



The Development of AntiRetroviral Therapy in Africa (DART) trial

Comparison of
routine vs clinically driven laboratory monitoring
in HIV-infected African adults over 5 years on ART:
Final results of the DART trial

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Main objective of DART



- To evaluate the need for routine laboratory monitoring of ART
 - in African adults who fulfilled clinical and CD4 criteria for ART initiation
 - in terms of clinical effectiveness, safety and costs
- Primary endpoints
 - *Efficacy*: new WHO stage 4 HIV event (AIDS) or death
 - *Safety*: any Serious Adverse Event which is not only HIV-related



Trial design

3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease,
CD4 < 200 cells/mm³ initiating triple drug ART

randomise

Laboratory and Clinical Monitoring (LCM)

12 weekly biochemistry,
FBC & CD4

Other investigations & concomitant medications if clinically indicated

Switch to second-line for

- new/recurrent WHO 4
(or multiple WHO 3)
- CD4 < 100 cells/mm³

Clinically Driven Monitoring (CDM)

12 weekly biochemistry,
FBC & CD4,

FBC & biochemistry only returned if clinically indicated (or grade 4 toxicity);
CD4 never returned

Other investigations & concomitant medications if clinically indicated

Switch to second-line for new/recurrent WHO 4
(or multiple WHO 3)



Trial status

- 6578 patients screened
- 3316 patients randomised to CDM or LCM
 - between 15 January 2003 and 28 October 2004
- Final data to 31 December 2008 (max 6, median 4.9 years)
 - during Jan 2009, all laboratory tests returned to CDM participants
 - participants transitioned care into Ugandan and Zimbabwean national ART programmes (except those in second-line studies)
 - results of second-line studies expected early 2010



Characteristics at baseline (ART initiation)



		LCM N=1656	CDM N=1660
Women		1092 66%	1064 64%
Age (years)	median (range)	36 (18-67)	36 (18-73)
CD4 count (cells/mm ³)	median	86 (0-199)	86 (1-199)
	<50 cells/mm ³	554 33%	555 33%
HIV-1 RNA (log ₁₀ copies/ml)	mean (SD)*	5.4 (0.7)	5.4 (0.7)
WHO stage	2	363 22%	310 19%
	3	916 55%	948 57%
	4	377 23%	402 24%
On cotrimoxazole before/at ART initiation		1014 61%	1034 62%
ART: ZDV+3TC plus	TDF	1232 74%	1237 75%
	ABC	150 9%	123 9%
	NVP	274 16%	273 16%
Identified at any time (including post-baseline) as having previously received ART		65 4%	65 4%
Previous ART for MTCT (% of women)		23 2%	38 4%

* assayed in a subset (N=968) at baseline only



Follow-up



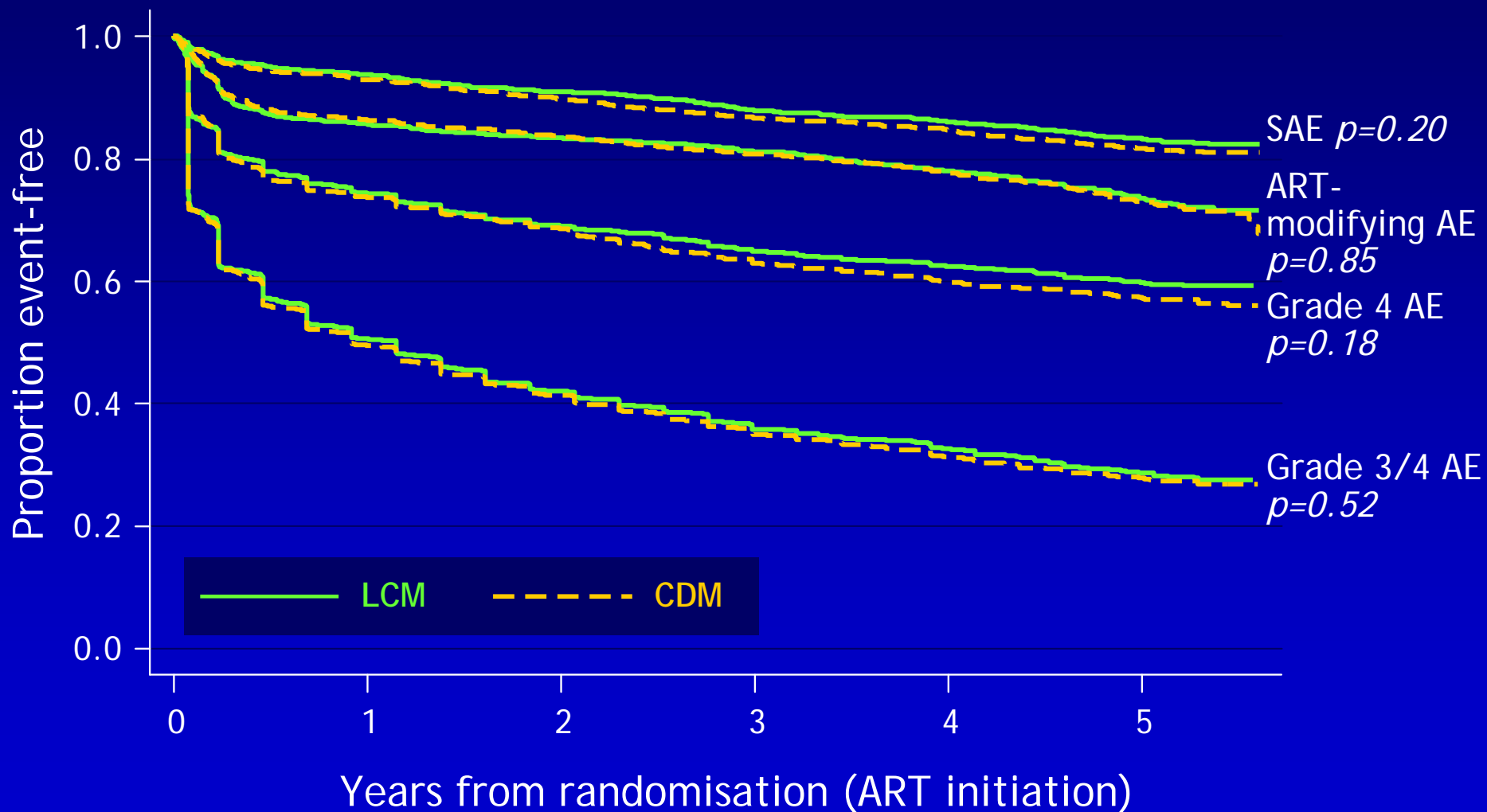
- Median follow-up to 31 December 2008 4.9 years (IQR 4.5-5.3)
 - 14,937 person-years
 - 236 (7%) lost to follow-up
 - 98% and 99% of expected nurse and doctor visits attended
 - high patient-reported adherence

Blinding of laboratory test results in the CDM arm

- Few CDM participants sought external CD4 counts
 - clinicians remained blinded
 - at DART exit, 81/1281 (6%) reported having CD4s done privately
 - 43/81 had 1 CD4 test only
 - 3/81 had 6 or more



