Optimizing High Dose Therapy
Results from MRC Myeloma IX randomized trial

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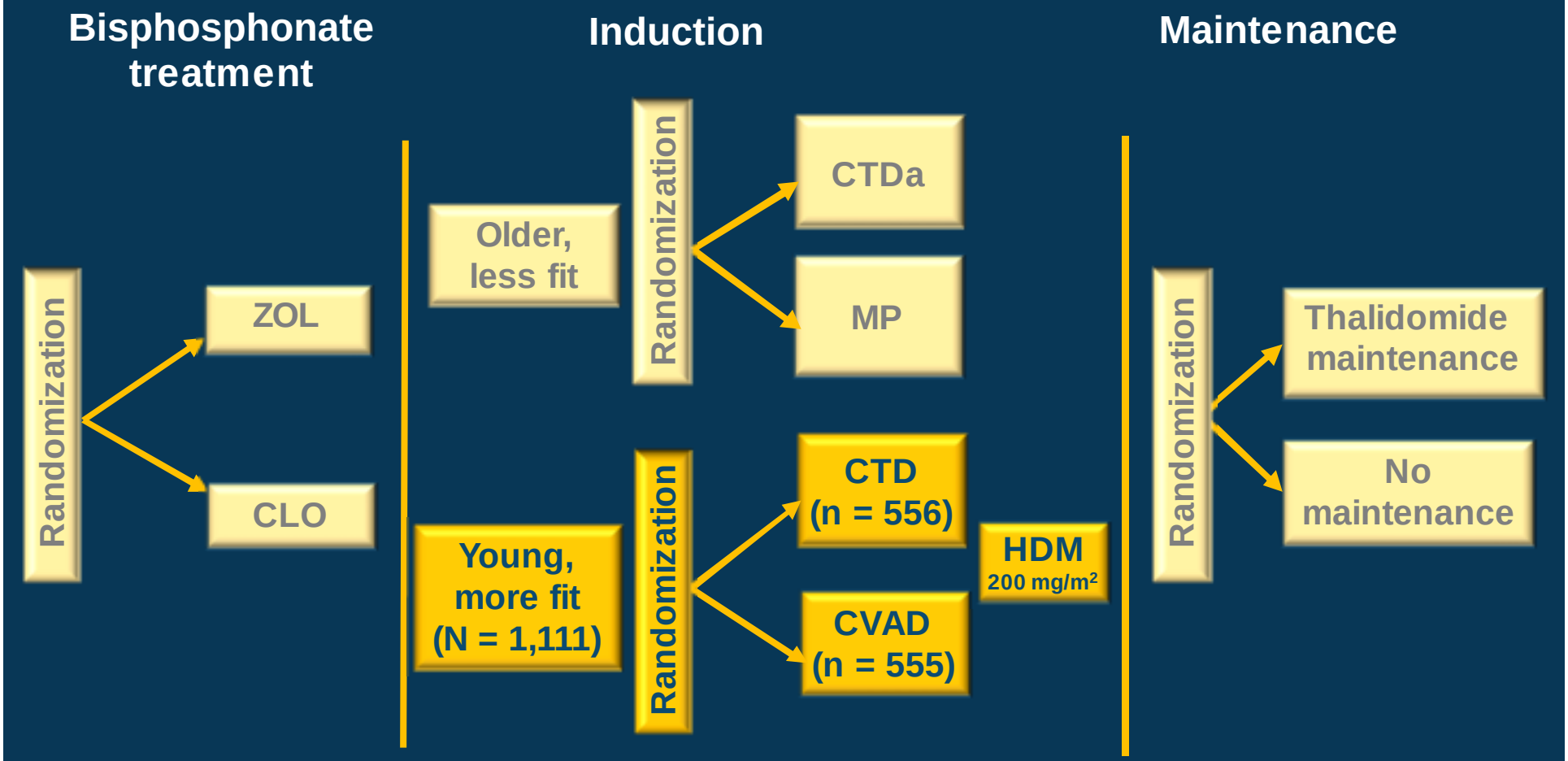
EMN Trialist Group

What is role of High Dose Therapy in NDMM?

- Younger patients show the most significantly reduced life expectancy and most potential for improved outcomes.
- HDT is the treatment associated with the best outcomes in MM.
- How can these outcomes be improved further with the use of “novel” agents?
- We have assessed comprehensively how HDT performs currently.
- Having defined the current best strategy, we can ask how can this be improved.

