2021 ASCO ANNUAL MEETING

ASCO DIRECT HIGHLIGHTS™: HIGHLIGHTS IN BREAST CANCER

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor Sammons Cancer Center
Texas Oncology
US Oncology

Disclosure of Conflict(s) of Interest

Joyce O'Shaughnessy, MD reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months.

Consultant:

AbbVie Inc.
Agendia
Amgen Biotechnology
Aptitude Health
AstraZeneca
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Daiichi Sankyo
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G1 Therapeutics
Genentech
Gilead Sciences
GRAIL
Halozyme Therapeutics
Heron Therapeutics
Immunomedics
Ipsen Biopharmaceuticals
Lilly
Merck
Myriad
Nektar Therapeutics
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Pierre Fabre Pharmaceuticals
Puma Biotechnology
Prime Oncology
Roche
Samsung Bioepis
Sanofi
Seagen
Syndax Pharmaceuticals
Synthon
Taiho Oncology
Takeda

Objectives

- Review long-term follow-up of MINDACT trial
- Discuss BCI and prediction of benefit from extended AI therapy
- Compare outcomes of de-escalated neoadjuvant trastuzumab and pertuzumab with or without weekly paclitaxel
- Analyze results from OlympiA trial
- Introduce new regimen of dalpiciclib plus fulvestrant
- Compare efficacy of trastuzumab plus endocrine therapy or chemotherapy as first-line for metastatic breast cancer
- Discuss patient survey results about tolerability of treatment and individualized dosing options

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Outcome of patients with an ultralow risk 70-gene signature in the MINDACT trial

Josephine Lopes Cardozo, MD

PhD Candidate Netherlands Cancer Institute

Medical Fellow EORTC

June 6, 2021

NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

EORTC
European Organisation for Research and Treatment of Cancer

The future of cancer therapy

MINDACT

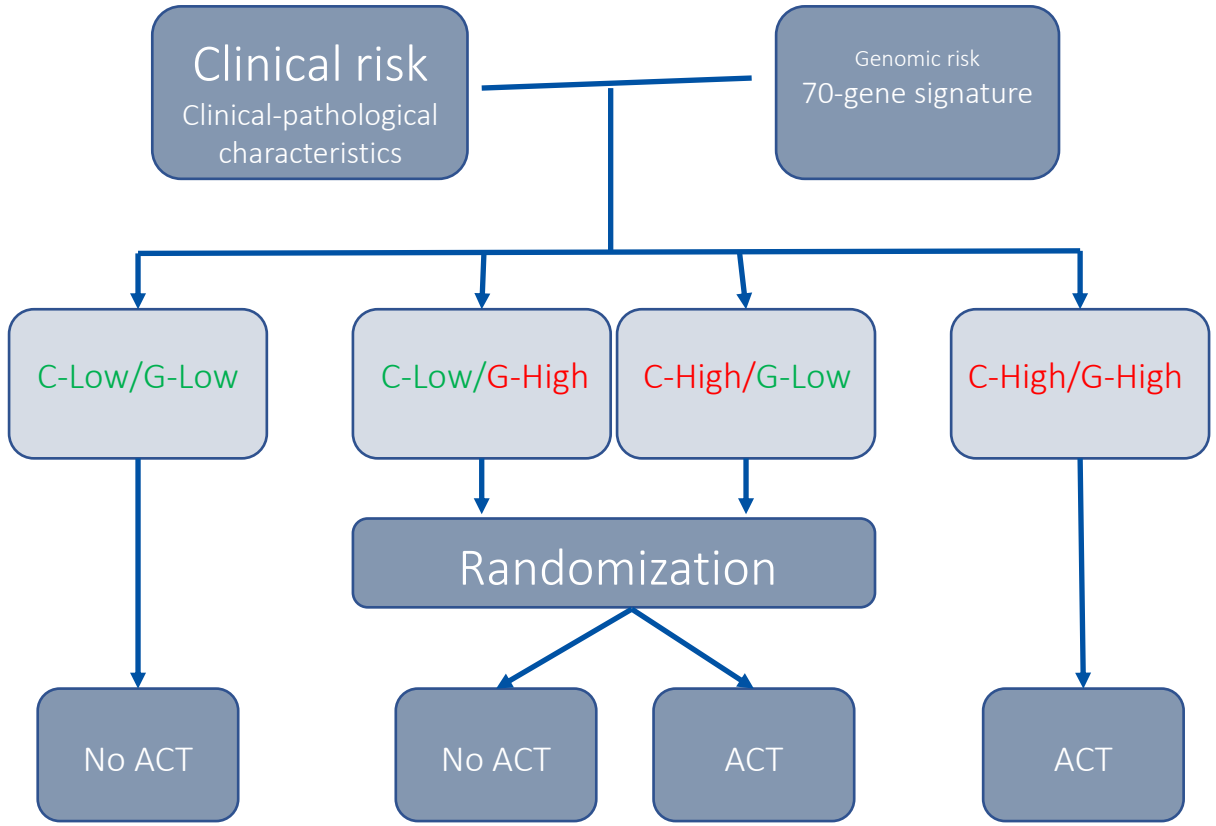
EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

MINDACT

NETHERLANDS CANCER INSTITUTE ANTONI VAN LEEUWENHOEK

- Inclusion criteria
- Women aged 18-70
- Operable invasive breast cancer
- Tumor size max 5 cm
- 0-3 positive lymph nodes
- No distant metastasis

MINDACT trial design



Cardoso (2016) NEJM;375:717-729. ; Piccart (2021) Lancet Oncol. 2021; 22:476–488

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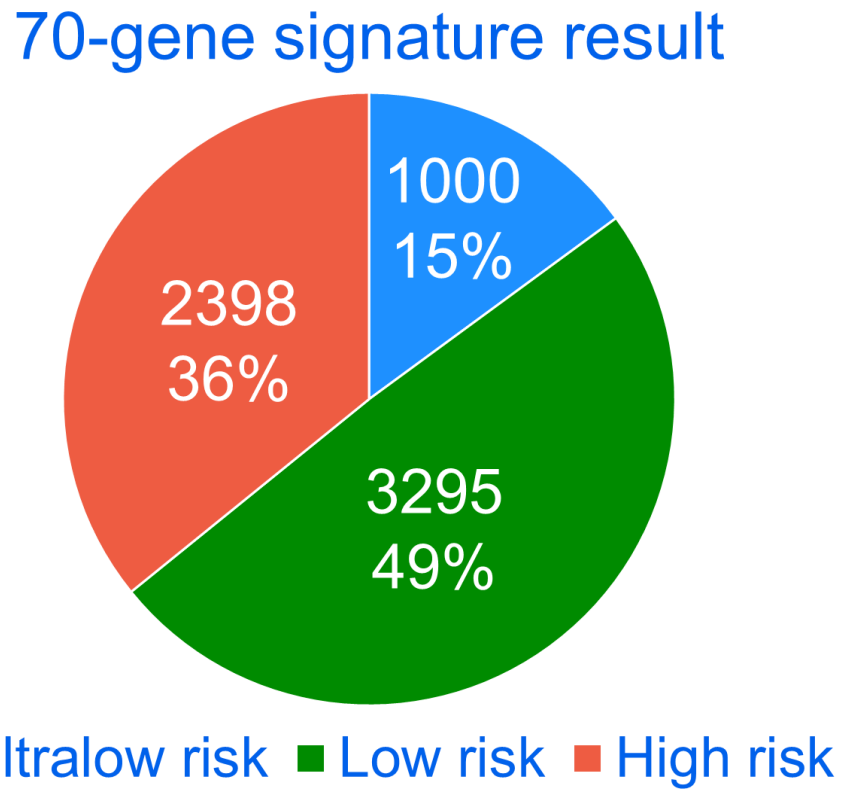
15% of MINDACT patients genomic ultralow risk



Total N=6693

- HR+/HER2- subtype
- ~95% of Low* and Ultralow risk patients
- 57% of High risk patients

- Adjuvant systemic treatment
- 76-85% endocrine therapy or no AST in Low and Ultralow risk
- 83% chemotherapy in High risk

- *Low risk also referred to as Low not Ultralow

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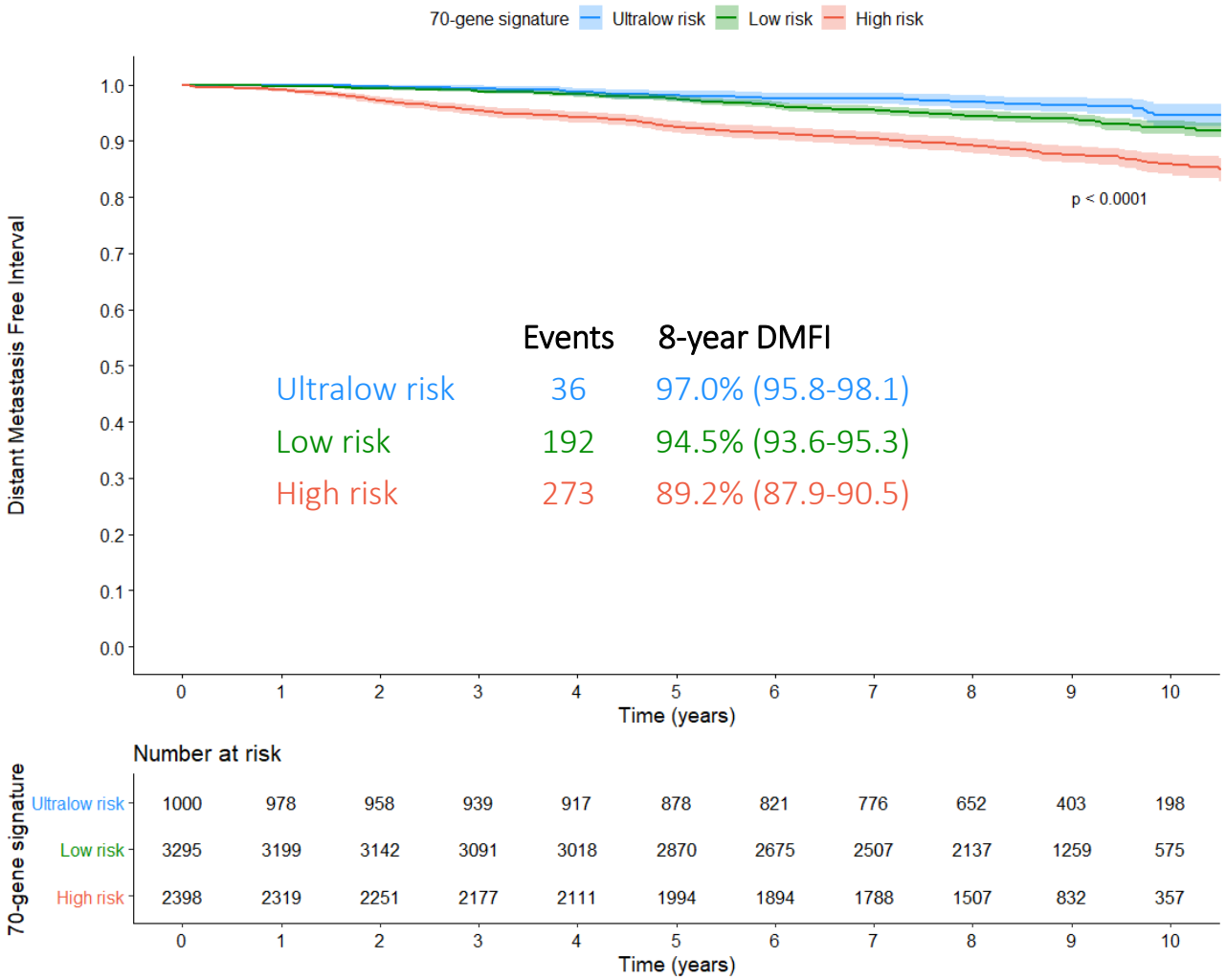
Excellent Distant Metastasis Free Interval rates for genomic Low and Ultralow risk patients



Median follow-up: 8.7 years

Risk of distant metastasis or BC-death	
	Adj* HR (95% CI)
Ultralow risk vs low risk	0.65 (0.45-0.94)
High risk vs low risk	2.17 (1.68-2.80)