Adverse events





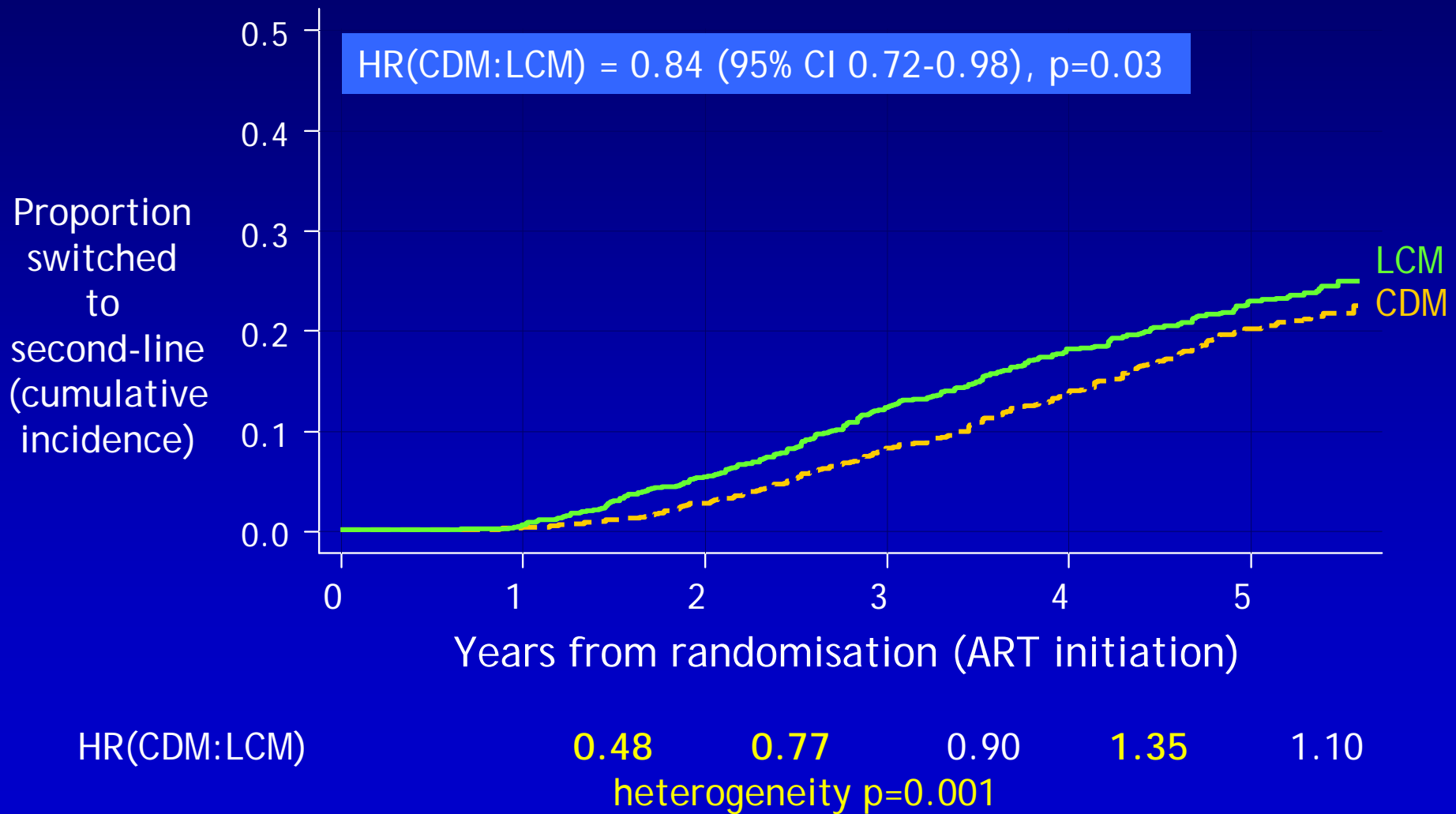
Antiretroviral therapy



At last follow-up/31 December 2008	LCM N=1656		CDM N=1660	
Remained on first-line	1295	78%	1346	81%
- still taking original first-line regimen	1014	61%	1059	64%
- substituted CBV <u>only</u>	113	7%	98	6%
- substituted third drug (\pm CBV)	162	10%	179	11%
- off ART for >90 days	6	0.4%	10	0.6%
Had switched to second-line	361	22%	314	19%

