2024 ASCO® ANNUAL MEETING

Association of MammaPrint index and 3-year outcome of patients in the FLEX Registry trial with HR+HER2- early-stage breast cancer treated with chemotherapy with or without anthracycline

Joyce O'Shaughnessy[1], Cathy Lynne Graham[2], Pat Whitworth[3], Peter D. Beitsch[4], Cynthia R. C. Osborne[5], Rakhshanda Layeequr Rahman[6], Eric Allen Brown[7], Linsey P. Gold[7], Nathalie McDowell Johnson[8], Adam Brufsky[9], Harshini Ramaswamy[10], Nicole Stivers[10], Andrea Menicucci[10], William Audeh[10], **FLEX Investigators' Group**

[1]Baylor University Medical Center, Texas Oncology, The US Oncology Network, Dallas, TX; [2]Emory University, Atlanta, GA; [3]Nashville Breast Center, Nashville, TN; [4]Dallas Surgical Group, Dallas, TX; [5]Texas Oncology PA, Dallas, TX; [6]Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX; [7]Comprehensive Breast Care, Troy, MI; [8]Legacy Health System, Portland, OR; [9]University of Pittsburgh, Pittsburgh, PA; [10]Medical Affairs, Agendia, Inc., Irvine, CA

Lead with the End: Conclusions

- In the real-world FLEX Registry trial, patients with MammaPrint High 2, BluePrint Luminal B, HR+ HER2- EBC have higher 3-yr RFS rate with AC-T than with TC therapy (non-randomized)
- AC-T-treated High 1 and High 2 patients were significantly more likely to be premenopausal, node-positive and have larger cancers (adverse prognostic features) than those treated with TC. Thus, some High 1 pts may benefit from AC-T > TC
- These real-world data suggest that MammaPrint High 2 HR+ HER2- EBC pts may benefit from the addition of doxorubicin to taxane/cyclophosphamide therapy. However, validation within other studies is needed

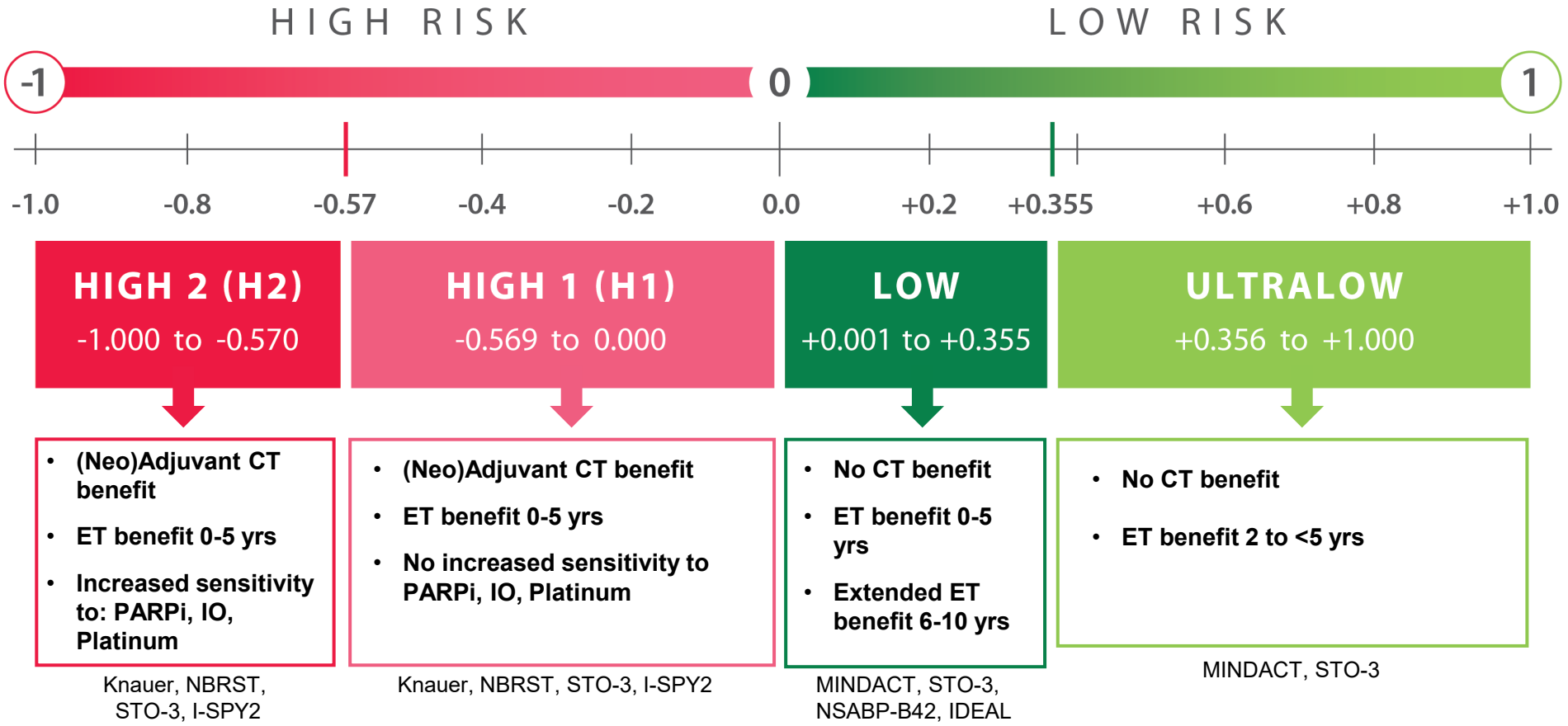
Background: Who benefits from adjuvant anthracyclines?