*Adjusted for clinical-pathological and treatment characteristics

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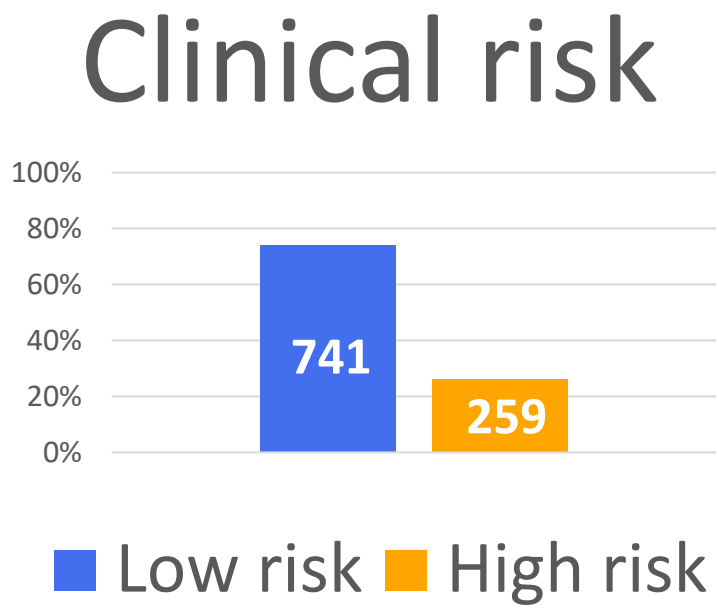
Characteristics 1000 genomic Ultralow risk patients

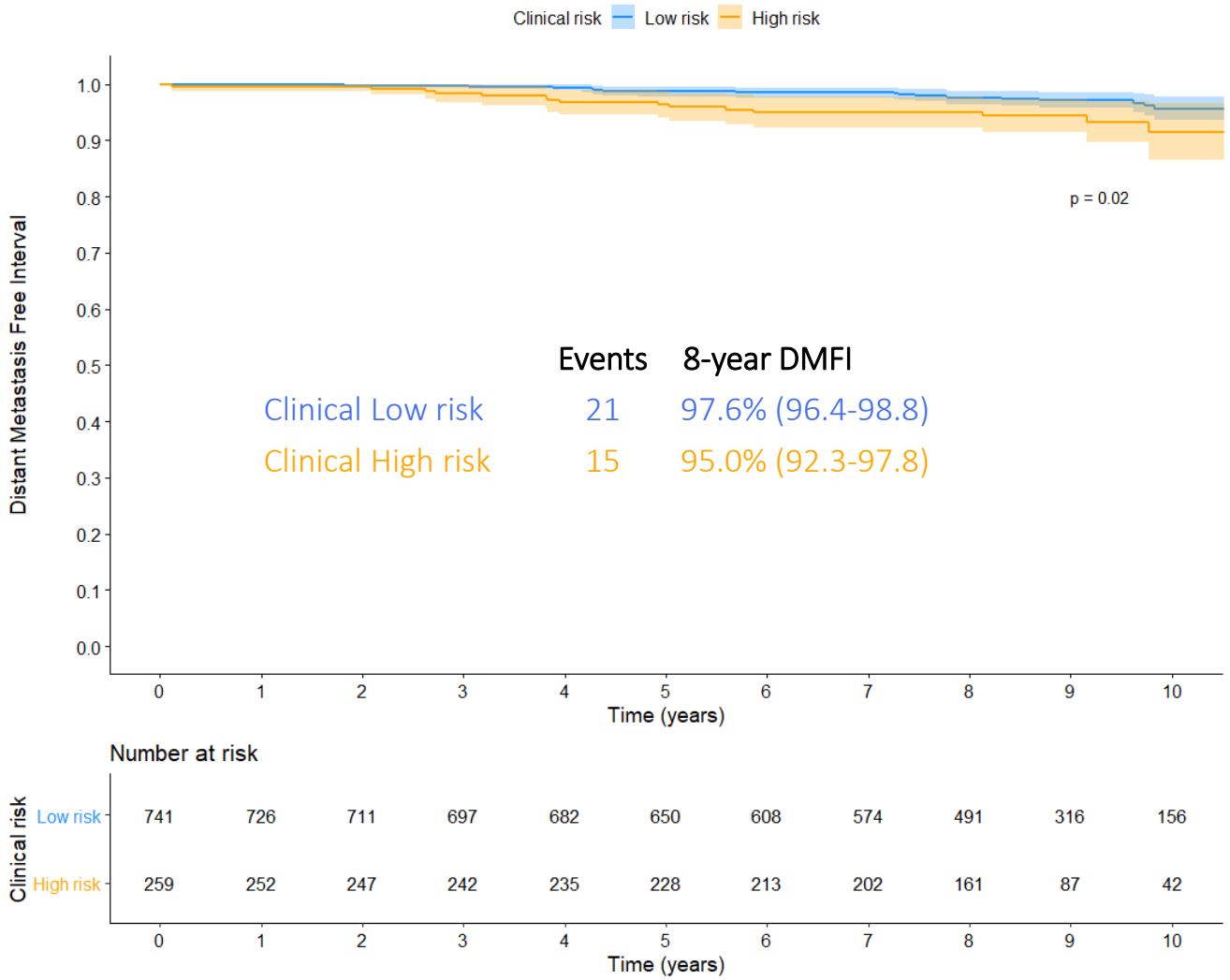
- 67% >50 years
- 80% lymph node negative
- 81% tumors ≤2 cm
- 96% Grade 1 or 2
- 97% HR+/HER2- subtype

- 16% no adjuvant systemic treatment
- 69% endocrine therapy
- 14% chemotherapy

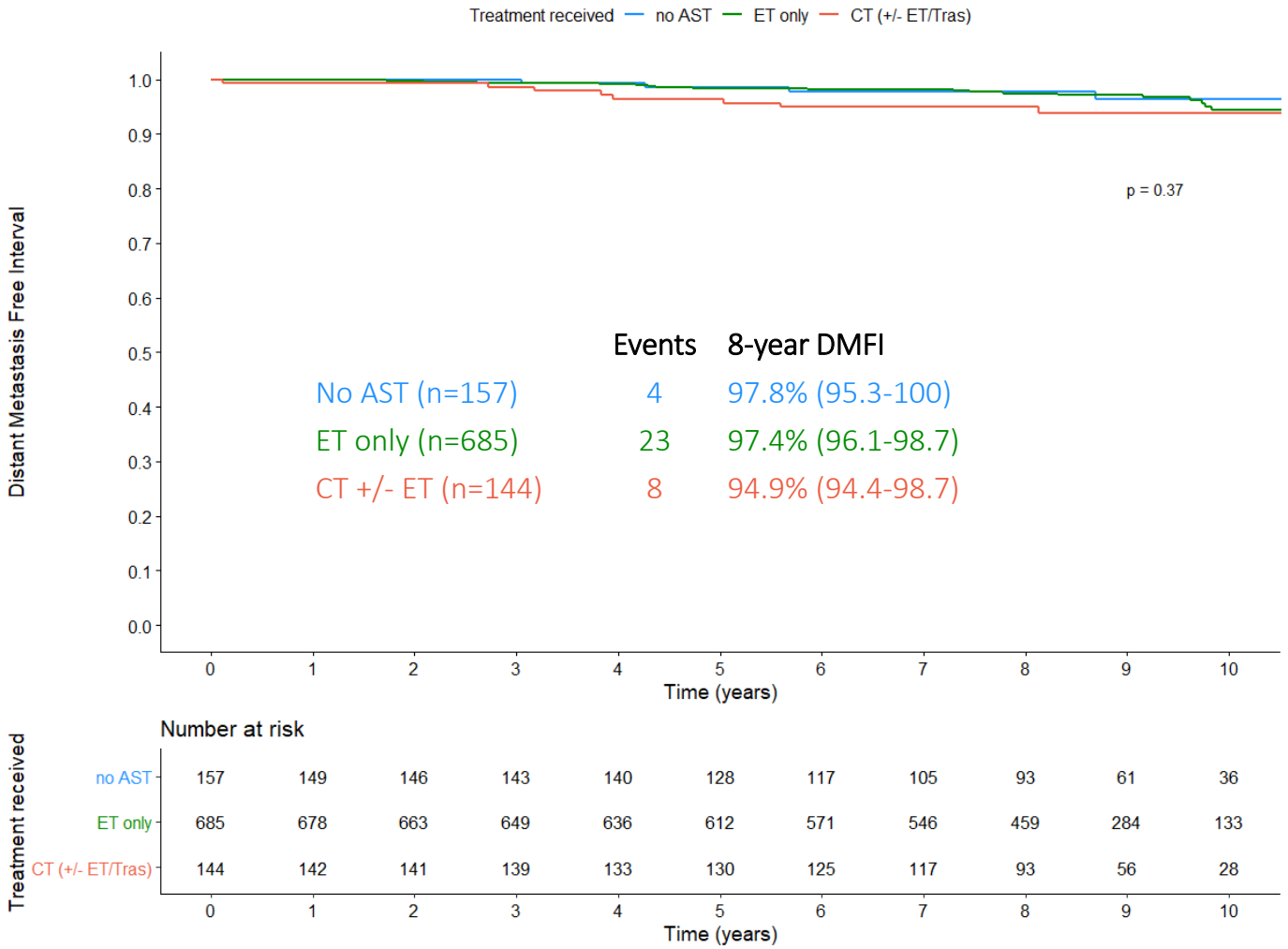


Clinical High risk tumors
- Larger size
- Higher grade
- Lymph node positive

Small difference in Distant Metastasis Free Interval in genomic Ultralow risk patients by Clinical risk



Excellent outcomes for genomic Ultralow risk patients receiving only endocrine therapy or no adjuvant systemic treatment



Risk of distant metastasis or BC-death (Ultralow risk patients only)	
	Adj* HR (95% CI)
CT vs no CT	0.98 (0.37-2.61)
ET vs no ET	0.59 (0.27-2.13)

*Adjusted for clinical-pathological characteristics

Note: 92% of patients receiving chemotherapy were Clinical High risk

Clinical implications

- The 70-gene signature MammaPrint can identify patients with an ultralow risk of distant recurrence

- Patients with ultralow risk tumors could be candidates for further de-escalation of treatment, further reducing overtreatment and the risk of side-effects

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Breast Cancer Index (BCI) and Prediction of Benefit from Extended Aromatase Inhibitor (AI) Therapy in HR+ Breast Cancer: NRG Oncology/NSABP B-42

EP Mamounas[1,2], H Bandos[1,3], P Rastogi[1,3,4], Y Zhang[5], K Treuner[5], PC Lucas[1,3,4], CE Geyer, Jr.[1,6], L Fehrenbacher[1,7], ML Graham[1,8], SL Chia[1,9], AM Brufsky[1,3,4], JM Walshe[1,10], GS Soori[1,11], SR Dakhil[1,12], S Paik[1,13], SM Swain[1,14], DC Sgroi[15], CA Schnabel[5], N Wolmark[1,3,4]

[1]NRG Oncology, Pittsburgh, PA; [2]Orlando Health Cancer Institute, Orlando, FL; [3]University of Pittsburgh, Pittsburgh, PA; [4]UPMC Hillman Cancer Center, Pittsburgh, PA; [5]Biotheranostics, Inc, San Diego, CA; [6]Houston Methodist Cancer Center, Houston, TX; [7]Kaiser Permanente Oncology Clinical Trials Northern CA, Novato, CA; [8]Waverly Hematology Oncology, Cary, NC; [9]British Columbia Cancer Agency, Vancouver, BC, Canada [10]Cancer Trials Ireland (Formerly known as Irish Clinical Oncology Research Group – ICORG), Dublin, Ireland; [11]Florida Cancer Specialists, City?, FL; [12] CCOP Wichita via Christi Reg. Med. Ctr., Wichita, KS; [13]Yonsei University College of Medicine, Seoul, Republic of South Korea; [14]Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC; [15] DS, Massachusetts General Hospital, Boston, MA.

