Results of Chemotherapy Alone, with Sequential or Concurrent Addition of 52 weeks of Trastuzumab in the NCCTG N9831 HER2-positive Adjuvant Breast Cancer Trial

- **Dr. Perez has no relevant financial relationships to disclose.**

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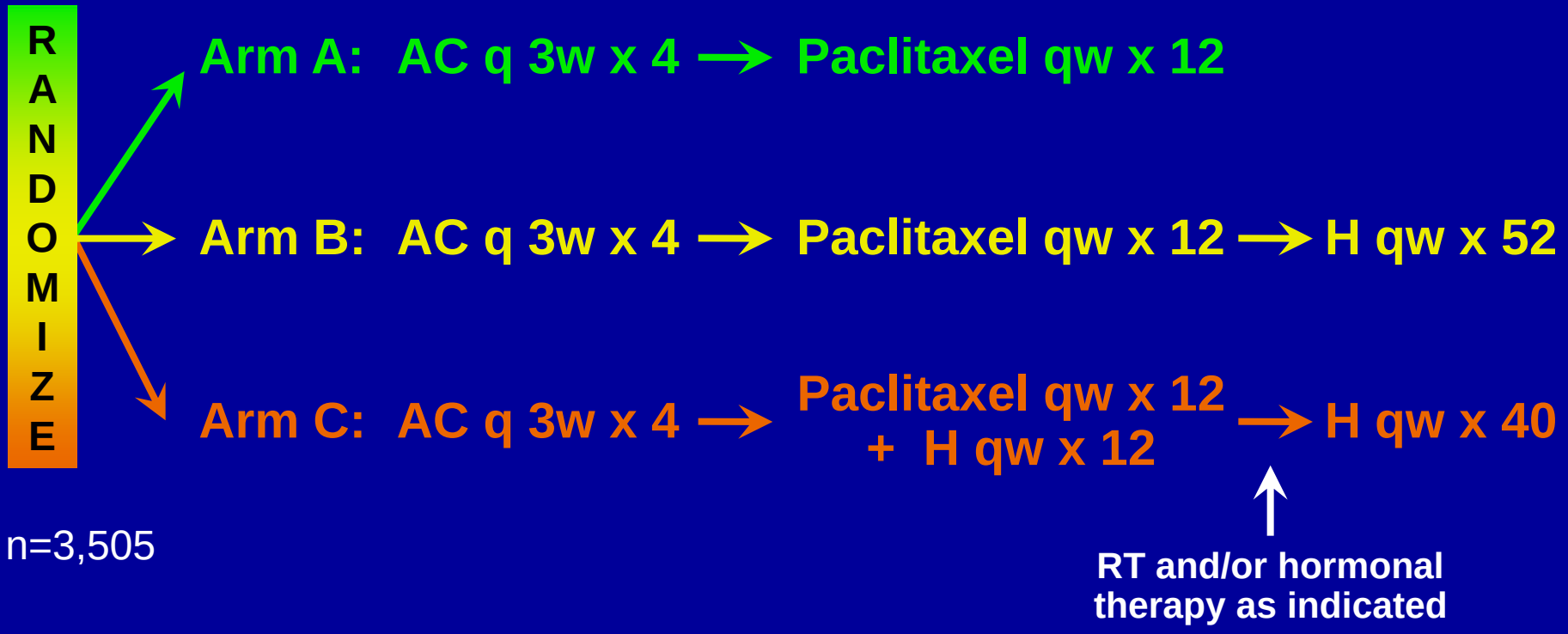
Schema: N9831



n=3,505

Perez EA

H=trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg); A=doxorubicin dose 60 mg/m^2; C=cyclophosphamide, 600 mg/m^2; paclitaxel, 80 mg/m^2; q 3w=every 3 weeks; qw=weekly

Relevant Study Milestones

2000
- Study activated

2002
- Eligibility based on central HER2 testing
- 8 mo temporary closure of **Arm C** due to cardiac analysis

2005
- Release of joint data (N9831+ B-31)
- Pts on **A** could crossover to receive H
- Pts on **B** could crossover to concurrent H

2009
- IDMC data release based on 2nd Interim Analysis of **A** vs **B**
- Events for 1st Interim Analysis of **B** vs **C** reached afterwards

N9831 Patients

- N=3,505 originally enrolled
- 372 ineligible or cancelled before treatment
  - 344 ineligible (283 due to not HER2+)
  - 28 cancelled before treatment
- 3,133 patients eligible