- The Anthracyclines in Early Breast Cancer (ABC) Trials showed that docetaxel-cyclophosphamide (TC) was **not** non-inferior to an anthracycline-based regimen (TaxAC) regarding invasive disease-free survival (IDFS) in high risk HER2- breast cancer
- However, benefit from the anthracycline was modest:
  - 1.6% improvement in 5-year IDFS ($p = 0.08$)
  - 2.8% improvement in 5-year Recurrence-Free Interval (RFI) ($p = 0.0003$)
- 5-year RFI with TaxAC vs TC stratified by ER status:
  - Significant for ER- HER2- breast cancer (HR=1.90 [1.39-2.61]; $p < 0.0001$)
  - Non-significant for ER+ HER2- (HR=1.19 [0.96-1.47]; $p = 0.11$)
- Genomic classifiers that predict risk of recurrence may identify subsets of patients with HR+HER2- early breast cancer (EBC) who could benefit from addition of an anthracycline

References: Geyer et al., J Clin Oncol 2024

70-gene MammaPrint test: Implications for ET and CT Decisions

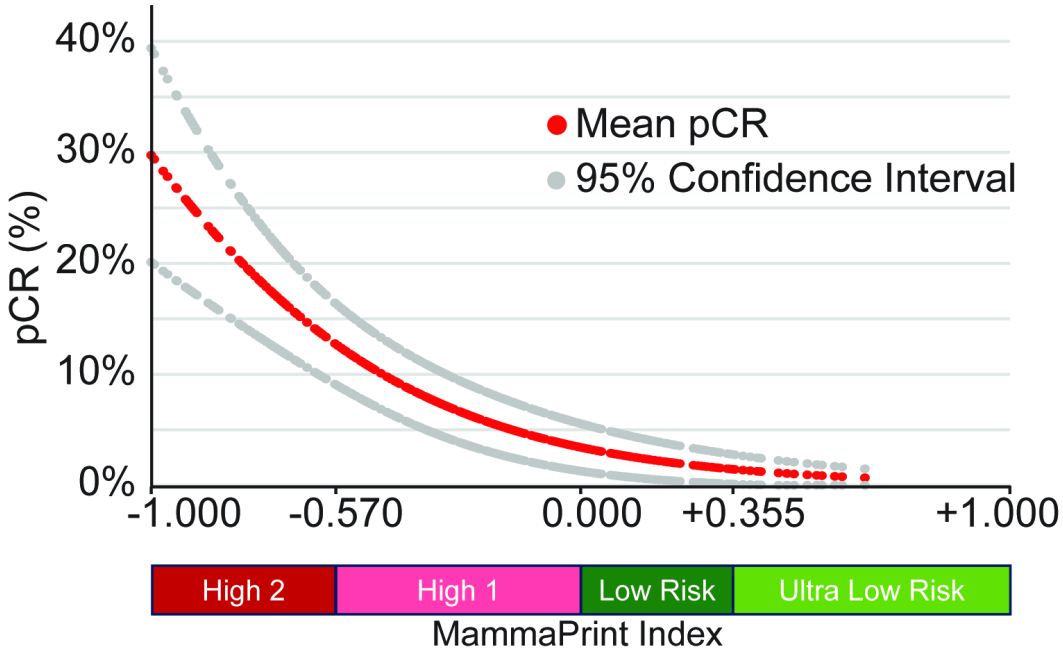
- MammaPrint classifies patients with HR+HER2- EBC as having an Ultra Low, Low, High 1, or High 2 risk of distant recurrence