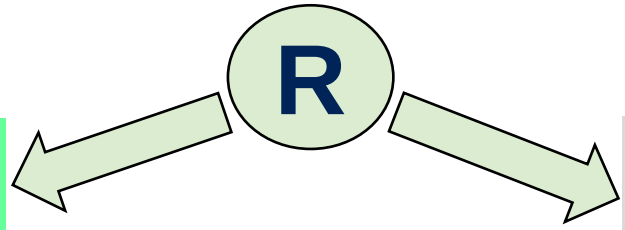
NSABP B-42

- **Postmenopausal pts with ER+ or PR+ breast cancer**
- **Stage I, II, or IIIa invasive BC at diagnosis**
- **Disease-free after 5 years of endocrine therapy**

AI x 5 years **or** **TAM x ≤ 3 years** **AI to Complete 5 years**

Stratification:

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



Letrozole x 5 yrs

Placebo x 5 yrs

NSABP B-42: Results

- Ten-year results (SABCS 2019) and further updated as of 04/30/2020
  - **Statistically significant improvement in DFS with extended L therapy: HR = 0.85, p = 0.01, 3.3% absolute improvement**
  - **No significant difference in overall survival with L *vs.* P**
  - **Extended L provided statistically significant reduction in:**
    - **BCFI events: HR = 0.75, p = 0.003, 2.7% absolute benefit**
    - **DR: HR = 0.72, p = 0.01, 1.8% absolute benefit**
- **Genomic classifiers that predict risk of late recurrence and/or benefit from extended endocrine therapy may further assist with the decision to recommend extended aromatase inhibitor therapy**

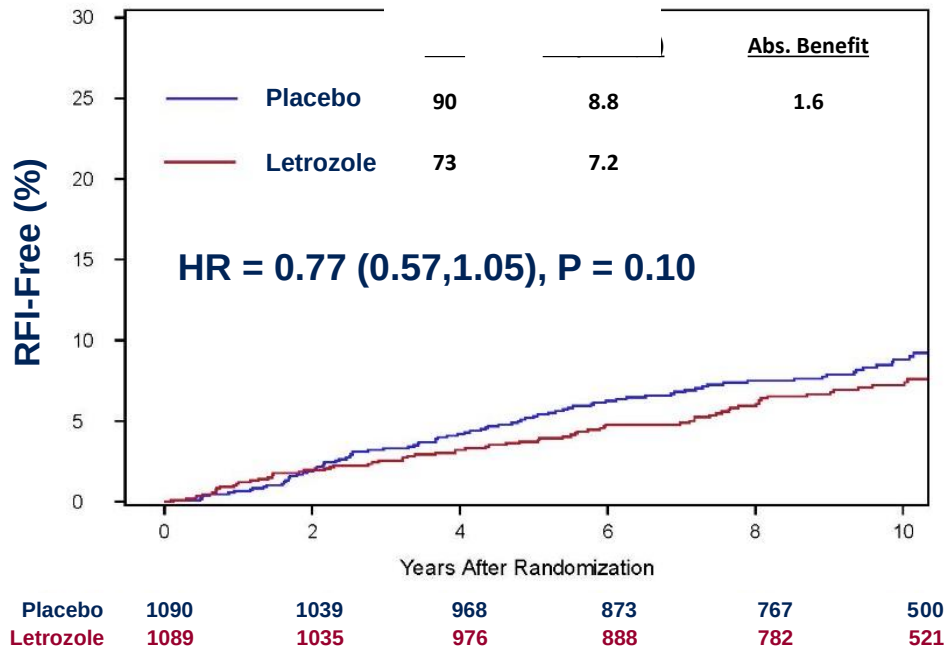
Breast Cancer Index (BCI)

- BCI is an 11-gene expression molecular signature comprised of two functional panels:
  - **Molecular Grade Index (MGI) – 5 genes measuring tumor proliferative status**
  - **HOXB13 and IL17BR (H/I) – 2 gene ratio measuring estrogen signaling**
- The BCI test provides both a prognostic BCI score for the risk of cumulative (0-10 years) and late (post-5 years) distant recurrence, and a prediction of the likelihood of extended endocrine therapy benefit based on BCI (H/I)
- BCI (H/I) predicted endocrine benefit across several different endocrine treatment backgrounds in the Stockholm, MA.17, Trans-aTTom and IDEAL studies with significant treatment to biomarker interaction[1-5]

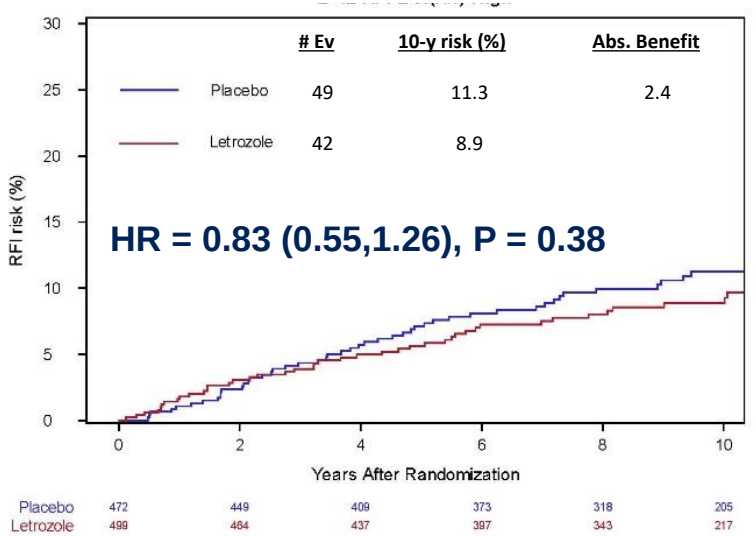
1.Sgroi DC et al JNCI 2013; 105(14):1036-42. 2. Zhang Y et al. CCR 2013; 19(15):4196-205. 3. Sgroi DC et al. Cancer Res 2012; 72 (Suppl.): Abstract P2-10-5. 4. Bartlett JMS et al. Ann Oncol 2019 Nov 1;30(11):1776-83. 5. Noordhoek I et al. Clin Cancer Res 2021 Jan 1;27(1):311-9.

Results: RFI

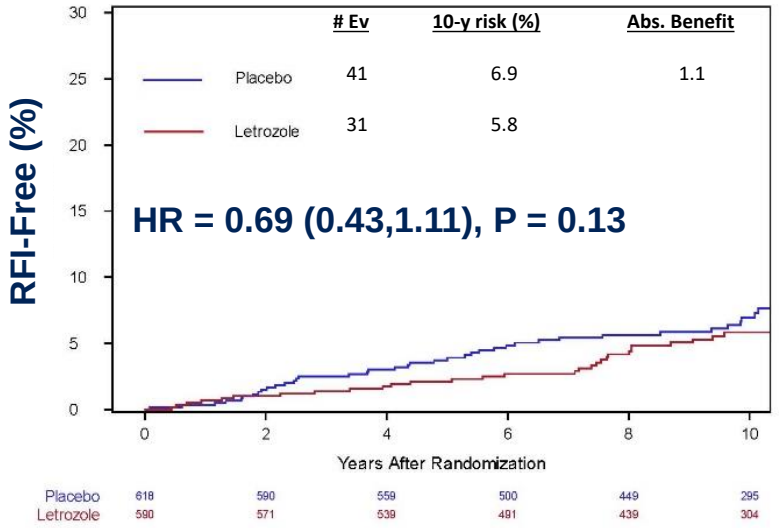
All Patients



BCI (H/I) High



BCI (H/I) Low

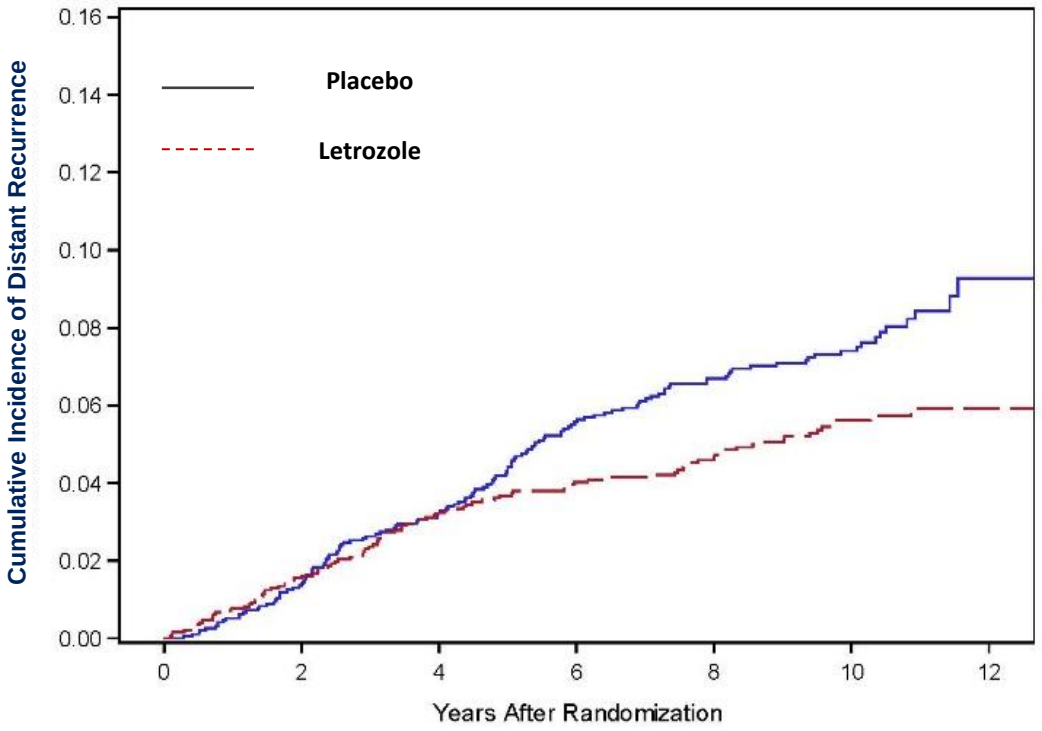


Test for Treatment-by-BCI (H/I) Interaction p = 0.55

ELT effect in subgroups (nodal status, prior tam use, HER2 status) was not different by BCI (H/I)

