

Evaluation of
Subcutaneous Proleukin® in a
Randomized International Trial

ESPRIT[™]

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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 ≥ 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

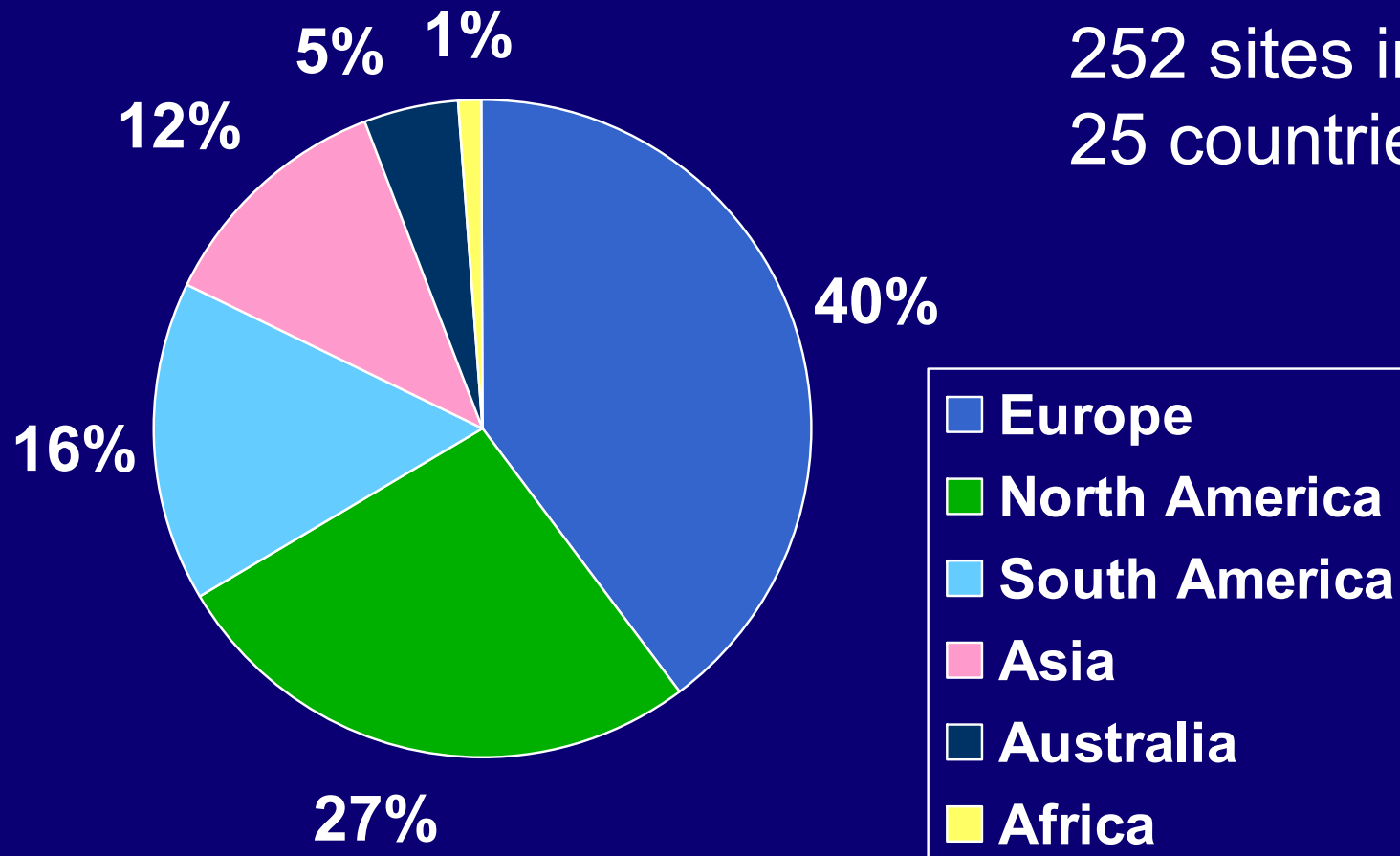
Primary :

