Penn Medicine
Abramson Cancer Center

Review of Breast Cancer Highlights from the 2020 International Oncology Meeting

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I have nothing to disclose

2020 Annual ASCO meeting: Locoregional

- Abstract LBA2: A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: A trial of the ECOG-ACRIN Research Group (E2108). Khan et al.

- Abstract 508: Primary results of NRG Oncology/NSABP B-43: Phase III trial comparing concurrent trastuzumab (T) and radiation therapy (RT) with RT alone for women with HER2-positive ductal carcinoma in situ (DCIS) after lumpectomy. Cobleigh et al.

*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. Thank you.

Abstract LBA2:Early Local therapy in Stage IV breast cancer

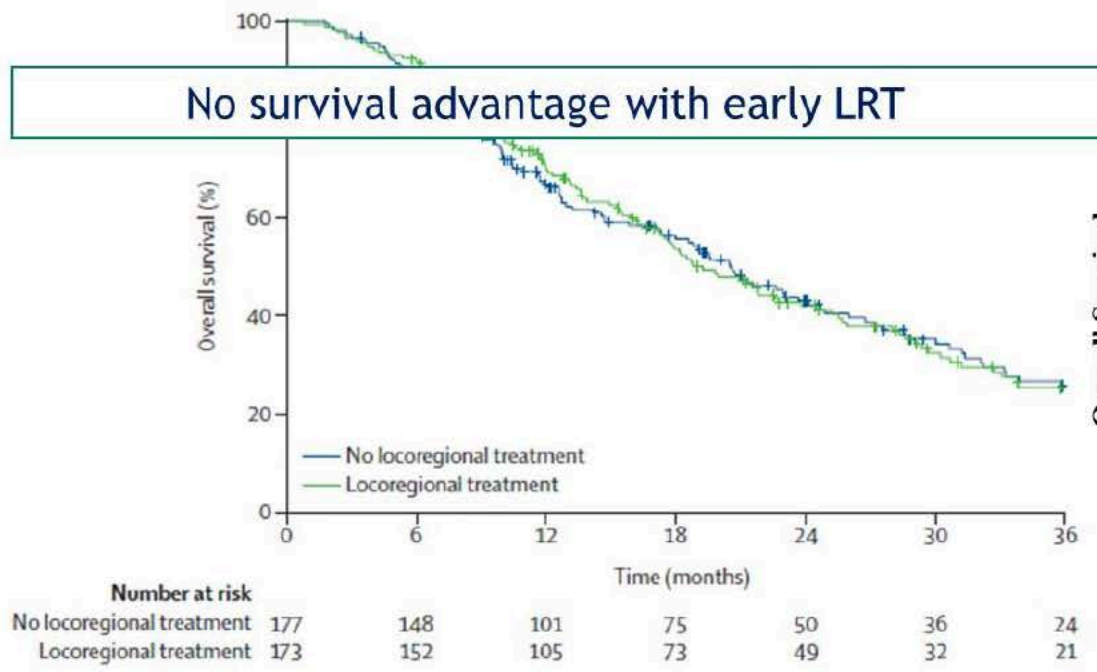
- About 6% of newly diagnosed breast cancer patients present with Stage IV disease and and an intact primary tumor (IPT)

- Locoregional treatment (LRT) for the IPT is hypothesized to improve survival based on retrospective analyses.
  - Studies were biased: women receiving surgery were younger, had smaller tumors, more ER + disease and lower metastatic burden.

Completed randomized trials testing the value of LRT in *de novo* Stage IV breast cancer have provided conflicting data.

Tata memorial Hospital, Mumbai, India

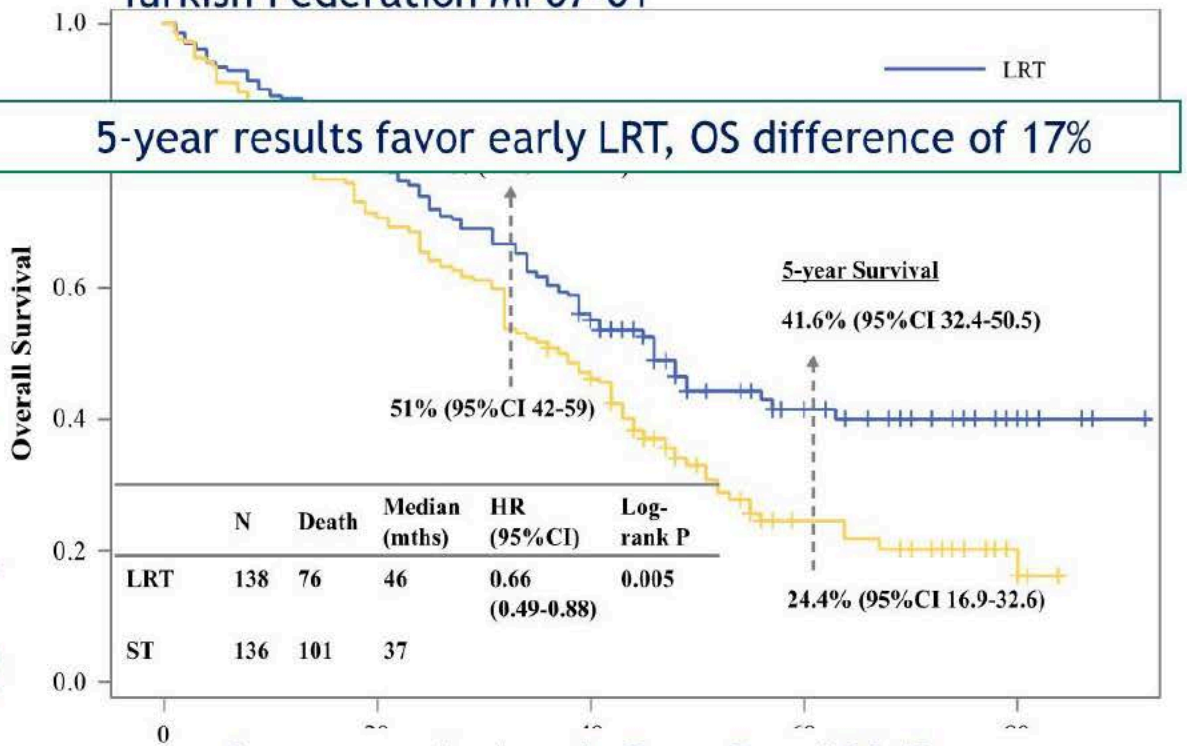
No survival advantage with early LRT



Badwe et. al. *Lancet Oncol* 2017

Turkish Federation MF07-01

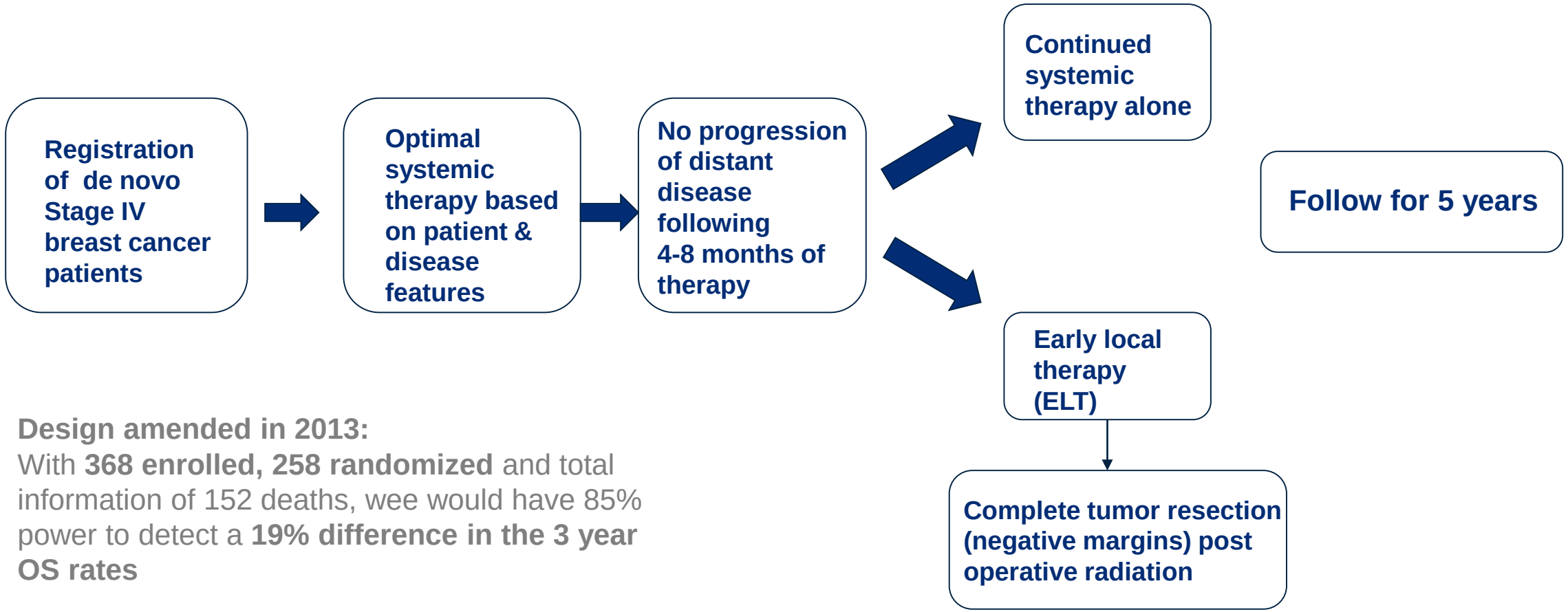
5-year results favor early LRT, OS difference of 17%



Soran et. al. *Annals Surg Oncol* 2018

Design of E2108

- Opened in 2011, last patient enrolled 2015



Design amended in 2013:
With **368 enrolled, 258 randomized** and total information of 152 deaths, wee would have 85% power to detect a **19% difference in the 3 year OS rates**