References: **Knauer (**Breast Cancer Res Treat 2010**), NBRST** (Whitworth, Ann Surg Oncol 2022), **STO-3** (van't Veer, Breast Cancer Res Treat, 2017; Esserman, JAMA Onc, 2017), **I-SPY2** (https://www.ispytrials.org/i-spy-platform/i-spy2; Pusztai, Cancer Cell 2021), **MINDACT** (Piccart, Lancet Oncol, 2021; Lopes Cardozo, JCO, 2022), **NSABP-B42** (Rastogi, ASCO, 2021), **IDEAL** (Liefers, SABCS, 2022)

MammaPrint High 2 predicts increased chemosensitivity in HR+HER2- Early Breast Cancer

- About 1/3 of MP high risk HR+HER2- EBCs are High 2 and 2/3 are High 1
- Patients with HR+HER2- EBC were more likely to achieve pCR with neoadjuvant chemotherapy with MP High 2 than with MP High 1 disease (NBRST, Whitworth et al., 2017)

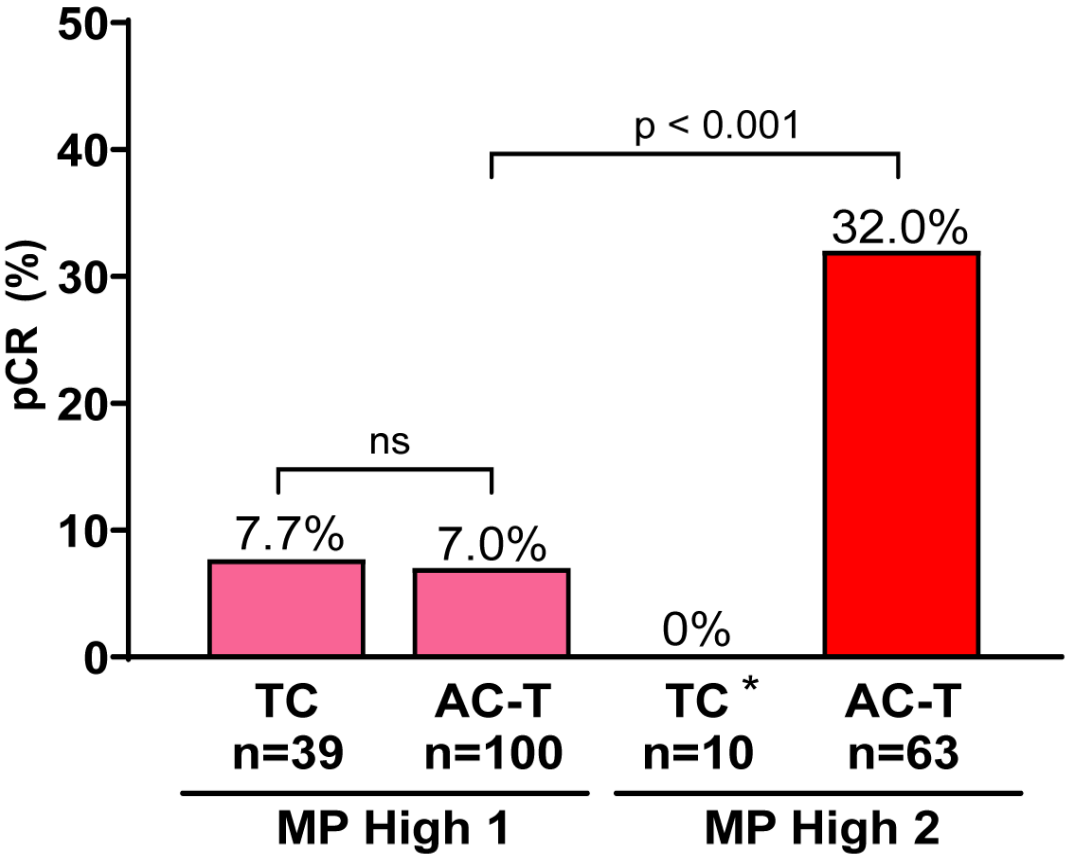


MP High 2 cancers had significantly higher pCR rates compared to MP High 1 cancers

