

# Evaluation of Subcutaneous Proleukin® in a Randomized International Trial

## ESPRIT<sup>✶</sup>

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# Background and Rationale

- High CD4+ cell counts are associated with lower risks of opportunistic disease (OD), serious non-AIDS events, and death.
- In combination with ART, subcutaneous recombinant interleukin-2 (IL-2) raises CD4+ cell counts greater than ART alone.
- It is not known if the CD4+ cell count increase seen with IL-2 results in a lower rate of clinical disease.

# Study Design

Patients taking ART with CD4+ counts  $\geq 300/\mu\text{L}$

N = 2071

**IL-2**

ART plus:

- 3 cycles of IL-2 (7.5 MIU twice daily for 5 days, 8 wks apart)
- additional cycles to maintain goal (2x baseline or  $\geq 1000$  CD4+ cells)

N = 2040

**Control**

ART without IL-2

**Plan: 320 primary events**

**Closure date 15 Nov 2008**

**323 primary events observed**

**Median follow-up = 7 years**

# Major Endpoints

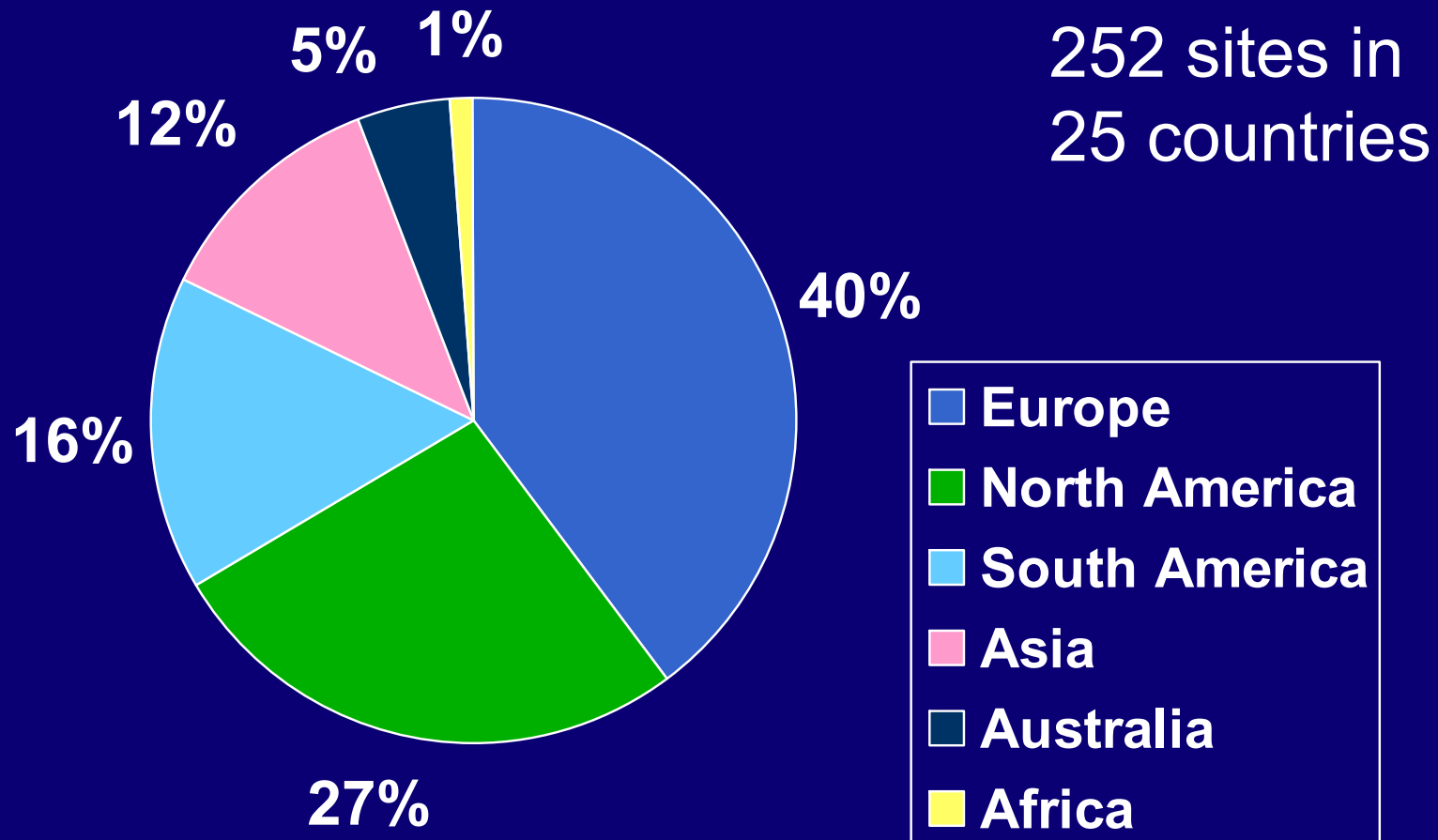
*Primary :*

- Opportunistic disease (OD) or death

*Other key endpoints:*

- Death
- Grade 4 clinical adverse events
- Serious non-AIDS events
  - Non-fatal renal, cardiovascular, liver, malignancy
  - Death from non-AIDS causes