  A: 1,087

  B: 1,097

  C: 949
- Patient characteristics and safety already reported – cardiac: **0.3**, **2.8**, **3.3**%

Perez EA et al: J Clin Oncol 2008;26:1231-8

N9831

Control (A)* **vs** **Sequential (B)***

AC → T **AC → T → H**

Efficacy Analysis

*Patients eligible for crossover censored

Data frozen on 11/3/2009

A vs B Comparison
2nd Interim Analysis

At 67% of planned number of events (386 events)

- 2,184 pts, median follow-up: 5.5 yr
- 75% of pts followed for a minimum of 5 yr

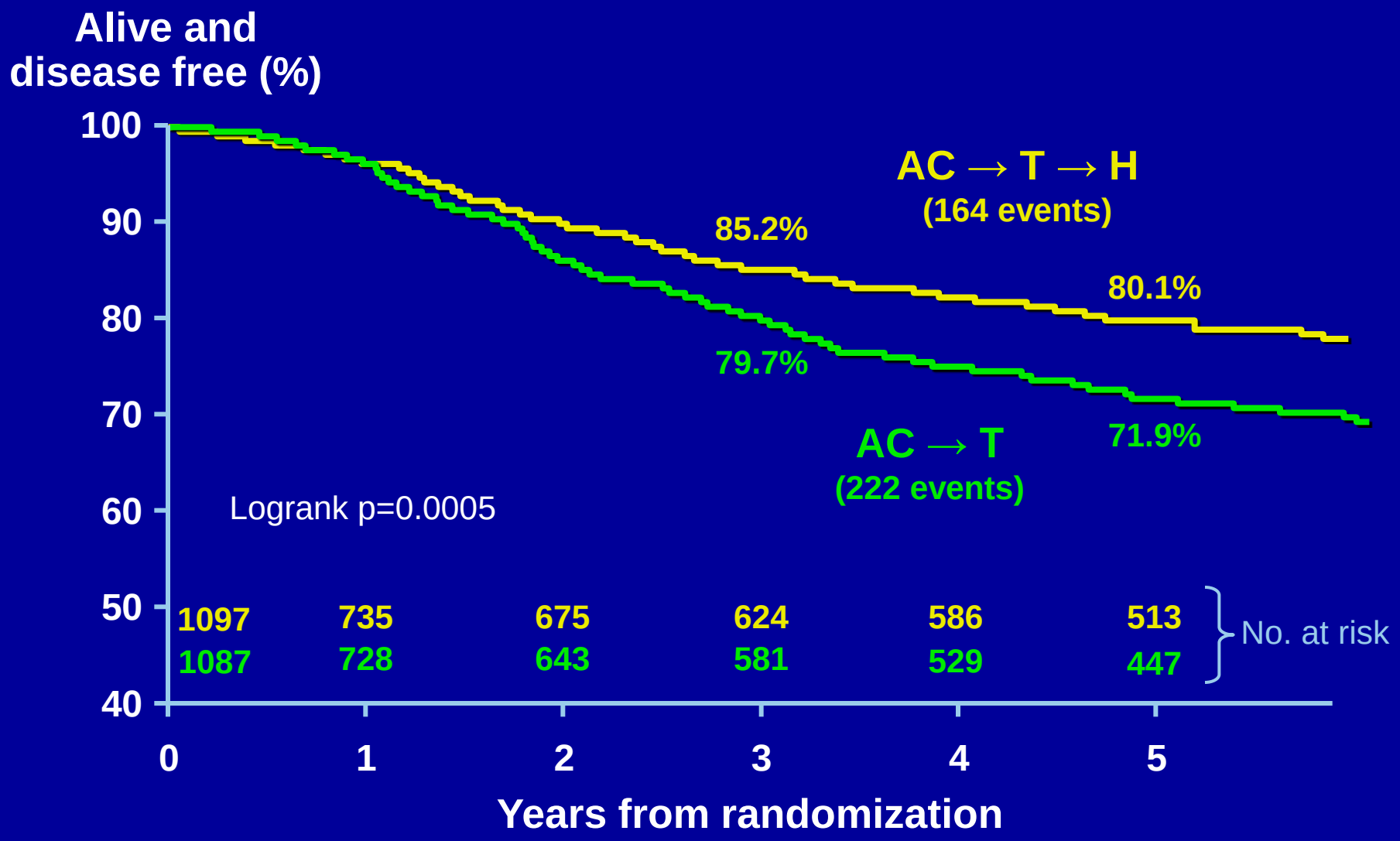
DFS improved with addition of trastuzumab sequential to AC → T chemotherapy