Study	pCR% to neoadjuvant chemotherapy		
	High 1	High 2	P-Value
I-SPY2 (Pusztai et al, Cancer Cell, 2021)	10.0% (n=109)	22.0% (n=49)	<0.05
NBRST (Beitsch et al, ASCO 2023)	6.1% (n=198)	23.3% (n=129)	<0.0001
FLEX (O'Shaughnessy et al, SABCS 2023)	6.3% (n=142)	29.2% (n=72)	<0.01

MammaPrint High 2 associated with increased sensitivity to neoadjuvant anthracycline therapy in HR+HER2- EBC in the FLEX Registry Trial

- Among High 1 cancers, pCR rates with AC-T/TAC vs TC were comparable
- No High 2 cancer (n=10) developed pCR with TC
- pCR rate with AC-T/TAC was significantly higher in High 2 compared to High 1 (p<0.001) cancers



*insufficient sample size in TC treated group for High 2 comparison

Reference: Figure adapted from Audeh et al., 2024, Miami Breast Cancer Conference, Poster #36

Evaluating the association between MammaPrint and anthracycline benefit using real world data

Objective: Evaluate association of MP Index and 3-year Recurrence-Free Survival in HR+HER2- EBC patients treated with taxane and cyclophosphamide (TC) or with anthracycline + taxane (AC-T) chemotherapy (CT)

Methods

- **FLEX Registry Trial** (NCT03053193): Prospective observational study enrolling stage I-III patients whose breast cancers are analyzed for MammaPrint Index and who consent to full somatic genome evaluation and clinical data collection
- **Patients**: 614 patients with HR+HER2- early breast cancer with MP High Risk, BluePrint Luminal B-Type tumors who received CT and had at least 3 years of follow-up since diagnosis. High Risk cancers were classified as High 1 or High 2. Patients treated with SOC CT at physician discretion
- **Endpoint**: Recurrence Free Survival (RFS) defined as time from diagnosis to local-regional recurrence, distant recurrence, or breast cancer-specific death (STEEP 2.0, Tolaney et al., 2021)
- **Statistical Considerations**: Differences in clinical characteristics and 3-year RFS shown using Chi-squared or Fisher's Exact Test, or Kaplan-Meier analysis and log-rank test, respectively

