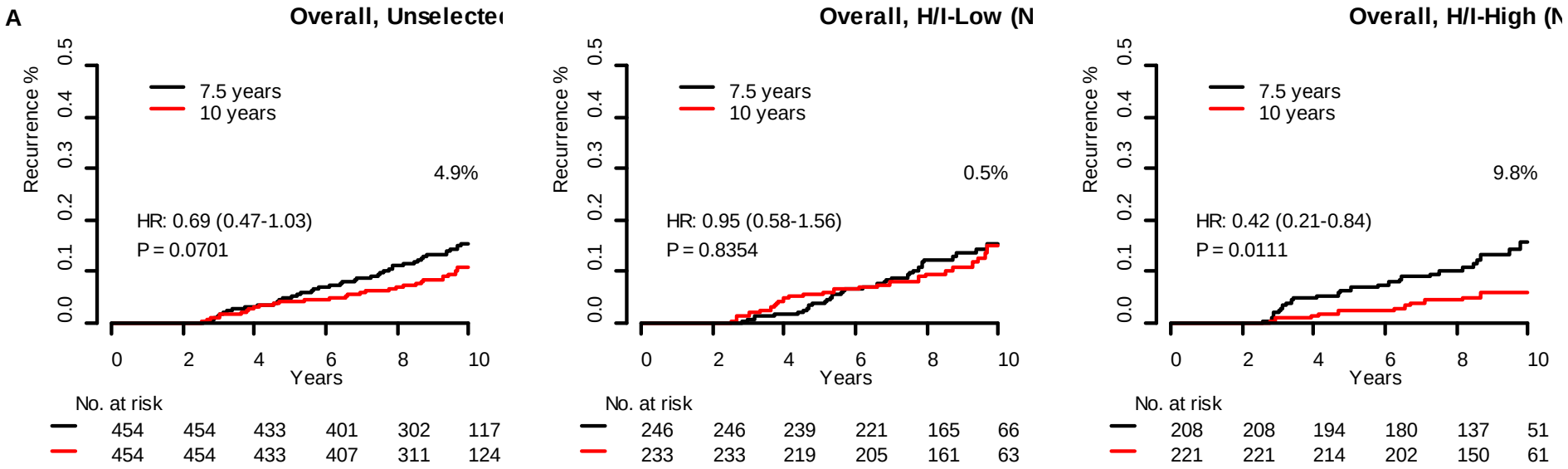
Blok et al 2018 JNCI 110(1): djx134

Breast Cancer Index IDEAL Study

- The primary endpoint was recurrence-free interval (RFI)
  - Events during first 2.5 years not counted (both arms on therapy)
- Median follow-up was 9.3 years after randomization
- Overall cohort (n=908) represents ~50% of parent trial and included LN- and LN+ patients
- Secondary objective was to determine if BCI (H/I) is predictive of extended AI benefit in patients treated with AIs in the primary adjuvant setting (n=794; 29% AI only primary adjuvant, 59% sequence of TAM/AI primary adjuvant)



Benefit from an Additional 2.5y vs 5y of Extended Endocrine Therapy is Dependent on Classification by BCI (H/I): Overall Cohort