Design of E2108: Endpoints

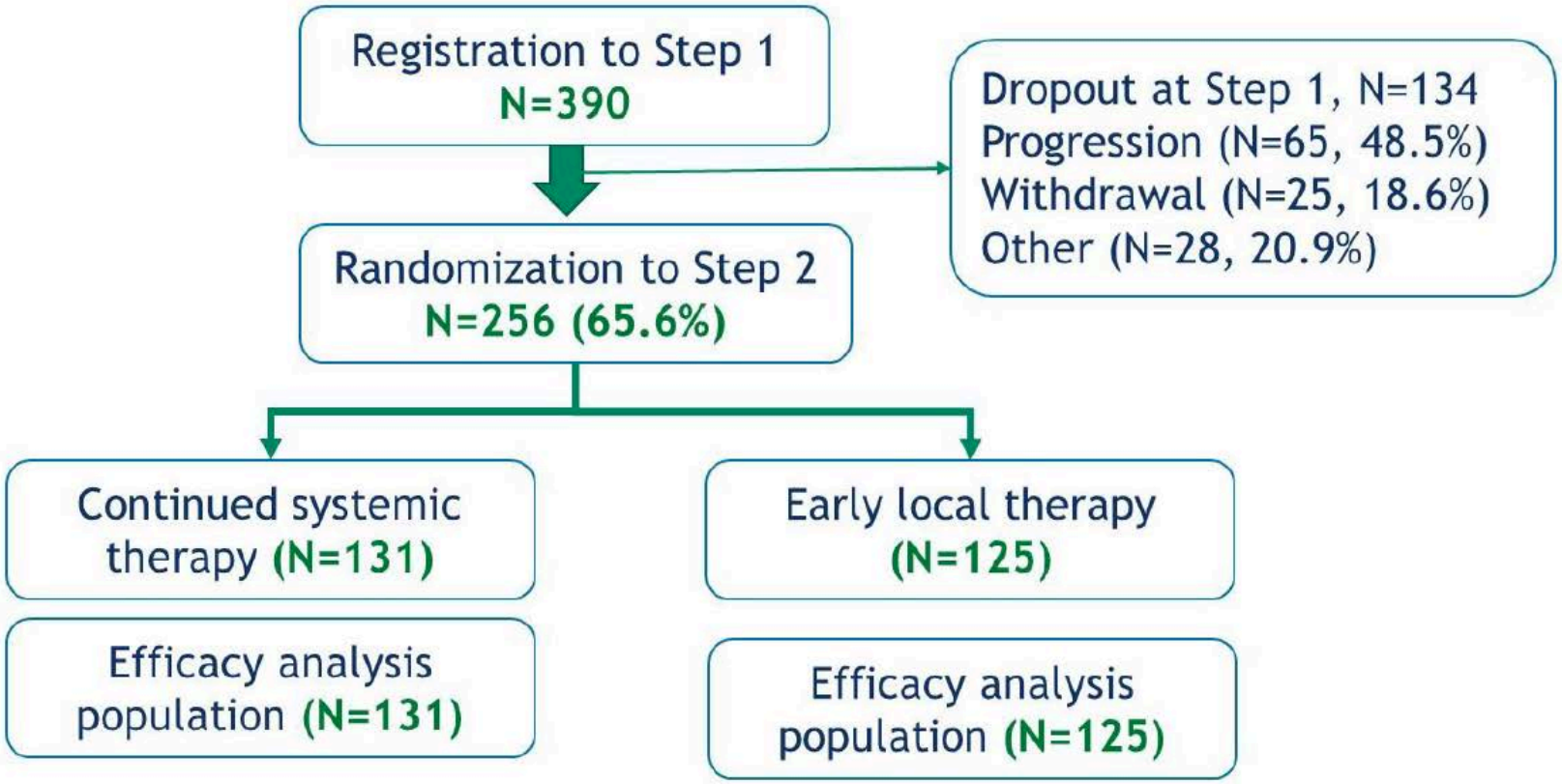
Primary

- Overall Survival

Secondary

- Time to locoregional progression
- Health related quality of life
- Absolute value of circulating tumor cell burden
- Collection of biological samples

E2108 study: Consort Diagram



Participant Characteristics

	Registered (N=390)	Not randomized (N=134)	Randomized (N=256)	P
Median Age in years (range)		57 (29-84)	56 (25-86)	0.54
Race/ethnicity	% of 390	% of 134	% of 256	
European	77.3	104 (80.6)	200 (82.3)	0.51
African	15.8	24 (18.6)	38 (15.6)	
Latina	8.4	9 (7.2)	24 (10.3)	0.33
Postmenopausal	249/390	68.7%	63.9%	0.45
Breast cancer subtype	% of 393	% of 134	% of 256	0.07
HR positive & HER2 negative	54.2	58.5	59.6	
Triple negative	10.2	15.4	8.2	
HER2 positive	28.8	26.2	32.2	

Results: Distant disease patterns and initial systemic therapy used

	Registered (N=390)	Not randomized (N=134)	Randomized (N=256)	P
Metastatic sites	% of 390	% of 134	% of 256	
Bone only	31.5	27.1	37.9	0.51
Visceral only	26.4	32.3	24.2	
Bone & visceral	27.2	40.6	40.9	0.33
	% of 373	% of 126	% of 247	
Initial systemic therapy				0.93
Only endocrine therapy	27.2	31.7	31.2	
Chemotherapy ± HER2-directed agent*	54.2	54.8	53.8	
Both endocrine and chemotherapy	13.7	13.5	15.0	

*HER-2 directed therapy was used in 103/113 patients with HER-2 positive tumors

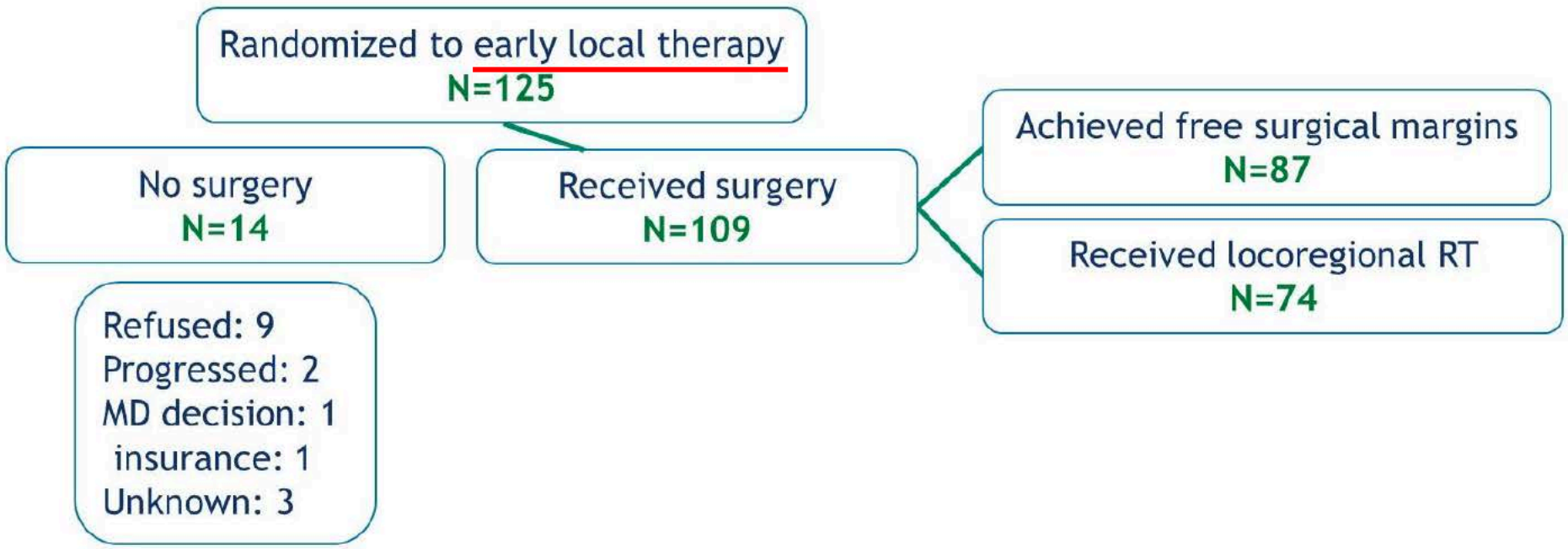
Results: Primary tumor characteristics

	Drop-out during Initial systemic therapy N=134	Randomized to Step 2 Distant disease stable or responding N=256	
Primary tumor	% of 134	% of 256	
T1-3, N0-1	50.4	52.0	
T4 and/or N2-3	49.6	48.0	
Primary tumor palpable	87.2	86.1	0.763
Direct invasion into skin	23.3	11.6	0.003
Skin nodules present	13.5	6.4	0.019
Attached to fascia	24.2	17.9	0.358
No skin involvement or pain	59.1	66.1	0.173

Results: Characteristics of randomized participants, by arm

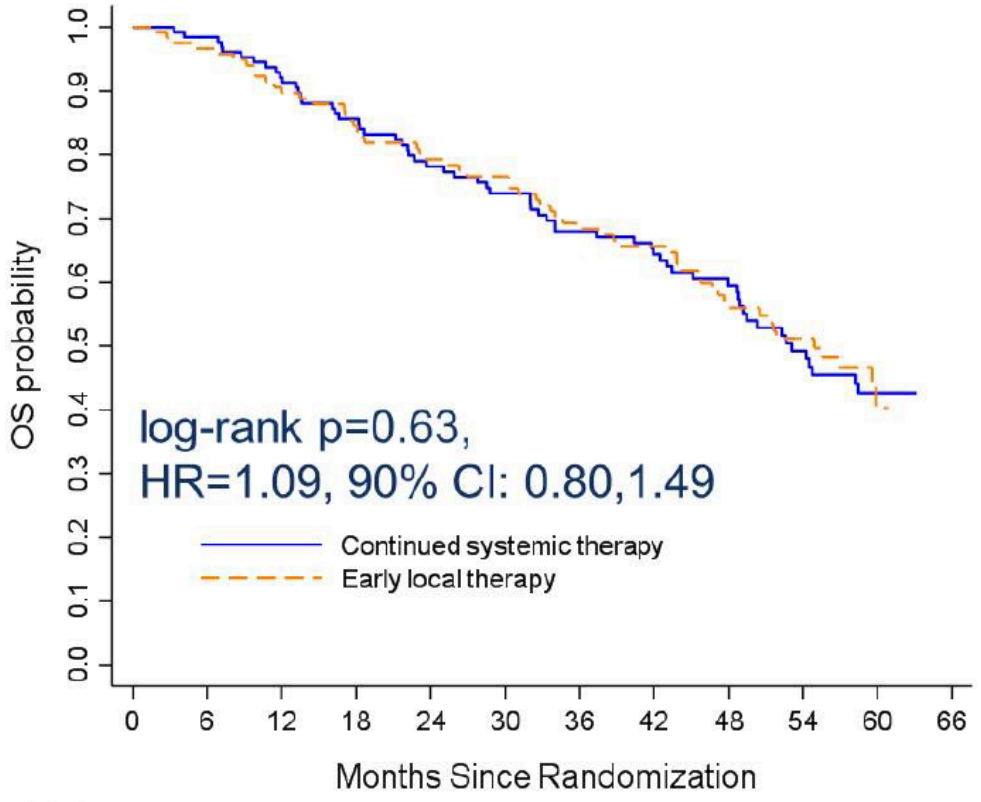
	Continued systemic therapy (N=126)	Early local therapy (N=121)
Median Age in years (range)	56 (25-86)	55 (30-81)
	% of 126	% of 121
Race/ethnicity		
European	82.0	82.0
African	15.3	16
Latina	12	8.6
Single organ system involved	60.3	52.1
Breast cancer subtype		
HR positive & HER2 negative	57	59.0
Triple negative	9.1	7.8
HER2 positive	33.9	33.0