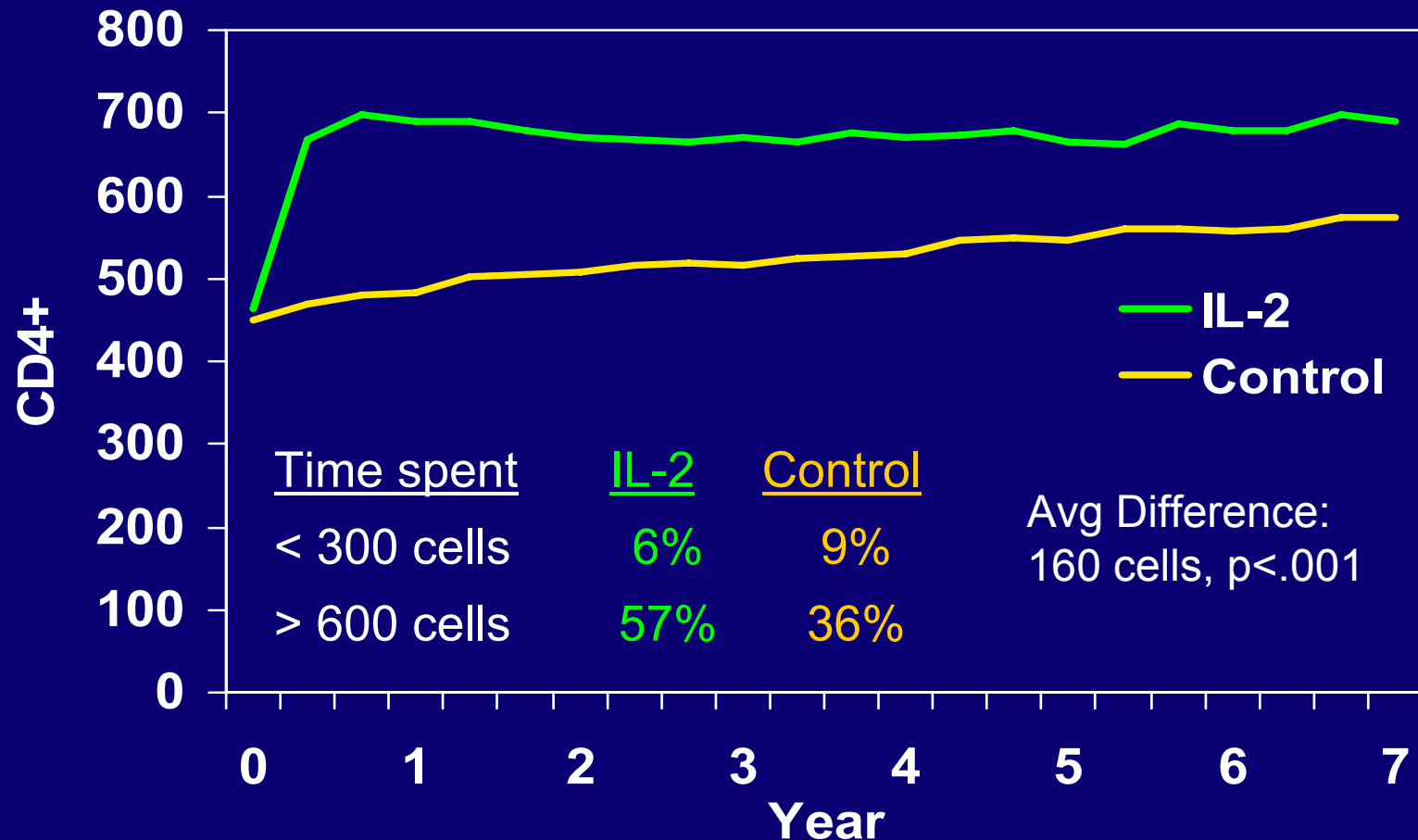
# Geographic Distribution of Patients



# Baseline Characteristics

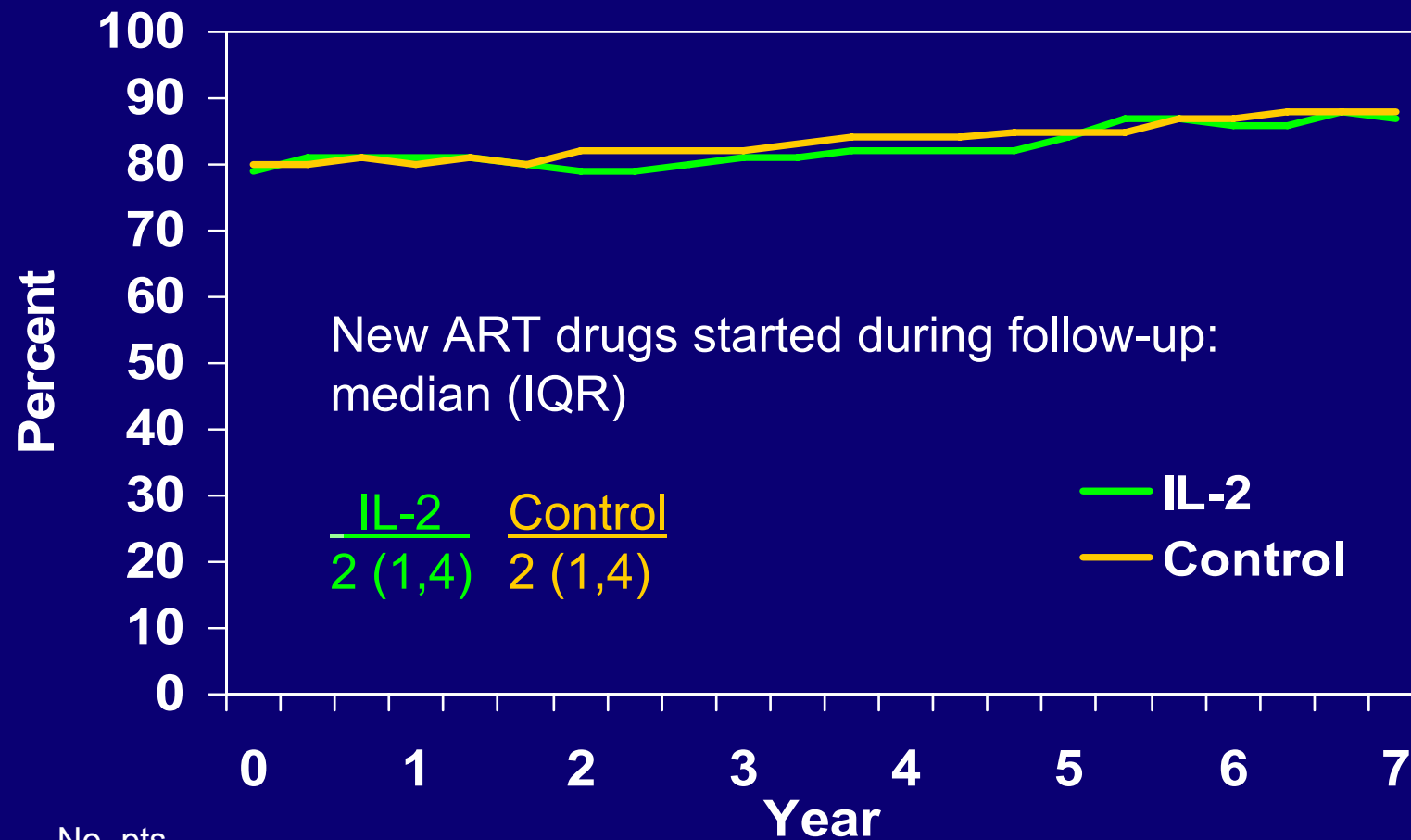
|                               | <u>IL-2</u> | <u>Control</u> | <u>Total</u>   |
|-------------------------------|-------------|----------------|----------------|
| Age (mean)                    | 41          | 41             | 41             |
| Female (%)                    | 19%         | 19%            | 19%            |
| Non-white race (%)            | 25%         | 24%            | 24%            |
| Median CD4+ (IQR)             | 464         | 450            | 457 (372, 584) |
| Nadir CD4+ (IQR)              | 200         | 194            | 197 (91, 306)  |
| HIV-RNA $\leq$ 500 copies (%) | 79%         | 80%            | 80%            |
| Prior clinical AIDS (%)       | 25%         | 26%            | 26%            |
| Years prior ART (IQR)         | 4.1         | 4.3            | 4.2 (2.2, 6.4) |