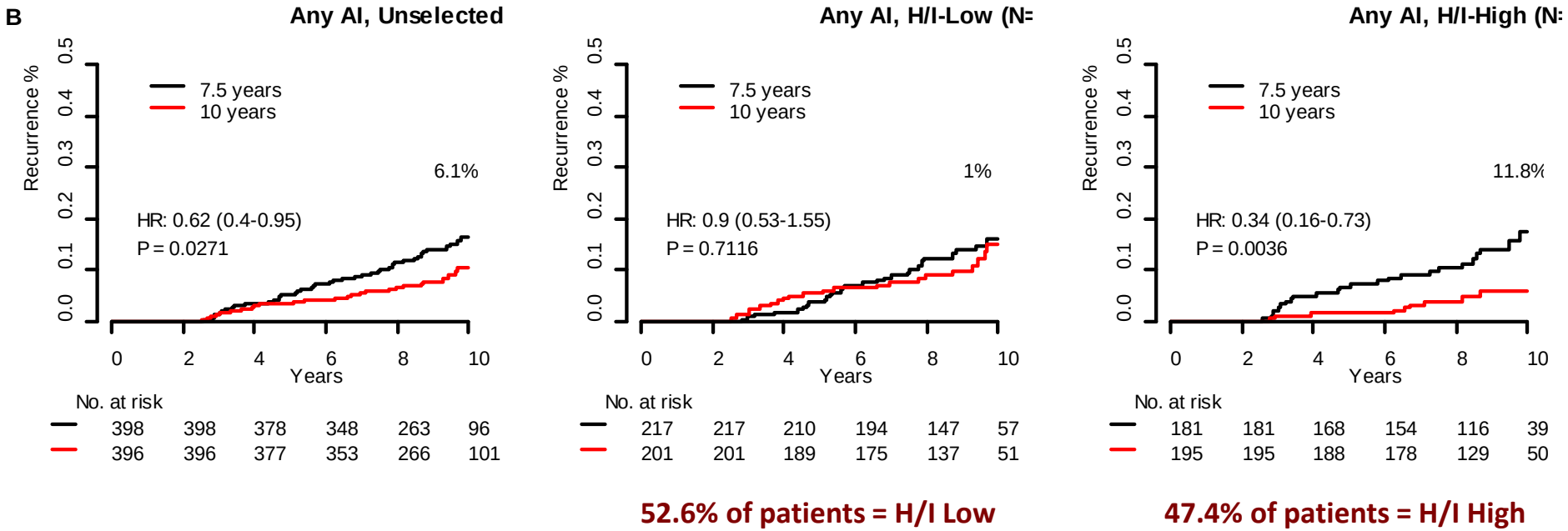


52.8% of patients = H/I Low

47.2% of patients = H/I High

- Overall cohort included both N0 (27%) and N+ (73%) patients
- BCI (H/I) patients demonstrate a 58% relative risk reduction and a 9.8% absolute RFI benefit from an additional 2.5 years of endocrine therapy (full 10 years of therapy)

Benefit from an Additional 2.5y vs 5y of Extended Endocrine Therapy is Dependent on Classification by BCI (H/I): Any AI Cohort



52.6% of patients = H/I Low

47.4% of patients = H/I High

- Any AI cohort= 5 y of adjuvant AI monotherapy (27% of patients) or 2-3 y tamoxifen followed by 2-3 yrs. of adjuvant AI (60% of patients)
- BCI (H/I) patients demonstrate a 66% relative risk reduction and an 11.8% absolute RFI benefit from an additional 2.5 years of AI therapy (full 10 years of therapy)

Summary of BCI Clinical Evidence For Prediction of Endocrine Benefit

- BCI (H/I) has consistently and significantly predicted preferential benefit from endocrine therapy in HR+ early stage breast cancer across multiple studies
- BCI (H/I) patients have consistently demonstrated a ~58-66% relative risk reduction from additional endocrine therapy
- The current IDEAL study demonstrates that BCI predicts benefit of extended AI therapy in patients previously treated with primary adjuvant AI, which is relevant for the current standard of care for the majority of HR+ early stage breast cancer patients

Study Cohort	Relative Risk Reduction	Absolute Benefit (High H/I)†	Interaction P-Value
Treatment: Adjuvant TAM vs none			
Stockholm (n=600)[1]	**H/I-High HR: 0.35** (0.19-0.65); p=0.0005 H/I-Low HR: 0.67 (0.36-1.24), p=0.204	**17.5%**	0.003
Treatment: Extended AI vs Placebo			
MA.17 (n=249)[2]	**H/I-High OR: 0.35** (0.16-0.75); p=0.007 H/I-Low OR: 0.68 (0.31-1.52), p=0.35	**16.5%**	0.03
Treatment: Extended TAM vs Stop			
Trans-aTTom N+ (n=583)[3]	**H/I-High HR: 0.35** (0.15-0.86); p=0.027 H/I-Low HR: 1.07 (0.69-1.65), p=0.768	**10.2%**	0.01
Treatment: 5y vs 2.5y Extended AI			
IDEAL (n=908)[4]	**H/I-High HR: 0.42** (0.21–0.84); p=0.0111 H/I-Low HR: 0.95 (0.58-1.56), p=0.835	**9.8%**	0.045

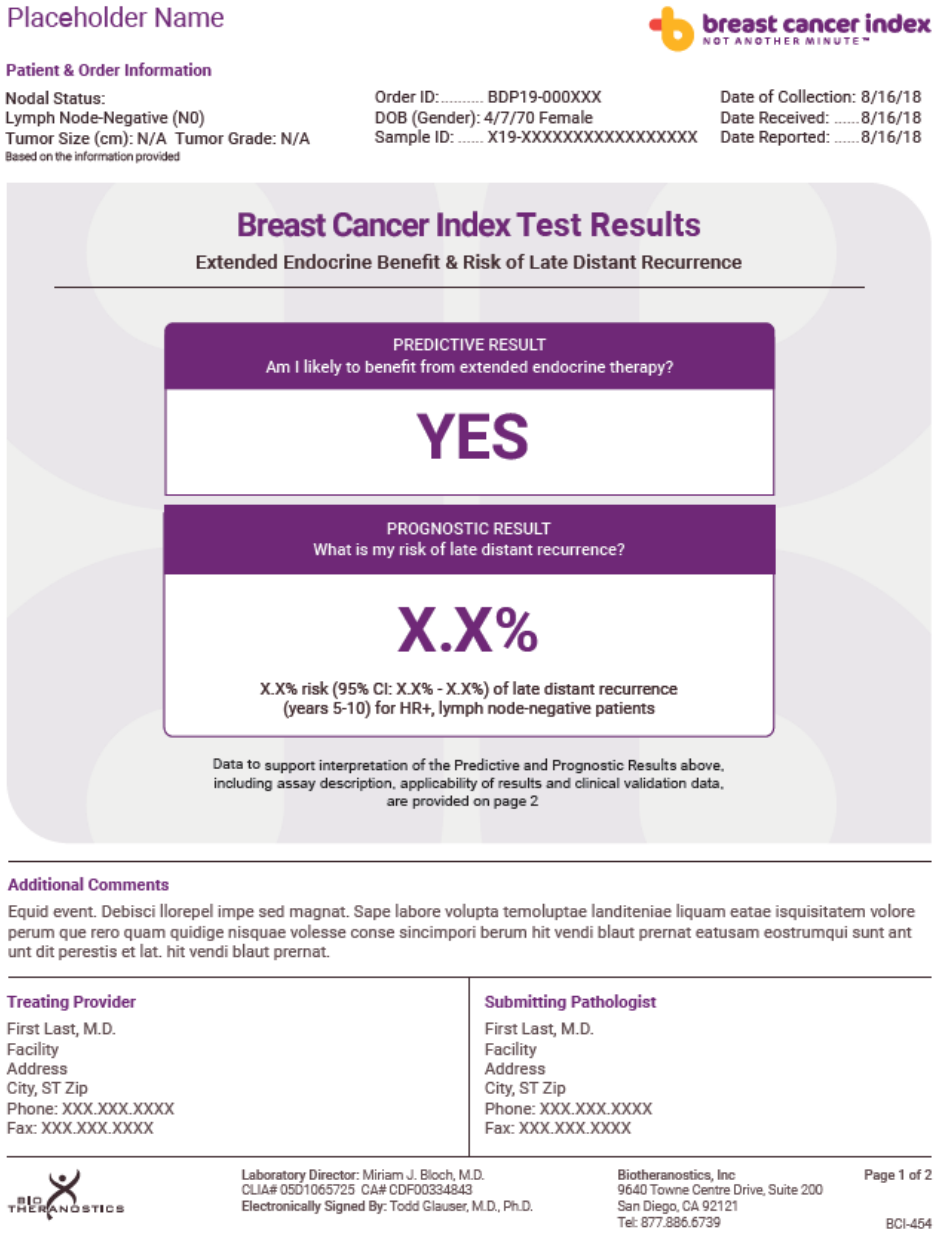
*Hazard Ratios were reported for all studies, except in MA.17 where odds ratios were reported due to nested case-controlled study