Delivery of locoregional therapy (LRT) in early local therapy arm



Continued systemic therapy: 25 women received surgery (13 the year following randomization and 12 at a later time)

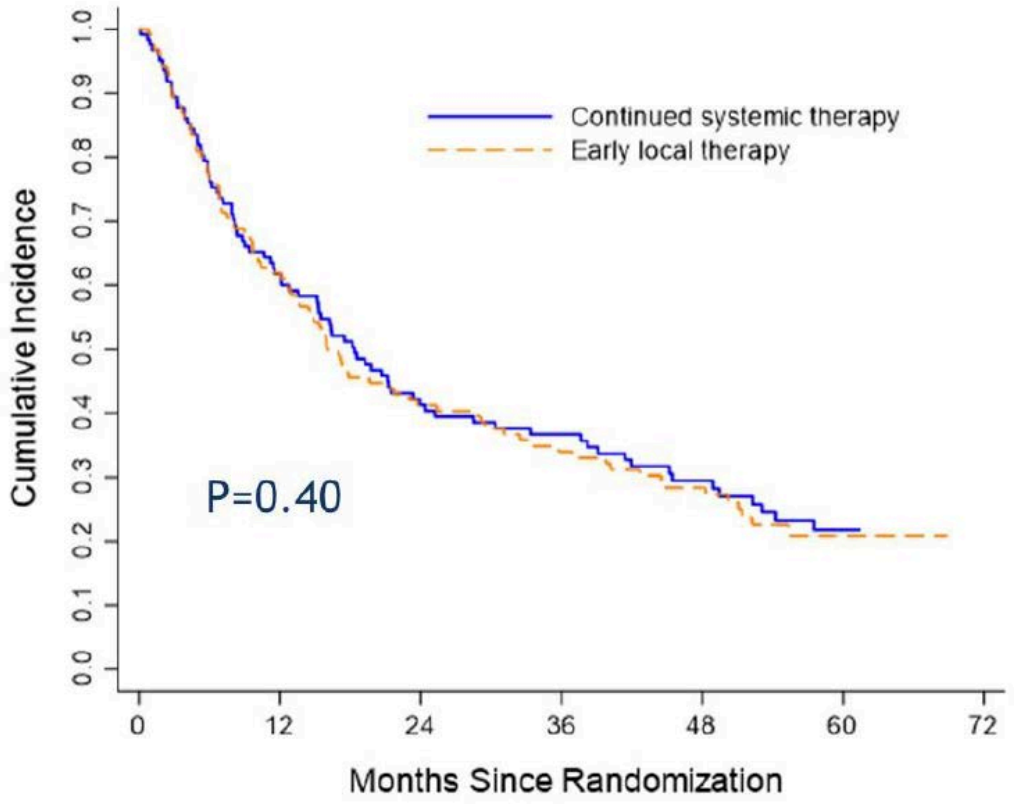
Results: Overall survival



Number at risk												
Continued systemic therapy	129	125	115	105	93	87	77	71	58	40	12	3
Early local therapy	124	111	103	97	91	85	75	70	54	36	8	2

- As of December 10, 2019: 121 patients had died
- Median follow up time was 53 months (0-91)
- Median survival was 54 months
- Stratified log rank test and Cox proportional hazard model were used to compare OS between treatment groups.

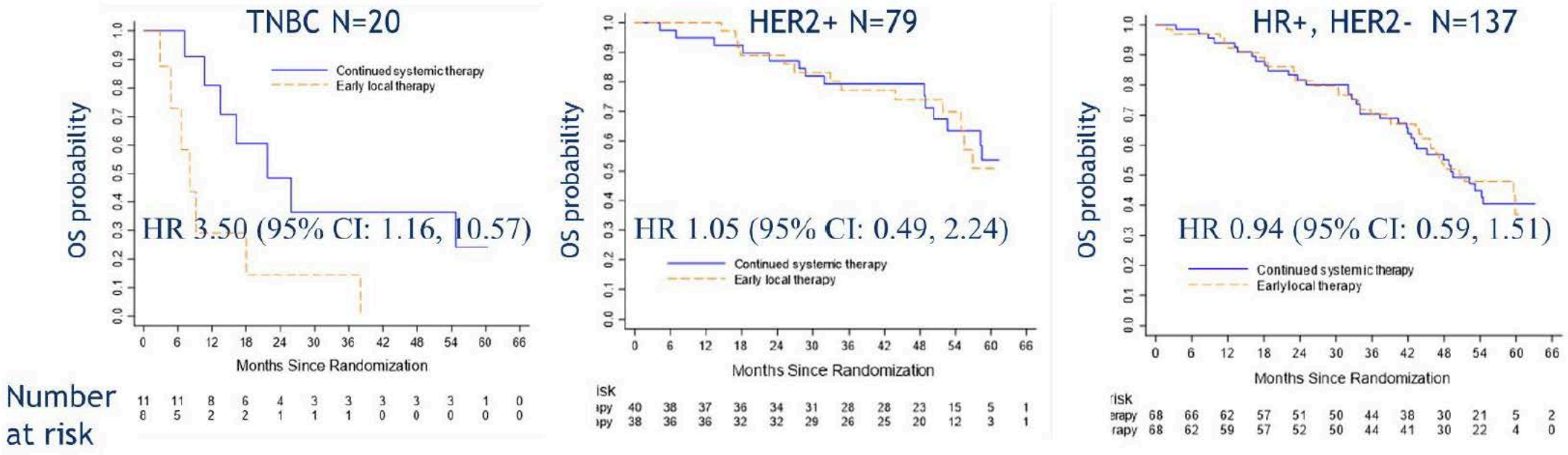
Results: Progression free survival



Number at risk							
Continued systemic therapy	125	71	45	37	26	5	0
Early local therapy	123	72	47	37	27	3	0

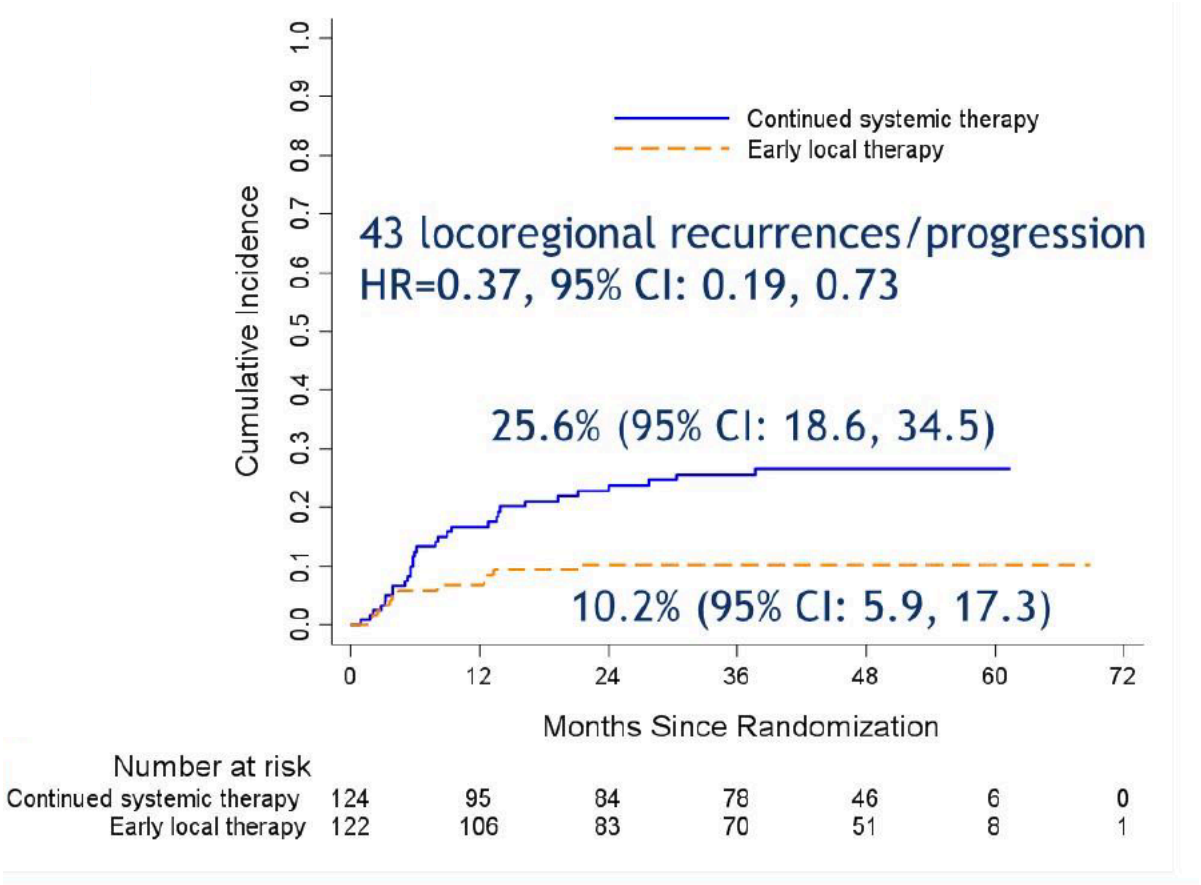
- 178 patients had disease progression of death
- 89 patients on each arm
- Kaplan-Meier estimates of PFS were compared by treatment arm using a stratified log-rank test