# Median CD4+ During Follow-up



|          |      |      |      |      |      |      |      |     |
|----------|------|------|------|------|------|------|------|-----|
| No. pts  |      |      |      |      |      |      |      |     |
| IL-2:    | 2071 | 1846 | 1829 | 1797 | 1757 | 1721 | 1410 | 878 |
| Control: | 2040 | 1928 | 1861 | 1803 | 1739 | 1648 | 1350 | 824 |

# Percent with HIV-RNA $\leq 500$ Copies/ml



No. pts

|          |      |      |      |      |      |      |      |     |
|----------|------|------|------|------|------|------|------|-----|
| IL-2:    | 2065 | 1943 | 1864 | 1827 | 1770 | 1735 | 1418 | 889 |
| Control: | 2036 | 1921 | 1856 | 1791 | 1724 | 1643 | 1350 | 821 |

# Primary Endpoint

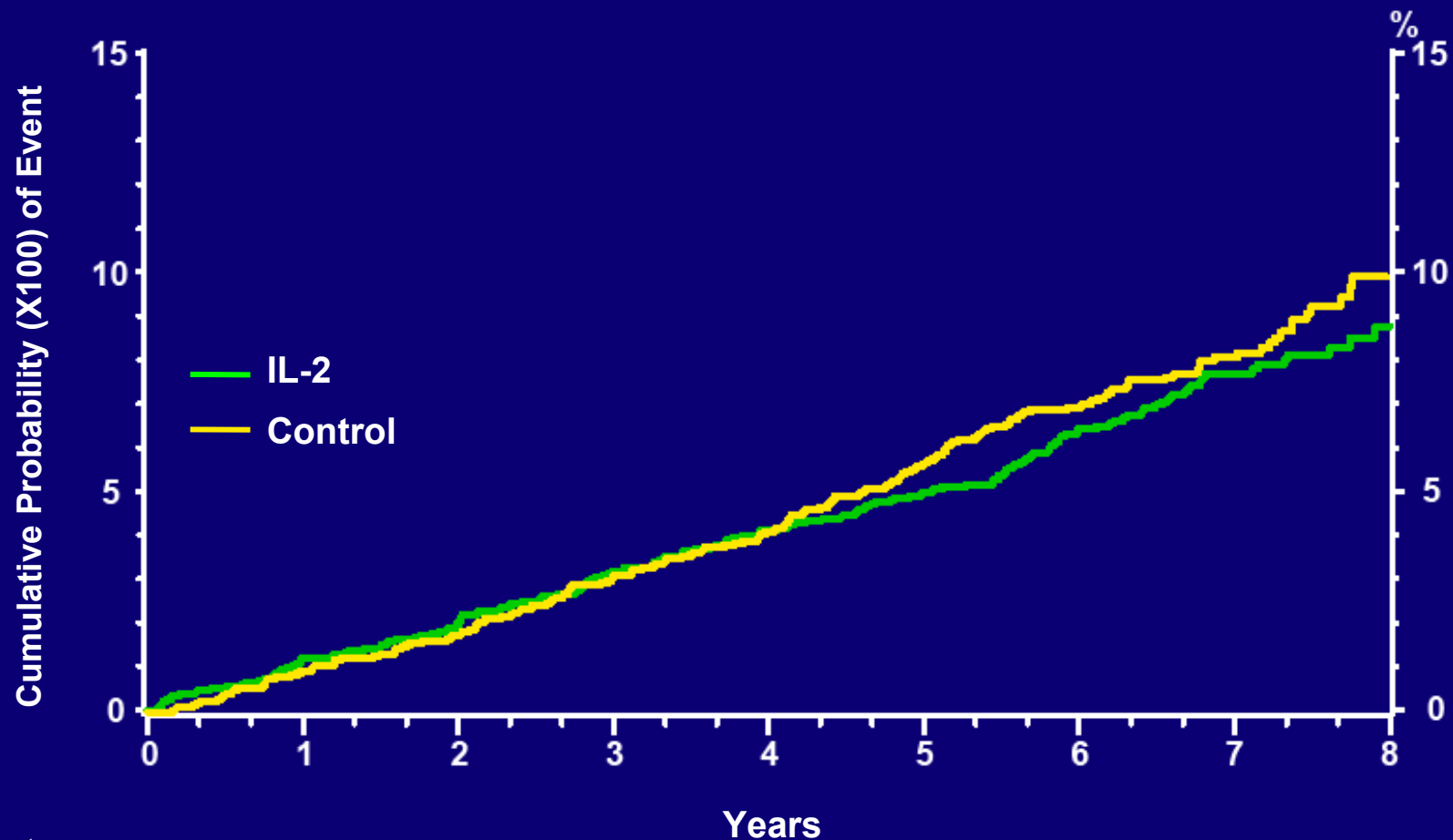
## Opportunistic Disease or Death

| <u>IL-2</u> |              | <u>Control</u> |              | <u>HR (95% CI)</u> | <u>p-value</u> |
|-------------|--------------|----------------|--------------|--------------------|----------------|
| <u>No.</u>  | <u>Rate*</u> | <u>No.</u>     | <u>Rate*</u> |                    |                |
| 158         | 1.13         | 165            | 1.21         | 0.93 (0.75, 1.16)  | .52            |