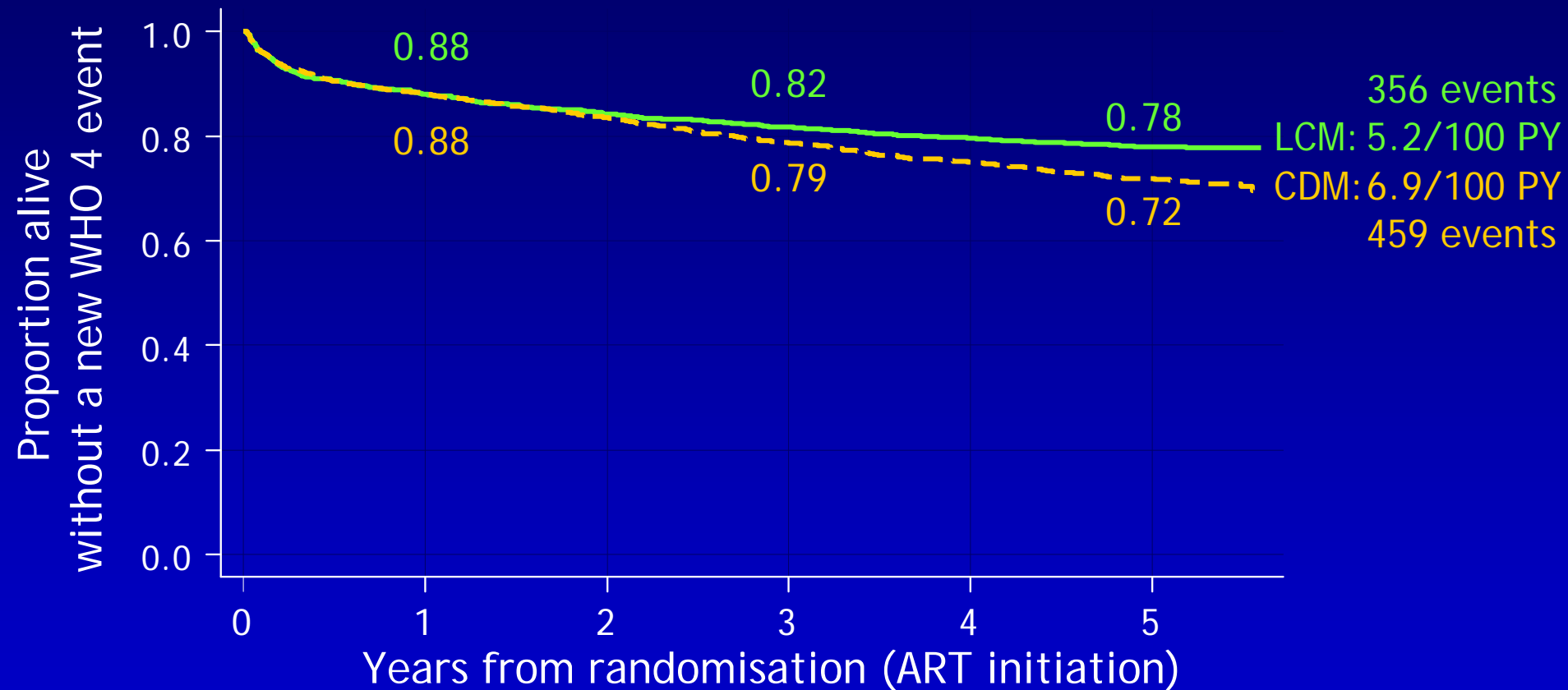


Switch to second-line





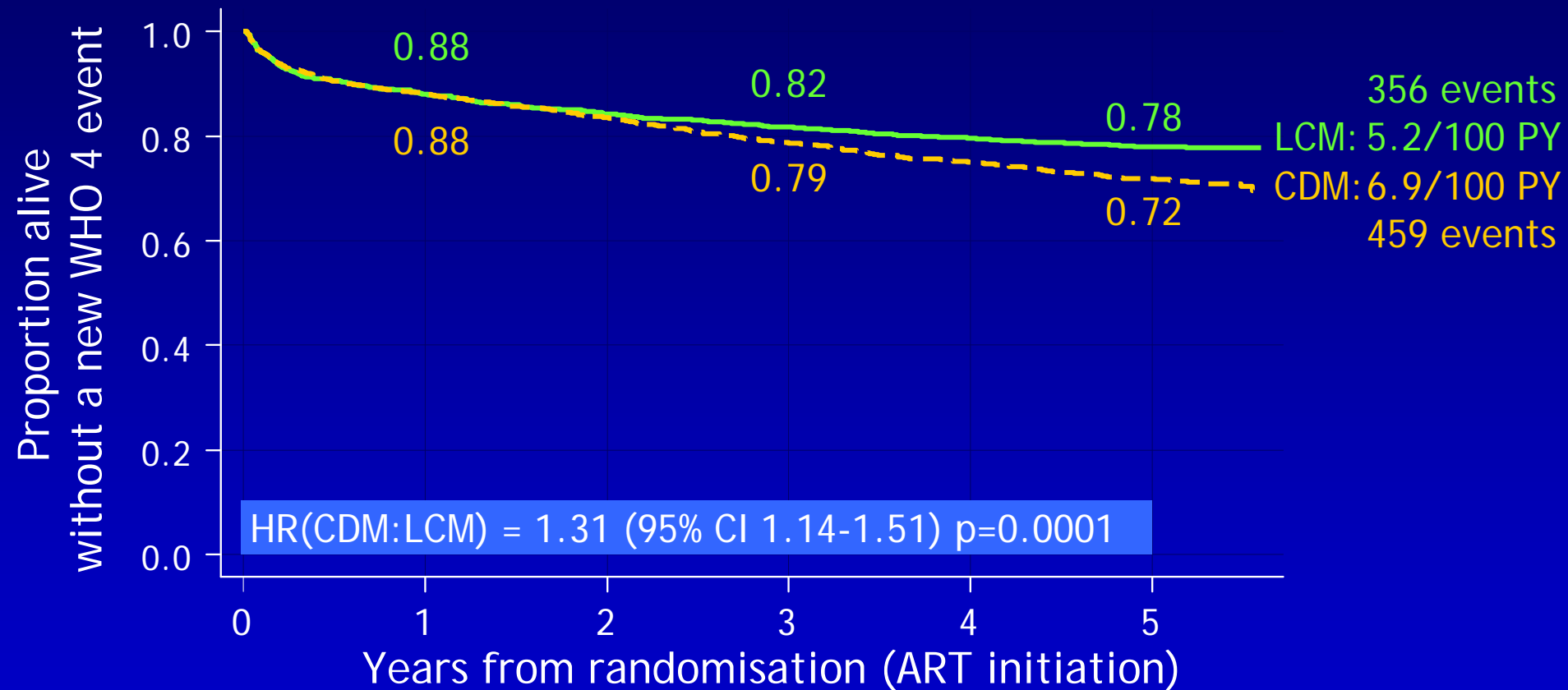
Progression to new WHO 4 event or death (primary endpoint)



LCM: n=	1656	1438	1364	1306	1255	682
CDM: n=	1660	1443	1354	1262	1184	613
IAS July 2009						



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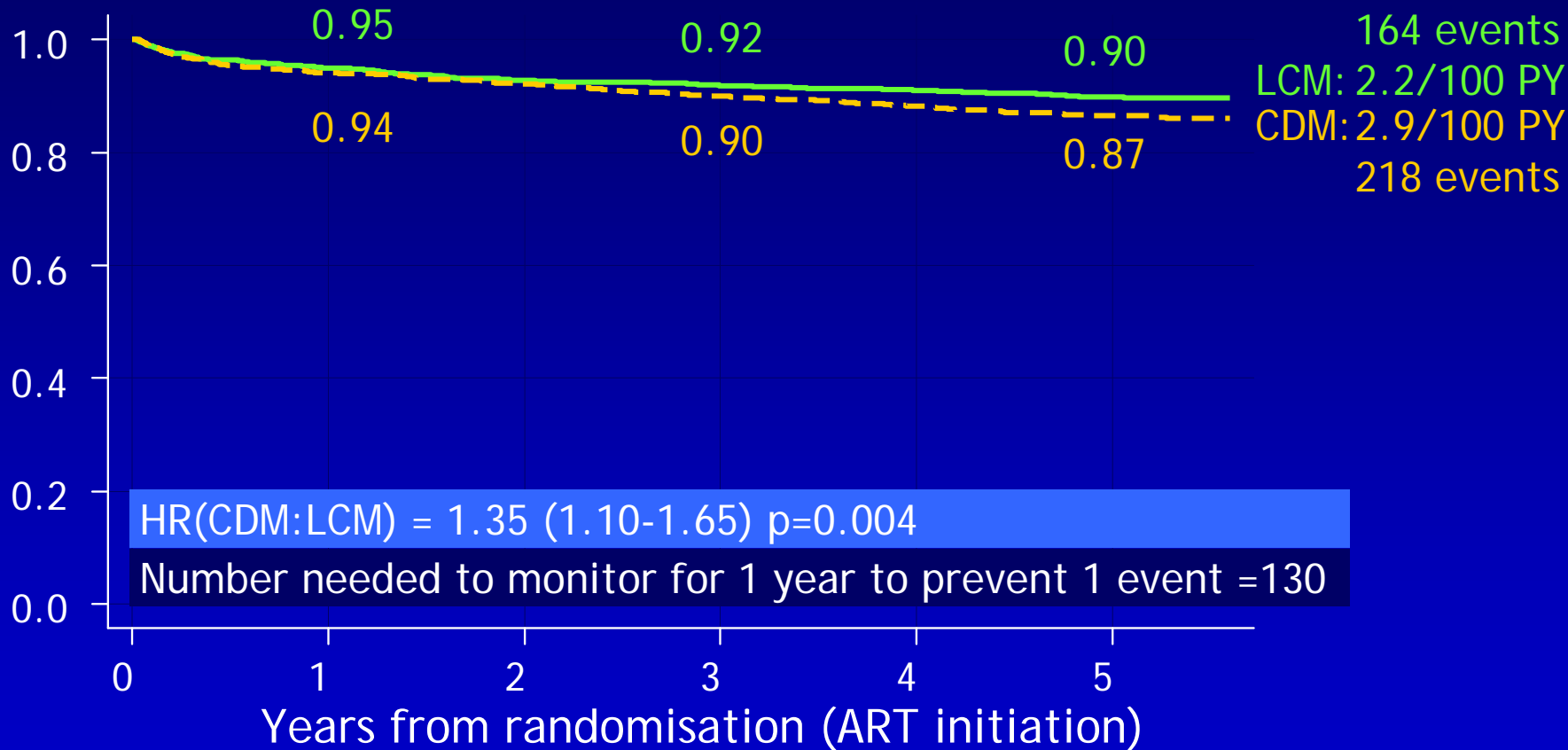
IAS July 2009