- 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

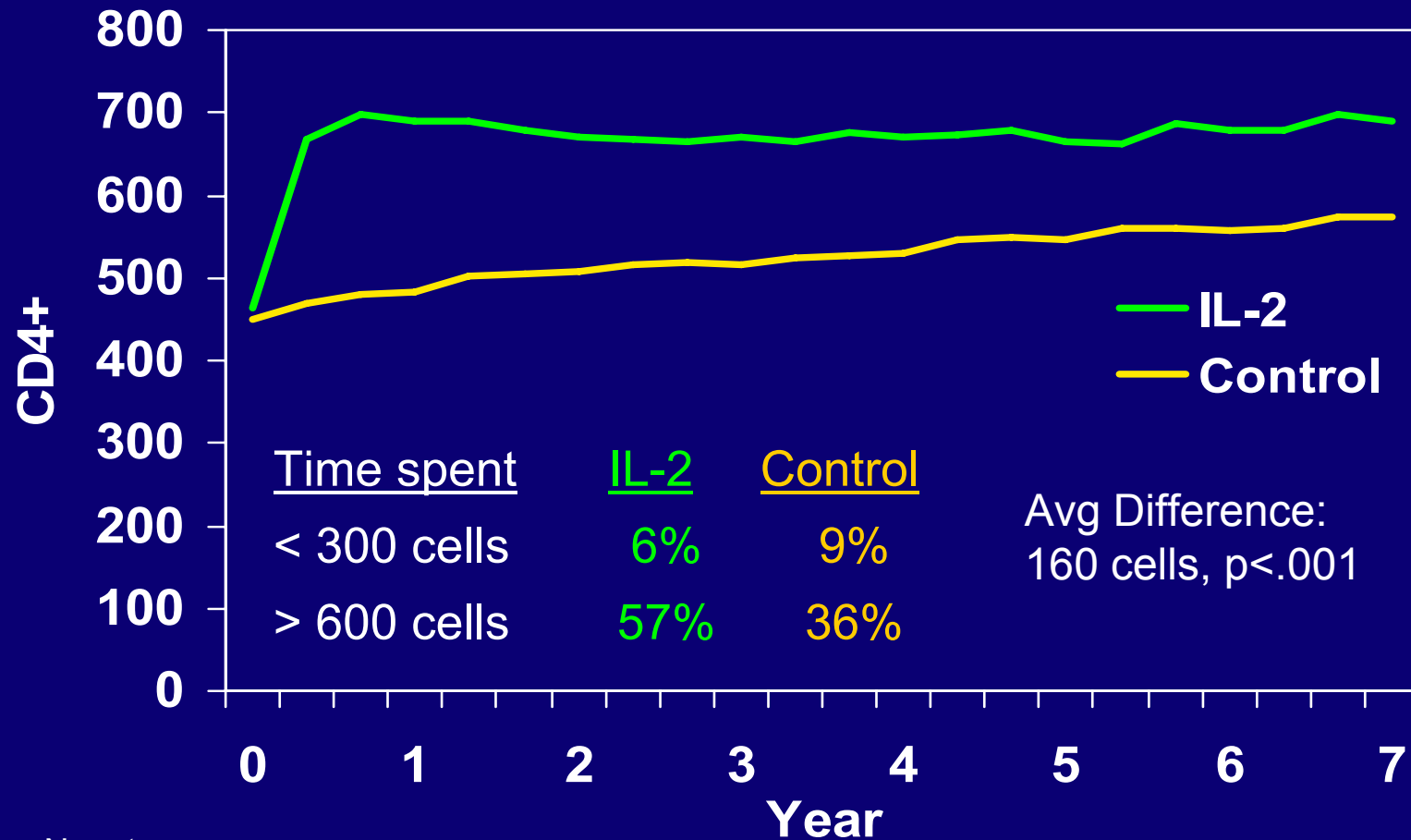
Geographic Distribution of Patients



Baseline Characteristics

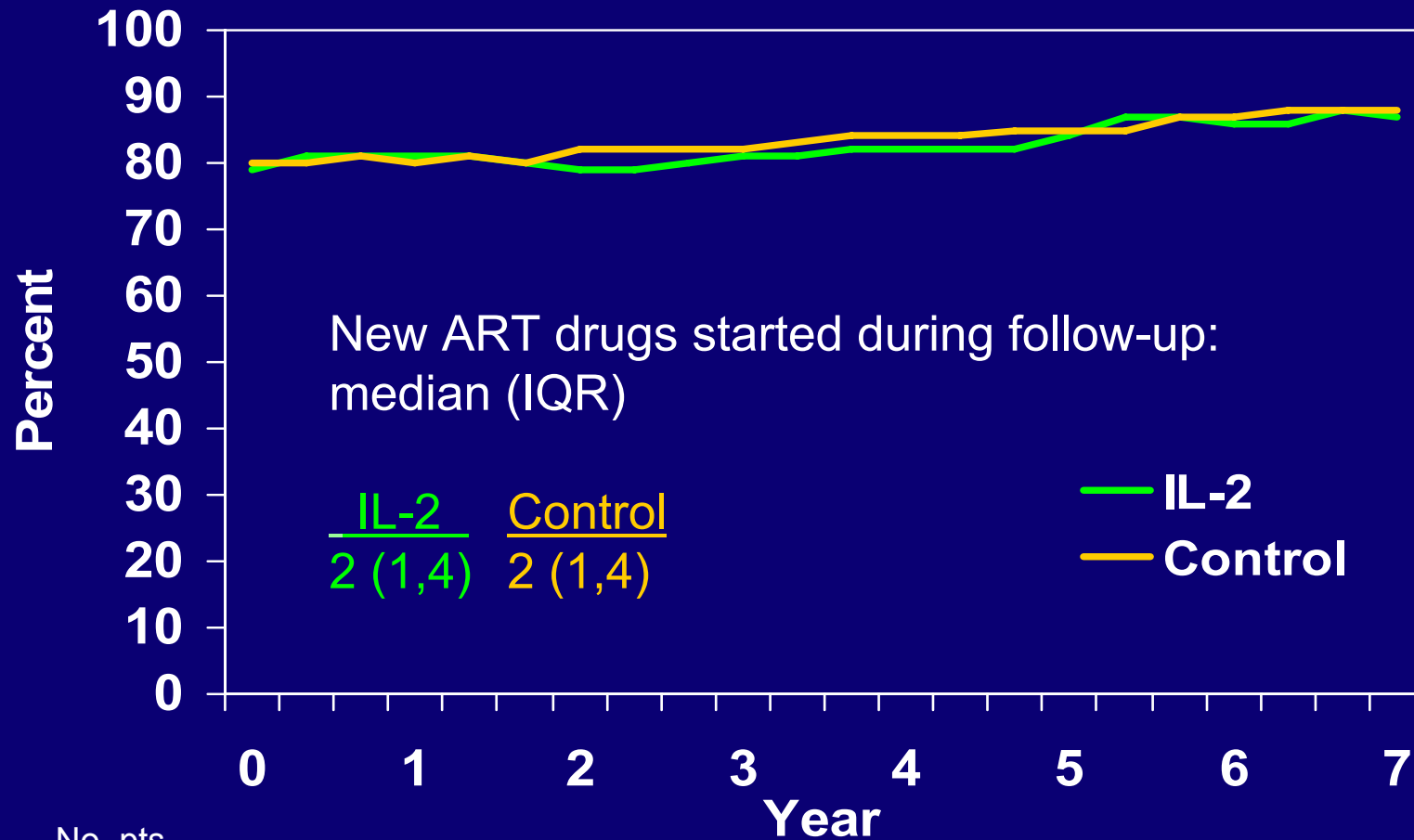
	<u>IL-2</u>	<u>Control</u>	<u>Total</u>
Age (mean)	41	41	41
Female (%)	19%	19%	19%
Non-white race (%)	25%	24%	24%
Median CD4+ (IQR)	464	450	457 (372, 584)
Nadir CD4+ (IQR)	200	194	197 (91, 306)
HIV-RNA \leq 500 copies (%)	79%	80%	80%
Prior clinical AIDS (%)	25%	26%	26%
Years prior ART (IQR)	4.1	4.3	4.2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