*Predicted HR based on CD4+ difference = 0.74*

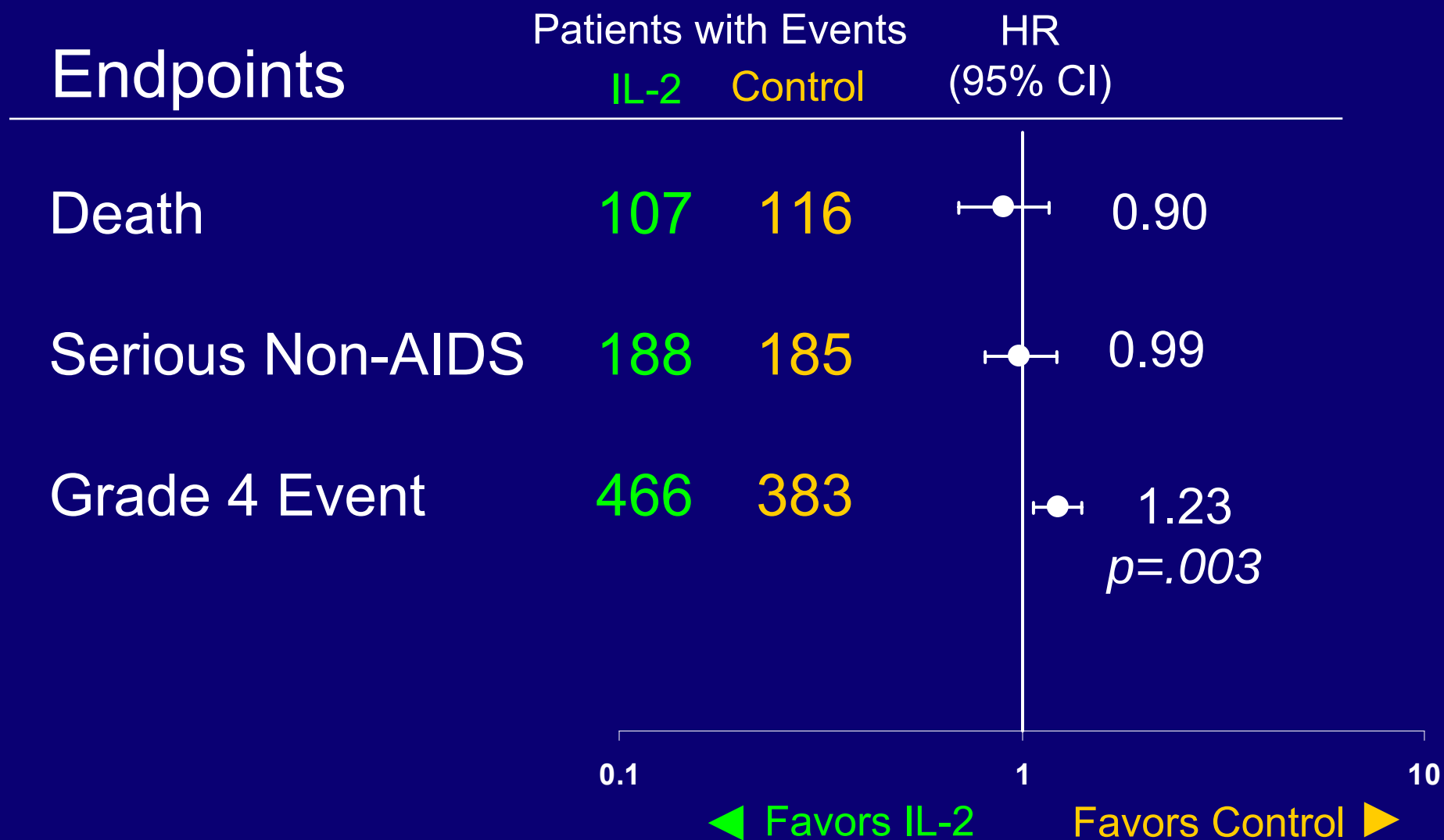
*\* rate per 100 person years*

# Opportunistic Disease or Death

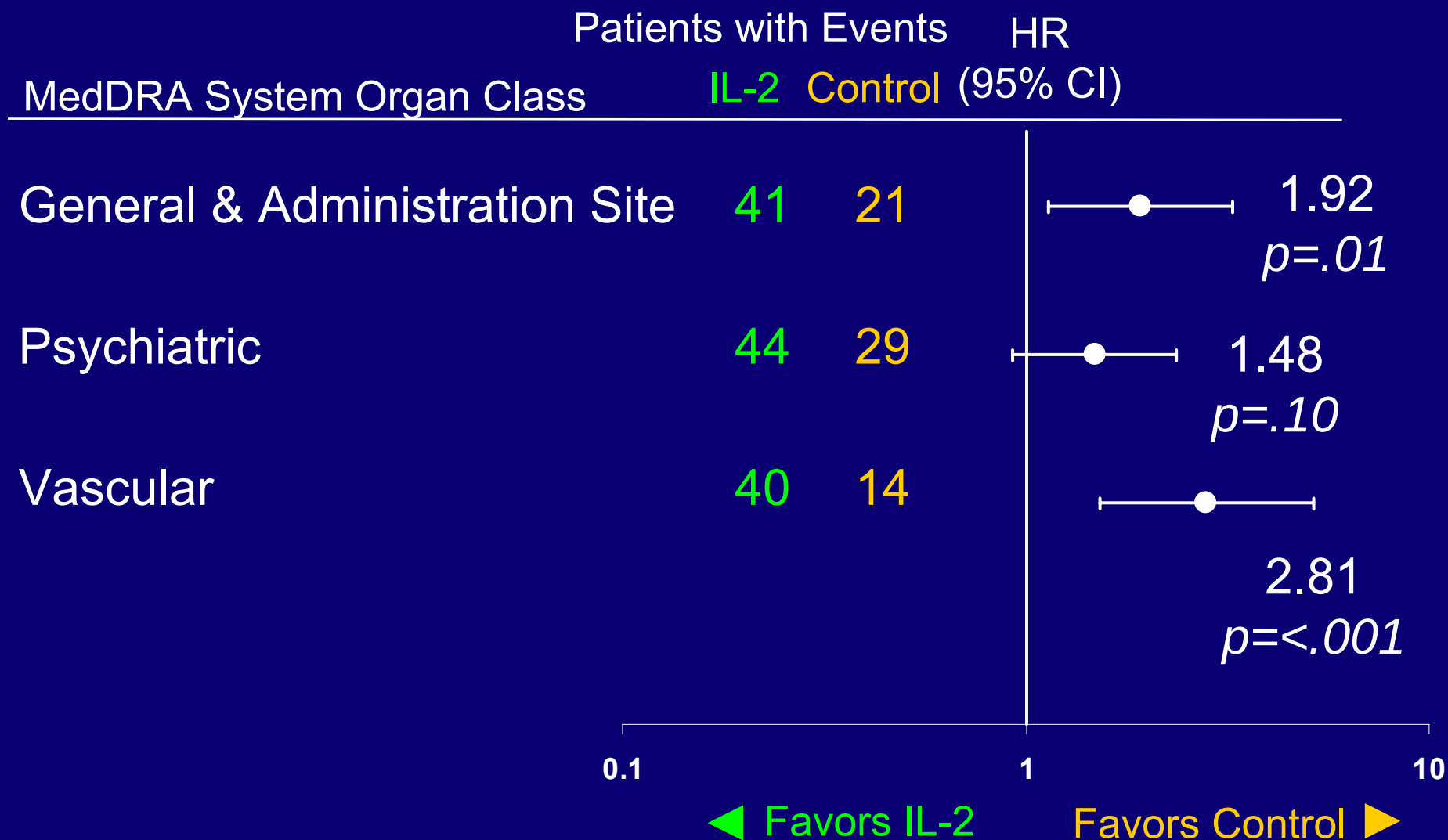


| No. pts  | Years |      |      |      |      |      |      |     |     |
|----------|-------|------|------|------|------|------|------|-----|-----|
| IL-2:    | 2071  | 2030 | 1997 | 1947 | 1909 | 1873 | 1552 | 971 | 322 |
| Control: | 2040  | 2003 | 1962 | 1918 | 1883 | 1825 | 1483 | 910 | 272 |

## Other Major Endpoints



# Grade 4 Events of Note



# **Why did we not observe an overall reduction in OD/death with IL-2, in spite of a substantial difference in CD4 counts between groups?**

Possible explanations:

- CD4+ cells expanded by IL-2 are not functionally equivalent to CD4+ cells arising as a result of viral load suppression with ART.
- There may be harmful effects of IL-2 counterbalancing beneficial effects of IL-2.

# Conclusions

- IL-2 plus ART produces a substantial and sustained CD4+ cell increase compared with ART alone.
- IL-2 plus ART provides no additional clinical benefit compared to ART alone.
- The addition of IL-2 to ART was associated with more grade 4 clinical events.
- CD4+ cell count is not a reliable surrogate marker for clinical outcomes in the evaluation of IL-2.
- Clinical endpoint trials are needed to evaluate the clinical impact of novel therapeutic approaches to treat HIV infection.

# Acknowledgements

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hundreds of investigators.

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Merci!