NCIC CTG MA.17
Final Analysis of Updated Data

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A Placebo-controlled Trial of Letrozole Following Tamoxifen as Adjuvant Therapy in Postmenopausal Women with Early Stage Breast Cancer

North American Breast Intergroup
NCIC CTG, NCCTG, CALGB, ECOG, SWOG
Breast International Group (BIG)
EORTC, IBCSG

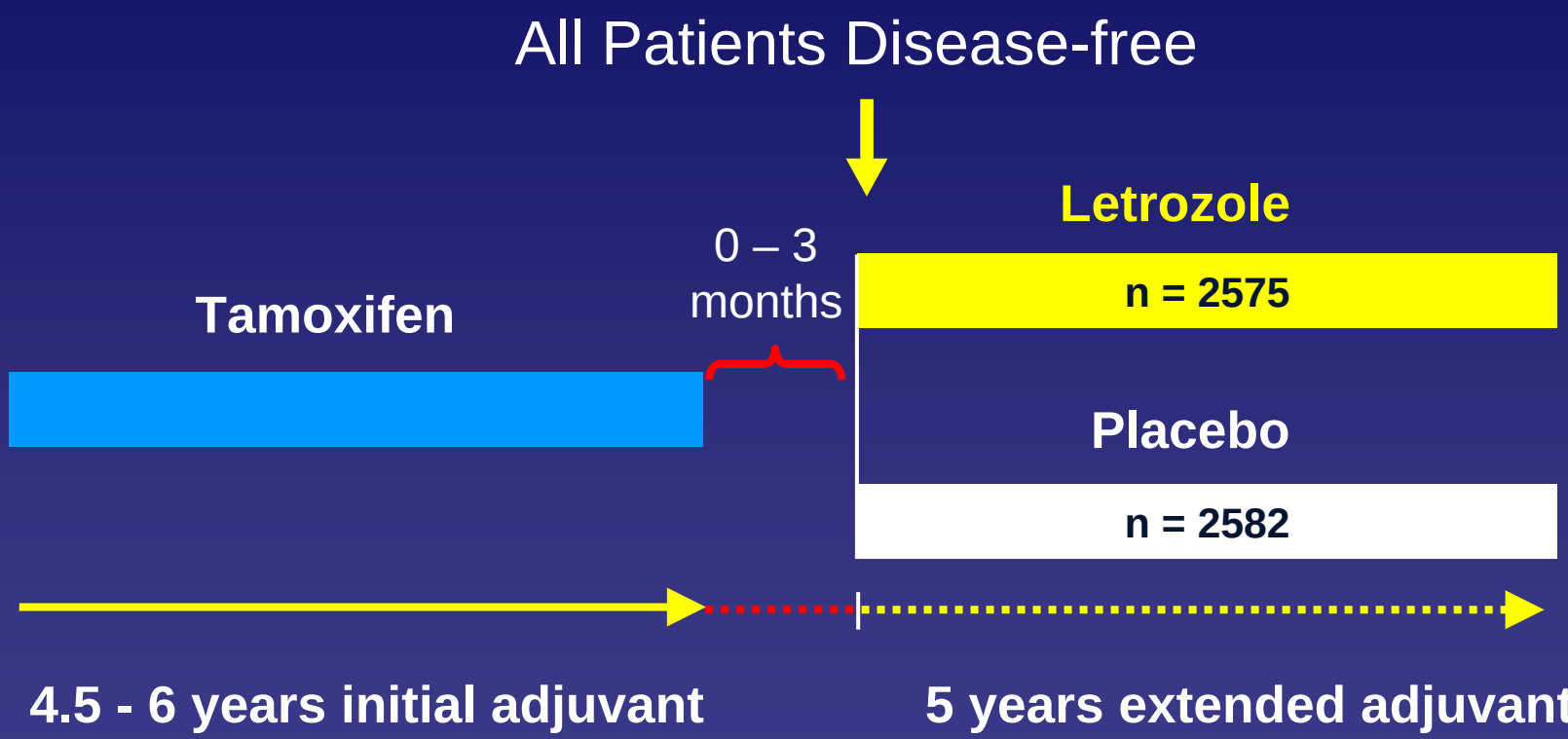
National Cancer Institute of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe des essais cliniques

Extended Adjuvant Therapy
Letrozole (LET) following 5 years of Tamoxifen

- > 5 years of Tamoxifen confers no added benefit
- Recurrence after Tamoxifen is ~ 2% and ~ 4% per annum in node –ve and +ve pts
- LET after Tamoxifen shrinks existing tumors / prevents tumors in animal models
- LET after Tamoxifen induces remissions in advanced breast cancer

NCIC CTG Intergroup Trial MA.17 Design

Goss PE et al., *N Engl J Med* 2003;349 (Nov 6)



Stratification: Receptors +ve / unknown
Lymph Node + ve, - ve, unknown
Adjuvant Chemo Y / N

MA.17: Primary End Point

- Disease-Free Survival:
  - Recurrence in:
    - ipsilateral breast
    - chest wall
    - locoregional nodal
    - metastatic sites
  - Occurrence of contra lateral new primary breast cancer

MA.17: Secondary End Points

- Overall survival
- Rate of contra lateral breast cancer
- Long-term safety/tolerability
  - Lipid profile
  - Cardiovascular morbidity / mortality
  - Bone fractures / BMD
  - Clinical / Laboratory
- QOL SF-36 / Menqol

MA.17 Eligibility Criteria

- Patients enrolled
  - Postmenopausal
  - ER + ve and/or PR +ve or Unknown
  - Node – ve, + ve or unknown
  - Completed 4.5 - 6 years of initial tamoxifen
  - No evidence of recurrent cancer
  - ECOG 0,1,2

MA.17: Statistical Assumptions

- Primary end point (DFS)