Non-proportionality of Hazard Rates in DR

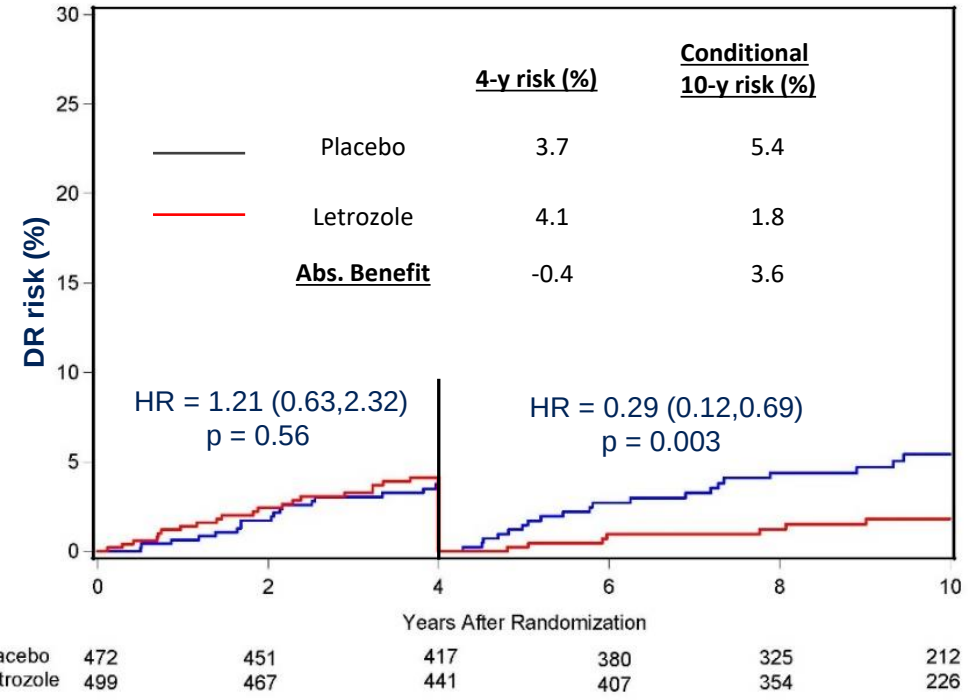
B-42, Parent Trial



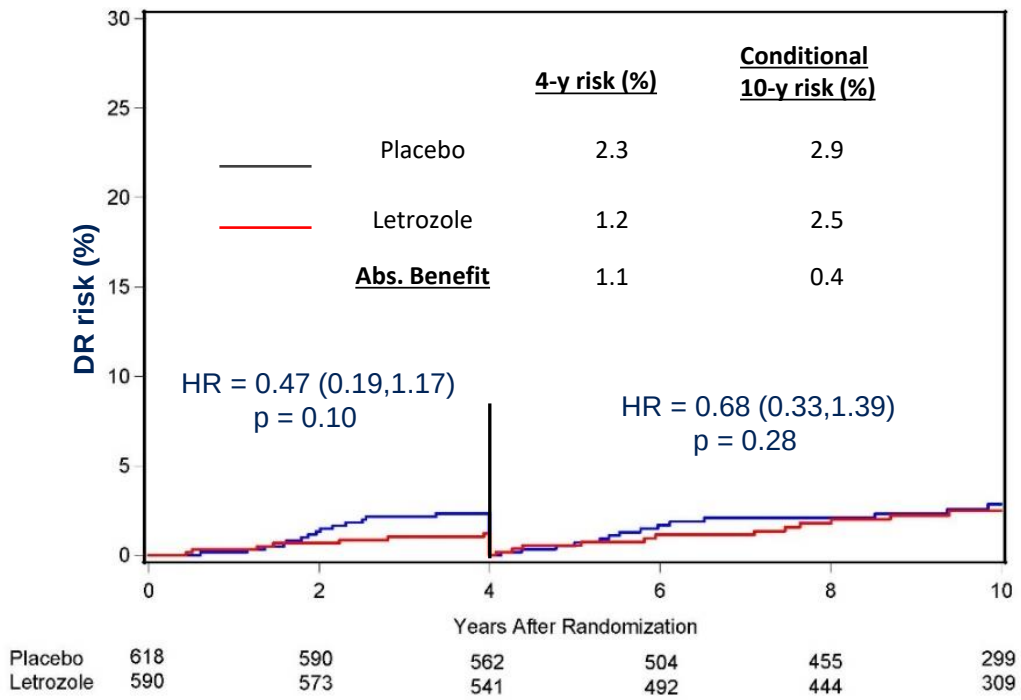
- In the B-42 parent trial a delayed treatment effect of ELT on DR at around year 4 after randomization was observed
- Proportional hazards assumption was not satisfied for BCI (H/I)-High group (p = 0.016)
- Based on that, time dependent secondary analyses for DR were performed

Time-dependent Secondary Analysis of DR

BCI (H/I)-High



BCI (H/I)-Low



- **Statistically significant ELT benefit for DR in BCI (H/I)-High after Year 4**
- **ELT-by-BCI (H/I) interaction was not statistically significant for any of the time intervals: ≤ 4 y (p=0.09), >4 y (p=0.14)**

Summary/Conclusions

- BCI (H/I) prediction of ELT benefit on RFI was not confirmed:
  - **RFI absolute benefit was 1.6% in the B-42 BCI translational cohort**
- In time-dependent DR analyses, BCI (H/I)-High cohort showed statistically significant benefit from ELT after 4y, while BCI (H/I)-Low did not.
  - **Absolute benefit after 4y comparing BCI (H/I)-High (3.6%) vs. the unselected cohort (1.7%) is consistent with previous validation results**
  - **BCI (H/I) prediction of ELT benefit after 4y was more apparent in the HER2 negative subset (treatment-by-BCI (H/I) interaction p=0.043)**
- Additional follow-up may enable further characterization of BCI (H/I) predictive ability in B-42

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DE-ESCALATED NEOADJUVANT PERTUZUMAB+TRASTUZUMAB WITH OR WITHOUT WEEKLY PACLITAXEL IN HER2+/HR- EARLY BREAST CANCER: ADAPT HER2+/HR- BIOMARKER AND SURVIVAL RESULTS

N. Harbeck, O. Gluz, M. Christgen, S. Kuemmel, E.-M. Grischke, M.W. Braun, D. Augustin, J. Potenberg, K. Krauss, C. Schumacher, H. Forstbauer, T. Reimer, A. Stefek, H.H. Fischer, E. Pelz, M. Graeser, C. zu Eulenburg, R. Kates, R. Wuerstlein, H. Kreipe, U. Nitz

On behalf of the ADAPT-Investigators,
West German Study Group, Moenchengladbach

06JUN2021

WSG
Westdeutsche Studiengruppe
West German Study Group

ADAPT

WSG-ADAPT HER2+/HR-

Study Design
(NCT01779206)

- HER2+, ER- and PR-
- M0
- ECOG ≤1 or KPS ≥80%

(n=134)

R 5:2

A

Trastuzumab
8 mg/kg → 6 mg/kg q3w x4
+
Pertuzumab
840 mg → 420 mg q3w x4

(n=92)

12 weeks

B

Trastuzumab
8 mg/kg → 6 mg/kg q3w x4
+
Pertuzumab
840 mg → 420 mg q3w x4
+
Paclitaxel
80 mg/m^2 q1w x12

(n=42)

Surgery within 3 weeks

In histologically confirmed non-pCR: standard neoadjuvant therapy followed by surgery

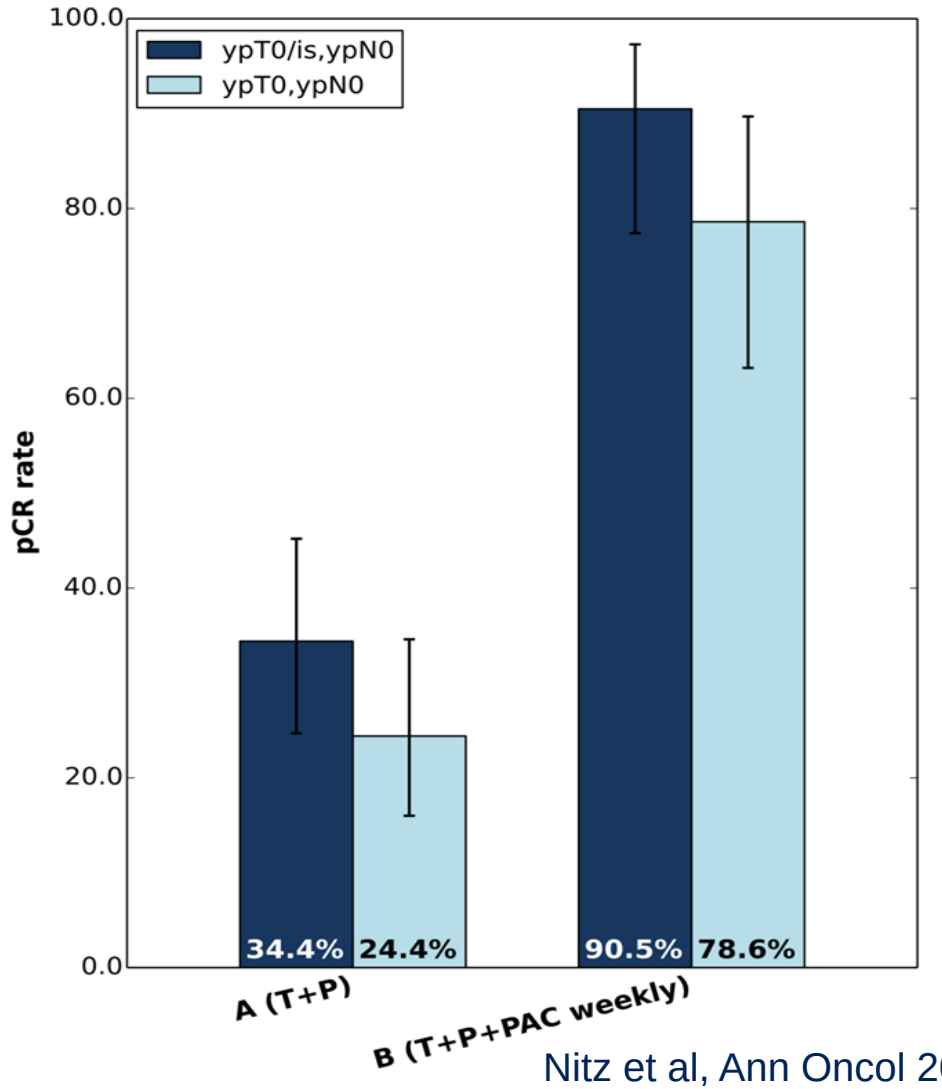
Adjuvant therapy according to national guidelines; if pCR was achieved after 12 weeks of study therapy, additional chemotherapy could be omitted at investigator's discretion

3-week biopsy for **early response assessment** (defined as Ki67 decrease ≥ 30% vs baseline or low cellularity, i.e. < 500 invasive tumor cells)

Hofmann et al, Trials 2013; 14: 261
Nitz et al, Ann Oncol 2017; 28(11): 2768-72

WSG-ADAPT HER2+/HR-

pCR rates (ypT0/is ypN0; ypT0 ypN0)



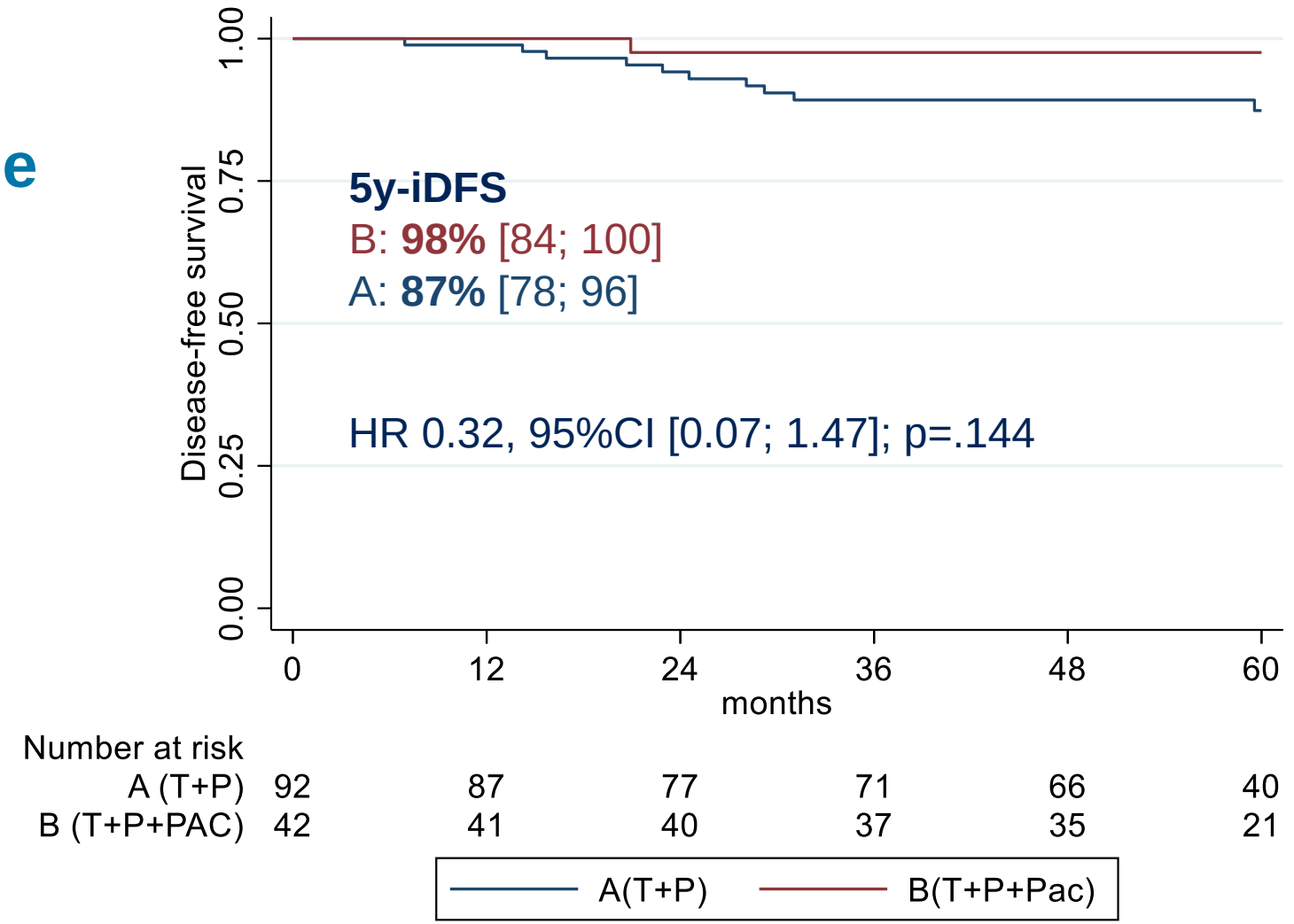
Patients with
no further CT after pCR

Arm A	Arm B
9 (29.0%)	30 (79.0%)

Nitz et al, Ann Oncol 2017; 28(11): 2768-72

WSG-ADAPT HER2+/HR-

Invasive disease-free survival by trial arm



WSG-ADAPT HER2+/HR-

(NCT01779206)

Conclusions

- For the first time, we have shown in a prospective multicenter trial both excellent pCR and survival in patients treated by de-escalated 12-week neoadjuvant weekly paclitaxel and dual HER2 blockade (T+P), irrespective of additional chemotherapy (CT) use.
- CT-free regimens are promising in highly sensitive tumors with early response.
- Future investigation of CT-free regimens needs to be focused on selected patients (e.g. HER2 3+, non-basal-like, early responders, predictive RNA signatures such as immune signatures).
- In WSG-ADAPT HER2+/HR-, early pCR after only 12 weeks of neoadjuvant Pac+P+T was strongly associated with improved outcome and may thus serve as a predictive clinical marker for further treatment (de)-escalation.
- WSG-ADAPT TP II has already reported a pCR rate of 57% in HER2+/HR+ EBC after 12 weeks of neoadjuvant Pac+P+T[1]; survival results are being awaited.
- Further de-escalation trials with similar concepts (e.g. COMPASS, DECRESCENDO) are ongoing[2].