HDT, high dose therapy; NDMM, newly diagnosed multiple myeloma.

MRC Myeloma IX study – factorial design



CLO, sodium clodronate; CTD, cyclophosphamide + thalidomide + dexamethasone; CTDa, CTD attenuated (low-intensity); CVAD, vincristine + doxorubicin + dexamethasone + cyclophosphamide; HDM, high-dose melphalan; MP, melphalan + prednisone; OS, overall survival; PFS, progression-free survival; SRE, skeletal-related event; ZOL, zoledronic acid.

Morgan GJ, et al. Lancet 2010; 376: 1989–99.
Morgan GJ, et al. Lancet Oncol. 2011;in press.
Morgan GJ, et al. Haematologica 2011;in press.

Maximizing response pre- and post-HDT is a therapeutic aim. What is the optimal induction strategy?

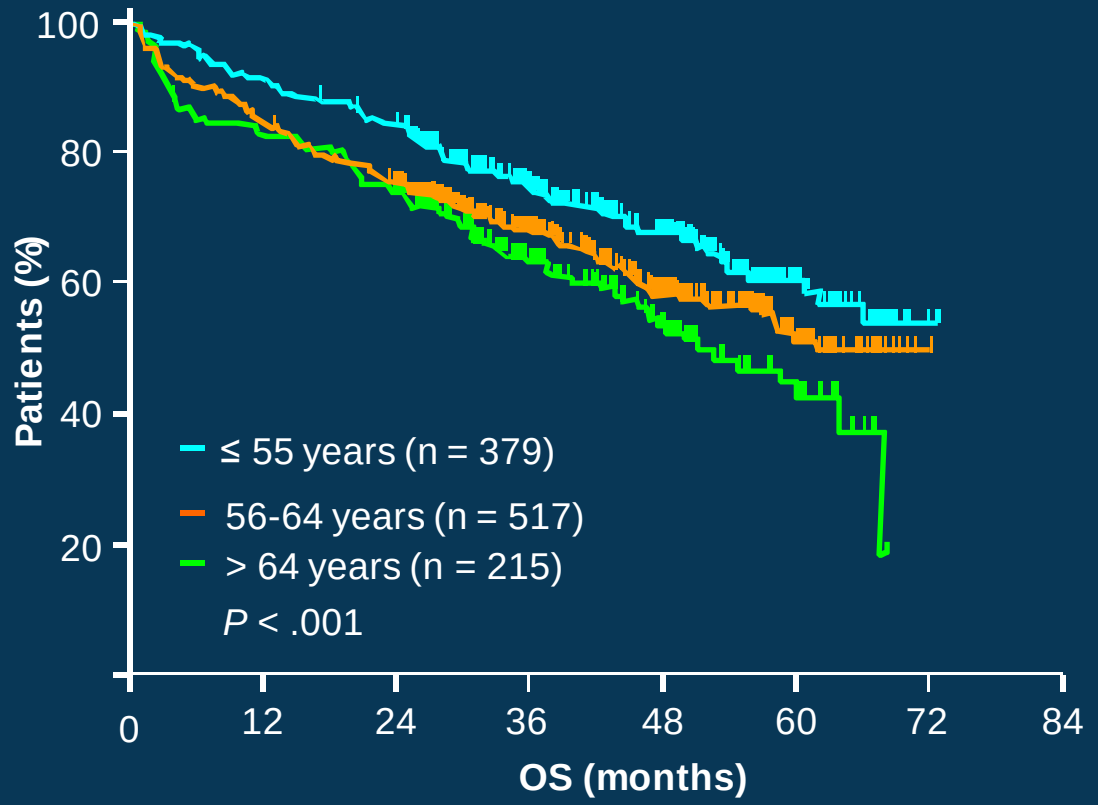
Hypothesis 1.
CTD not inferior to CVAD (OS and PFS)

MRC Myeloma IX HDT pathway: baseline patient characteristics

Characteristic	CVAD (n = 556)	CTD (n = 555)
Female sex, n (%)	208 (37.4)	211 (38)
Median age, years (range)	59 (31–74)	59 (33–78)
ISS stage at initial randomization, n (%)		
I	124 (22.3)	151 (27.2)
II	191 (34.4)	189 (34.1)
III	183 (32.9)	160 (28.8)
Missing data	58 (10.4)	55 (9.9)
Median β_2-microglobulin, mg/L (range)	4.1 (0.1–66.0)	3.9 (0.1–114.0)

ISS, International Staging System.