Results: overall survival by tumor subtype

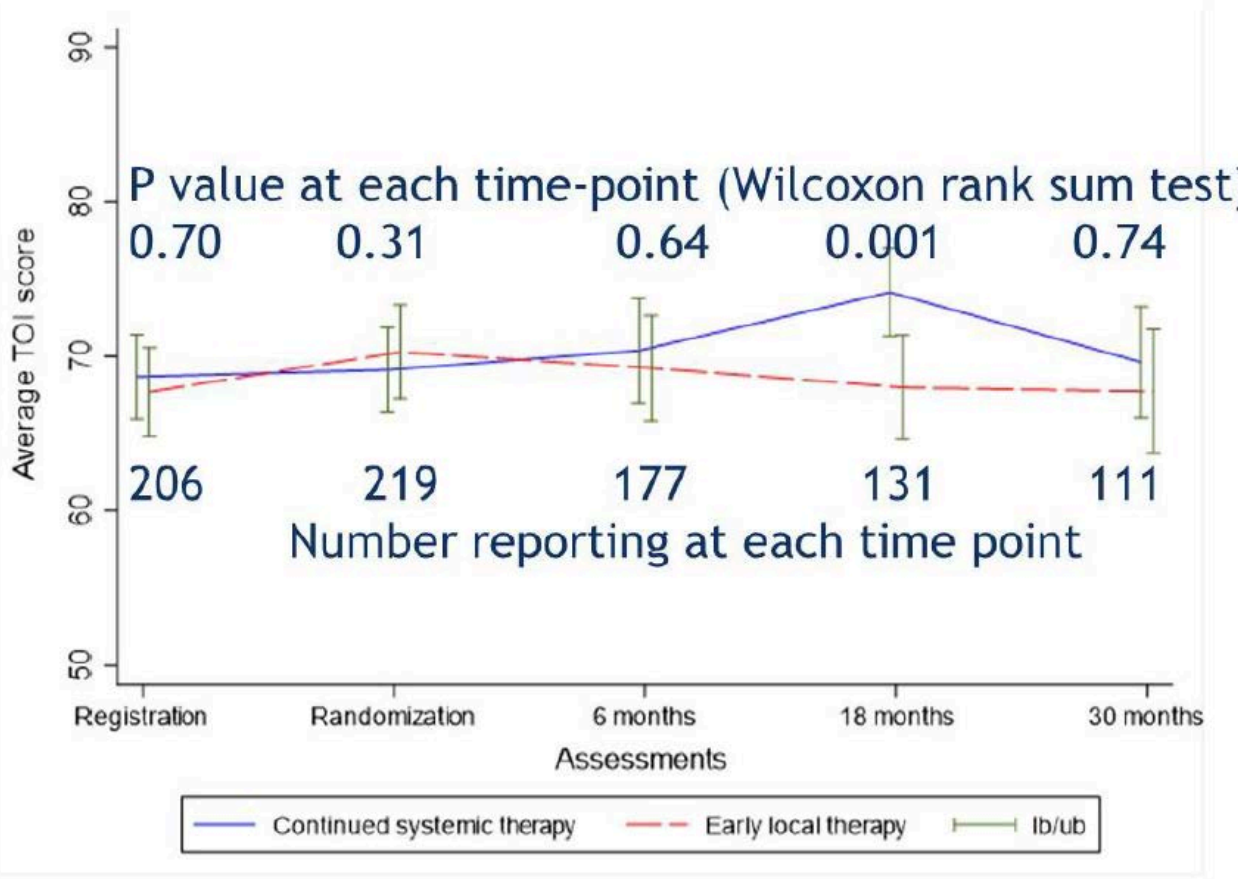


Locoregional progression

- Continued systemic therapy:
  - Development of symptoms leasing to a decision for local therapy.
- Early local therapy:
  - Regional nodal progression
  - Chest wall disease or invasive in-breast recurrence



Results: Health-related quality of life



- FACT-B trial outcome index- 37 item questionnaire focusing on physical, social, emotional and functional well-being.
- FACT-TOI was significantly lower in patients receiving ELT at 18 months post randomization.
- No significant difference was found between early local therapy and continued system therapy at the other assessment points to the study

Conclusions

- Early local therapy (ELT) does not improve survival in patients with de novo metastatic cancer and intact primary tumor.
- Although we saw a 2.5 fold higher risk of local disease progression with LRT, the use of LRT for the primary site did not lead to improved HRQOL.
- Based on available data, LRT for the primary tumor should not be offered to women with Stage IV breast cancer with the expectation of a survival benefit.
- When systemic disease is well controlled with systemic therapy but the primary site is progressing, LRT may be considered.

Abstract #508

Results of the NRG Oncology/NSABP B-43: A Phase III Clinical Trial Comparing Trastuzumab Given Concurrently with Radiation therapy and Radiation Therapy alone for Women with HER2-positive Ductal Carcinoma in Site Resected by Lumpectomy

Cobleigh et al

NSABP B-43 Background:

- 48,500 DCIS cases expected in 2020
- DCIS gives rise to ~85% of invasive breast cancers
- DCIS treatment: mastectomy or lumpectomy +RT (+/- endocrine therapy)
- A proportion of DCIS overexpresses HER 2
- Trastuzumab, a monoclonal antibody is widely used to treat HER 2 positive invasive cancer.

NSABP B-43: Background

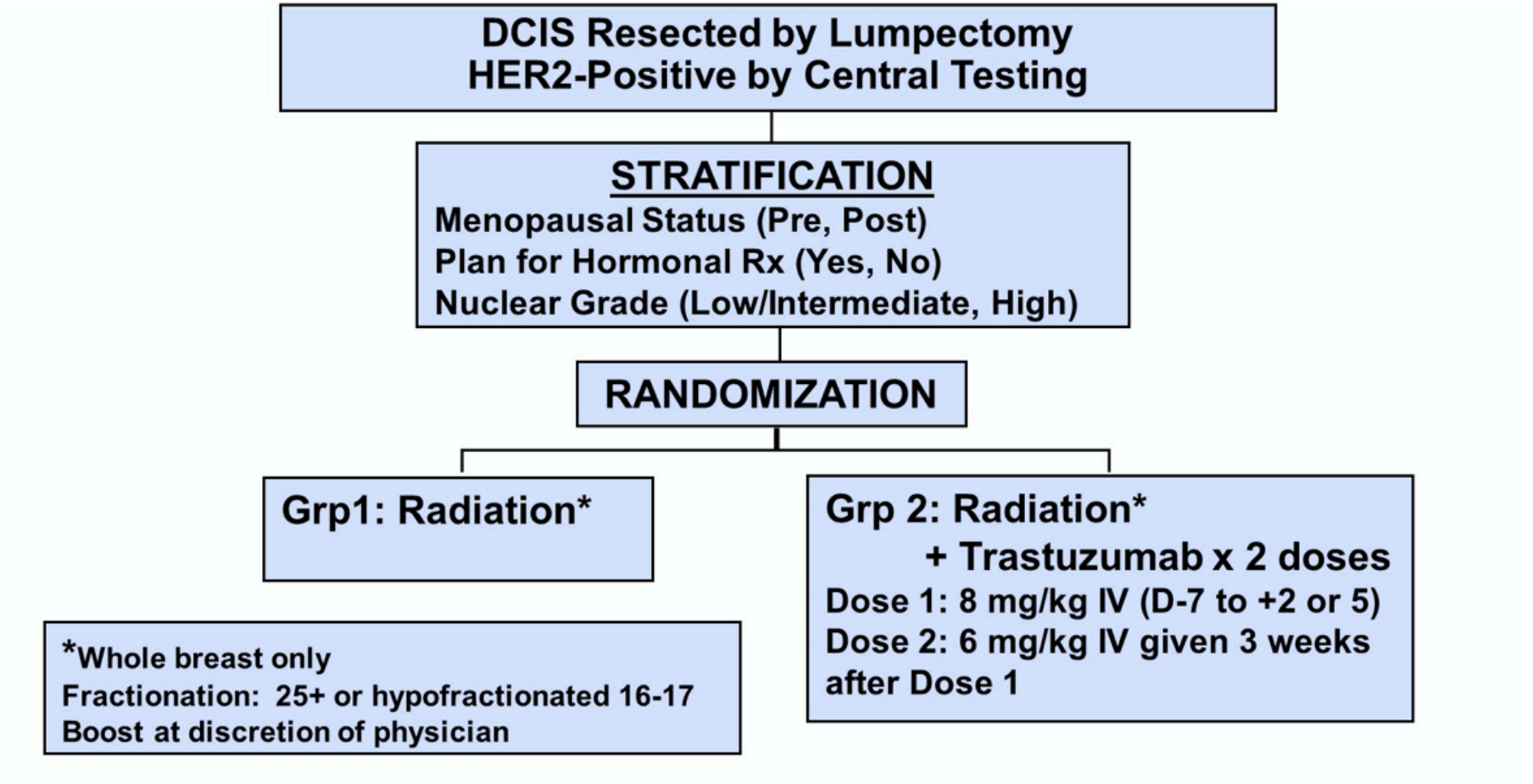
- Preclinical studies-HER2 targeted Rx and RT
  - HER-2 targeted MoAbs +/or TKIs boost the effectiveness of radiation in xenograft models and in cell lines, without producing a detrimental effect on irradiated HER 2 normal cells

- Human studies
  - Apoptosis occurs quickly
  - Suggests short treatment durations with trastuzumab +RT, should be investigated
  - Combining trastuzumab and RT is safe
    - N9831: No significant differences among arms in radiation-related acute skin reaction, pneumonitis, dyspnea, cough dysphagia, neutropenia or cardiac events regardless of treatment side.