- Log rank P=0.0005
  - Crossing boundary for statistical significance, pre-set at 0.001
- Estimated hazard ratio: 0.70
  - 95% CI: 0.57- 0.86

N9831: A vs B Comparison
DFS Adjusted for Pt Characteristics

Parameter	Categories	N	HR	P-value
Age at registration	40-59 yrs <40 yrs or ≥60 yrs	1,433 751	0.73 1	0.0025
Number of positive nodes	10 or more 4-9 0-3	296 583 1,305	3.11 1.86 1	<0.0001 <0.0001
Tumor size	>5cm ≤5cm	1,995 189	1.61 1	0.0016
Estrogen receptor	Negative Positive	1,062 1,122	1.48 1	0.0001
Treatment arm	**AC → T → H** **AC → T**	1,087 1,097	0.67 (0.55-0.82) 1	<0.0001

Control (A) vs Sequential (B)
Disease Free Survival



N9831

Sequential (B)* **vs** **Concurrent (C)**

AC → T → H **AC → T+H → H**

Efficacy Analysis

*Censoring based on temp closure of **C**, and eligibility for crossover

Data frozen on 11/3/2009

B vs C Comparison
1st Interim Analysis

At 50% of planned number of events (312 events)

- 1,903 pts, median follow-up: 5.3 yr
- 75% of pts followed for 5 yr

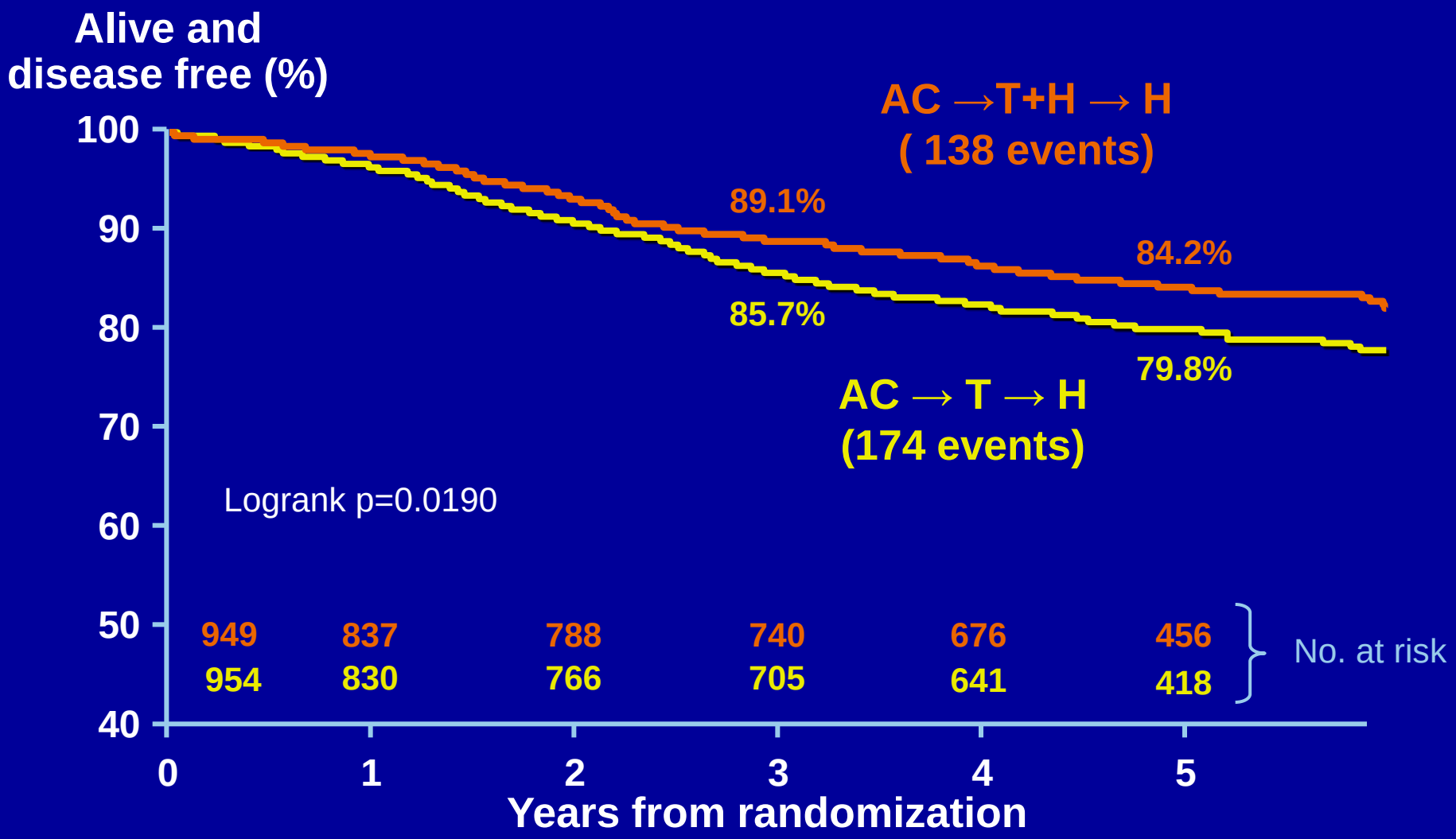
DFS differs with respect to the timing of trastuzumab's addition to AC → T