Impact of age on OS in patients receiving HDT



≤ 55 years	379	344	316	225	130	42	6
56-64 years	517	441	387	261	154	61	1
> 64 years	215	178	159	99	52	21	0

- HDT is safe even in patients older than 64 years, although there are significant differences in survival according to age group.

Characteristic of transplant group (1)

- A total of 749 (67%) underwent transplantation (median age 58 years).
  - The median age of patients not undergoing transplantation was 61 years
  - Taking into account age, the outcome for these patients was the same as those in the non-intensive pathway
- A small proportion of patients (17/1,111 [1.5%]) over the age of 70 were included in the study.
  - 9 patients were randomised to receive CTD induction and 8 were randomised to CVAD induction
  - Only 3 patients (CTD: 2 patients; CVAD: 1 patient) received subsequent HDT

Characteristic of transplant group (2)

- Taking early mortality of 8.5% we show that there was no difference between the arms in favour of CTD:
  - CVAD, 52/556 (9.4%) and CTD, 41/555 (7.4%) (p = 0.28 Fisher's exact test)
- During HDT and the peritransplant period a transplant-related mortality rate of 1.5% was seen that was independent of the induction pathway followed:
  - CVAD, 6/379 (1.6%) vs CTD 5/370 (1.4%; p = 1.0, Fisher's exact test)
- An improvement in CR rate was noted after ASCT in both arms of the study:
  - 30.5% increase in CR rate in the CVAD arm and 39.1% in the CTD arm

CR, complete response.

Response rates

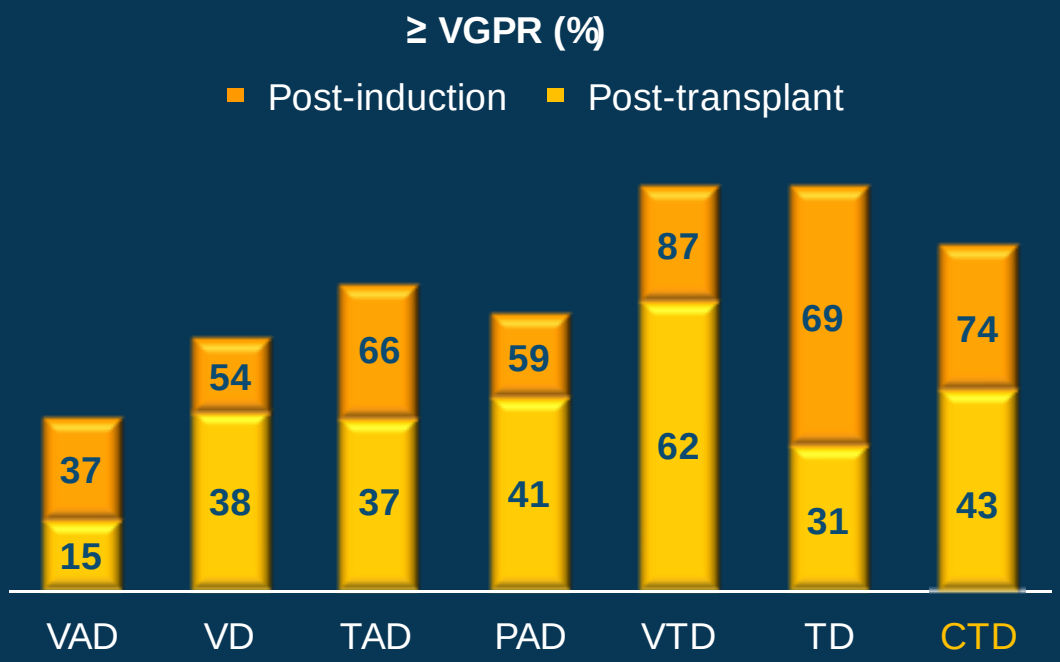
Response, %	After induction therapy			After HDT with ASCT		
	CVAD (n = 556)	CTD (n = 555)	p*	CVAD (n = 379)	CTD (n = 370)	P*
Overall response	71.2	82.5	< 0.0001‡	90.0	91.6	0.45
CR	10.4	16.0	0.0061	40.9	55.1	0.0001
VGPR	17.1	27.2	< 0.0001	21.4	18.6	0.36
PR	43.7	39.3	0.14	27.7	17.8	0.0017
Minimal response	7.6	3.2	0.0020	1.8	0.5	0.18
No change	6.5	2.5	0.0021	1.8	0.8	0.34
Disease progression	2.7	3.2	0.60	2.4	3.2	0.51
Early death	4.1§	2.2§	0.085	0.8¶	1.6¶	0.34
Unable to determine	7.9	6.3	0.35	3.2	2.2	0.50

* Fisher exact test; ‡ Logistic regression; §Within 60 days of randomization; ¶Within 100 days of high-dose therapy date.