NSABP B-43: Background

- Hypothesis
  - Trastuzumab, administered during RT, would improve the results of lumpectomy +irradiation in women with HER2-positive DCIS

NSABP B-43 Schema



NSABP B-43: Eligibility Criteria

- Women > or = 18 yo
- ECOG performance status 0 or 1
- Breast tumor is DCIS
  - Mixed DCIS and LICS eligible
- HER2 positive DCIS
- ER and/or PR status determined prior to randomization
- DCIS resected by lumpectomy
- No history of major cardiac disease or uncontrolled hypertension
- No multicentric DCIS

NSABP B-43 : Endpoints

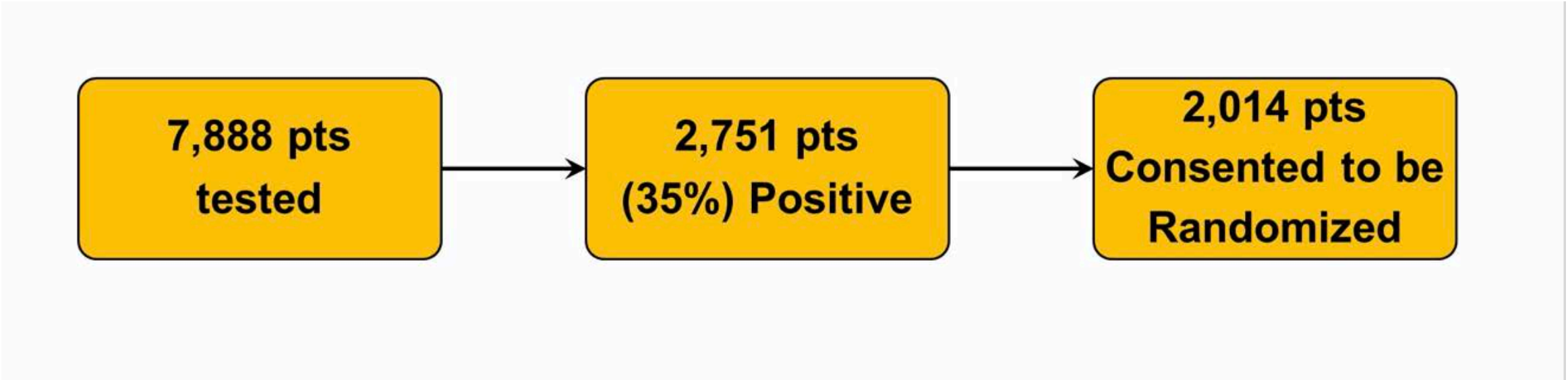
- Primary endpoint
  - Ipsilateral Breast Tumor Recurrence (Invasive or DCIS)

- Secondary Endpoints:
  - Disease Free Survival (DFS)
    - Invasive or non invasive local, regional, distant recurrence, contralateral BC, 2nd non-breast primary cancer and death from any cause as first events
  - Relapse-free Interval (RFI)
    - Invasive or noninvasive recurrence of BC as first event.
  - Overall Survival (OS)
    - All deaths

NSABP B-43: Statistical Design

- To estimate the rate of IBTR in the control arm, we used the IBTR rates for patients in B-24 with comedo necrosis (as a proxy for HER2+ status)
- Definitive analysis of the primary endpoints would be performed when 163 ipsilateral breast cancer events were observed, which was expected by 10.5 years after protocol start
- With 163 IBTRs, the study had 80% power to detect a hazard reduction of 36%, assuming a two-sided log-rank test with α=.05
  - HR=0.64 was based on reducing 1.73 ipsilateral breast cancer events per 100 patient-years to 1.11 events per 100 patient-years
- Protocol amendment, submitted in 2014 and approved by CTEP, required that definitive analysis be performed when all pts had been on study for ≥5 yrs if the required number of events had not been reached
- Definitive analysis was triggered at the 5-yr cut-off, when only 114 IBTRs had occurred

NSABP B-43 Schema HER 2 Testing



NSABP B-43: Patient Population

- Between Dec 2008 and Dec 2014, 2014 patients were randomly assigned to RT or RT +T
- Of these 1,998 patients (99.2%) had follow up information
- 10 pts (0.5%) were ineligible
- Median follow up time: 79.2 months

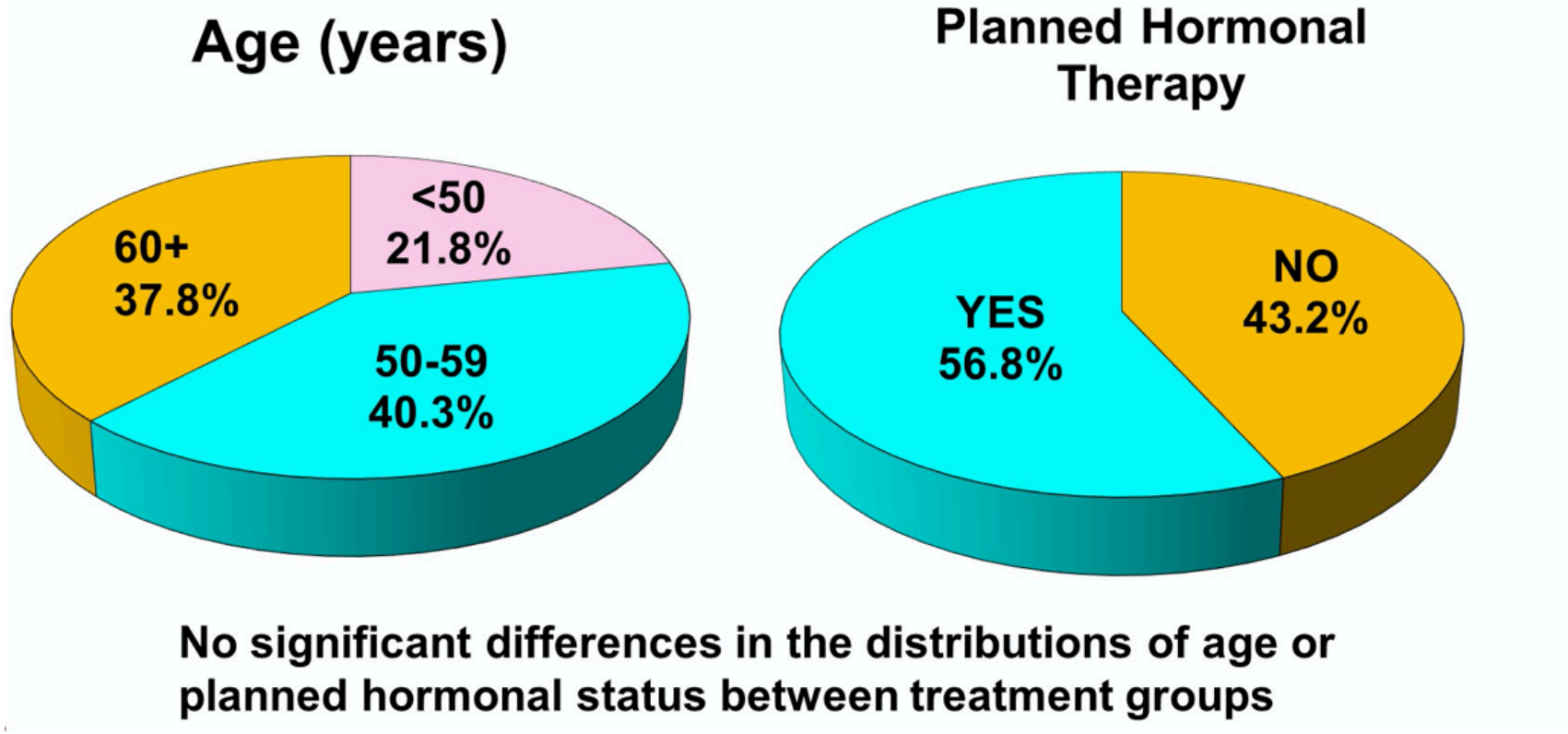
NSABP B-43: Treatment and Compliance

- **1,965/2,001 pts (98.2%) with RT information completed their radiation therapy per protocol criteria**
  - **988/1,005 (98.3%) in the RT arm**
  - **977/996 (98.1%) in the RT+T arm**
- **1,679/2,001 pts (83.9%) with radiation information had a radiation boost**
  - **846/1,001 (84.5%) in the RT arm**
  - **833/1,000 (83.3%) in the RT+Trastuzumab arm**
- **In the RT+Trastuzumab arm**
  - **964/996 (96.8%) received at least one dose**
  - **939/996 (94.3%) received both doses**