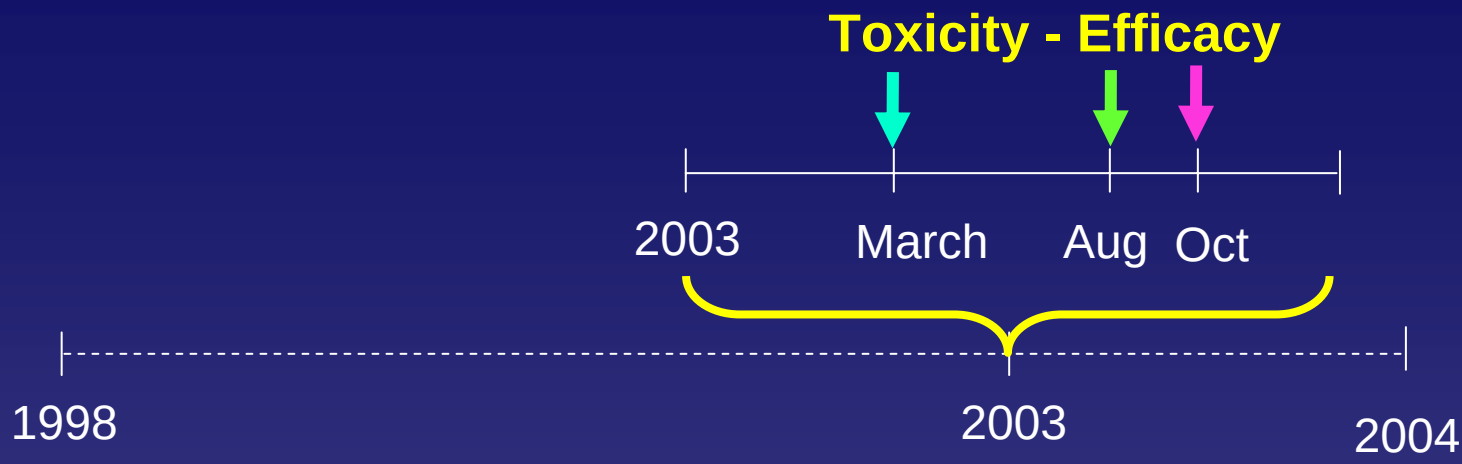
  To detect an improvement in DFS of 22%, equivalent to reducing the estimated risk of relapse at four years by 2.5% (12% to 9.5%)

- Interim analyses
  - Prospectively planned at 171 and 342 events
  - Stopping boundary nominal significance, *P*=0.0008

Five Pre-Planned Subset Analyses for the Final Analysis

1. Tumor Receptors +ve, Unknown
2. Lymph Node Status +ve, -ve, Unknown
3. Prior Chemo Y / N
4. Menopausal Status at start of Tamoxifen
5. Prior Tamoxifen < or > 5yrs

MA17 Final Analysis

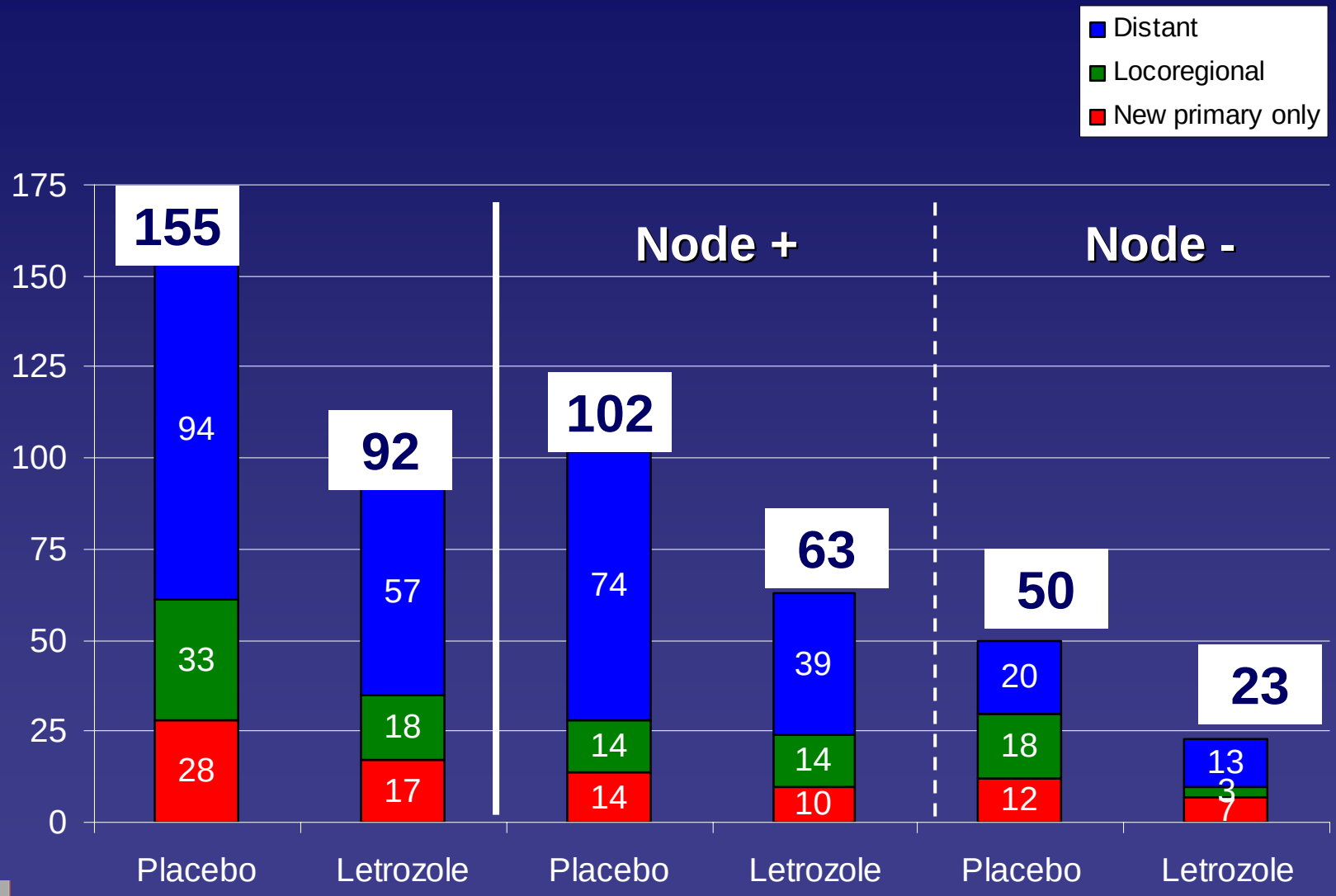


- Interim Analysis
  - DFS events: 207
  - Deaths: 73
  - # pts at 40 months = 384
  - Median follow-up: 2.4 yrs
- Final Analysis
  - DFS events: 247
  - Deaths: 113
  - # pts at 40 months = 1115
  - Median follow-up: 2.5 yrs