- CTD is associated with higher ORR rates post-induction.
  - The quality of response improves significantly post-ASCT

ASCT, autologous stem-cell transplantation; ORR, overall response rate; PR, partial response; VGPR, very good partial response.

Response rates following induction with novel agent-containing regimens and post-transplantation



Induction regimens of interest not shown: CVD, RVD, RD and Rd.

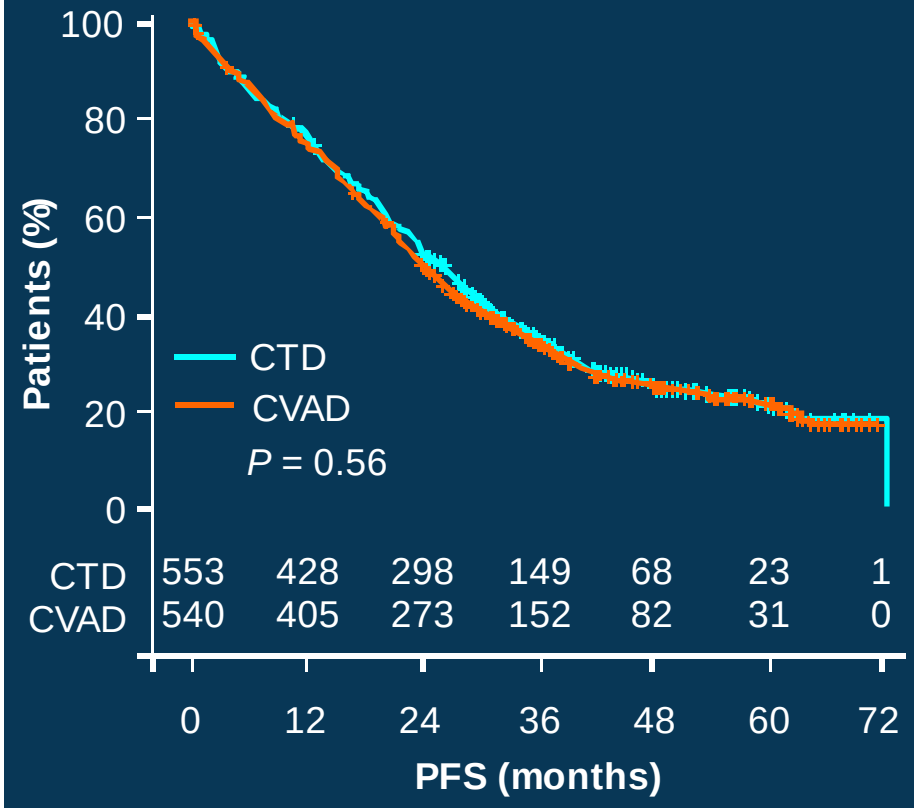
- Exact comparisons with current alternative drug combination require formal randomized studies.

CVD, cyclophosphamide + bortezomib + dexamethasone; PAD, bortezomib + doxorubicin + dexamethasone; Rd, lenalidomide + low-dose dexamethasone; RD, lenalidomide + high-dose dexamethasone; RVD, lenalidomide + bortezomib + dexamethasone; TAD, thalidomide + doxorubicin + dexamethasone; TD, thalidomide + dexamethasone; VAD, vincristine + doxorubicin + dexamethasone; VD, bortezomib + dexamethasone; VTD, bortezomib + thalidomide + dexamethasone.