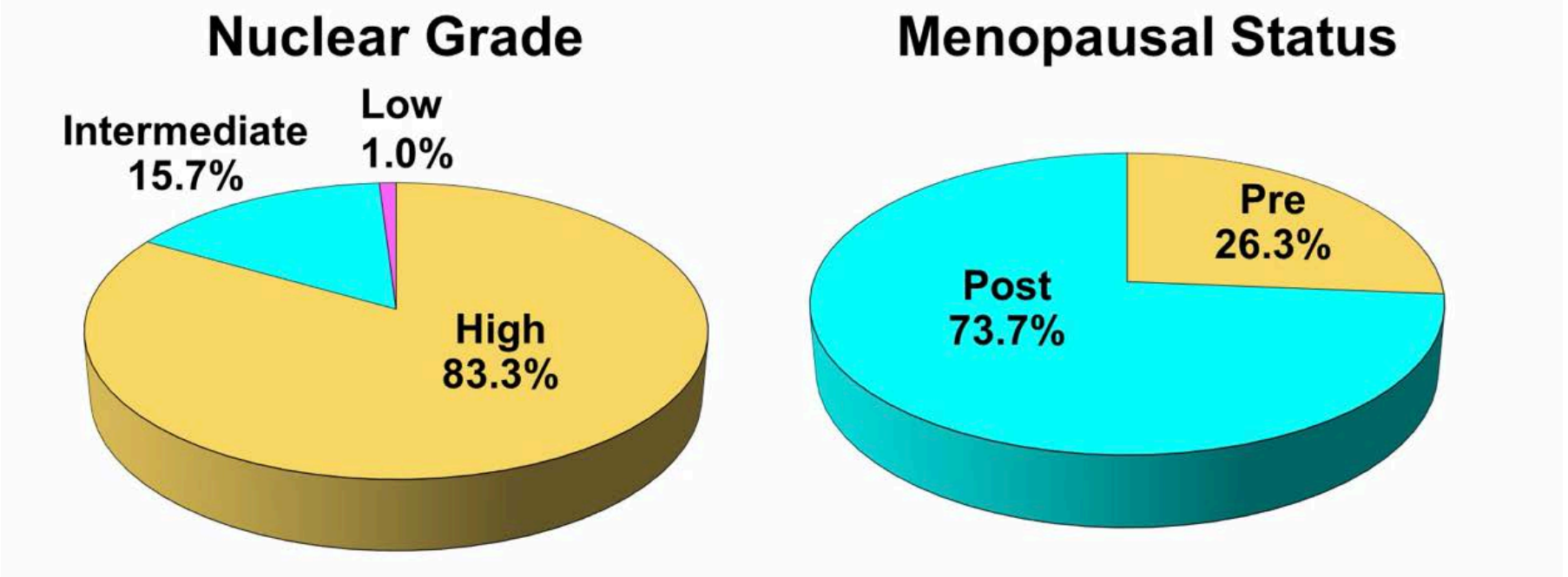
NSABP B-43:Adverse Events

- **Acute toxicity was quite low in both arms**
  - **No acute toxic deaths occurred**
  - **Two pts (both in the RT+T arm) experienced Grade 4 AEs, both deemed unrelated to therapy**
  - **39 (3.9%) in the RT arm and 49 (4.9%) in the RT+T arm experienced Grade 3 AEs. 2 pts in each group had G3 cardiac AEs**
- **Long-term AEs:**
  - **One pt in the RT arm developed invasive HER2+ IBTR, received adjuvant AC-TH, and later succumbed to AML**

NSABP B-43: Patient Characteristics



NSABP B-43: Patient Characteristics continued

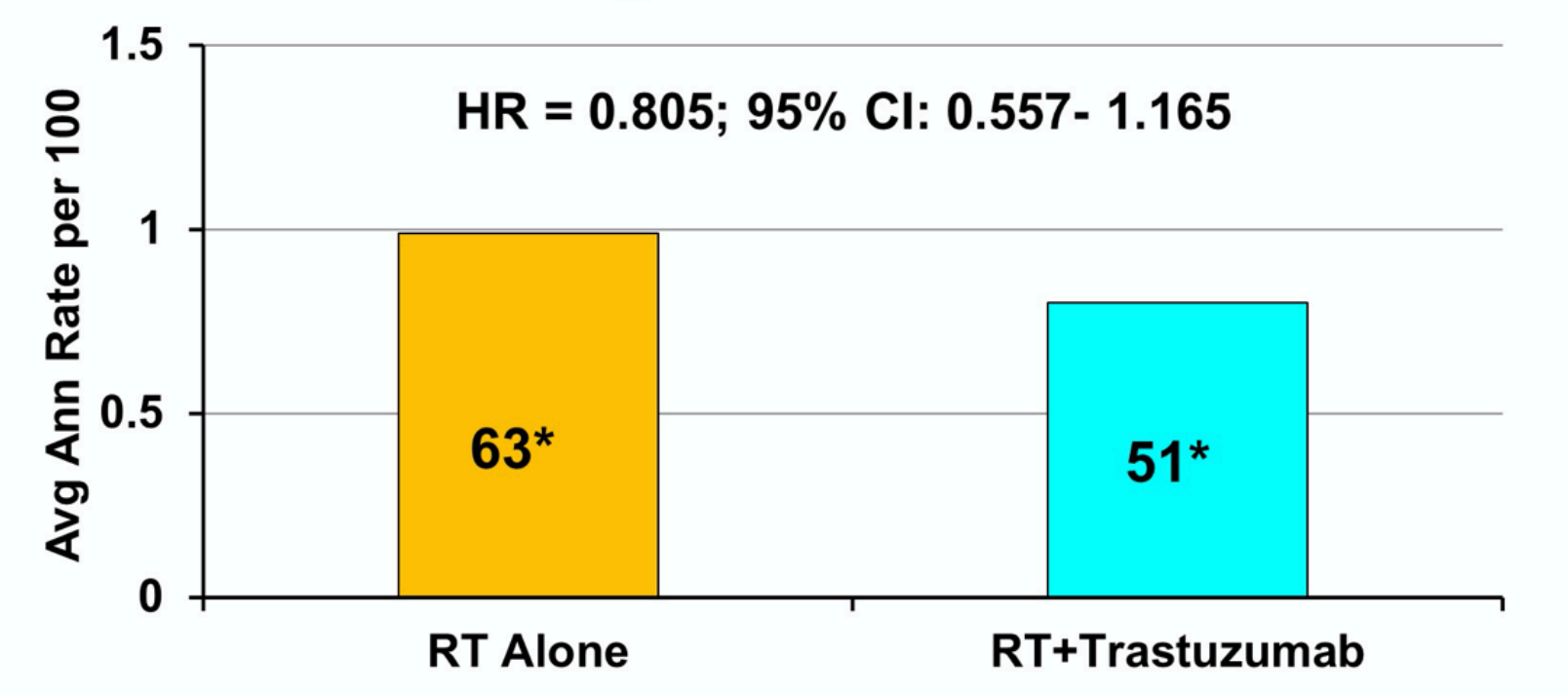


No significant differences in the distributions of Nuclear Grade or Menopausal Status between treatment groups

B-43: Events by Site of First Tumor Recurrence

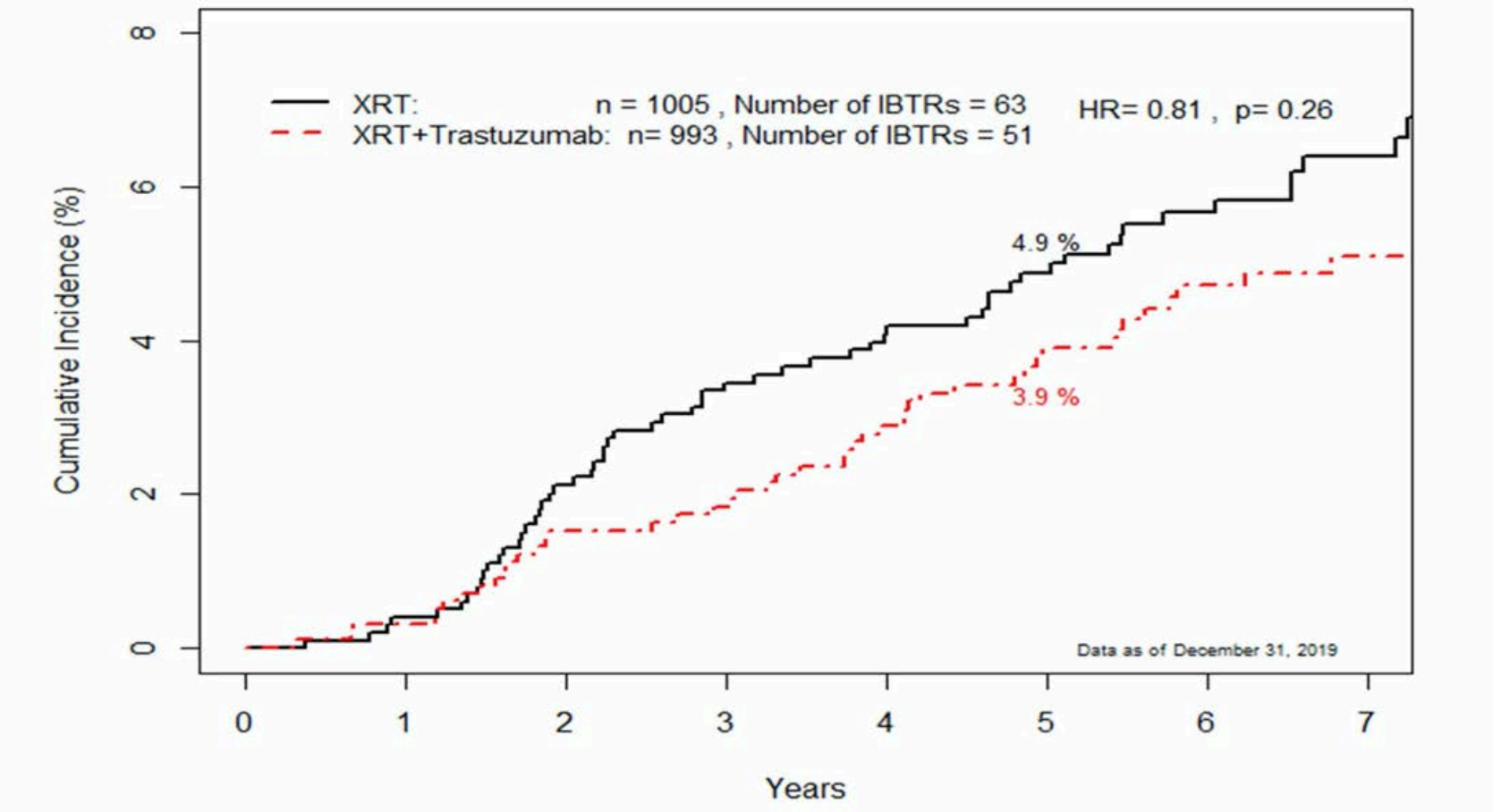
	RT		RT + Trastuzumab	
	No.	%	No.	%
Ipsilateral Breast Tumor Rec.	63	6.3	50	5.0
– Noninvasive	45	4.5	30	3.0
– Invasive	18	1.8	20	2.0
Other Loc-Reg. Recurrence	1	0.1	0	0.0
Distant Recurrence	0	0.1	2	0.2
Second Primary Cancer	77	7.7	72	7.3
Death, NED	14	1.4	9	0.9
Total events	155	15.4	133	13.4
Event free	850	84.6	860	86.6
Total	1005	100.0	993	100.0