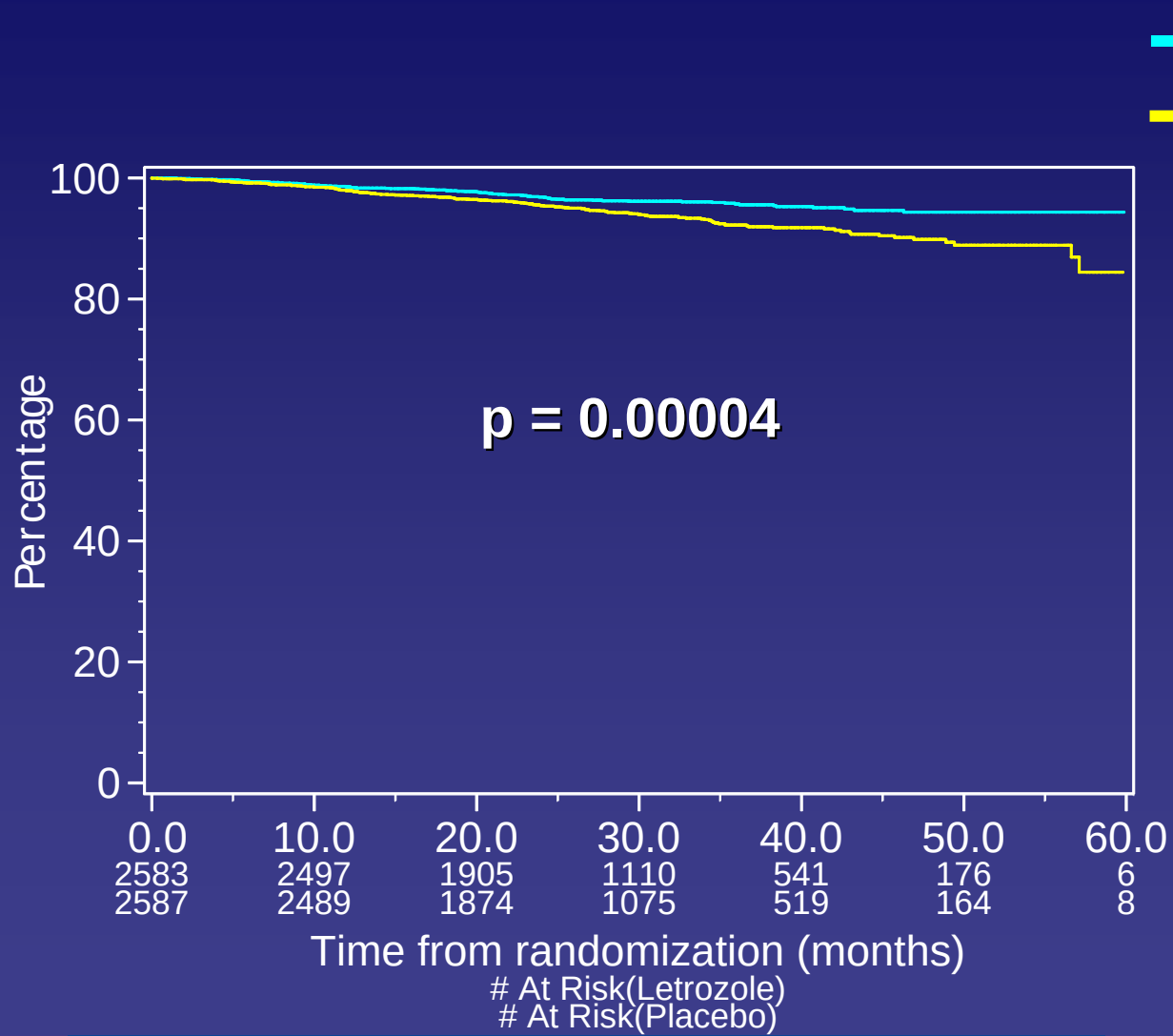
MA.17 Patient Demographics

	Letrozole	Placebo
Median age (y)	62	62
ER+ and/or PgR+ (%)	98	98
ECOG 0 (%)	90	90
T1 (%)	58	58
Node – ve	50	49
Breast-conserving surgery	57	57
Radiotherapy	60	59
Chemotherapy	46	46