[1]Gluz et al, ASCO 2020; [2]Piccart et al, JCO 2020

BIG Breast International Group

frontier science

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NIH NATIONAL CANCER INSTITUTE

A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline *BRCA1/2* mutations and high-risk HER2-negative early breast cancer

OlympiA: Trial schema

- Local genetic testing or on-study central screening
  (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

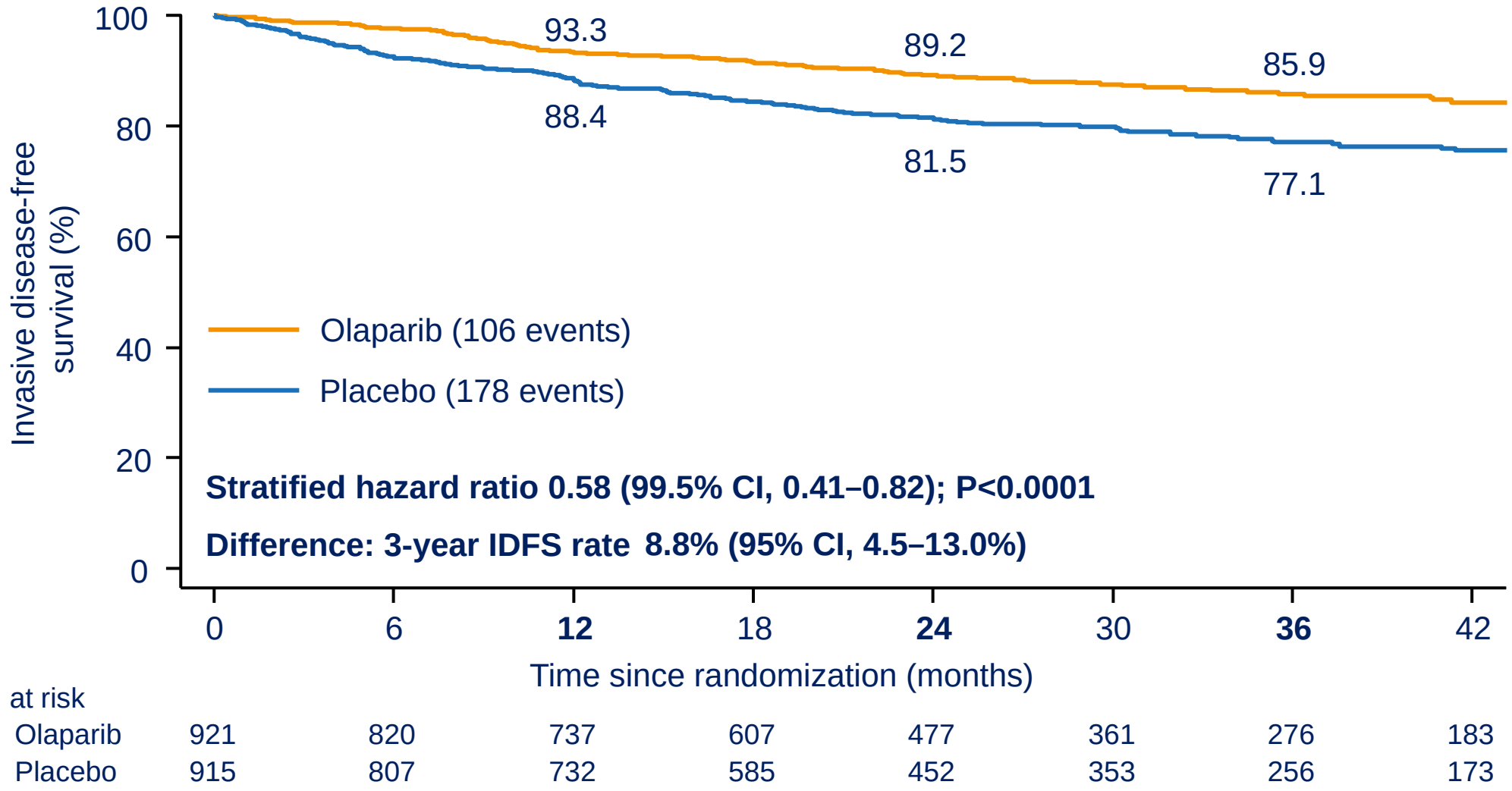
Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

OlympiA: Invasive disease-free survival (ITT)