†. Low H/I patients demonstrated no significant benefit across all study cohorts

DISCUSSION

- BCI IDEAL STUDY
  - BCI predictive assay was able to predict the benefit of EET with AI for 10 years over 7.5 years in 47% of patients treated with AI during the first 5 years of treatment
  - However, IDEAL was not the best trial to determine whether a patient previously treated with 5 years of an AI would benefit from any additional AI. This is probably one of our most important clinical questions.
    - NSABP B42
    - AERAS

BCI Report



Placeholder Name

breast cancer index
NOT ANOTHER MINUTE™

Patient & Order Information

Nodal Status:
Lymph Node-Negative (N0)
Tumor Size (cm): N/A Tumor Grade: N/A
Based on the information provided

Order ID:..... BDP19-000XXX
DOB (Gender): 4/7/70 Female
Sample ID: X19-XXXXXXXXXXXXXXXX

Date of Collection: 8/16/18
Date Received: 8/16/18
Date Reported: 8/16/18

Breast Cancer Index Test Results

Extended Endocrine Benefit & Risk of Late Distant Recurrence

PREDICTIVE RESULT
Am I likely to benefit from extended endocrine therapy?

YES

PROGNOSTIC RESULT
What is my risk of late distant recurrence?

X.X%

X.X% risk (95% CI: X.X% - X.X%) of late distant recurrence (years 5-10) for HR+, lymph node-negative patients

Data to support interpretation of the Predictive and Prognostic Results above, including assay description, applicability of results and clinical validation data, are provided on page 2

Additional Comments

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Treating Provider

First Last, M.D.
Facility
Address
City, ST Zip
Phone: XXX.XXX.XXXX
Fax: XXX.XXX.XXXX

Submitting Pathologist

First Last, M.D.
Facility
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City, ST Zip
Phone: XXX.XXX.XXXX
Fax: XXX.XXX.XXXX

BIOTHERANOSTICS

Laboratory Director: Miriam J. Bloch, M.D.
CLIA# 05D1065725 CA# CDF00334843
Electronically Signed By: Todd Glauser, M.D., Ph.D.

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Page 1 of 2

BCI-454

Abstract 1006:

BYLIEVE TRIAL

Is fulvestrant with alpelisib effective in patients with PIK3CA mutations previously treated with AI+CDK4/6 inhibition?

Alpelisib + Fulvestrant in Patients With *PIK3CA*-Mutated Hormone-Receptor Positive (HR+), Human Epidermal Growth Factor Receptor-2-Negative (HER2–) Advanced Breast Cancer (ABC) Previously Treated With Cyclin-Dependent Kinase 4/6 Inhibitor (CDKi) + Aromatase Inhibitor (AI): BYLieve Study Results

Hope S. Rugo,[1] Florence Lerebours,[2] Eva Ciruelos,[3] Pamela Drullinsky,[4] Manuel Ruiz-Borrego,[5] Patrick Neven,[6] Yeon Hee Park,[7] Aleix Prat,[8] Thomas Bachelot,[9] Dejan Juric,[10] Nicholas Turner,[11] Nickolas Sophos,[12] Juan Pablo Zarate,[12] Christina Arce,[12] Yu-Ming Shen,[13] Stuart Turner,[12] Hemanth Kanakamedala,[14] Wei-Chun Hsu,[14] Stephen Chia[15]