Total Recurrences of Breast Cancer



Disease Free Survival – All Patients

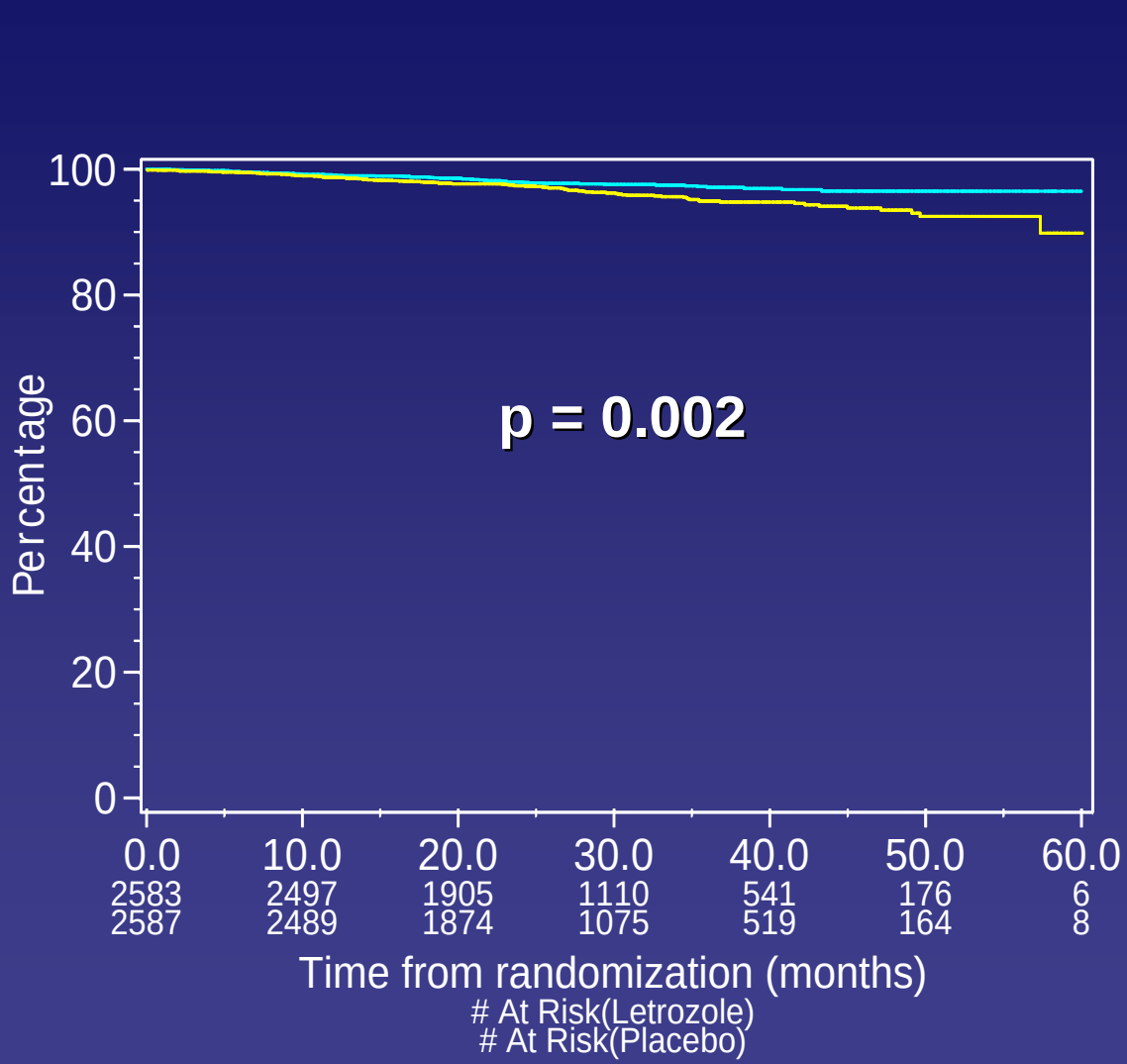


DFS by Treatment Duration

Year	Letrozole (N=2582) (%)	Placebo (N=2586) (%)		*P*-value
1	98.5	97.9		0.00004 (Overall)
2	96.9	95.4		
3	95.7	92.2		
4	94.7	89.8	4.8% (CI 2.1% - 6.9%)	**NNT = 21**
Node – ve	**96.3**	**93.6**	**2.7%**	**NNT = 37**
Node + ve	**92.3**	**84.8**	**7.5%**	**NNT = 13**

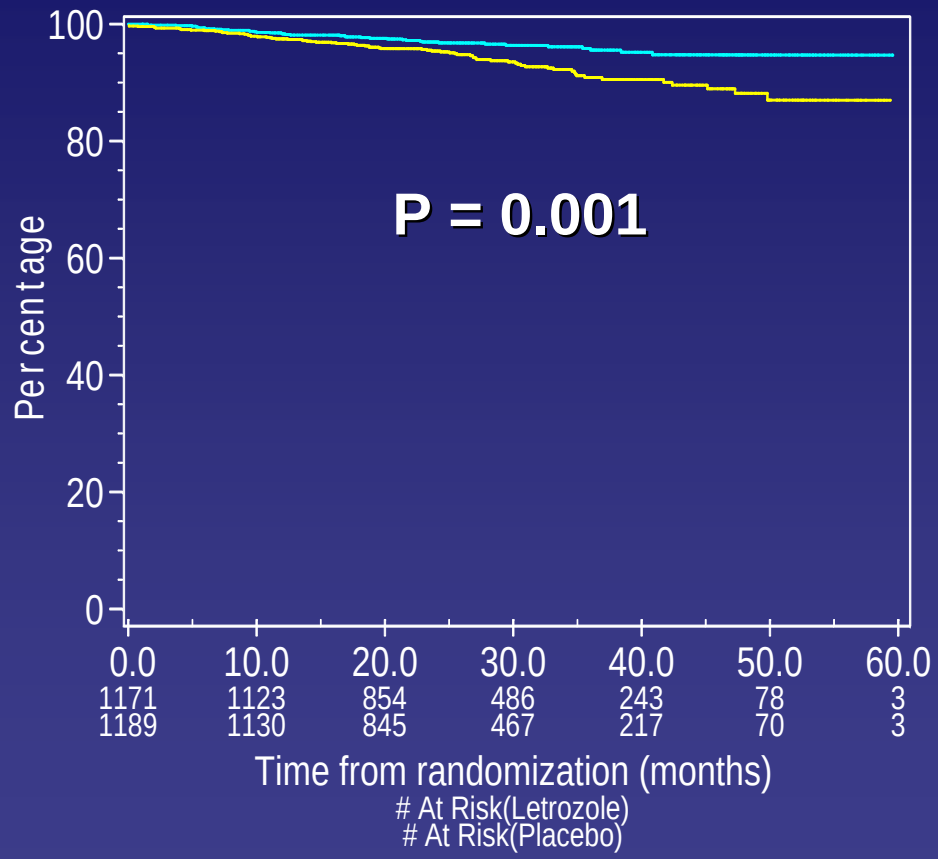
(NNT = Number Needed to Treat)