Median CD4+ During Follow-up



No. pts	0	1	2	3	4	5	6	7
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	0	1	2	3	4	5	6	7
IL-2:	2065	1943	1864	1827	1770	1735	1418	889
Control:	2036	1921	1856	1791	1724	1643	1350	821

Primary Endpoint

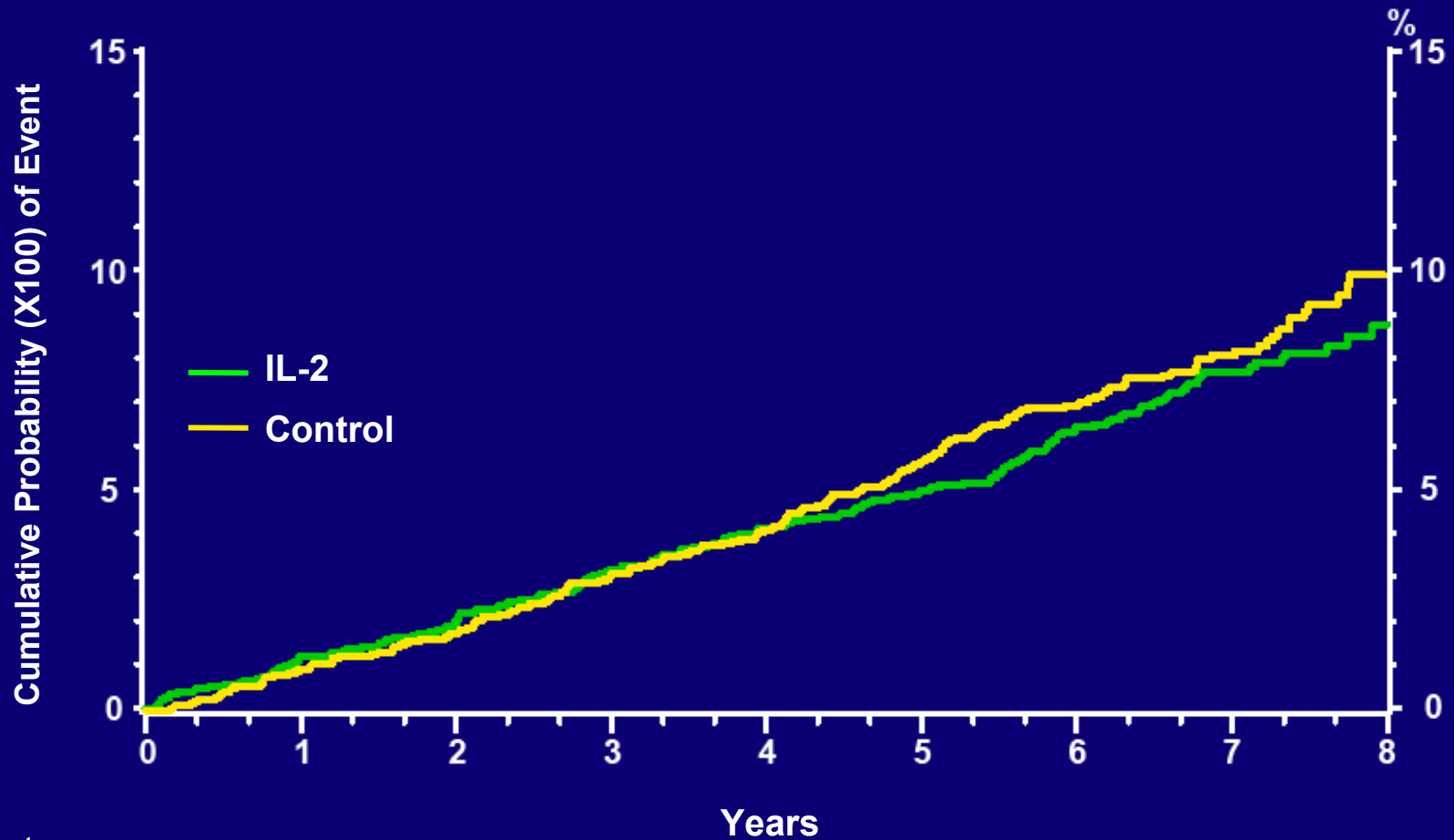
Opportunistic Disease or Death

<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