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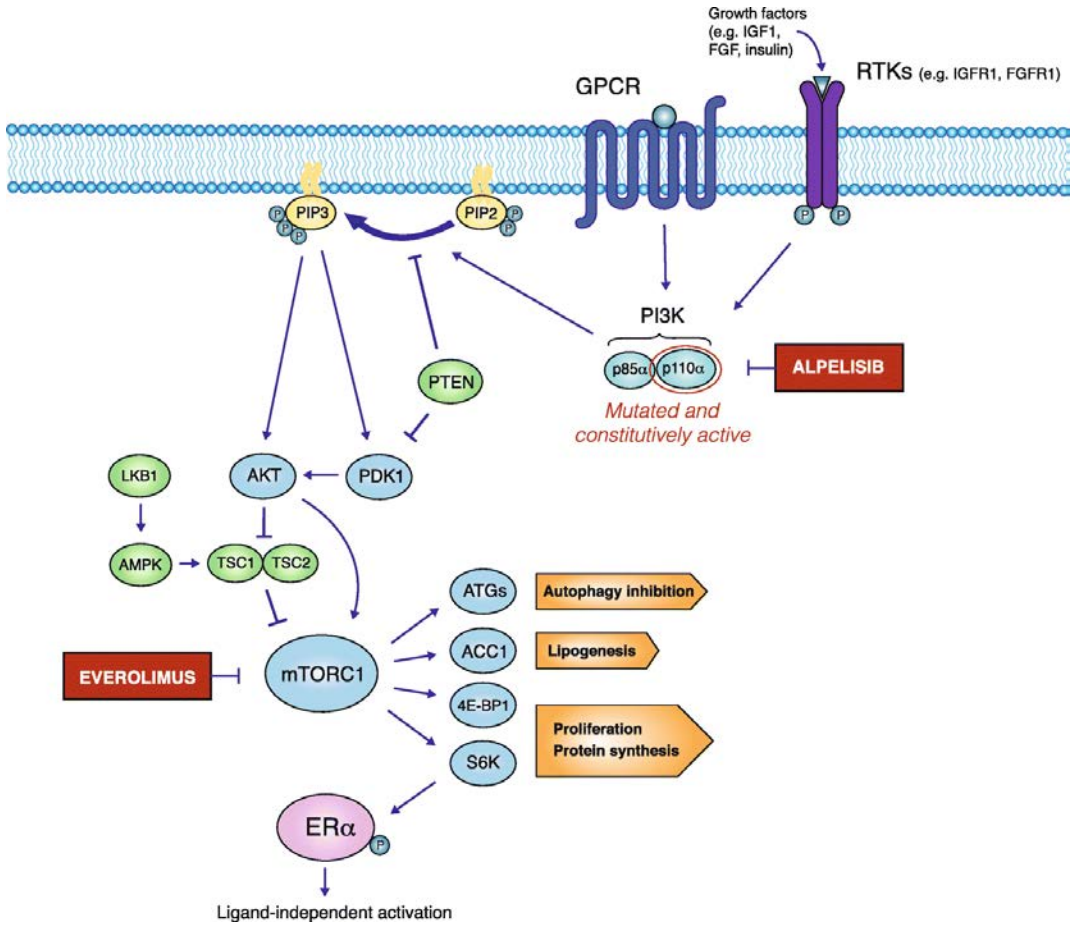
Abstract 1006