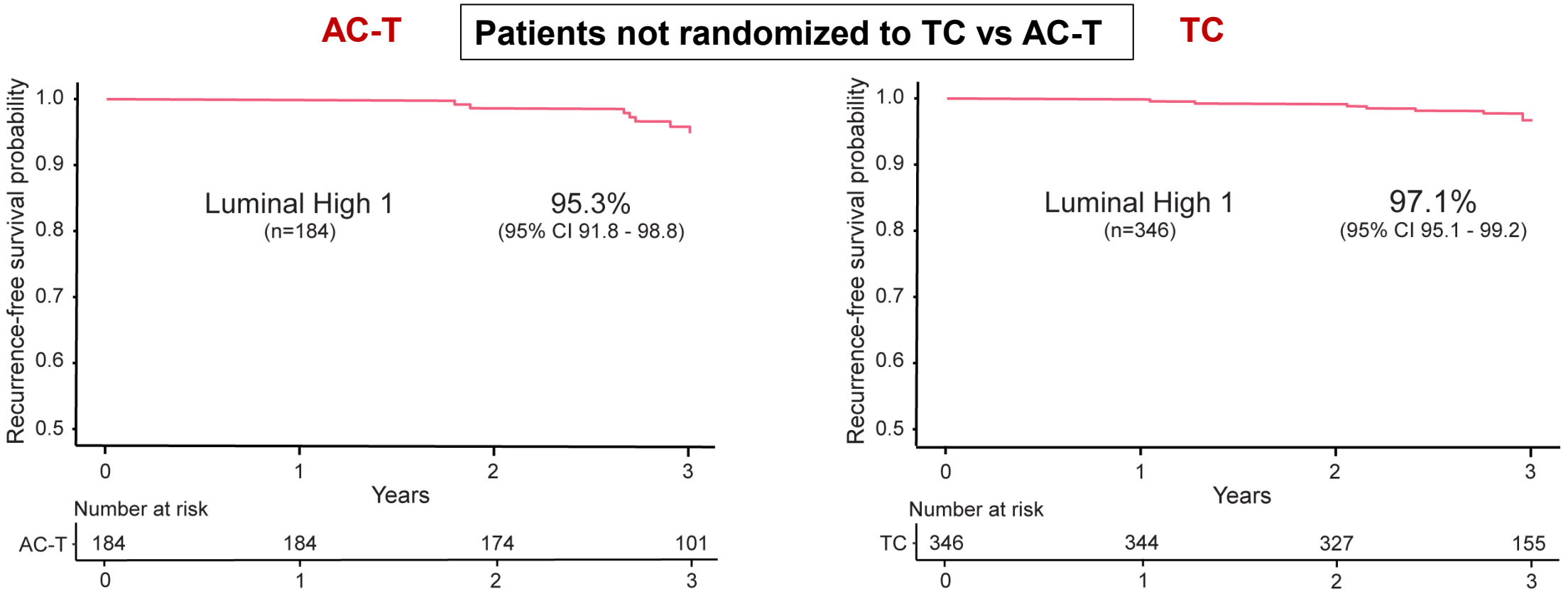
PRESENTED BY: Joyce O'Shaughnessy, MD, Texas Oncology, Sarah Cannon Research Institute

Characteristics of Luminal MP High Risk HR+ HER2- EBC Patients

- 86% of HR+ HER2- MP high risk cancers were MP High 1 (N=530); 14% were MP High 2 (N=84)
- Age, menopausal status, race, T stage, and lymph node status were comparable between patients with High 2 vs High 1 tumors
- 56% of MP High 2 were grade 3 vs 24% of MP High 1
- About 1/2 of High 2 pts received AC-T
- About 1/3 of High 1 received AC-T
- High 1 and High 2 AC-T-treated pts were significantly more likely to be premenopausal, and have higher T and N stage (data not shown)

Characteristic, n (%)	MP High1 (n=530)	MP High2 (n=84)	Overall (n=614)	P-value
Age (Years)				
Mean (SD)	58 (± 11)	55 (± 12)	58 (± 11)	0.131
Menopausal Status				
Post-	361 (74.3%)	54 (69.2%)	415 (73.6%)	0.618
Pre-/Peri-	125 (25.7%)	24 (30.8%)	149 (26.4%)	
Race				
White	410 (81.3%)	58 (72.5%)	468 (80.1%)	0.587
Black	53 (10.5%)	12 (15.0%)	65 (11.1%)	
Latin American	24 (4.8%)	8 (10.0%)	32 (5.5%)	
AAPI	14 (2.8%)	1 (1.3%)	15 (2.6%)	
Other	3 (0.6%)	1 (1.3%)	4 (0.7%)	
T Stage				
T1	227 (61.5%)	27 (45.8%)	254 (59.3%)	0.156
T2	126 (34.1%)	25 (42.4%)	151 (35.3%)	
T3	14 (3.8%)	6 (10.2%)	20 (4.7%)	
T4	2 (0.5%)	1 (1.7%)	3 (0.7%)	
N Stage				
Node Negative	275 (78.1%)	36 (65.5%)	311 (76.4%)	0.125
Node Positive	77 (21.9%)	19 (34.5%)	96 (23.6%)	
Grade				
G1	75 (14.9%)	3 (3.7%)	78 (13.4%)	<0.001
G2	308 (61.4%)	33 (40.7%)	341 (58.5%)	
G3	119 (23.7%)	45 (55.6%)	164 (28.1%)	
CT Regimen				
AC-T/TAC	184 (34.7%)	44 (52.4%)	228 (37.1%)	0.01
TC	346 (65.3%)	40 (47.6%)	386 (62.9%)	