Distant DFS – All Patients

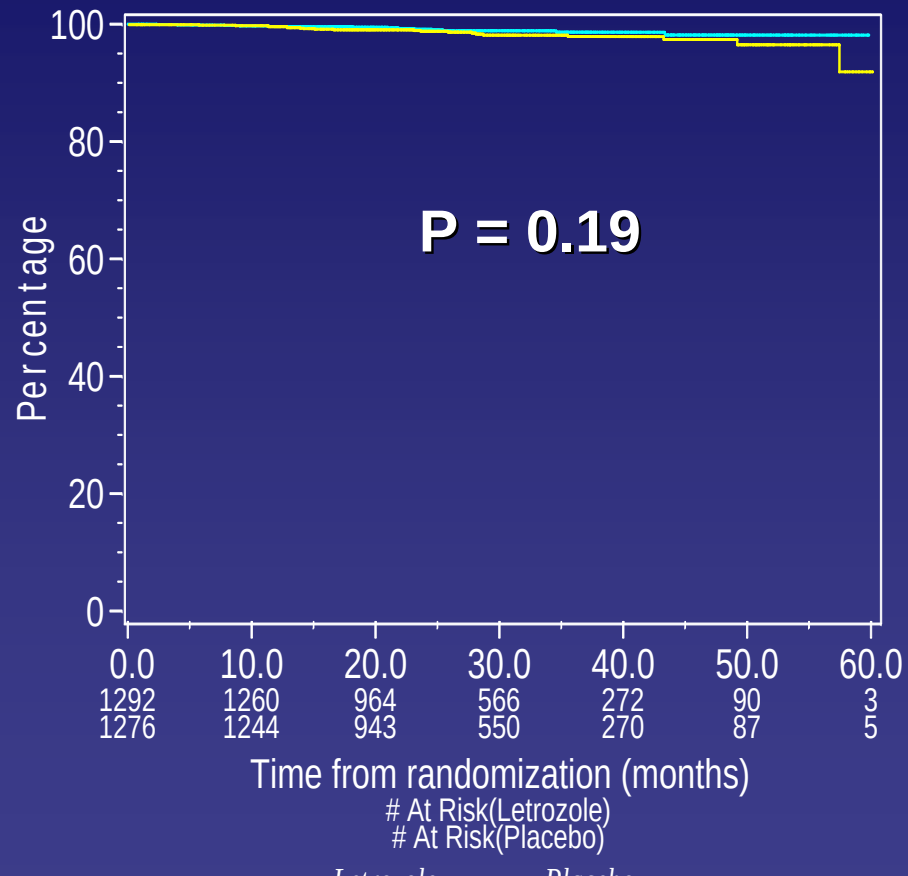


Distant DFS

Node Positive

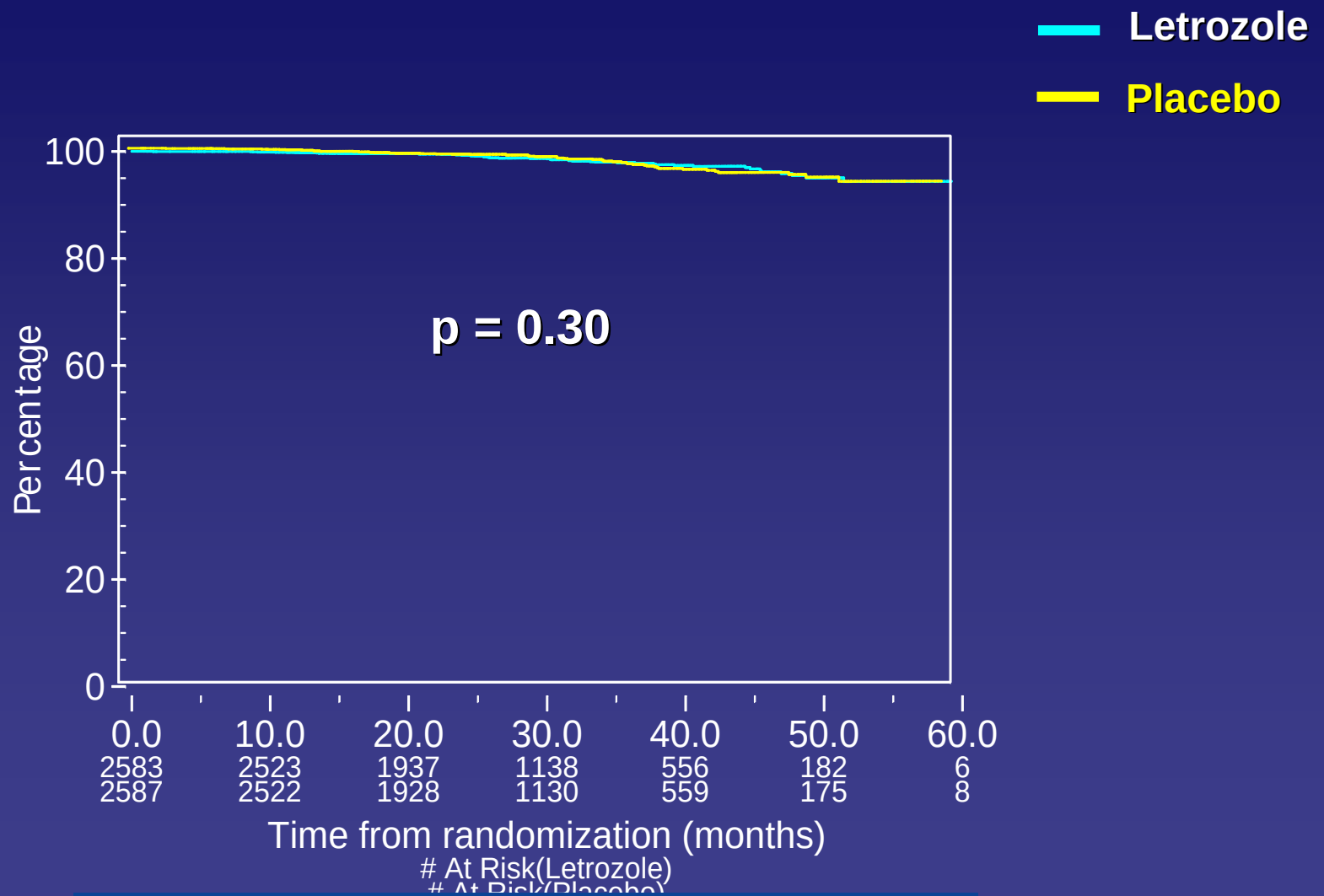


Node Negative



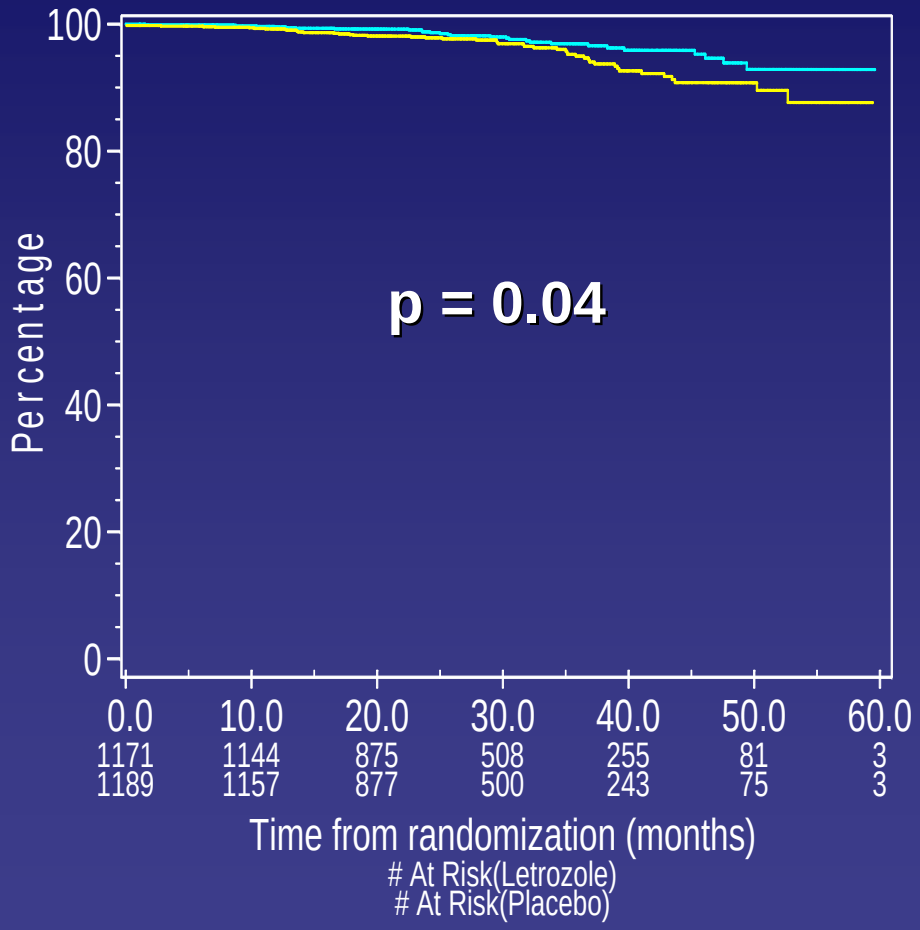
Letrozole Placebo

Overall Survival – All Patients

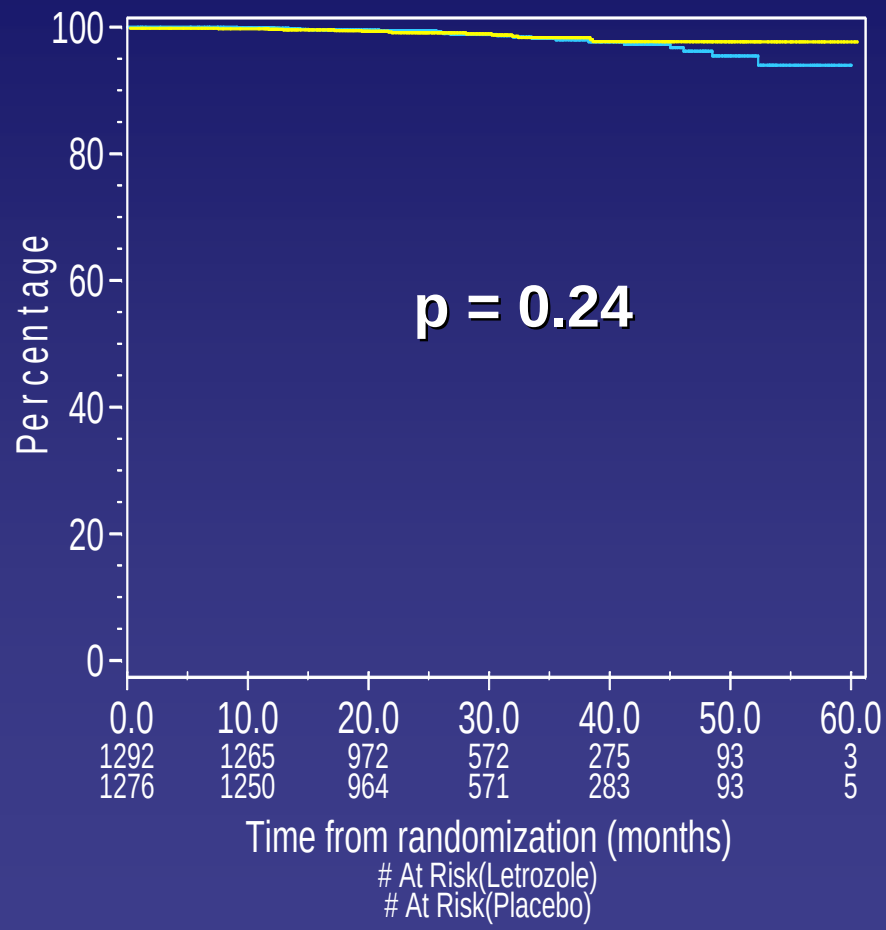