No. at risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

OlympiA: Distant disease-free survival

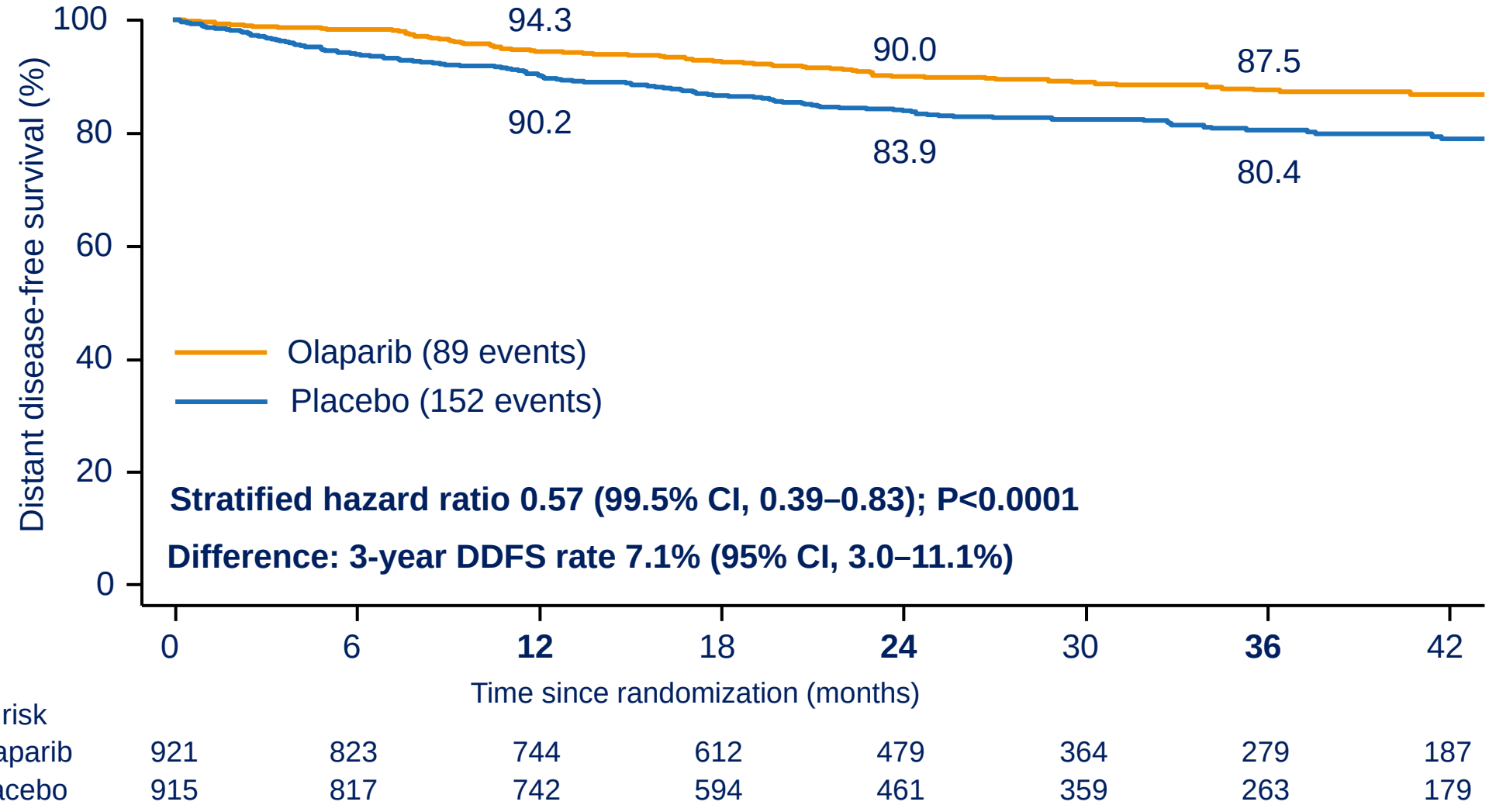
IDFS
P<0.005

DDFS and
OS only
tested if IDFS
significant

DDFS
P<0.005

Recycling of
alpha for
conservation
future
analyses

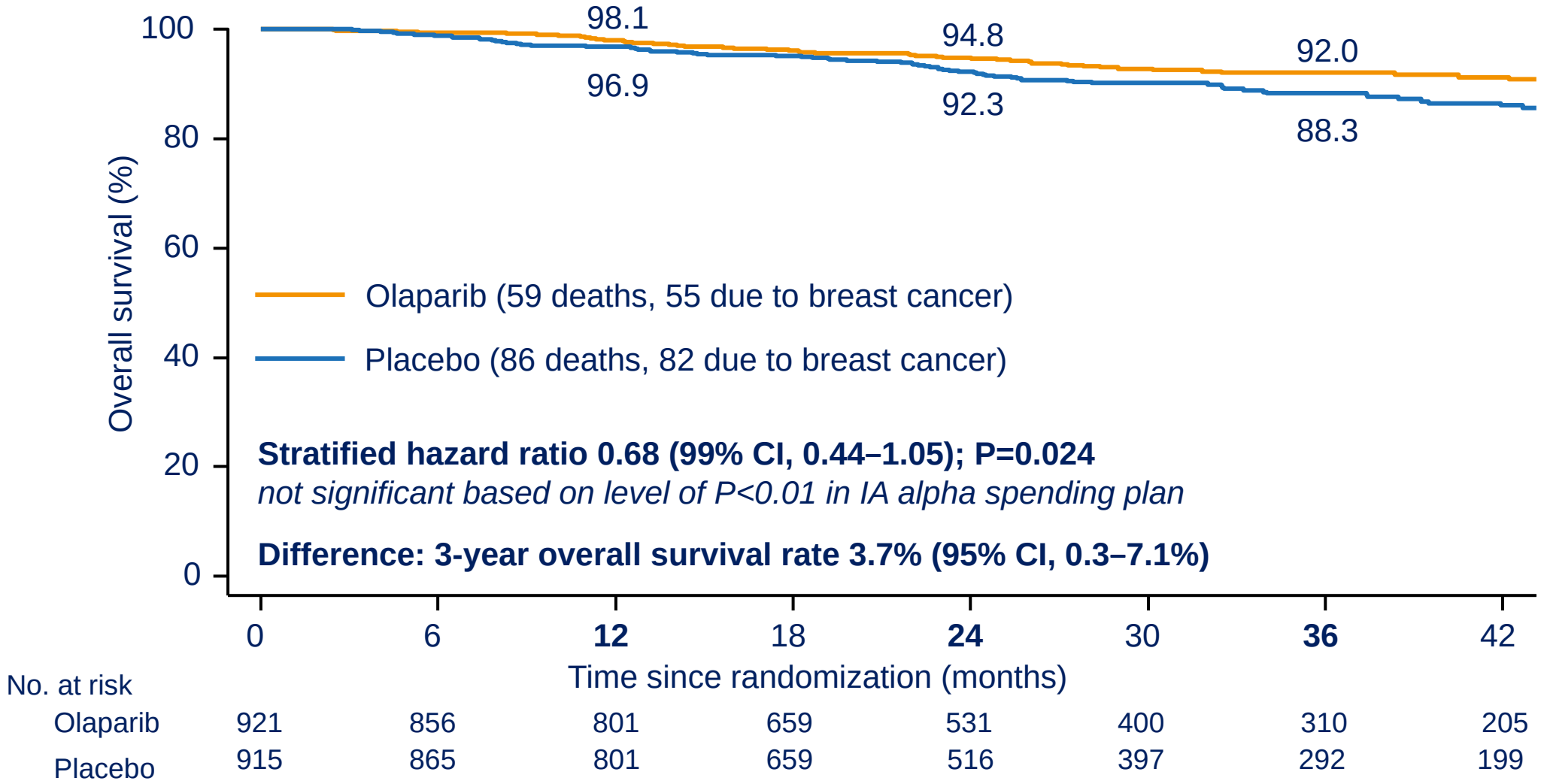
OS
P<0.01



No. at risk

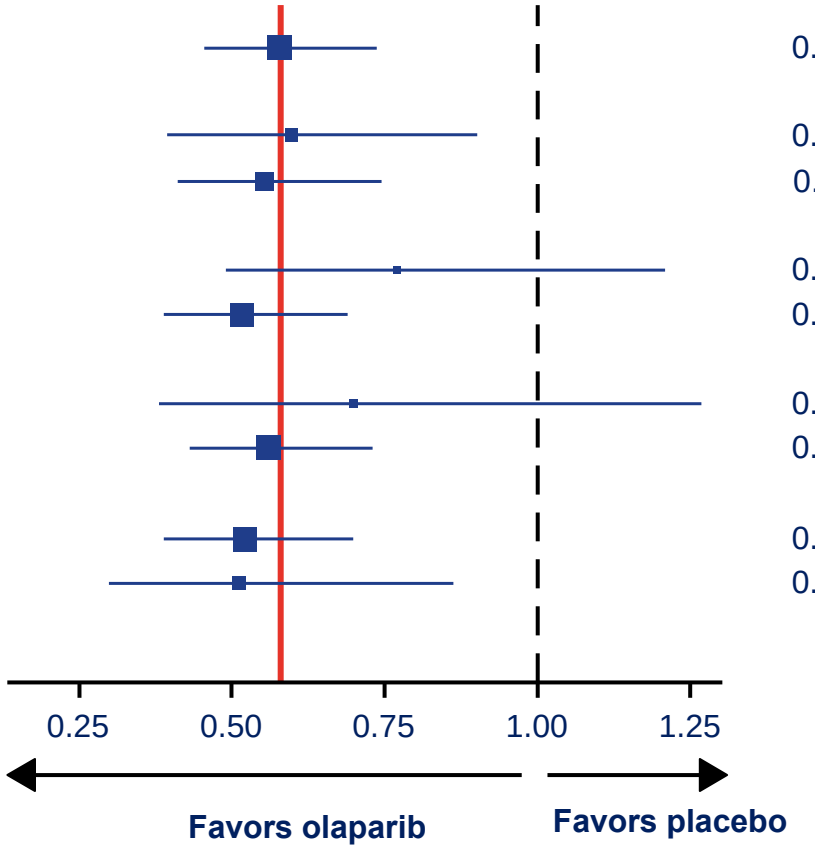
Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

OlympiA: Overall survival



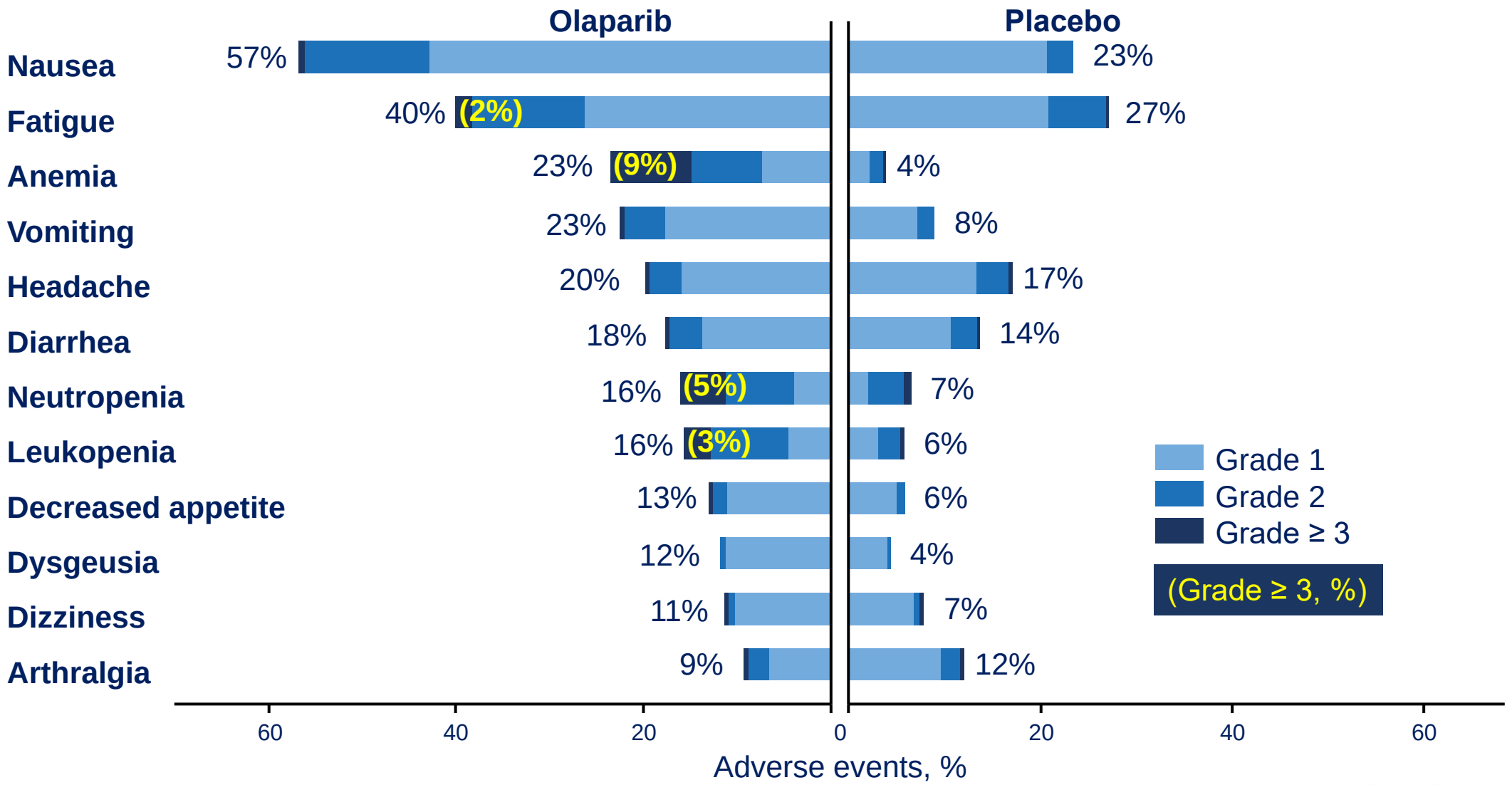
OlympiA: Subgroup analysis invasive disease-free survival

Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive-disease-free survival	P value for heterogeneity
	No. of patients with an invasive-disease event/total no.			
All patients	106 / 921	178 / 915	0.581 (0.455–0.737)	NA
Prior chemo				0.763
Adjuvant	36 / 461	61 / 455	0.601 (0.394–0.901)	
Neoadjuvant	70 / 460	117 / 460	0.555 (0.411–0.745)	
Prior platinum				0.144
Yes	34 / 247	43 / 239	0.773 (0.490–1.209)	
No	72 / 674	135 / 676	0.520 (0.389–0.689)	
HR status				0.509
HR+/HER2-	19 / 168	25 / 157	0.701 (0.381–1.268)	
TNBC	87 / 751	153 / 758	0.563 (0.431–0.730)	
BRCA				0.998
BRCA1	70 / 558	126 / 558	0.524 (0.389–0.699)	
BRCA2	22 / 230	38 / 209	0.515 (0.300–0.862)	
BRCA1/2 both	0 / 1	0 / 3	NC	



No statistical evidence of heterogeneity between any subgroup and the ITT IDFS treatment effect

OlympiA: Adverse events of any grade ≥ 10%



OlympiA: Summary of adverse events

	Olaparib (N = 911)	Placebo (N = 904)
Any adverse event	835 (91.7%)	753 (83.3%)
Serious adverse event (SAE)	**79 (8.7%)**	**76 (8.4%)**
Adverse event of special interest	**30 (3.3%)**	**46 (5.1%)**
MDS/AML	**2 (0.2%)**	**3 (0.3%)**
Pneumonitis	9 (1.0%)	11 (1.2%)
New primary malignancy	**20 (2.2%)**	**32 (3.5%)**
Grade ≥ 3 adverse event	221 (24.3%)	102 (11.3%)
Grade 4 adverse event	**17 (1.9%)**	**4 (0.4%)**
Adverse event leading to permanent discontinuation of treatment*	**90 (9.9%)**	**38 (4.2%)**
Adverse event leading to death†	1 (0.1%)	2 (0.2%)

Includes adverse events with an onset date on or after the first dose date and up to and including 30 days following date of last dose of study medication. AML denotes acute myeloid leukemia; MDS myelodysplastic syndrome

*Adverse events leading to permanent discontinuation of treatment in the olaparib group that occurring in > 1% were; nausea, anemia and fatigue

†Adverse events leading to death are cardiac arrest (olaparib, n = 1), AML (placebo, n = 1), and ovarian cancer (placebo, n = 1)

OlympiA: Conclusions

- Participants in OlympiA with high risk HER2-negative early breast cancer and germline *BRCA1/2* mutation had significant risk of IDFS and DDFS events despite standard therapies
- Adjuvant olaparib for 1 year after completion of local treatment and (neo)adjuvant chemotherapy, significantly improves both invasive and distant disease-free survival
- Fewer deaths were reported on olaparib, however OS benefit was not significant with median FU of only 2.5 years and as IA specified $P<0.01$; blinded follow-up continues
- Toxicity was limited and manageable without effect on global patient-reported quality of life
- Germline *BRCA1* and *BRCA2* sequencing is an important biomarker in early breast cancer

2021 ASCO ANNUAL MEETING

Dalpiciclib plus fulvestrant versus placebo plus fulvestrant in HR+/HER2− advanced breast cancer that relapsed or progressed on previous endocrine therapy (DAWNA-1): a multicenter, randomized, phase 3 study