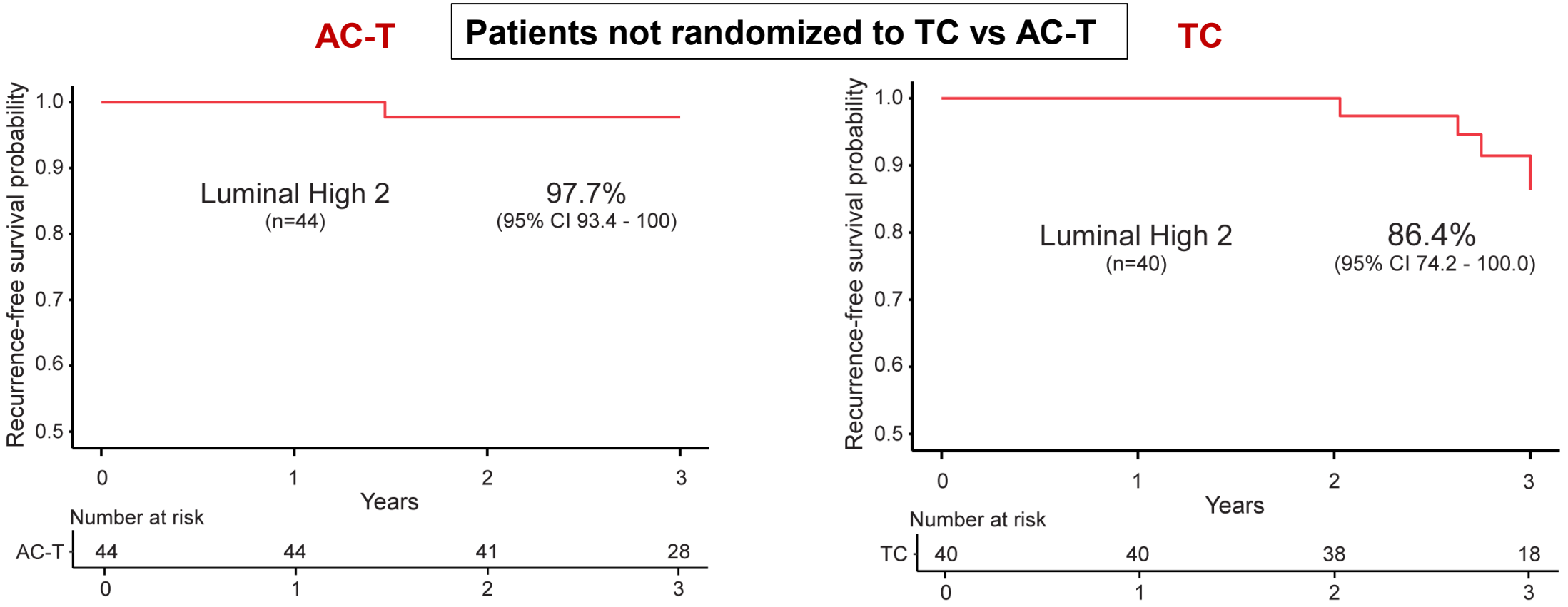
3-Year RFS in Luminal MP High 1 Patients with AC-T or TC



- Comparable 3-year RFS rates among High 1 tumors treated with TC or with AC-T

PRESENTED BY: Joyce O'Shaughnessy, MD, Texas Oncology, Sarah Cannon Research Institute