Overall Survival

Node Positive

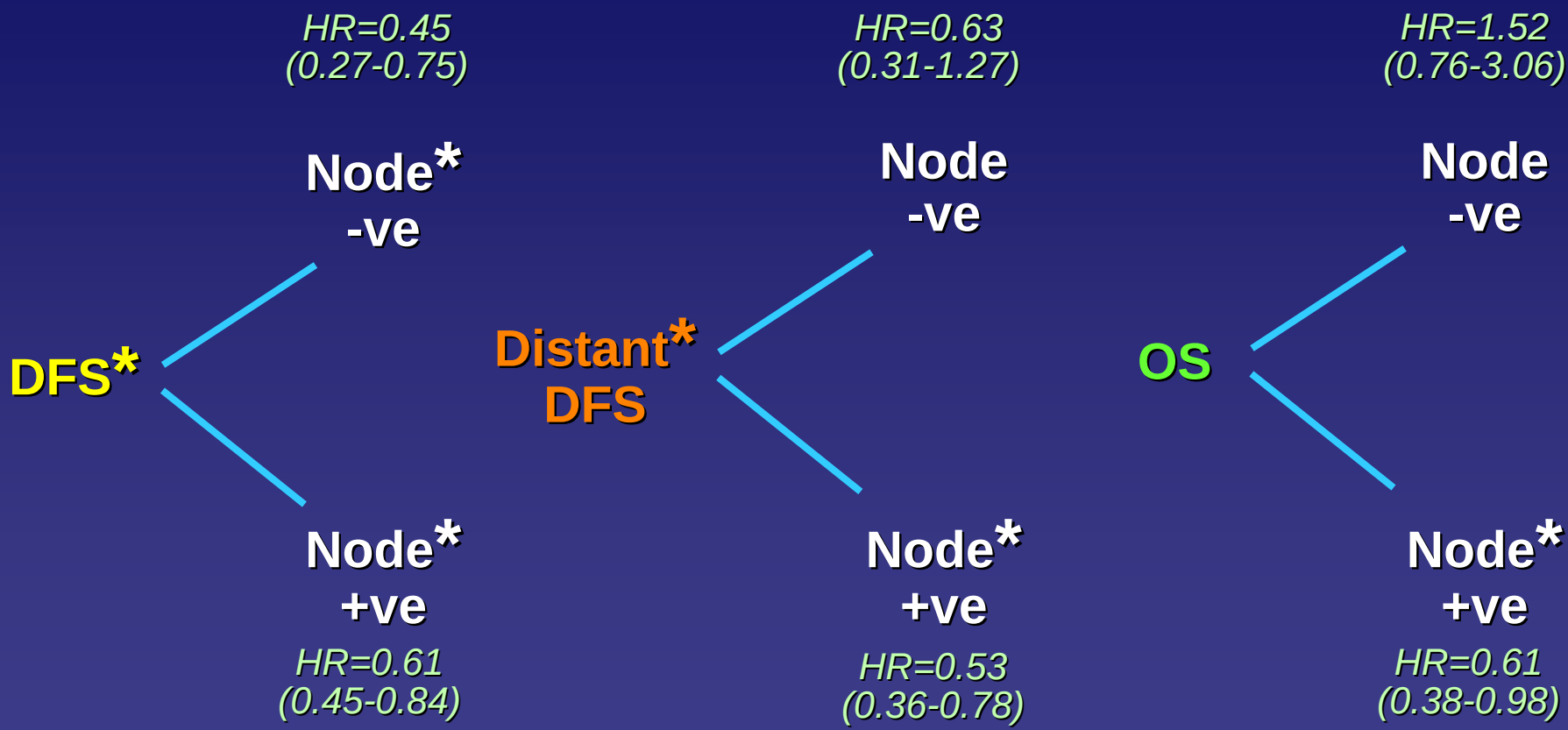


Node Negative



Letrozole Placebo

Summary of Key Endpoints in Nodal Subgroups



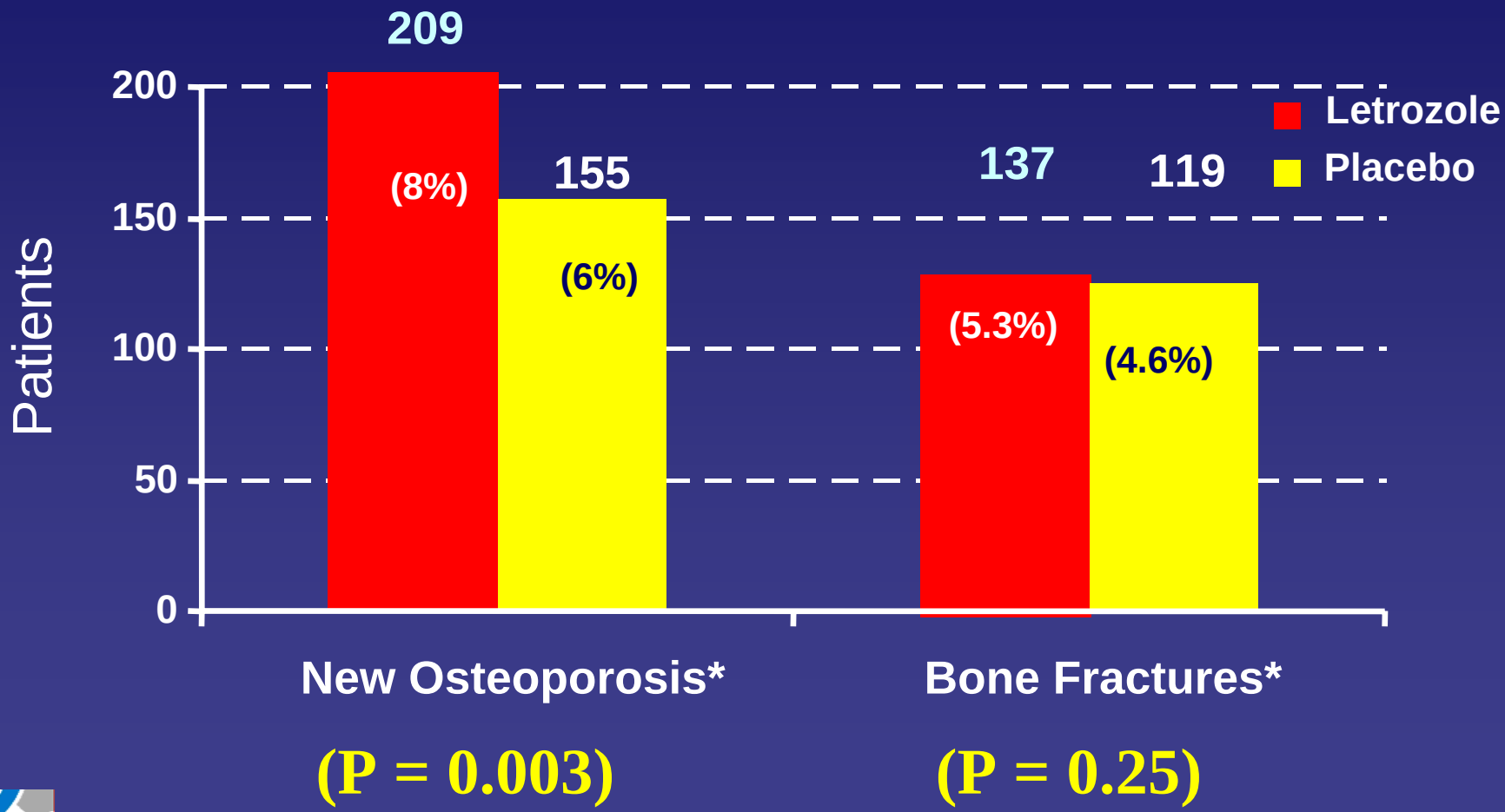
* = Statistically significant

MA.17: Incidence of Adverse Events (All Grades)

	Letrozole (%)	Placebo (%)	*P* value
Hot Flashes	58	54	0.003
Arthritis/Arthralgia	25	21	< 0.0001
Muscle pain	15	12	0.04
Vaginal bleeding	6	8	0.005
Hypercholesterolemia	16	16	0.79
Cardiovascular Events	6	6	0.76
Osteoporosis	8	6	0.003
Discontinuations due to adverse events	5	4	0.02
Discontinuations for other reasons	4	5	0.1