Survival



Proportion alive



	0	1	2	3	4	5
LCM	1656	1552	1501	1468	1436	796
CDM	1660	1542	1494	1445	1395	749

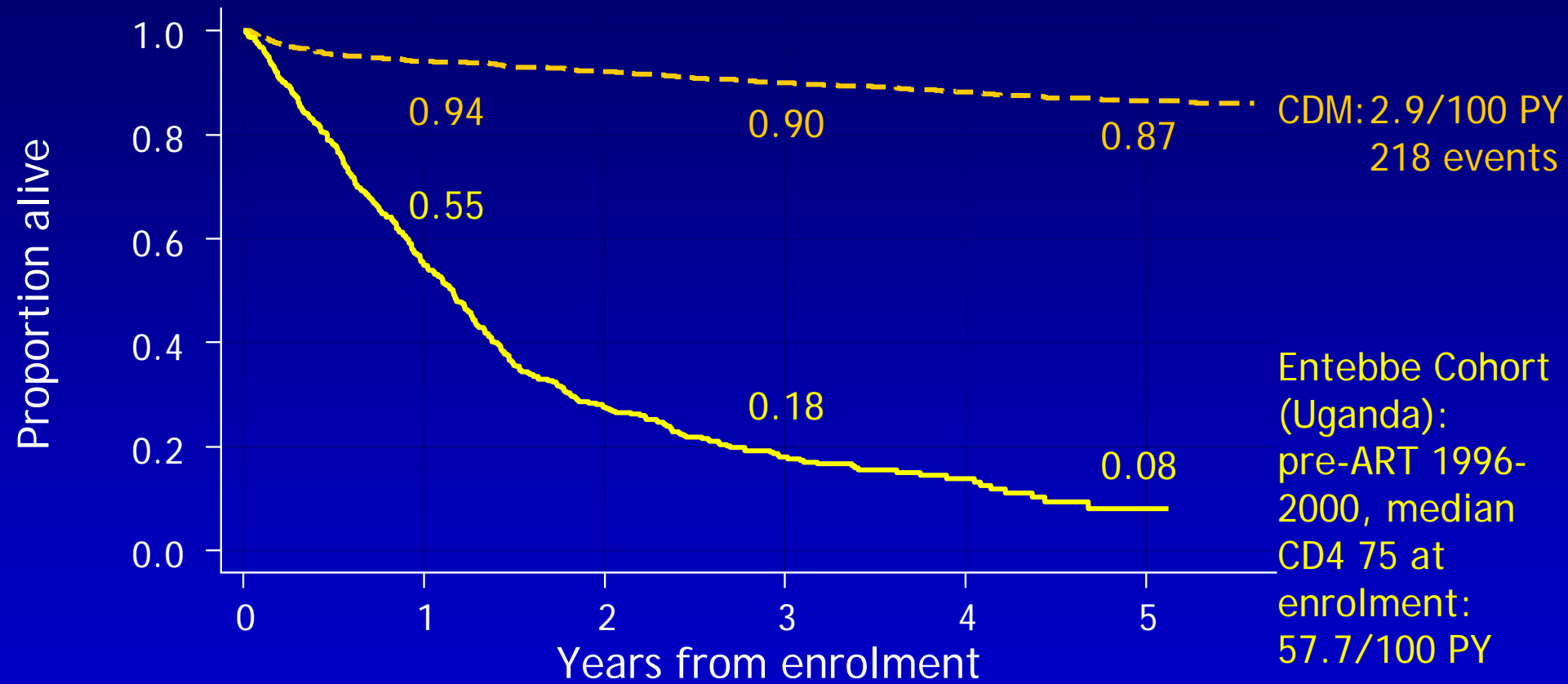


Survival





Survival



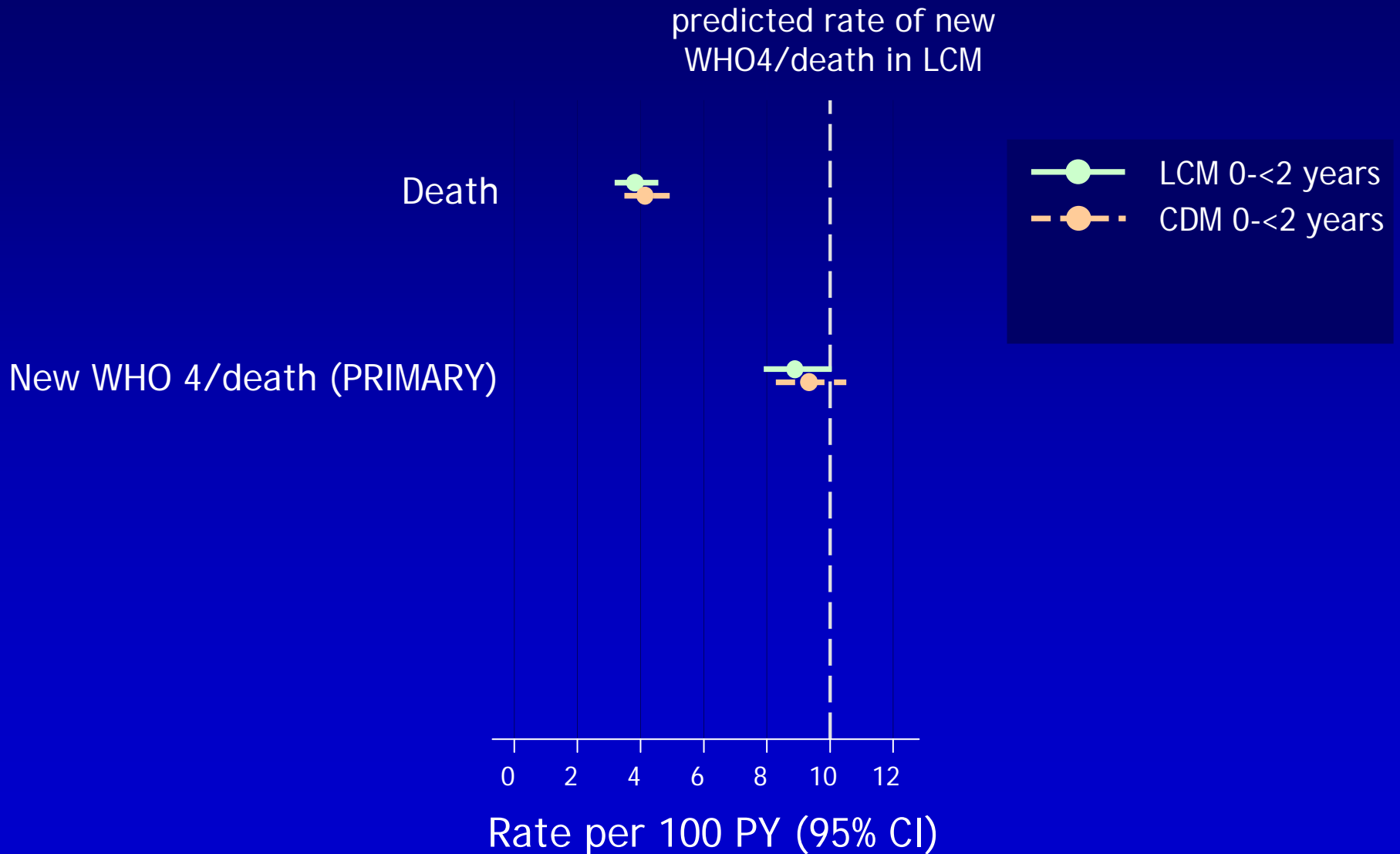


Survival



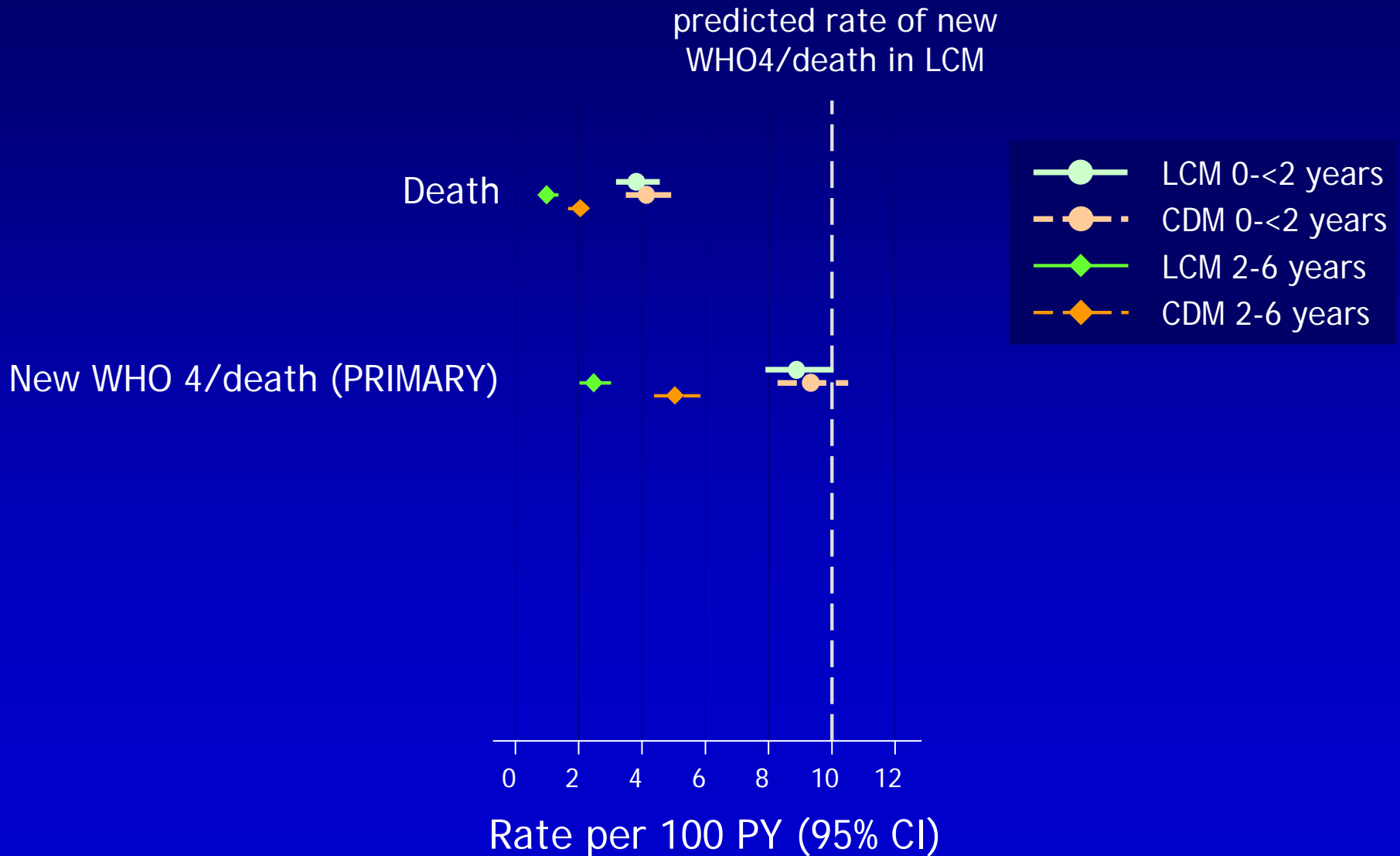


Absolute event rates over time on ART



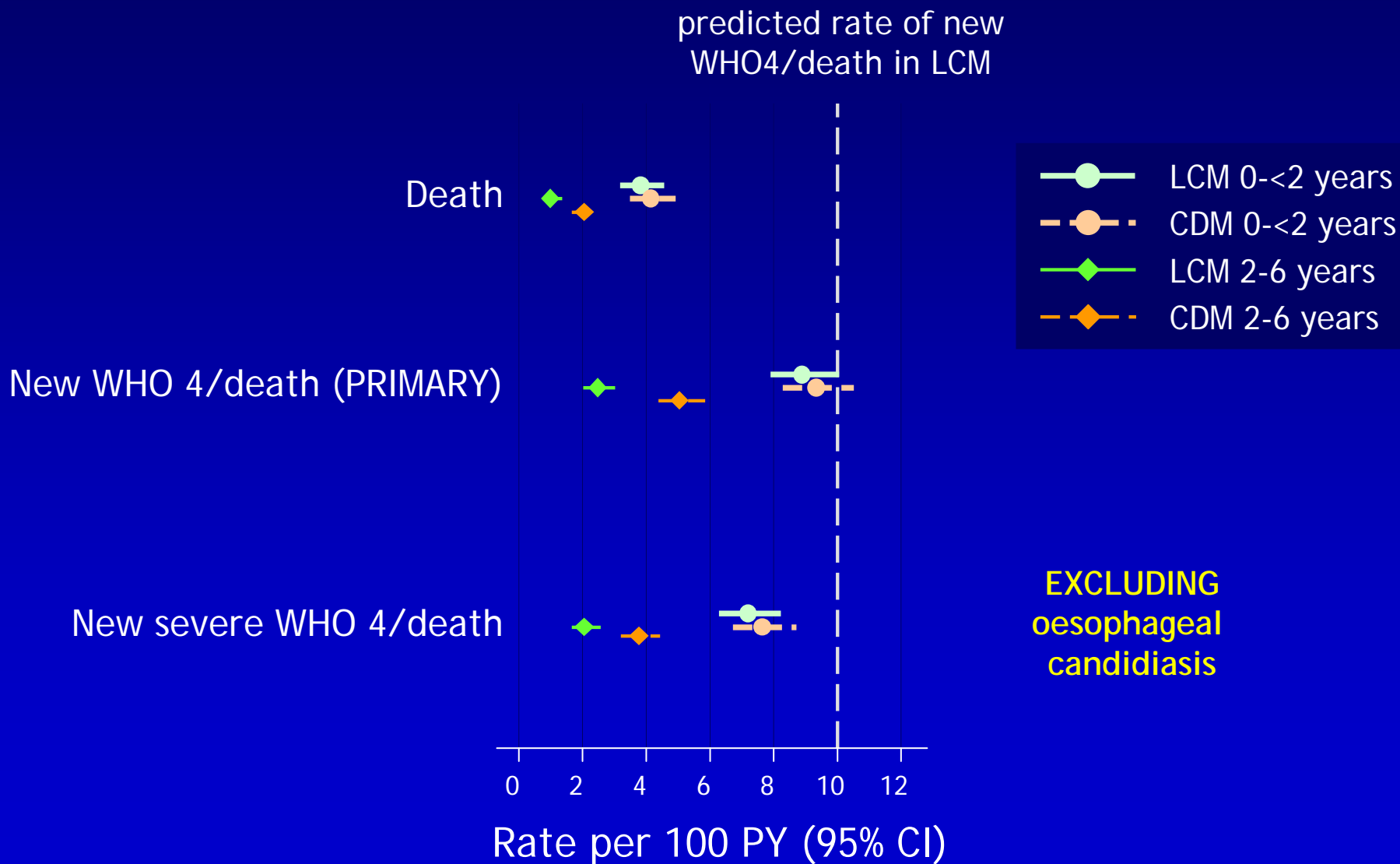


Absolute event rates over time on ART





Absolute event rates over time on ART





Main Finding