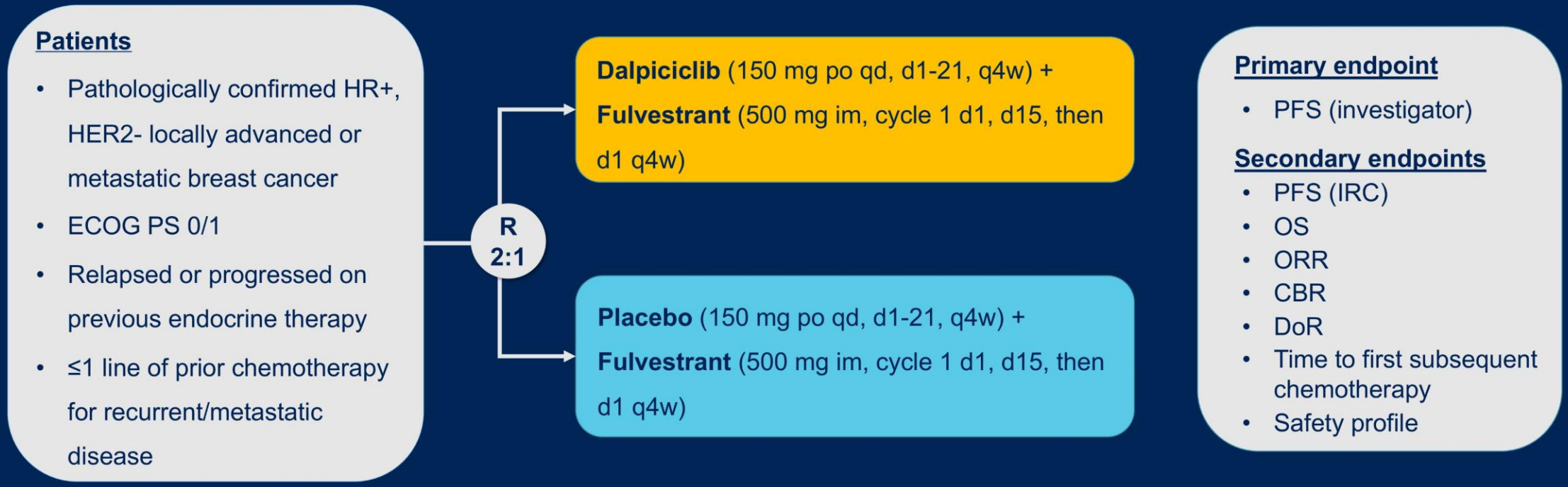
Binghe Xu, MD

National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College

On behalf of Qingyuan Zhang, Pin Zhang, Xichun Hu, Wei Li, Zhongsheng Tong, Tao Sun, Yuee Teng, Xinhong Wu, Quchang Ouyang, Xi Yan, Jing Cheng, Qiang Liu, Jifeng Feng, Xiaojia Wang, Xiaoyu Zhu, Fei Wu, Xiao Zhang, Jianjun Zou, the DAWNA-1 Study Group

June 5, 2021

DAWNA-1: study design



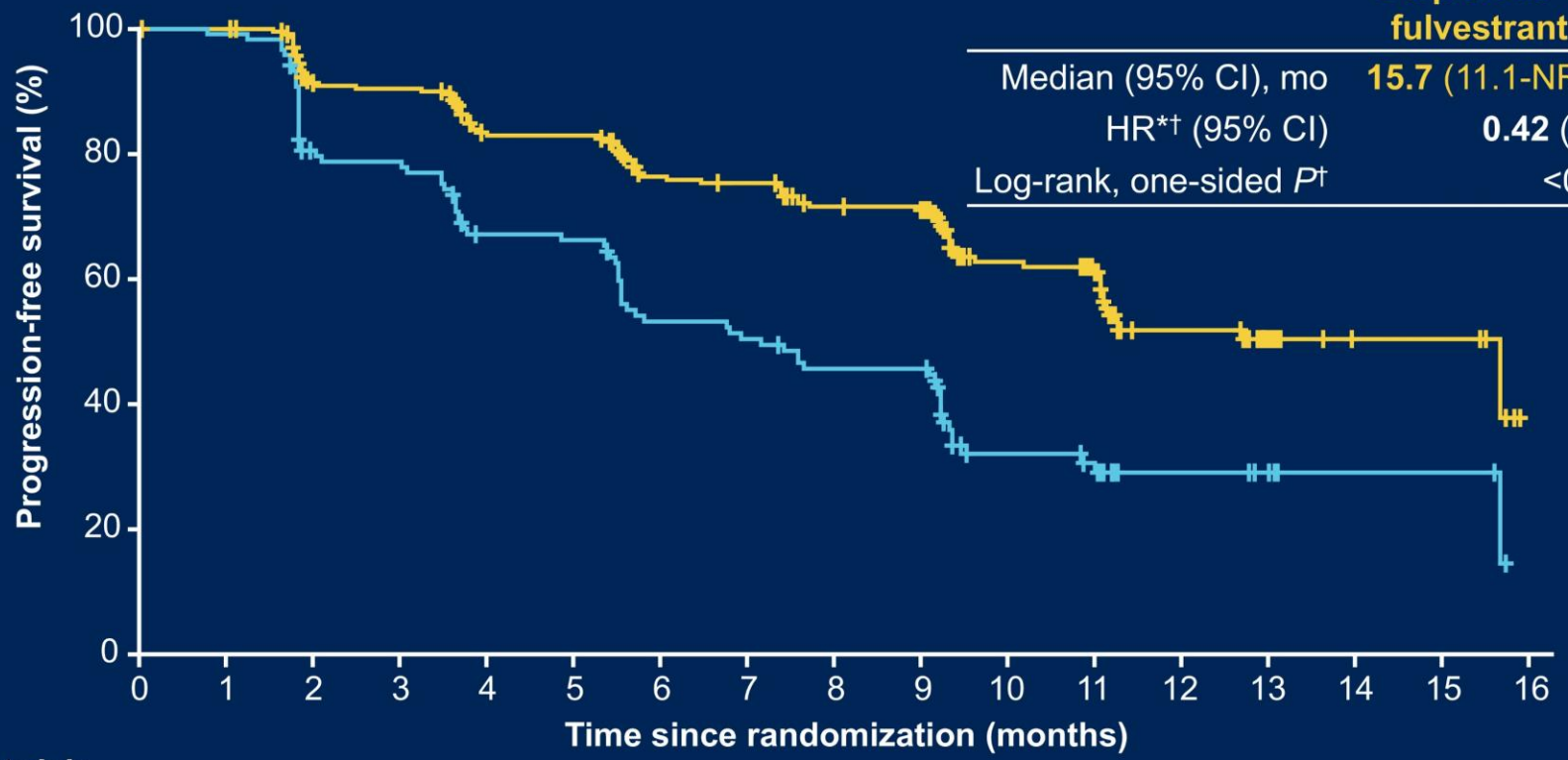
Stratification factors

- Visceral metastasis (yes vs no)
- Menopausal status (postmenopausal vs pre- or perimenopausal)

Tumor response was assessed per RECIST v1.1.
CBR, clinical benefit rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status

Primary endpoint: PFS per investigator

	Dalpiciclib + fulvestrant	Placebo + fulvestrant
Median (95% CI), mo	**15.7** (11.1-NR)	**7.2** (5.6-9.2)
HR*† (95% CI)	**0.42** (0.31-0.58)	
Log-rank, one-sided *P*†	<0.0001	



No. at risk																	
Dalpiciclib + fulvestrant	241	239	204	200	172	171	146	143	131	130	78	72	39	20	6	6	0
Placebo + fulvestrant	120	119	91	89	73	72	57	54	48	48	23	20	9	7	3	3	0

*Estimated using a stratified Cox proportional hazards model. †Analysis stratified by the randomization strata.

AEs occurring in ≥10% of patients in either group

Events, n (%)	Dalpiciclib + fulvestrant (n=240)			Placebo + fulvestrant (n=120)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Hematological toxicities						
Neutropenia	235 (97.9%)	156 (65.0%)	46 (19.2%)	15 (12.5%)	0	0
Leukopenia	233 (97.1%)	149 (62.1%)	0	12 (10.0%)	0	0
Anemia	147 (61.3%)	7 (2.9%)	0	14 (11.7%)	2 (1.7%)	0
Thrombocytopenia	135 (56.3%)	14 (5.8%)	0	10 (8.3%)	0	1 (0.8%)
Lymphopenia	40 (16.7%)	11 (4.6%)	1 (0.4%)	1 (0.8%)	0	0
Non-hematological toxicities						
AST increased	48 (20.0%)	1 (0.4%)	0	31 (25.8%)	1 (0.8%)	1 (0.8%)
Nausea	45 (18.8%)	1 (0.4%)	0	17 (14.2%)	1 (0.8%)	0
ALT increased	36 (15.0%)	0	0	32 (26.7%)	1 (0.8%)	1 (0.8%)
Asthenia	35 (14.6%)	1 (0.4%)	0	17 (14.2%)	0	0
Urinary tract infection	34 (14.2%)	0	0	18 (15.0%)	0	0
Rash	34 (14.2%)	0	0	5 (4.2%)	0	0
Hyperglycemia	29 (12.1%)	0	0	16 (13.3%)	0	0
Upper respiratory tract infection	28 (11.7%)	2 (0.8%)	0	12 (10.0%)	0	0
Hypertriglyceridemia	26 (10.8%)	0	1 (0.4%)	12 (10.0%)	2 (1.7%)	0
Headache	26 (10.8%)	0	0	8 (6.7%)	1 (0.8%)	0
Arthralgia	25 (10.4%)	0	0	8 (6.7%)	0	0
Hypoalbuminemia	25 (10.4%)	0	0	6 (5.0%)	0	0
Blood creatinine increased	25 (10.4%)	0	0	4 (3.3%)	0	0
Hypercholesterolemia	14 (5.8%)	0	0	13 (10.8%)	0	0

All grade 3 or 4 AEs occurring in ≥3% of patients in either group are listed. ALT, alanine aminotransferase; AST, aspartate aminotransferase

Conclusions

- The phase 3 DAWNA-1 met its primary endpoint at the interim analysis, with PFS significantly improved with dalpiciclib + fulvestrant vs placebo + fulvestrant
  - PFS: HR 0.42 (95% CI: 0.31-0.58)
- Benefit of dalpiciclib vs placebo extended beyond initial study treatment
  - Time to first subsequent chemotherapy: HR 0.47 (95% CI: 0.32-0.69)
- Dalpiciclib + fulvestrant demonstrated a tolerable safety profile

These findings support dalpiciclib + fulvestrant as a new treatment option in patients with HR+/HER2- advanced breast cancer who relapsed or progressed on prior endocrine therapy

2021 ASCO ANNUAL MEETING

Trastuzumab Plus Endocrine Therapy or Chemotherapy as First-line Treatment for Metastatic Breast Cancer with Hormone Receptor-positive and Her2-positive: the SYSUCC-002 Randomized Clinical Trial

Zhong-Yu Yuan

Sun Yat-sen University Cancer Center

June 5, 2021

Trial Design

Eligibility criteria

- Aged ≥18 years
- Histology-confirmed MBC
- HR+ HER2+
- Disease-free interval* >12 months

R
1:1

Stratification factors:

- previous adjuvant endocrine therapy (AI / ORM) and disease status (recurrent / *de novo*)

ET group
ORMs or AIs # + trastuzumab

CT group
taxanes, capecitabine, or vinorelbine + trastuzumab

Primary endpoint: Progression-free survival (PFS)

Secondary endpoints: Overall survival (OS), objective response rate (ORR), and Safety