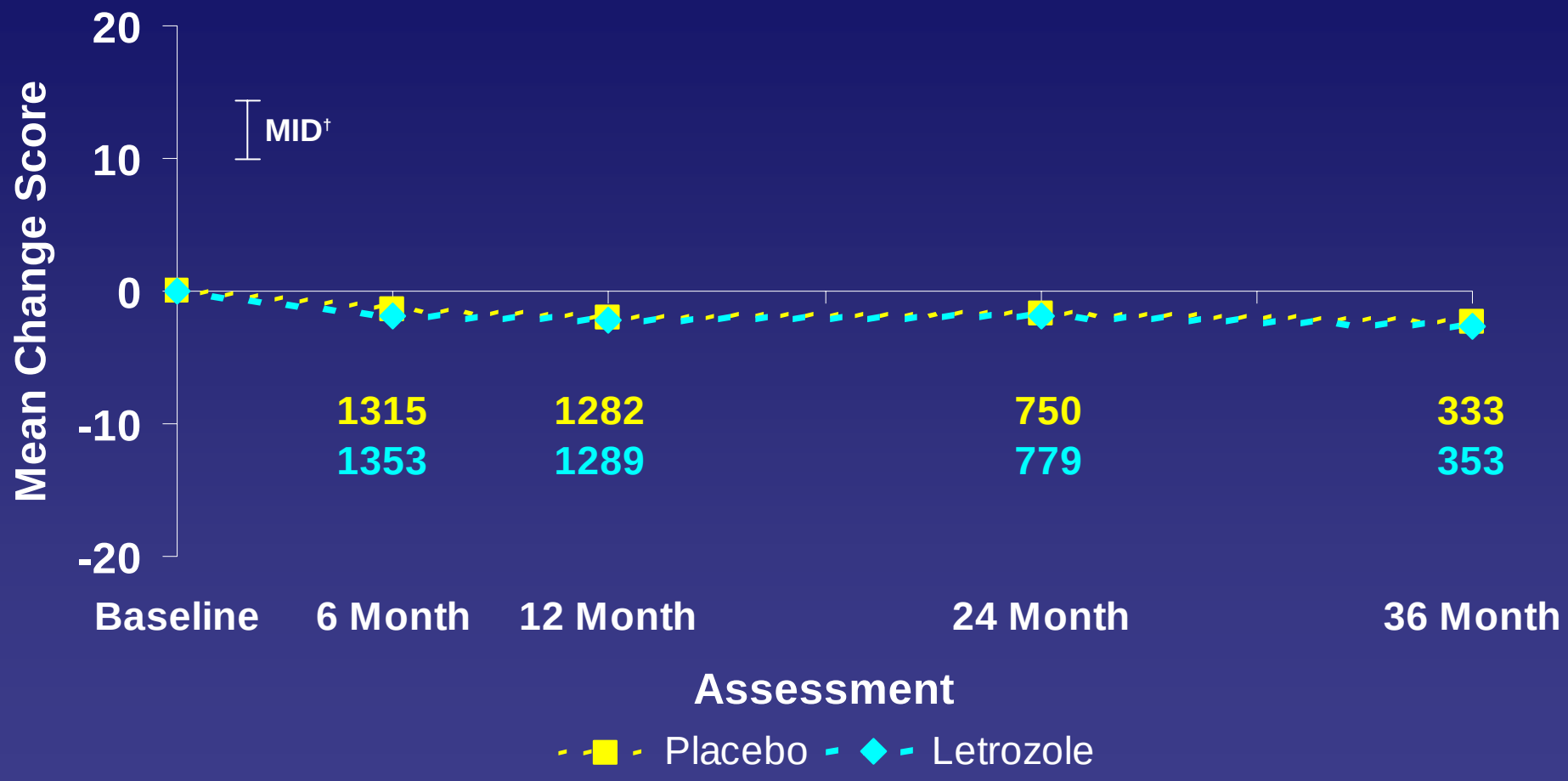
90% of AE's Grade 1 or 2

Numbers of patients who experienced osteoporosis or bone fracture



* patient reported

Quality of life substudy
SF-36 Physical Component



p = NS

† Minimally important difference = 5 pts

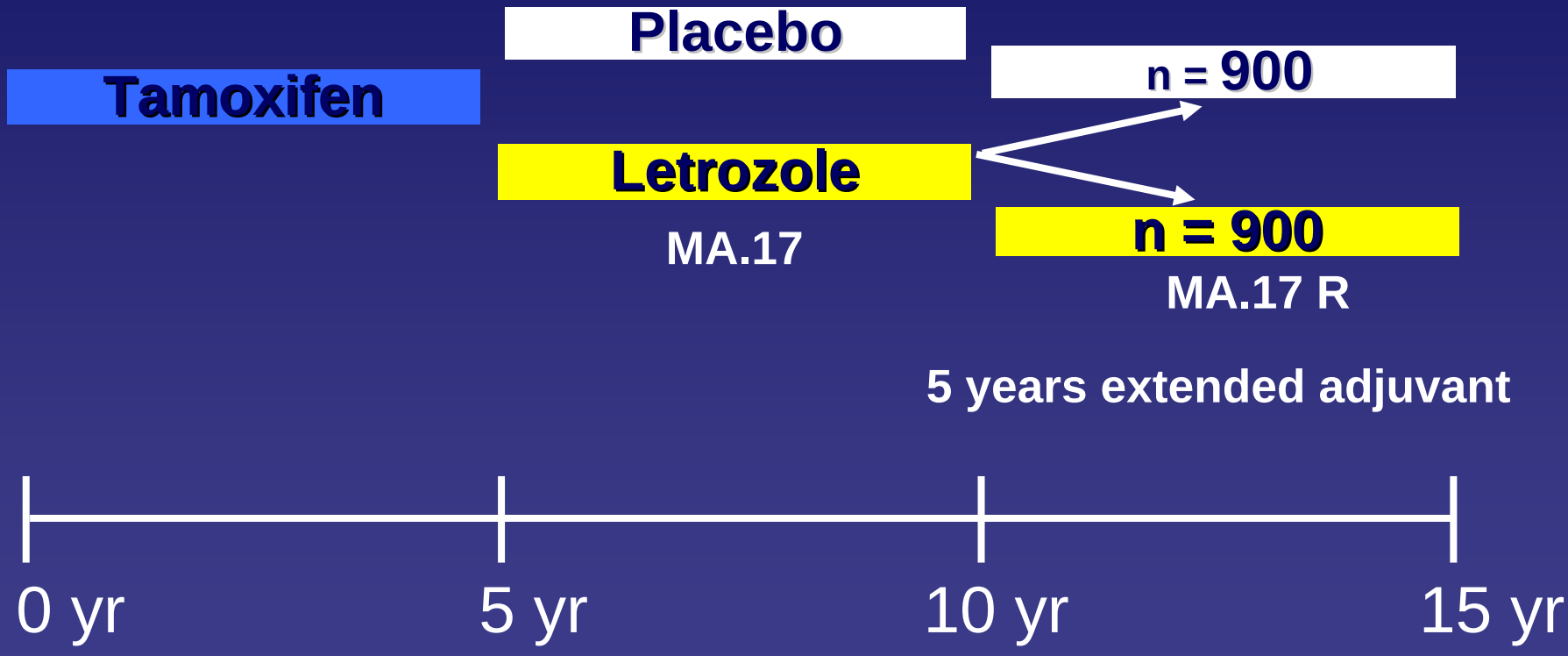
Conclusions MA.17 - Efficacy

- LET reduced recurrences (42%) and distant disease recurrence (40%) after 5 yrs of tamoxifen
- LET significantly reduced recurrences in both Node –ve and Node +ve pts
- LET reduced occurrences (37.5%) of new contra lateral breast cancers (prevention)
- LET improved OS in Node +ve patients
- OS was not improved in Node -ve patients but the same proportionate reduction in local recurrences, new primaries, and distant recurrences occurred as in the node +ve patients

Conclusions MA.17 – Safety & Tolerability

- Predictable but mild E2 deficiency symptoms occurred
- Global QOL was unaffected – mild QOL changes were noted related to reported menopausal symptoms and joint and muscle pains
- Bone metabolism was affected by LET as indicated by a minimal increase in osteoporosis detected over 4 yrs but no difference in clinical fractures occurred
- Evaluation of longer-term toxicities will be determined from MA.17 follow-up, re-randomization and sub studies of longer follow-up

MA.17R Re - Randomization Yr 10 – 15



MA.17 Acknowledgements

5187 Patients

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