- There is a small but statistically significant difference in mortality and disease progression between the two arms only from the third year on ART
- What causes this?



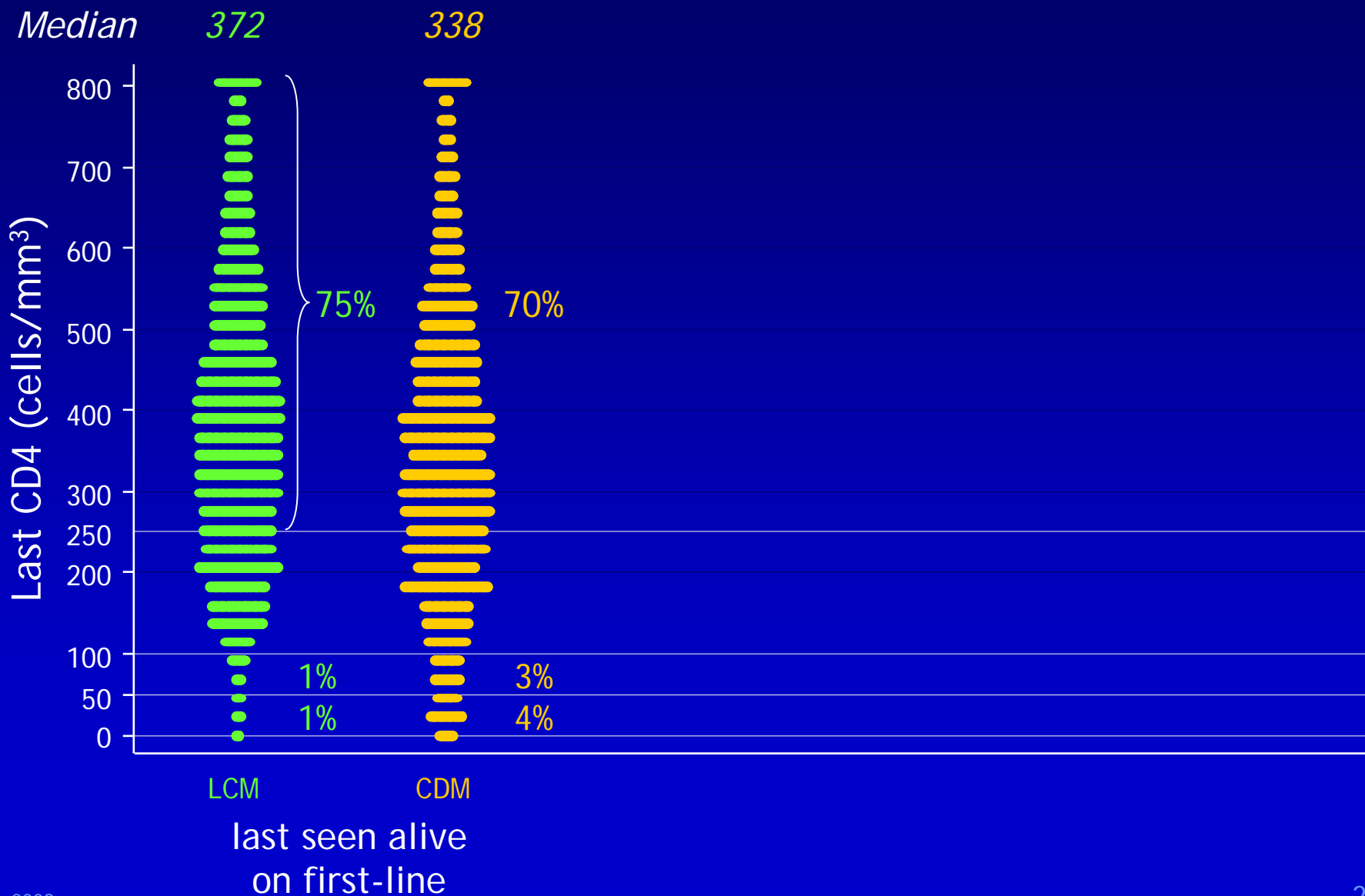
Explanation



- There is a small but statistically significant difference in mortality and disease progression between the two arms only from the third year on ART
- What causes this?
- Slightly later switching to second-line therapy in CDM leading to a few more patients in CDM living with lower CD4 counts on first-line and at increased risk of clinical events