PI3 Kinase Pathway



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Original Article

Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

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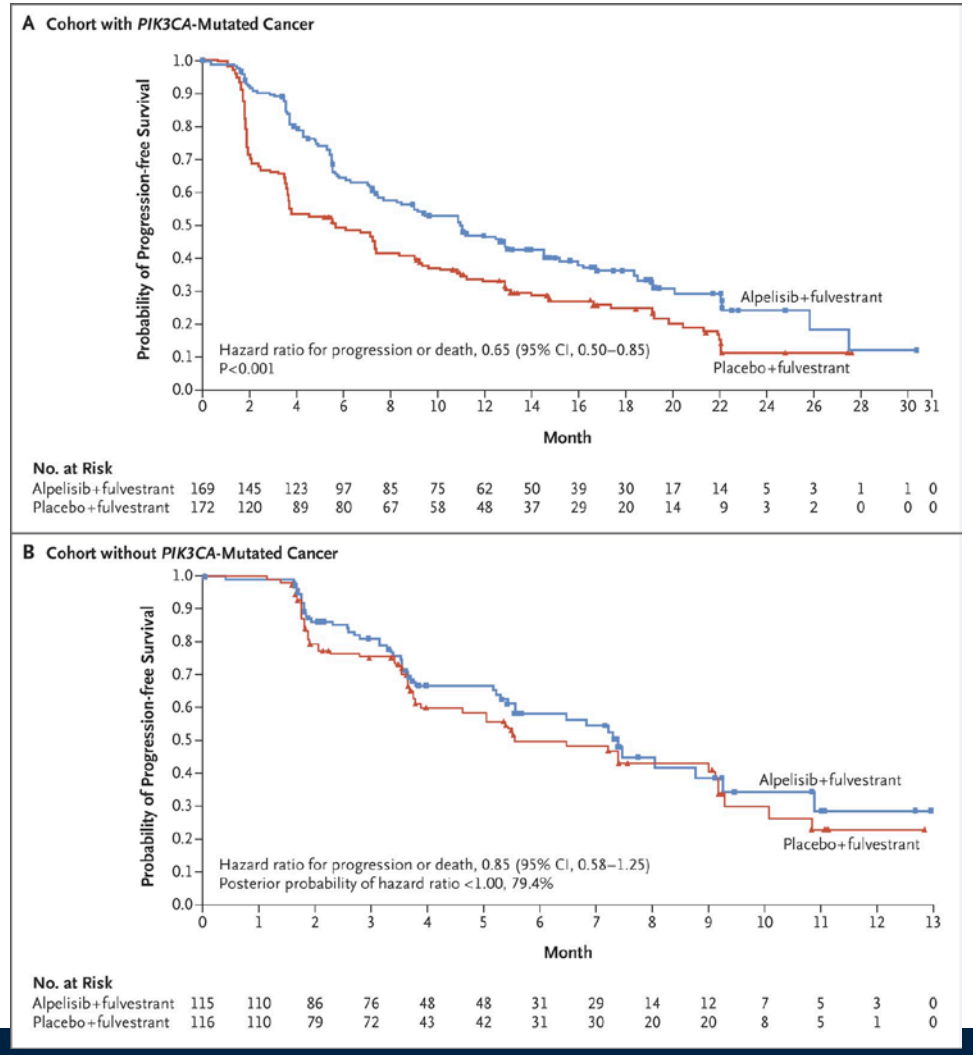
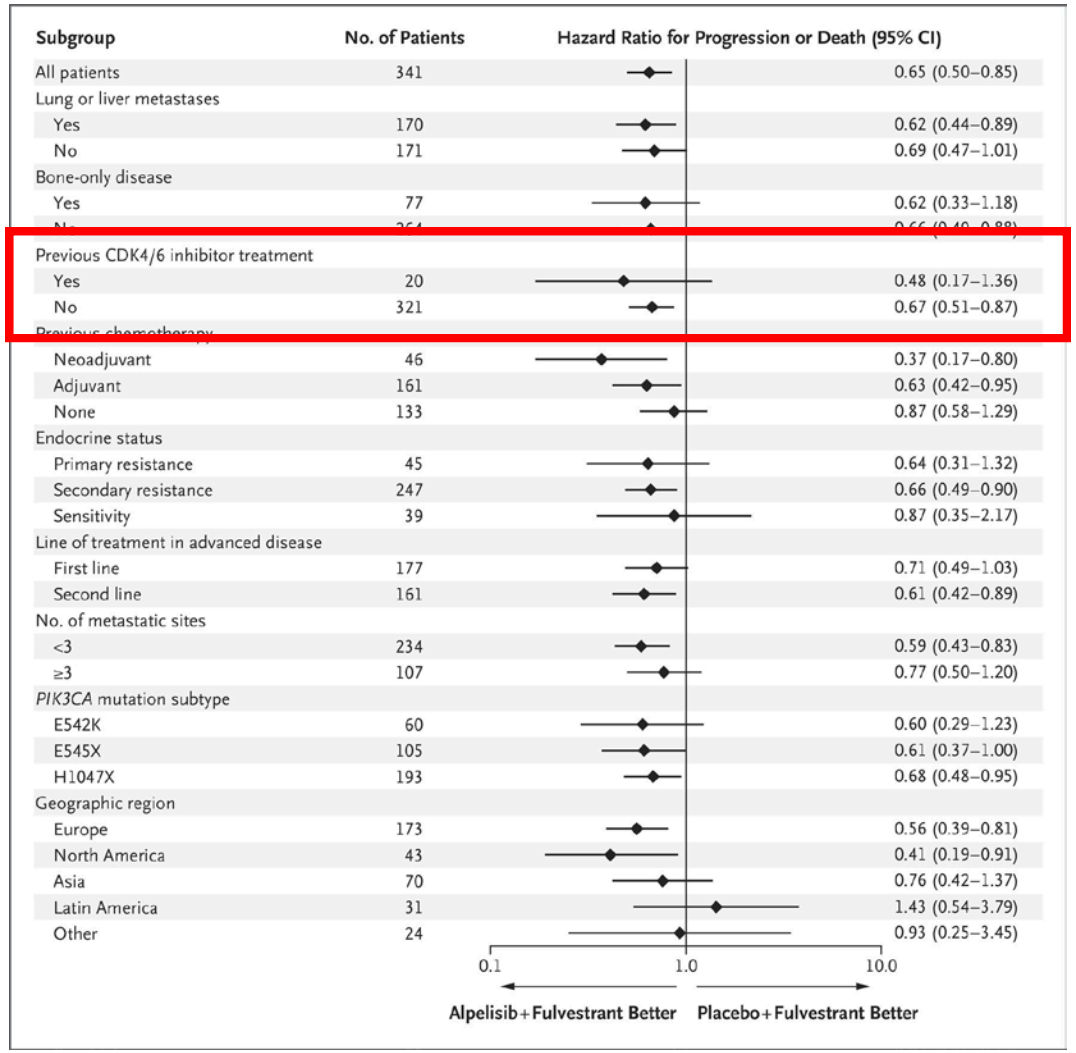
SOLAR-1 TRIAL

- In patients with PIK3CA mutation, alpelisib combined with fulvestrant led to a median progression-free survival of 11 months, compared with 5.7 months with fulvestrant plus placebo.
- Hyperglycemia, rash, and diarrhea were more common with alpelisib.