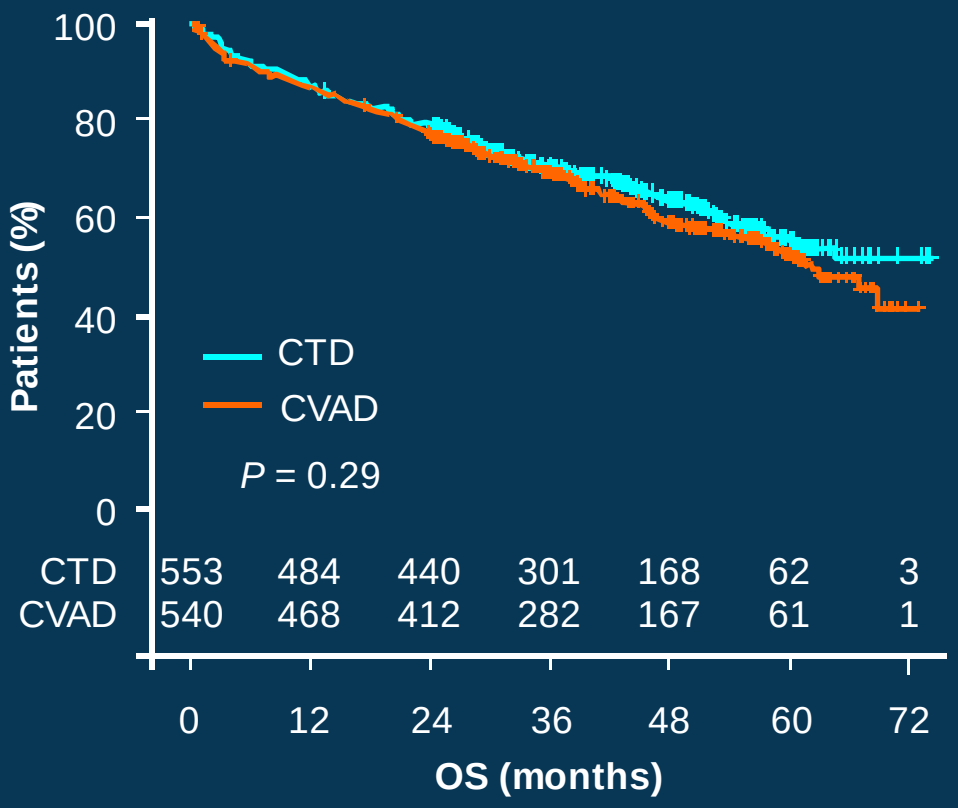
Harousseau JL, et al. J Clin Oncol. 2010;28:4621-29.
Rajkumar V, et al. Lancet Oncol. 2010;11:29-37.
Lokhorst H, et al. Blood. 2010;115:1113-20.
Sonneveld P, et al. Blood. 2008;112:abstract 653.
Cavo M, et al. Lancet. 2010;376:2075-85.
Kumar S, et al. Blood. 2010;116:abstract 621.
Richardson PG, et al. Blood. 2010;116:679-86.