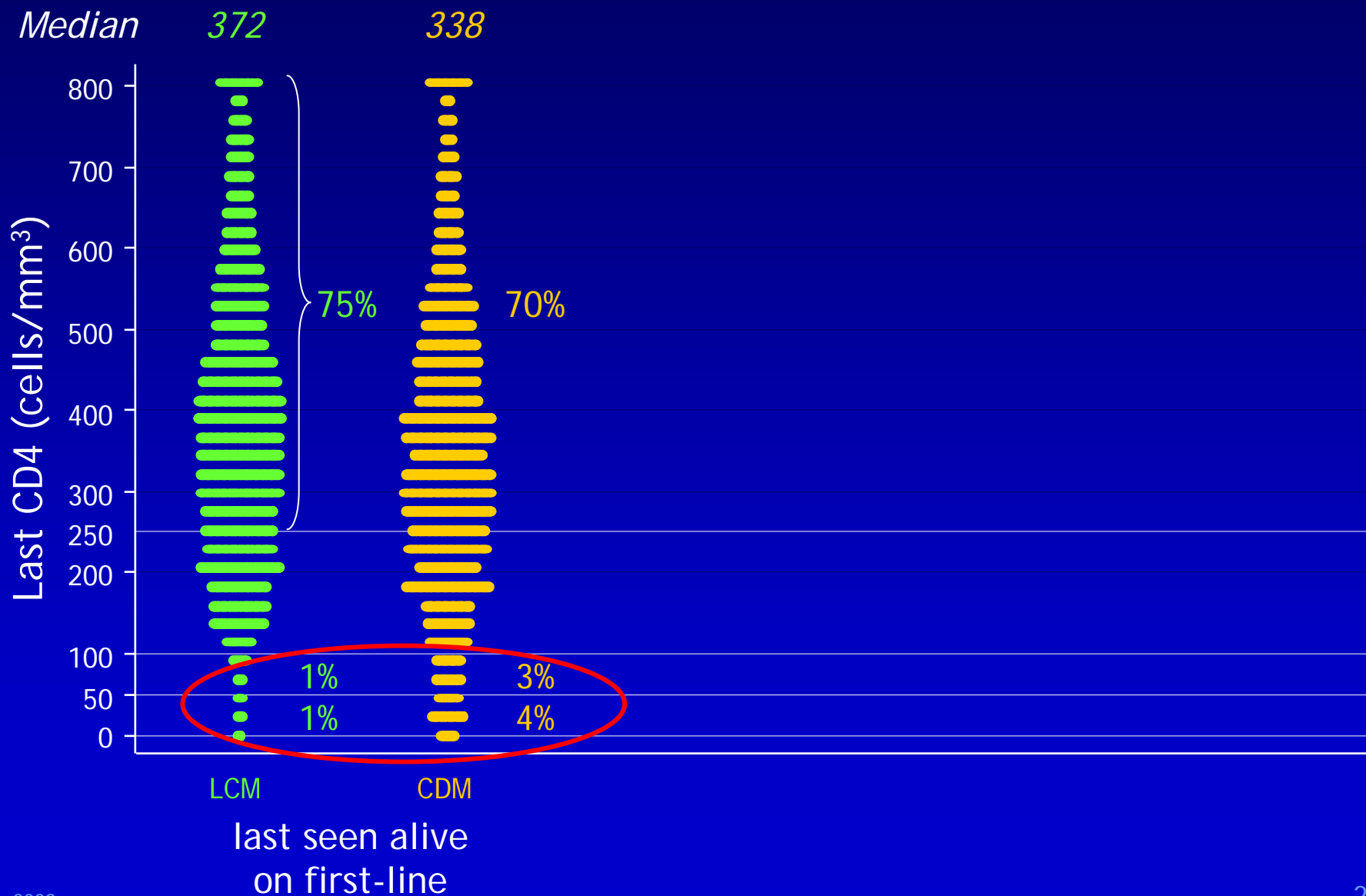


Most recent CD4 on first-line



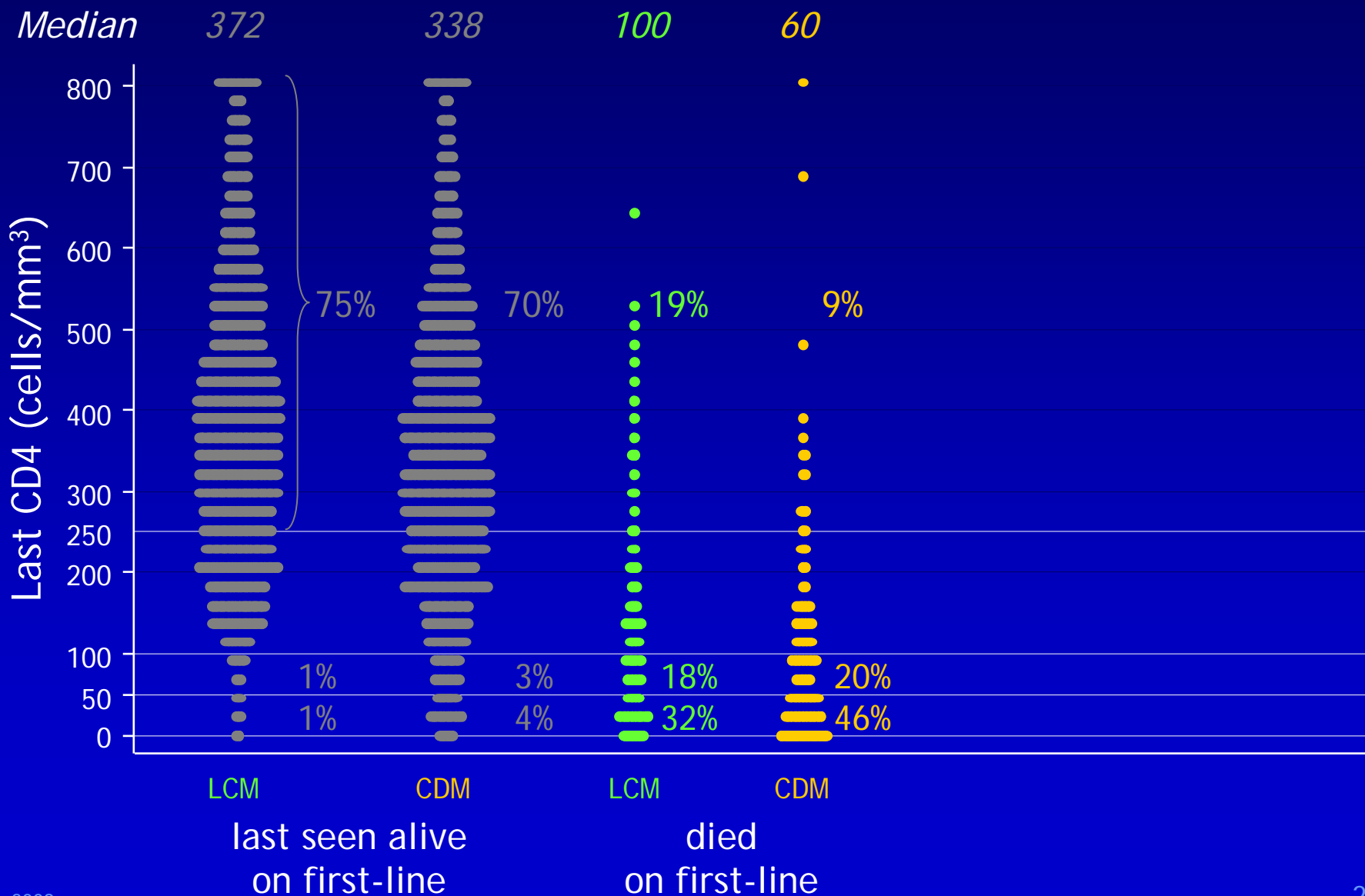


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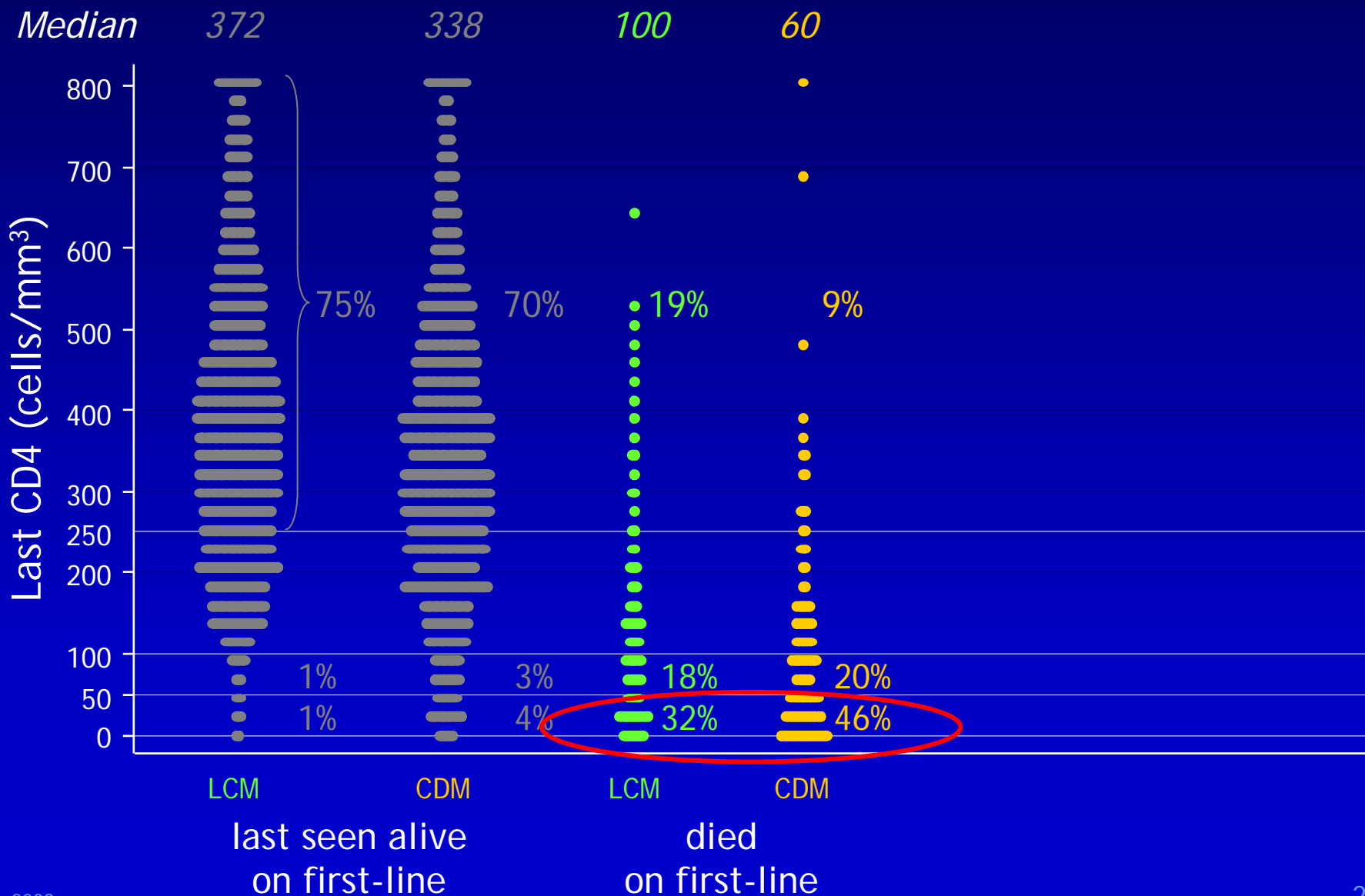