Subgroup Analysis of Progression-free Survival in the Cohort with *PIK3CA*-Mutated Cancer.



BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial (NCT03056755)

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)

Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

(assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

Treatment crossover between cohorts is not permitted

[a]Men in the letrozole cohort and premenopausal women also received goserelin 3.6 mg SC every 28 days or leuprolide 7.5 mg IM every 28 days for adequate gonadal suppression. [b]Enrollment in each cohort continued until at least 112 patients with a centrally confirmed *PIK3CA* mutation was reached. [c]IM on D1 and D15 of Cycle 1 and D1 for all other cycles thereafter. [d]Oral QD.
ABC, advanced breast cancer; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; CBR, clinical benefit rate; D, day; DOR, duration of response; IM, intramuscularly; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, PFS on next-line treatment; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneously; QD, once daily.

Statistical Analyses

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

- For efficacy endpoints, the primary population for analysis included patients who received one dose of study treatment and had a centrally confirmed *PIK3CA* mutation
  - *PIK3CA* mutation status was determined in tumor tissue by PCR analysis designed to detect mutations in the C2, helical, and kinase domains of *PIK3CA* (exons 7, 9, and 20, respectively)
  - Primary endpoint: Proportion of patients alive without disease progression[a] at 6 months based on local investigator assessment per RECIST v1.1, calculated with 2-sided 95% CIs
    - Clinically meaningful treatment effect and the primary endpoint would be met if the lower bound of the 95% CI was >30%
  - ORR and CBR were summarized with descriptive statistics (N, %) along with 2-sided exact binomial 95% CIs
- The safety set included all patients who received at least one dose of study treatment

[a]Disease progression refers to patients who progressed, died, or discontinued study by 6 months as failure.
CBR, clinical benefit rate; CI, confidence interval; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PFS2, PFS on next-line treatment; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RECIST, Response Evaluation Criteria In Solid Tumors.
1. Clopper CJ, Pearson ES. *Biometrika*. 1934;26(4):404-413.

Previous Treatments and Endocrine Status

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

Characteristic, No. (%); Full Analysis Set	Prior CDKi + AI (Cohort A) (N=127)
Lines of prior medication therapy in the metastatic setting	
0	15 (11.8)
1	89 (70.1)
2	21 (16.5)
3	2 (1.6)
Lines of prior ET in the metastatic setting	
0	15 (11.8)
1	98 (77.2)
2	14 (11.0)
Previous exposure to fulvestrant or chemotherapy as first-line treatment in the metastatic setting	
Fulvestrant	0
Chemotherapy	8 (6.3)
Endocrine status at study entry[a]	
Primary endocrine resistance	26 (20.5)
Secondary endocrine resistance	76 (59.8)
Endocrine sensitivity	1 (0.8)

15 patients received CDKi in the adjuvant setting

Primary endocrine resistance: relapse < 24 mos on ET (adjuvant) or progression < 6 months on ET (metastatic)
Secondary endocrine resistance: relapse ≥ 24 mos on ET or relapse < 12 mos after end of ET (adjuvant), or progression ≥ 6 mos on ET (metastatic).
Endocrine sensitivity: relapse ≥ 12 mos after the end of ET (adjuvant) or progression occurring ≥ 12 mos after the end of ET (metastatic setting).

[a]Endocrine status was defined as in SOLAR-1 (André F, et al. *N Engl J Med*. 2019) and per ESMO definitions (Cardoso F, et al. *Ann Oncol*. 2018).
AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; ET, endocrine therapy.

Efficacy: Primary Endpoint and PFS Results

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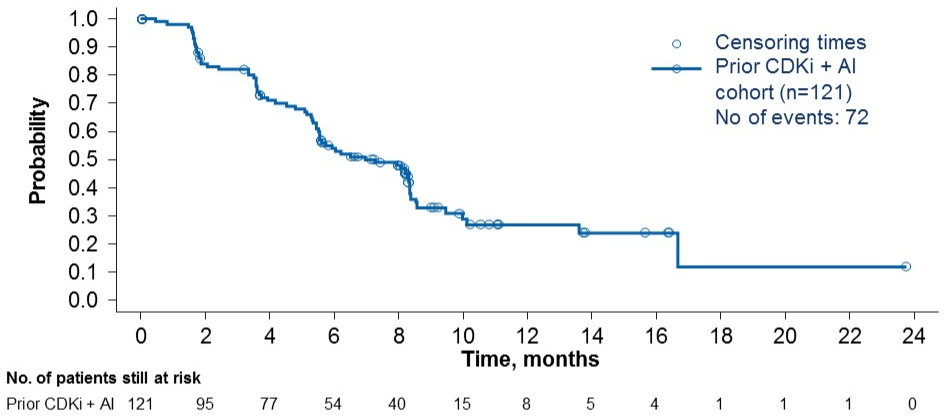
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