NSABP B-43: Number of IBTRs and Average Annual Rates

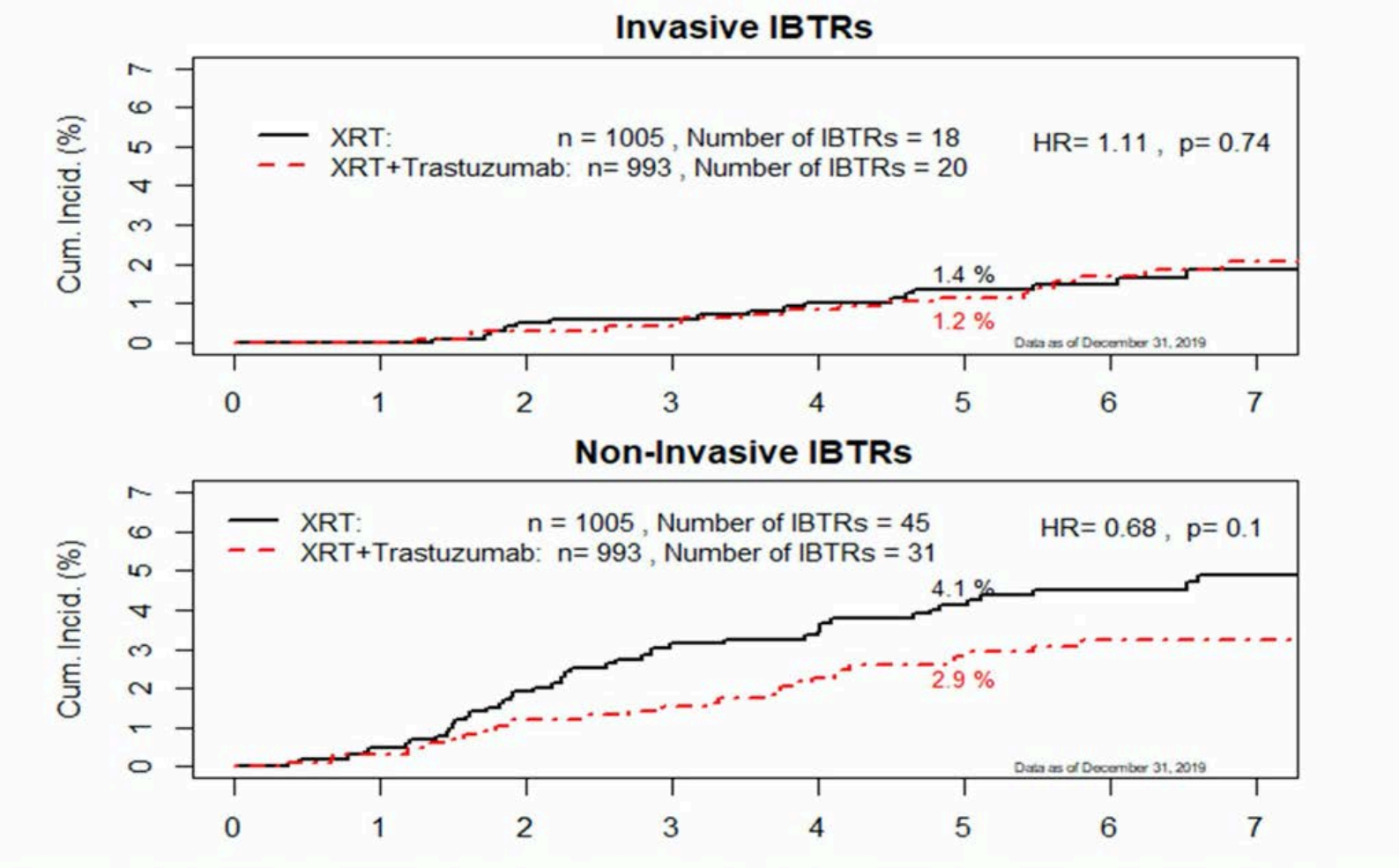


# of IBTRS

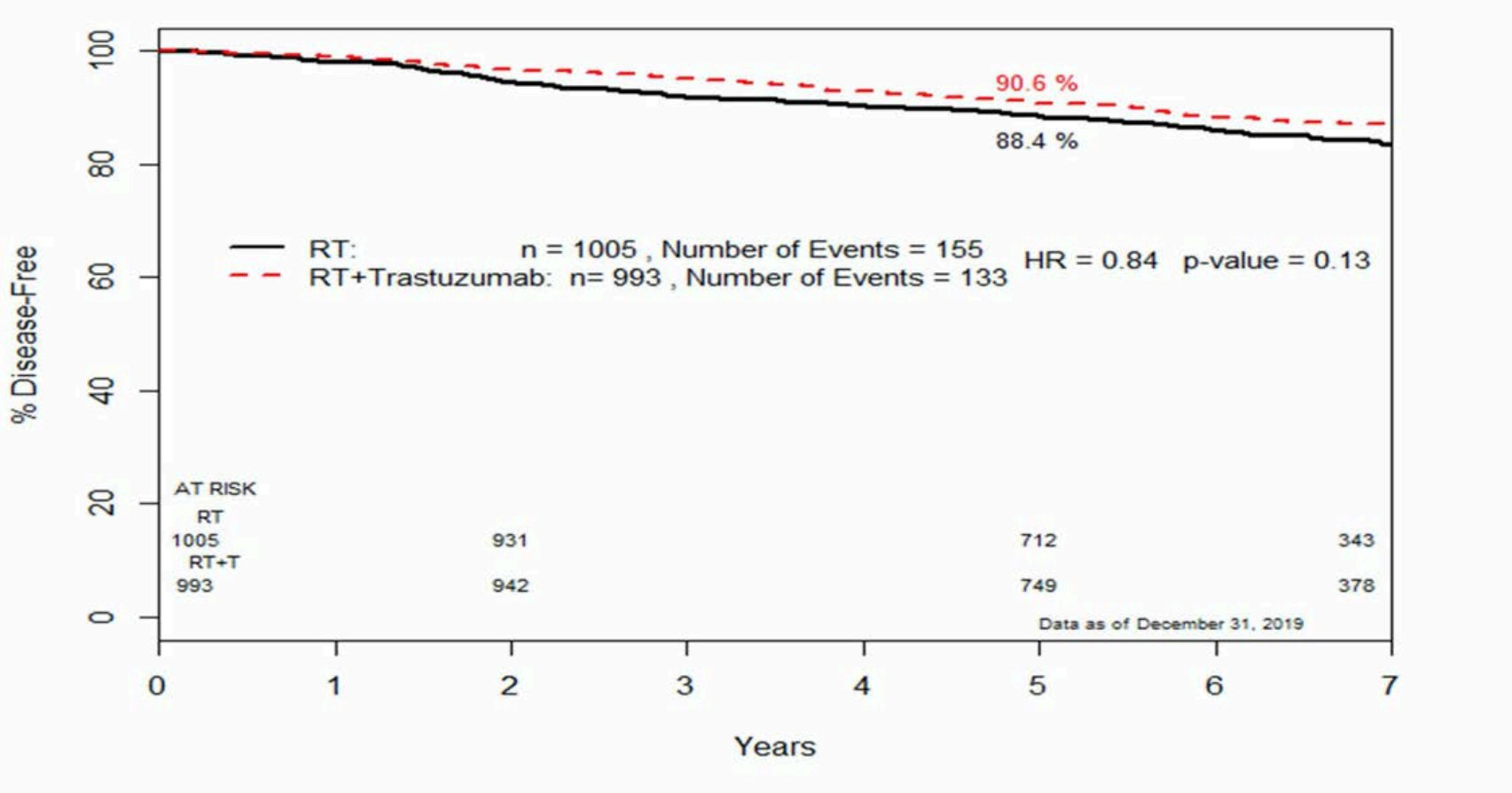
NSABP B-43: Cumulative Incidence of IBTRS



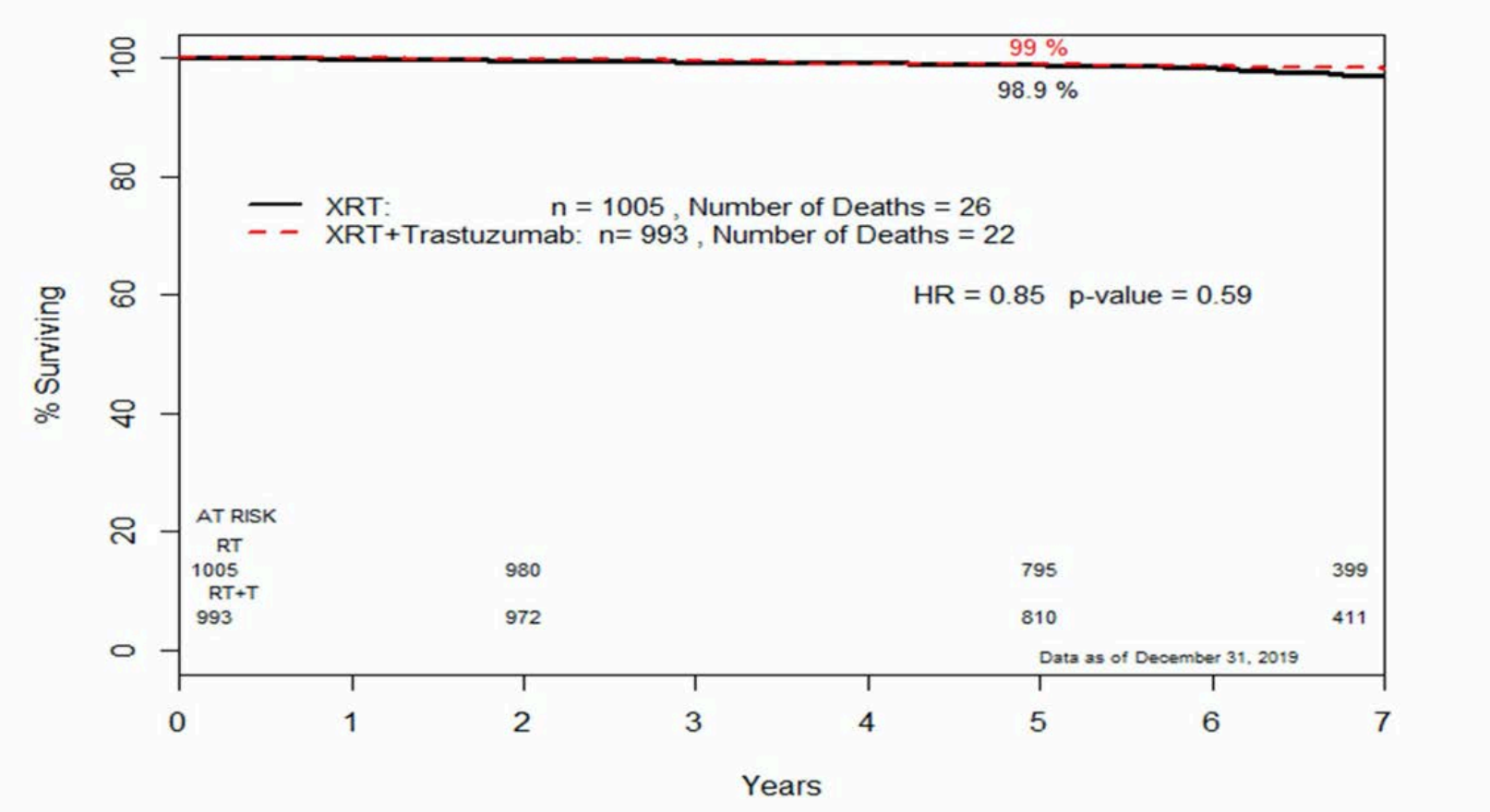
B-43: Cumulative Incidence of Invasive and Non-Invasive IBTRs