Impact of induction therapy on PFS and OS

Median PFS (95%, CI):
CTD, 27 (24-29) *vs.* CVAD, 25 (23-26) months

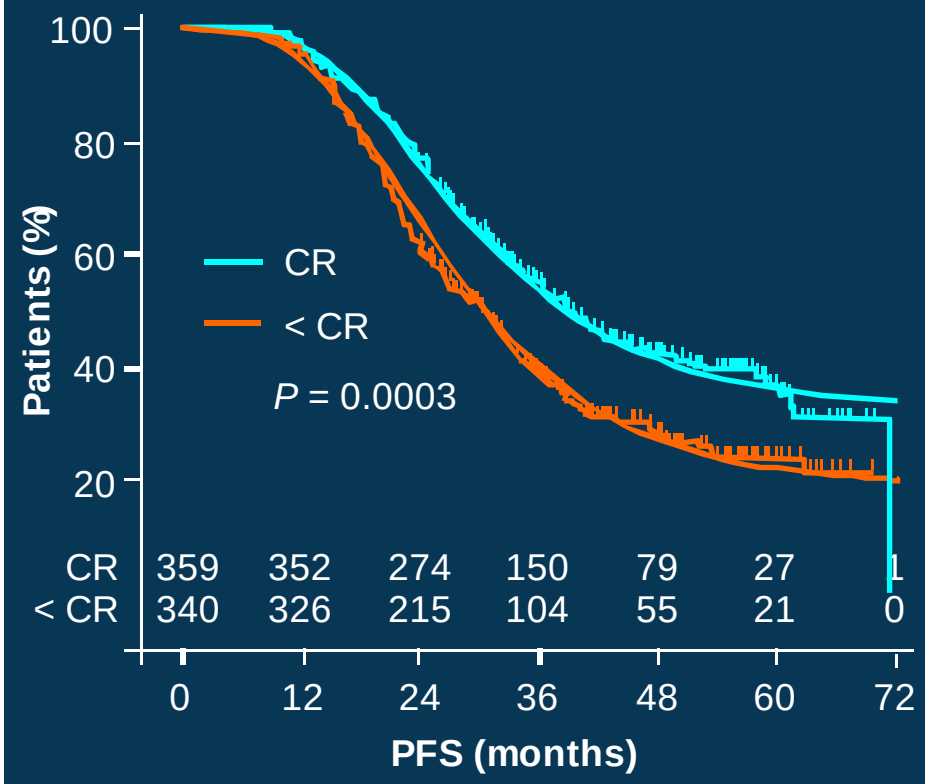


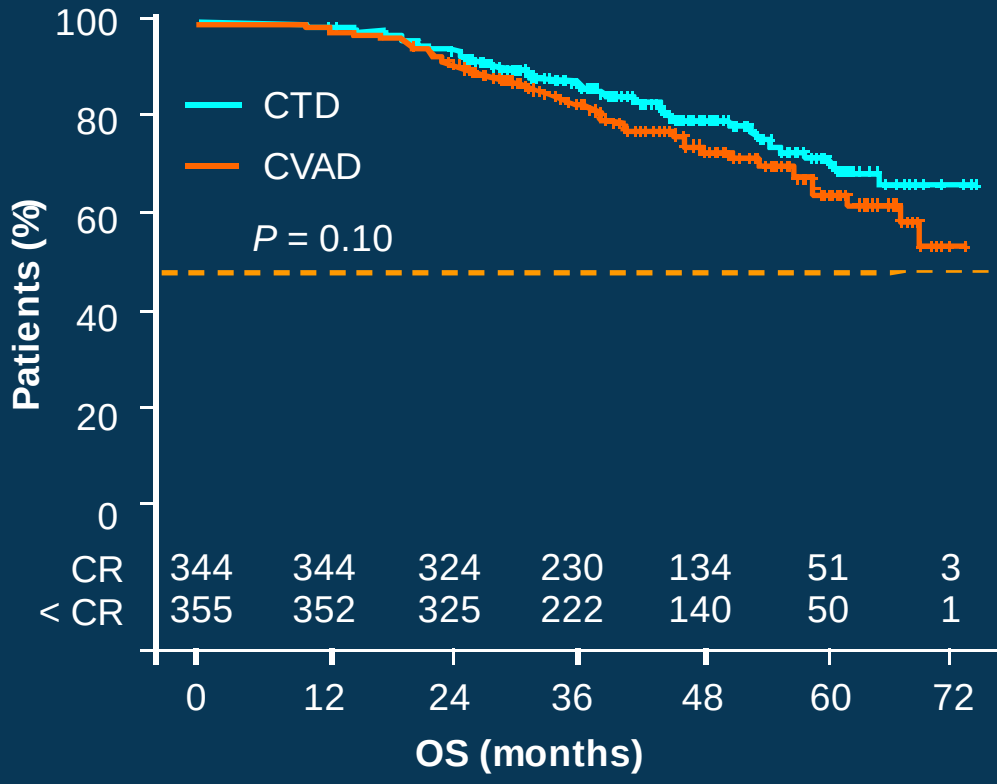
Median OS (95%, CI):
CTD, NR (61-NR) *vs.* CVAD, 63 (59-NR) months



- Median follow-up – 47 months.
- CTD is non-inferior to CVAD for PFS and OS.
  - OS benefit emerging after 2 years

Impact of CR/response status on survival outcomes





- PFS is greater in patients with a CR, regardless of treatment.
- There is a trend for OS with CTD in responding patients.
- With prolonged follow-up, the improvement in CR rates observed in the CTD arm translates to longer OS (3% improvement at 9 years).