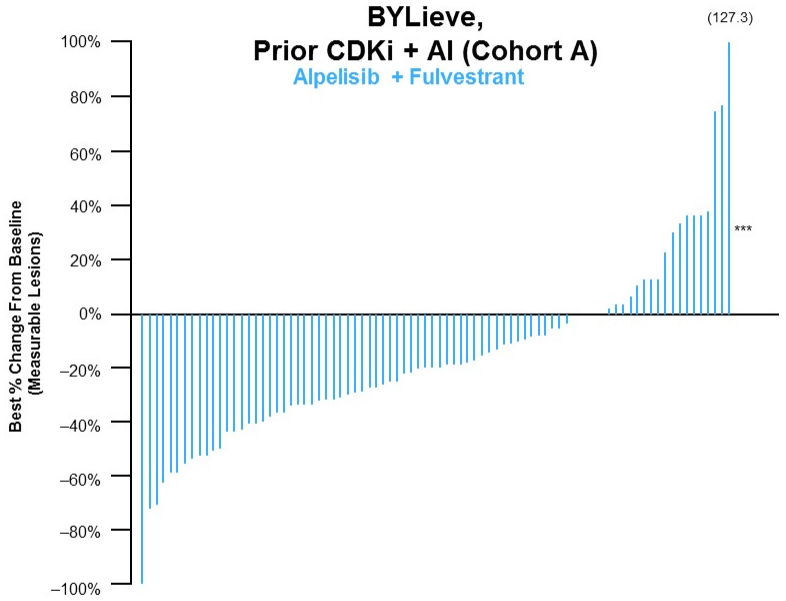
Endpoint	Prior CDKi + AI (Cohort A) (n=121)
Primary endpoint: Patients who were alive without disease progression at 6 mo	**50.4%** (n=61; 95% CI, 41.2-59.6)
Secondary endpoint: Median PFS	**7.3 mo** [n=72 (59.5%) with event]; 95% CI, 5.6-8.3)

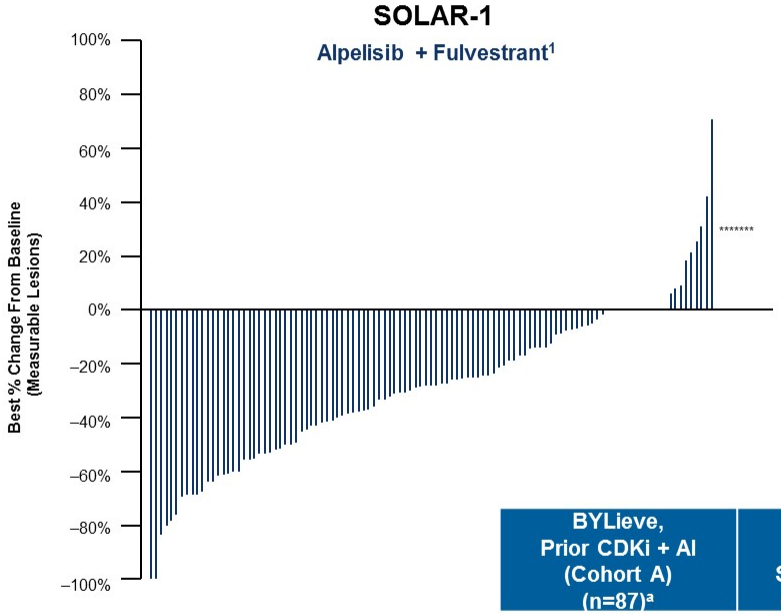


The primary endpoint for the prior CDKi + AI cohort was met (lower bound of 95% CI was > 30%), with 50.4% of patients alive without disease progression at 6 months

Efficacy: Best Percent Change From Baseline in Tumor Size

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer





	BYLieve, Prior CDKi + AI (Cohort A) (n=87)[a]	SOLAR-1 (n=116)[1]
Decrease in best % change from baseline	70.1%	75.9%
Increase/zero change in best % change from baseline	26.4%	18.1%

SOLAR-1 data cutoff date: June 12, 2018; BYLieve data cutoff date: December 17, 2019.
*Best percentage change in sum of diameters per investigator assessment, for patients with measurable disease at baseline.
[a]Patients with missing best percentage change or those with best percentage change in target lesion but overall response of Unknown are excluded'
1. Reprinted from Juric D, et al. SABCS 2018. Abstract GS3-08 (oral).

Safety of Alpelisib + Fulvestrant in the Prior CDKi + AI Cohort (Safety Set)

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Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

	CDKi + AI (Cohort A) (N=127)	
	All Grades, n (%)	Grade ≥3, n (%)
AEs	126 (99.2)	85 (66.9)
Treatment-related	126 (99.2)	79 (62.2)
SAEs	33 (26.0)	31 (24.4)
Treatment-related	20 (15.7)	18 (14.2)
Fatal SAEs	1 (0.8)	1 (0.8)
	Fatal SAE in 1 patient was respiratory failure	
AEs leading to discontinuation	26 (20.5)	15 (11.8)
Treatment-related[a,b]	23 (18.1)	13 (10.2)
AEs leading to dose adjustment/interruption	82 (64.6)	68 (53.5)

[a]Patients may have had more than one AE documented as leading to discontinuation.
[b]Adverse events leading to discontinuation included skin and subcutaneous tissue disorders (7), GI disorders (6), investigations (4), general disorders and administration site conditions (3), metabolism and nutrition disorders (2), infections and infestations (1), nervous system disorders (1), and respiratory, thoracic and mediastinal disorders (1).
AE, adverse event; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; GI, gastrointestinal; SAE, serious adverse event.