3-Year RFS in Luminal MP High 2 Patients with AC-T or TC



- High 2 tumors had worse outcomes treated with TC vs High 2 tumors with AC-T

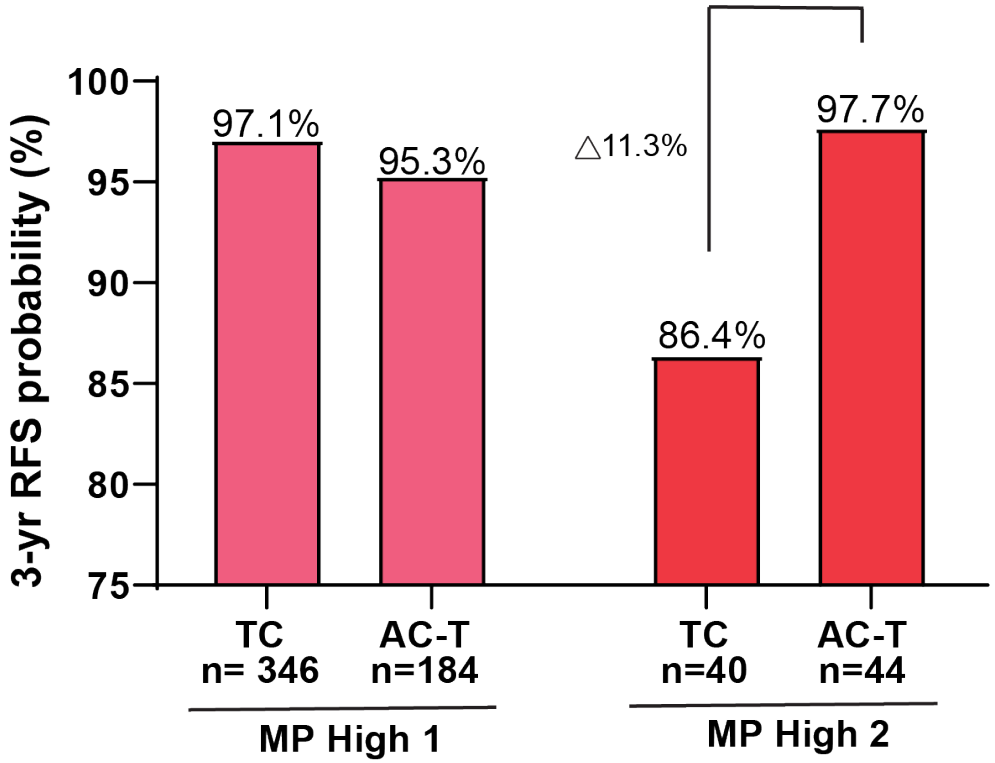
PRESENTED BY: Joyce O'Shaughnessy, MD, Texas Oncology, Sarah Cannon Research Institute

MammaPrint High 2 may be associated with benefit from anthracycline therapy

Chemotherapy Regimen	High 1	High 2
TC (N=386)	97.1% (95.1 - 99.2)	86.4% (74.2 - 100.0)
AC-T/TAC (N=228)	95.3% (91.8 - 98.8)	97.7% (93.4 - 100.0)
Difference in 3-yr RFS	-1.8%	11.3%

Patients not randomized to TC vs AC-T

- Similar 3-yr RFS rates for High 1 patients treated with AC-T or TC
- Higher 3-yr RFS rate for High 2 patients treated with AC-T than with TC



PRESENTED BY: Joyce O'Shaughnessy, MD, Texas Oncology, Sarah Cannon Research Institute

Conclusions

- In the real-world FLEX Registry trial, pts with MammaPrint High 2, BluePrint Luminal B, HR+ HER2- EBC have higher 3-yr RFS rate with AC-T than with TC therapy (non-randomized)
- Luminal MP High 1 patients have similar 3-yr RFS rates with adjuvant TC as with AC-T
- AC-T-treated High 1 and High 2 patients were significantly more likely to be premenopausal, node-positive and have larger cancers (adverse prognostic features) than those treated with TC. Yet, AC-T-treated High 2 patients had better outcome than TC-treated High 2 pts.
- Continued accrual to total of 30,000 EBC patients with 10-years follow-up is planned within the FLEX trial
- These preliminary findings are consistent with knowledge of High 2 Biology:
    - **Is similar to TNBC** → Rios-Hoyo et al., Poster #573 on 6/2 at 9am
    - **Has immune-activated state** → Cobain et al., Oral Session #506 on 6/3 3-6pm
- These real-world data suggest that MammaPrint High 2 HR+ HER2- EBC pts may benefit from the addition of doxorubicin to taxane/cyclophosphamide therapy. However, validation within other studies is needed

Acknowledgements

- We would like to thank the >16,000 patients enrolled in FLEX Trial to date
- FLEX study site investigators, coordinators, research nurses and personnel

FLEX Trial Information

- MammaPrint, BluePrint, and **F**ull-genome Data **L**inked With Clinical Data to **E**valuate New Gene E**X**pression Profiles (FLEX) (NCT03053193)
- Agendia, Inc.