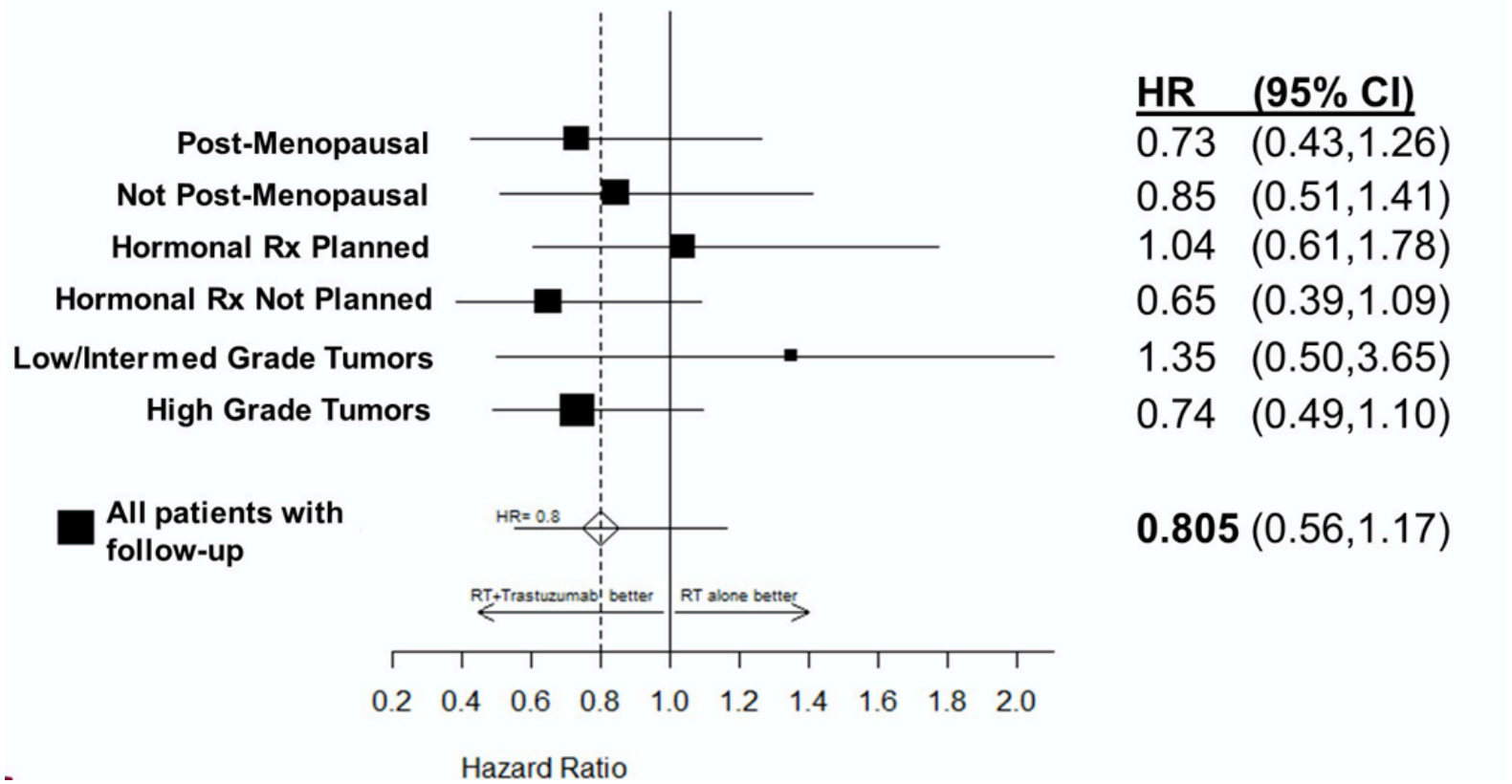
NSABP B-43: Disease-free Survival



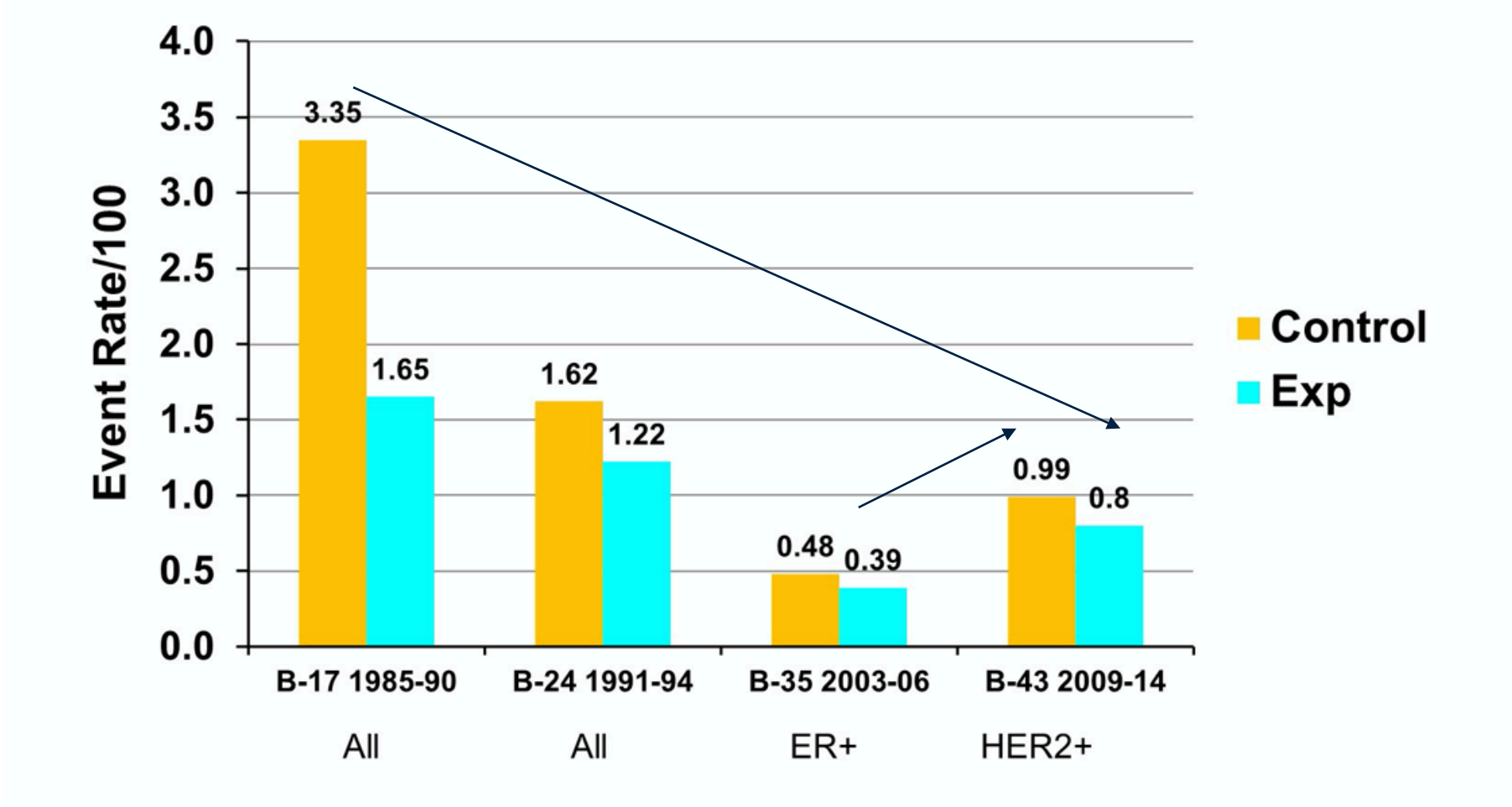
NSABP B-43: Overall Survival



B-43: Effect of trastuzumab on Risk of IBTR by Stratification Variable



NSABP B-43: Annual IBTR Event Rates/100



NSABP-B-43: Summary

- **Definitive analysis does not demonstrate statistically significant improvements in events with addition of two doses of trastuzumab:**
  - **19% reduction in IBTRs (not statistically significant)**
  - **17% reduction in recurrences (not statistically significant)**
  - **16% reduction in all DFS events (not statistically significant)**
- **Two doses of trastuzumab + RT has low toxicity**

NSABP B-43: Conclusions and Perspective

- **The rate of IBTR in clinical trials for DCIS pts has decreased over time.**
- **The primary endpoint of B-43 was not met.**
- **Future studies might focus on higher risk groups, e.g., HR-neg, high-grade HER2+ DCIS.**
- **Genomic classifiers that predict risk of IBTR may be helpful in identifying high-risk DCIS for future studies.**

Conclusions

- **E2108**
  - Early local therapy (ELT) does not improve survival in patients with de novo metastatic cancer and intact primary tumor.
  - The use of LRT for the primary site did not lead to improved HRQOL.
  - When systemic disease is well controlled with systemic therapy but the primary site is progressing, LRT may be considered.
- **NSABP-43**
  - No statistically significant improvements were seen in IBTRs or DFS with the addition of Trastuzumab with RT.

Thank you

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