AEs Leading to Discontinuation and Dose Intensity Compared With SOLAR-1

BYLieve
Alpelisib (BYL719) In patients with PIK3CA mutant, HR+, HER2- adVanced brEast cancer

BYLieve

AEs leading to discontinuation (≥ 1.5%)	Prior CDKi + AI (Cohort A) Alpelisib + fulvestrant (N=127)
	All grades, n (%)
Any adverse event	26 (20.5)
Rash	5 (3.9)
Urticaria	2 (1.6)
Colitis	2 (1.6)
Hyperglycemia	2 (1.6)
Vomiting	2 (1.6)

Median relative dose intensity for alpelisib in BYLieve was 89.9%

SOLAR-1[1]

AEs leading to discontinuation (≥ 1.5%)	Alpelisib + fulvestrant (N=284)
	All grades, n (%)
Any adverse event	71 (25.0)
Hyperglycemia	18 (6.3)
Rash	9 (3.2)
Diarrhea	8 (2.8)
Fatigue	6 (2.1)
Nausea	5 (1.8)

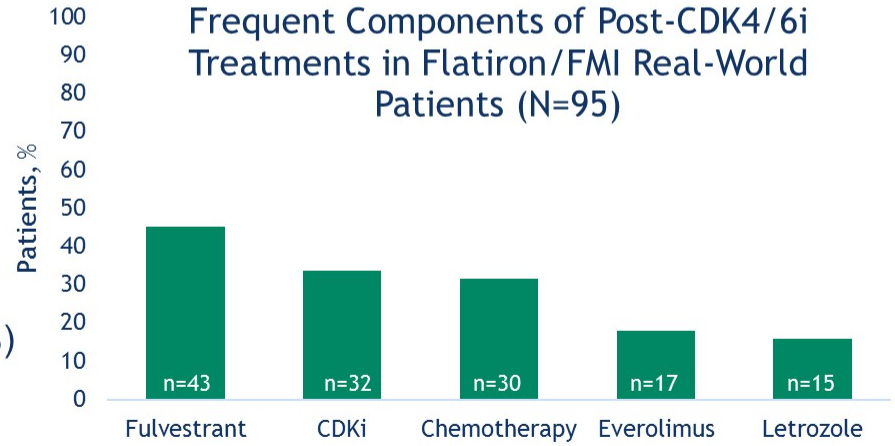
Median relative dose intensity for alpelisib in SOLAR-1 was 83.7%

AE, adverse event; AI, aromatase inhibitor; CDKi, cyclin-dependent kinase inhibitor; SAE, serious adverse event.

1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940.

Weighted/Matched PFS Analyses: BYLieve and a Real-World Cohort of Patients

- PFS results from BYLieve were compared with real-world PFS of a similar group of patients (N=95) with HR+, HER2–, *PIK3CA*-mutated ABC in the US after CDKi-based therapy from the de-identified US Flatiron Health-Foundation Medicine (FMI) clinicogenomics database
- Differences in prognostic factors for PFS between cohorts were mitigated by 3 different matching/weighting techniques that accounted for baseline covariates
- Treatments in the real-world setting varied, with 33 unique treatment regimens reported
  - The most common treatments regimens were
    - Capecitabine monotherapy (n=14, 14.7%)
    - Fulvestrant monotherapy (n=14, 14.7%)
    - Fulvestrant + palbociclib (n=13, 13.7%)
    - Everolimus + exemestane (n=11, 11.6%)
    - Fulvestrant + letrozole + palbociclib (n=5, 5.3%)



PFS Effect of Alpelisib Over Standard Treatments in Real-World Setting[a]

Analysis Method (In Patients With *PIK3CA* Mutation)	**BYLieve Prior CDKi +AI (Cohort A) Alpelisib + Fulvestrant median-PFS (mo)** (95% CI), n	**Flatiron/FMI Standard Treatment median-rwPFS (mo)** (95% CI), n
Unadjusted results	**7.3** (5.6-8.3), n=120	**3.6** (3.1-6.1), n=95
Weighting by odds	**7.3** (5.6-8.3), n=120	**3.7** (3.1-6.1), n=116
Propensity score matching	**8.0** (5.6-8.6), n=76	**3.5** (3.0-5.4), n=76
Exact matching	**6.5** (5.3-8.3), n=61	**3.4** (2.9-3.9), n=61

Matched analysis comparing BYLieve with RWE standard treatment in post-CDK4/6i setting further supports use of alpelisib + fulvestrant

[a]PFS comparison is based on PFS per RECIST v1.1 in BYLieve and real-world PFS in Flatiron/FMI.

DISCUSSION

- BYLIEVE TRIAL
  - Is a single-arm study that attempts to evaluate whether patients with PIK3CA mutations previously treated with an AI and CDK 4/6 inhibitor would benefit from alpelisib with ET.
    - Primary endpoint of lower bound CI >30% met (41.2%), with median PFS of 7.3 months
    - Results appear comparable to SOLAR-1 at face value
    - Authors compare efficacy to “real world” cohorts using statistical models, suggesting that the combination may be better than standard of care
  - Underscores the importance of management of side effects such as rash, hyperglycemia, and diarrhea, to maintain dose intensity
    - Overall discontinuation for AEs in BYLieve was 20.5%, compared to 25% in SOLAR-1
    - Fewer discontinuations for hyperglycemia in BYLieve (1.6%) compared to 6.3% in SOLAR-1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