Most recent CD4 on first-line



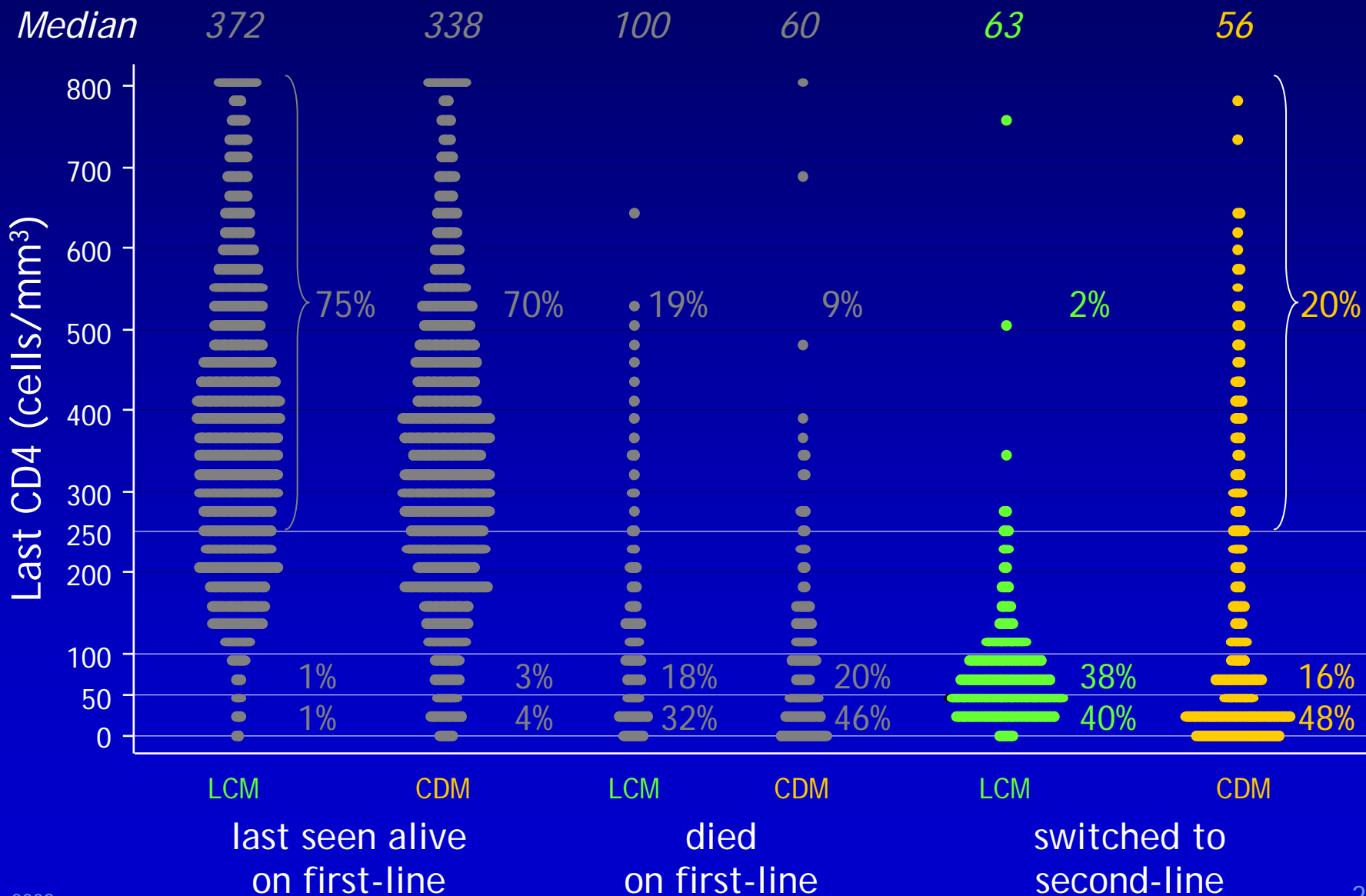


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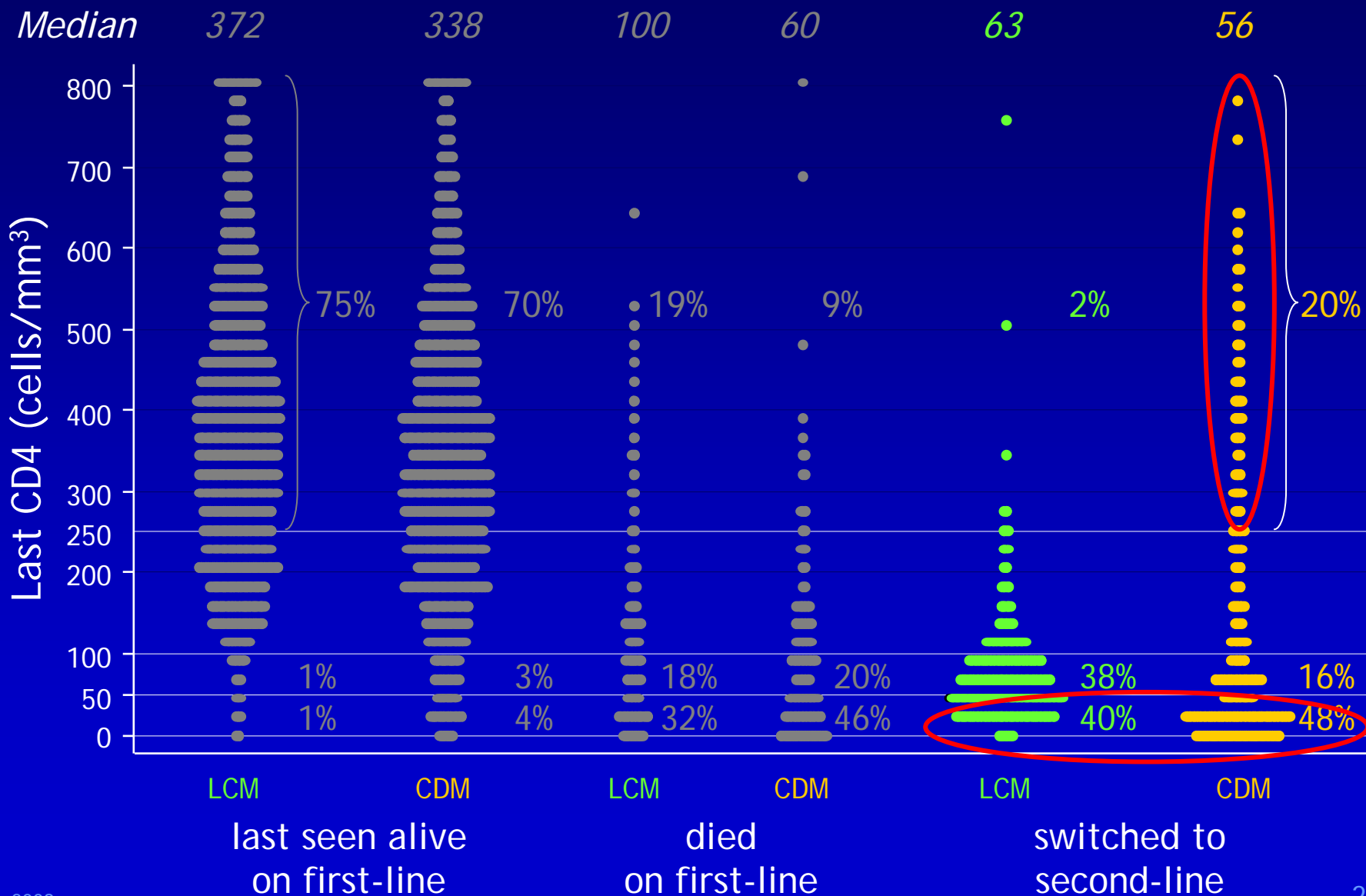


Most recent CD4 on first-line or at switch



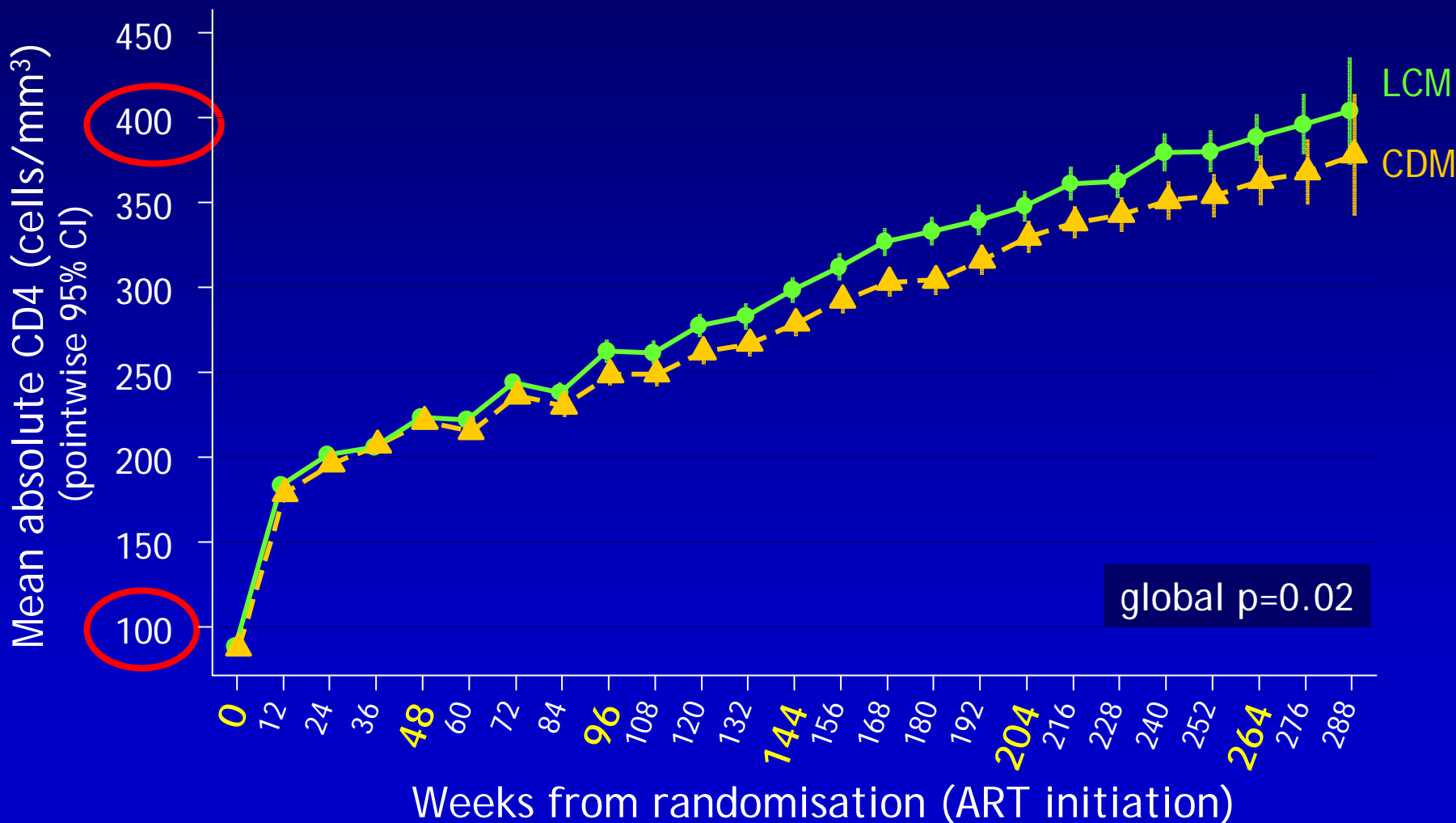


Most recent CD4 on first-line or at switch





Absolute change in CD4 over 5 years





Conclusions



- 5-year survival in 3316 participants with advanced HIV disease pre-ART was excellent (CDM 87%, LCM 90%)
- Loss to follow-up was very low
- Routine laboratory monitoring for toxicity did not impact adverse events or substitutions in first-line
- 12-weekly CD4 monitoring had no impact on disease progression during the first 2 years on ART
 - after 2 years, a small but significant impact on clinical disease progression favouring LCM appeared to be driven by later switch to second-line ART in CDM
 - there may be a role for targeted, as opposed to routine, CD4 monitoring from the second year on ART