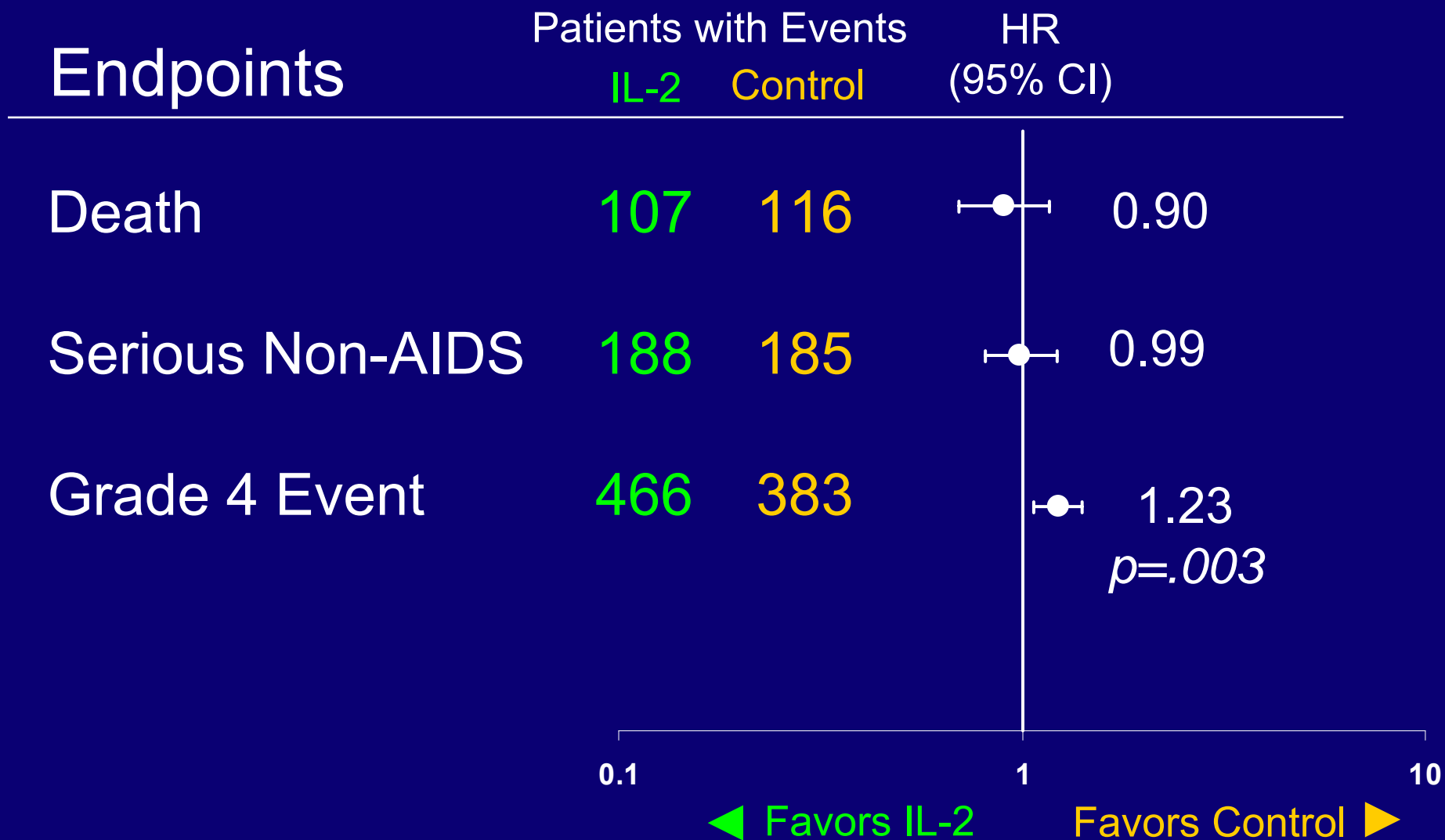
** rate per 100 person years*

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



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

Thanks to many thousands of patients and hundreds of investigators.

Supported by the Division of AIDS, NIAID, NIH.

This study was carried out by the INSIGHT group.

IL-2 was provided by Novartis and Chiron.

Merci!