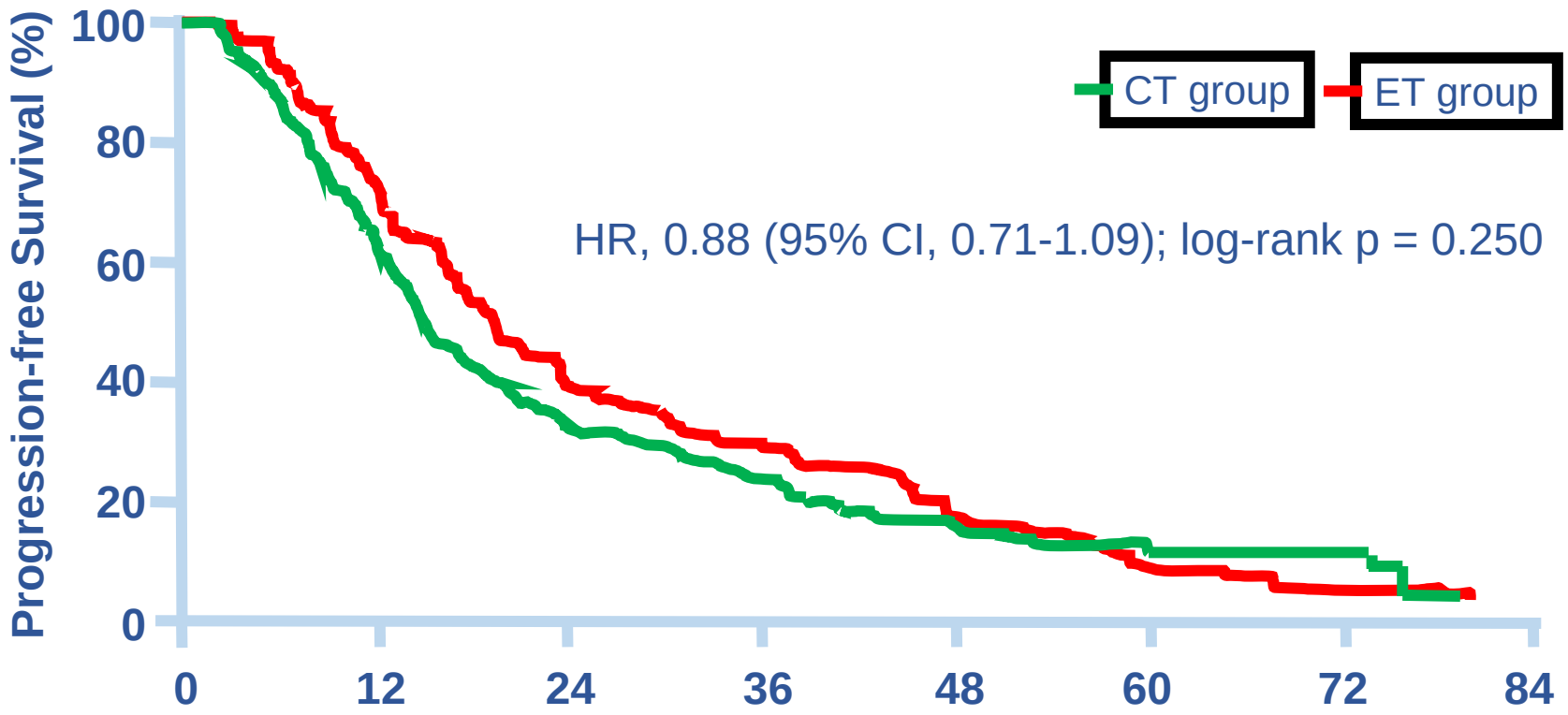
*Disease-free interval defined as the time from the diagnosis of the primary breast cancer to the first recurrence in patients who received (neo)adjuvant therapy) had to be >12 months

#ORMs: oestrogen-receptor modulators, including tamoxifen and toremifene; AIs: aromatase inhibitors, including anastrozole, letrozole, and exemestane

Baseline Patients Characteristics

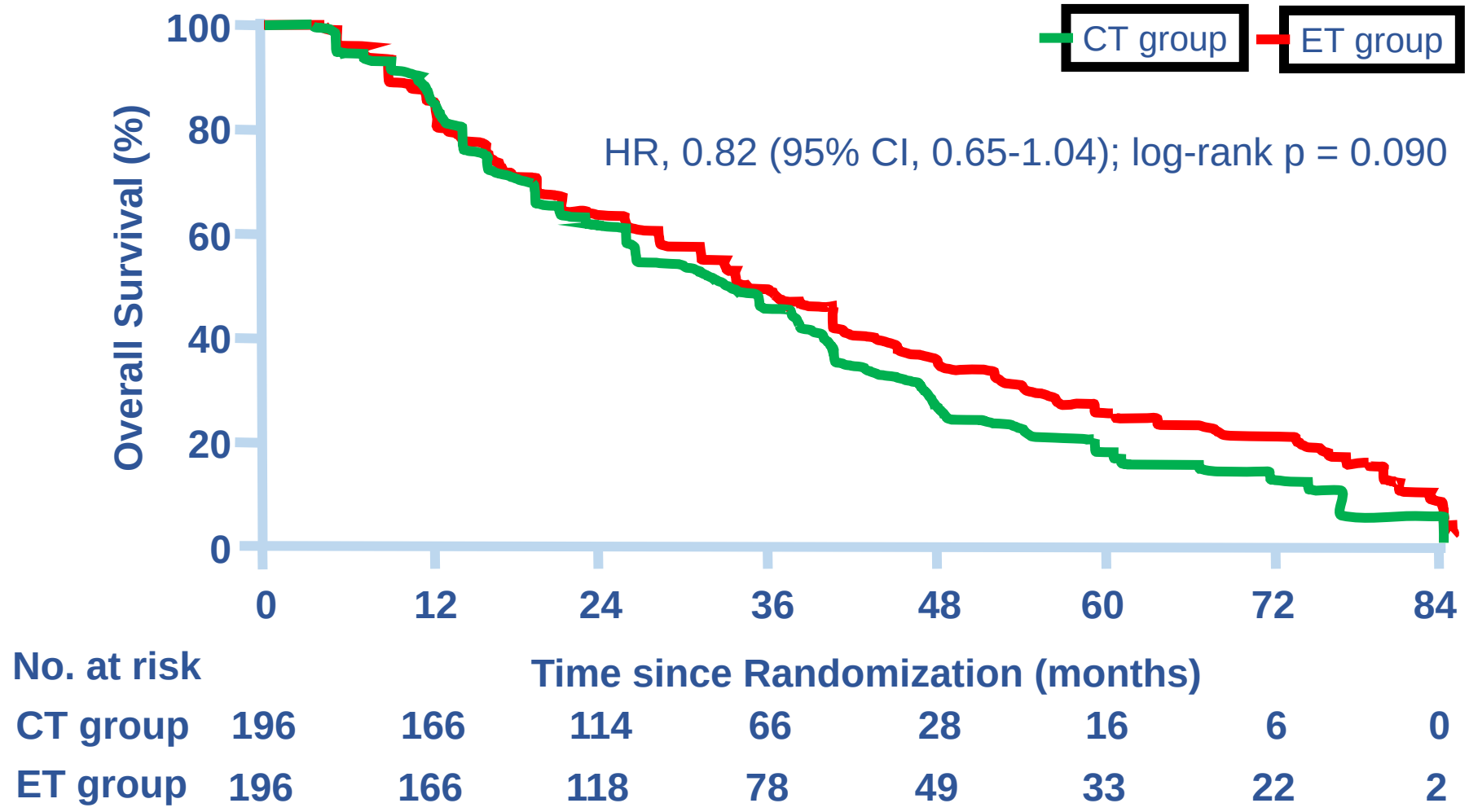
	ET group (N = 196)		CT group (N = 196)	
	n	%	n	%
Disease-free interval				
≤ 24 months	64	32.7	78	39.8
> 24 months	78	39.8	64	32.7
Previous anti-HER2 therapy				
Yes	41	20.9	48	24.5
No	101	51.5	94	48.0
Previous (neo)adjuvant chemotherapy	133	67.9	135	68.9
De novo metastases	54	27.6	54	27.6
Previous adjuvant endocrine therapy				
AIs	83	42.3	83	42.3
ORMs	59	30.1	59	30.1

Progression-Free Survival (primary endpoint)



No. at risk								
CT group	196	124	61	33	16	9	5	0
ET group	196	142	73	50	28	11	4	0

Overall Survival



Conclusion

- Trastuzumab plus endocrine therapy was non-inferior to and had fewer toxicities compared with trastuzumab plus chemotherapy in patients with HR+HER2+ MBC
- Exploratory analyses revealed that trastuzumab plus endocrine therapy was likely to be more beneficial in patients with a DFI >24 months
- Exploratory analyses revealed that trastuzumab plus chemotherapy was likely to be more beneficial in patients with a DFI ≤24 months

2021 ASCO ANNUAL MEETING

TREATMENT-RELATED SIDE EFFECTS AND VIEWS ABOUT DOSAGE ASSESSMENT TO SUSTAIN QUALITY OF LIFE:

RESULTS OF AN ADVOCATE-LED SURVEY OF PATIENTS WITH METASTATIC BREAST CANCER (MBC)

Anne Loeser,* Jeffrey Peppercorn, Mark E. Burkard, Kevin Kalinsky, Hope Rugo, Aditya Bardia

* Founder, Patient-Centered Dosing Initiative

SURVEY RATIONALE

BACKGROUND

- MBC is treatable, not curable
- Most patients remain on treatment indefinitely
- Usually no distinction between dosages for MBC vs. early-stage
- Recommended Starting Dose typically based on Phase 1 dose escalation trials
- Phase 1 trials → RP2D / Maximum Tolerated Dose (MTD)

- **PARADIGM: HIGHER DOSE/TOXICITY ~ GREATER EFFICACY**

PARADIGM CHALLENGES

- Toxicity not entirely relevant for targeted therapies
- "Real world" patient responses/tolerability may vary
- Treatment-related toxicities may
  - degrade QOL
  - occasionally be fatal
- MDA retrospective analysis - lower starting capecitabine dose improved tolerability / preserved efficacy

<u>NEW PARADIGM</u>: PERSONALIZE STARTING DOSE IN CLINICAL PRACTICE BASED UPON PATIENT ATTRIBUTES

PATIENT-CENTERED DOSING INITIATIVE (PCDI)

MBC patient advocates/Advisory Board of medical oncologists

WHAT WOULD PATIENTS SAY?

GOALS AND METHODS

SPECIFIC OBJECTIVES

1. Prevalence/severity of side effects
2. Physician-patient communication
3. Effect of dose reduction on QOL
4. Patients' willingness to discuss alternate allowed dosing opportunities

PREPARATION

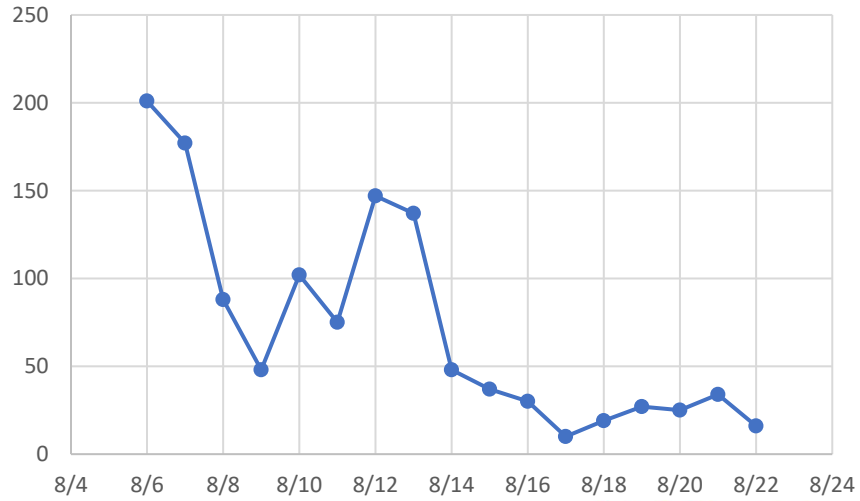
- Questions created by patient advocates
- "Piloted" the survey → 32 patients
- Final online, anonymous version
  - 27 questions
  - approved by Advisory Board
- Inclusion: US patients with MBC ≥ 18 ys.
- IRB Exempt Determination

GOAL: UNDERSTAND TOLERABILITY FROM PATIENTS' PERSPECTIVES + WILLINGNESS TO DISCUSS INDIVIDUALIZED DOSING OPTIONS

ROLLOUT

Social media, online support groups, email lists, breast cancer organization newsletters

Responses by Day Aug., 2020



SUMMARY

1,221 patients have spoken…

Objective 1: Prevalence/Severity of Side Effects:

- 86% had ≥ 1 bad side effect
  - 20% visited ER/hospital
  - 43% missed ≥ 1 treatment

Objective 2: Level of Physician/Patient Communication:

- 98% of patients with SE's told their doctor
- 82% received assistance

Objective 3: Effect of Dose Reduction on QOL:

- 83% given a dose reduction felt better

Objective 4: Patients' Willingness to Discuss Alternate Dosing Options:

- 92% would discuss dosages with physicians based on personal attributes

NEXT STEPS:
PATIENT-CENTERED DOSING INITIATIVE

"and more studies are needed…"

1) Medical Oncologists Survey

2) Compare Patient and Oncologists Survey Results

3) Engage Industry re: Dosage Level Efficacy

Retroactively

Outcomes of patients on lower doses due to Adverse Events vs. MTD

Proactively

Integrate comparative outcomes into clinical trial design