- Log rank P=0.019
  - Not crossing the boundary for statistical significance, pre-set at 0.00116
- Estimated hazard ratio: 0.77
  - 95% CI: 0.61- 0.96

N9831: B vs C Comparison
DFS Adjusted for Pt Characteristics

Parameter	Categories	N	HR	P-value
Number of positive nodes	10 or more 4-9 0-3	242 488 1,073	2.24 1.56 1	<0.0001 0.0008
Tumor size	>5 cm 2.1-5.0 cm ≤2 cm	166 989 748	1.84 1.57 1	0.0019 0.0005
Estrogen receptor	Negative Positive	934 969	1.78 1	<0.0001
Treatment arm	**AC → T+H → H** **AC → T →H**	949 954	0.75 (0.60-0.94) 1	0.0134

Sequential (B) vs Concurrent (C) Disease Free Survival



Results: Disease-Free Survival

Joint Analysis (N9831/B31) ~3 yr median follow-up[1]

Pairwise comparison	Number of events	P value	Adj HR (95%CI)
AC→T vs **AC → T+H → H**	619	<0.00001	**0.48** **(0.41-0.57)**

*Stratified – nodal status and receptor status

N9831 Analysis (N9831) >5 yr median follow-up[2]

	Pairwise comparison	Number of events	Log rank P value	Adj HR* (95%CI)
A **B**	**AC→T** vs **AC → T → H** (n=2,184)	386	0.0005	0.67 (0.55-0.82)
B **C**	**AC → T → H** vs **AC → T+H → H** (n=1,903)*	312	0.0190	0.75 (0.60-0.94)

*Excluding pts on **Arm B** entered when **Arm C** was closed

[1]Perez EA et al: J Clin Oncol 2007;25(18S):6S; Abstr #512
[2]Perez EA et al: SABCS 2009; Abstr #701

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Results: Overall Survival

Joint Analysis (N9831/B31) ~3 yr median follow-up[1]

Pairwise comparison	Number of events	P value	Unadj HR (95%CI)
AC→T vs **AC → T+H → H**	258	0.0007	**0.65** **(0.51-0.84)**

N9831 Analysis (N9831) >5 yr median follow-up[2]

	Pairwise comparison	Number of events	Log rank P value	Unadj HR* (95%CI)
A **B**	**AC→T** vs **AC → T → H** (n=2,184)	220	0.281	0.86 (0.65-1.13)
B **C**	**AC → T → H** vs **AC → T+H → H** (n=1,903)*	168	0.135	0.79 (0.59-1.08)

*Excluding pts on **Arm B** entered when **Arm C** was closed

[1]Perez EA et al: J Clin Oncol 2007;25(18S):6S; Abstr #512
[2]Perez EA et al: SABCS 2009; Abstr #701

Conclusions

- DFS is significantly improved with the addition of 52 wks of trastuzumab to AC → T
- There is a statistically significant 33% reduction in the risk of an event with the sequential addition of trastuzumab following AC → T
  - 5 yr DFS: 72% vs. 80%
- There is a strong trend for a 25% reduction in the risk of an event with starting trastuzumab concurrently with taxane relative to sequentially
  - 5 yr DFS: 80% vs. 84%

Implications for Practice

Based on a positive risk/benefit ratio

- We recommend that adjuvant trastuzumab be incorporated in a concurrent fashion with the taxane portion of chemotherapy
  - **AC → T+H → H**

Thank you…

Research Team

- Patients
- Medical personnel
- NCI, Genentech, BCRF