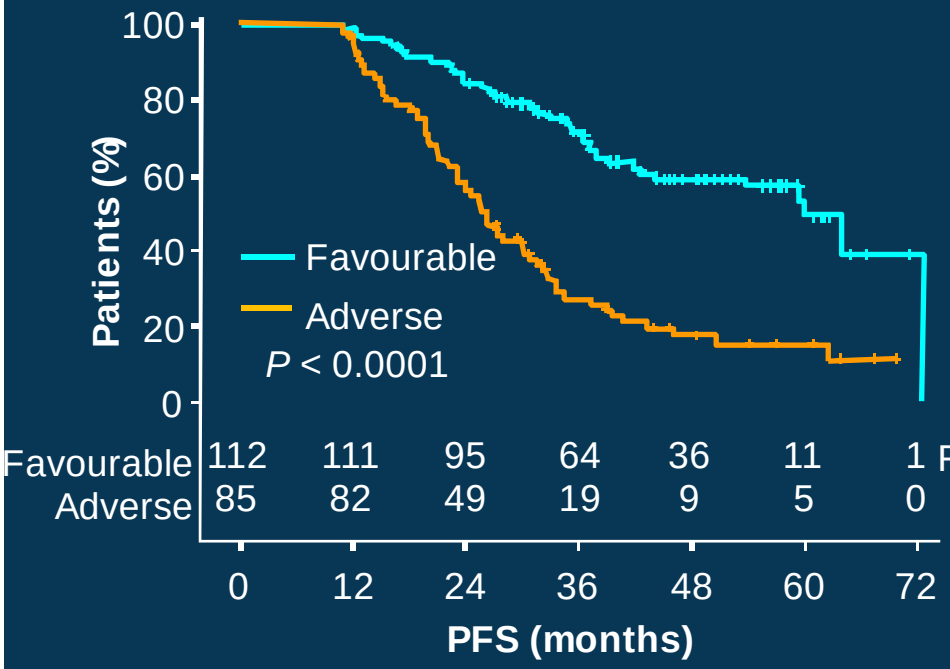
MRC Myeloma IX HDT pathway: iFISH at presentation

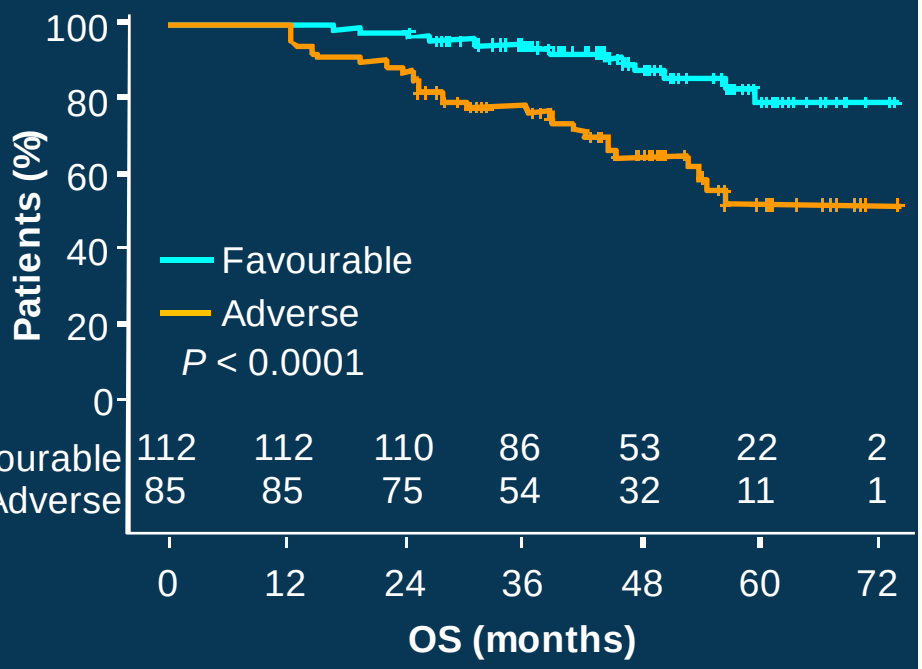
Cytogenetics	Prevalence		
	CVAD (n = 556)	CTD (n = 555)	Total
Adverse iFISH, n/N (%)	141/307 (46)	152/319 (48)	293/626 (47)
gain 1q21	98/267 (37)	101/264 (38)	199/531 (37)
t(4;14)	35/305 (11)	41/314 (13)	76/619 (12)
del1p32.1	**24/254 (9)**	**29/256 (11)**	**53/510 (10)**
17p-	20/292 (7)	26/299 (9)	46/591 (8)
t(14;16)	12/300 (4)	7/312 (2)	19/612 (3)
t(14;20)	4/301 (1)	7/311 (2)	11/612 (2)
Favourable iFISH, n/N (%)	166/307 (54)	167/319 (52)	333/626 (53)
del13q	128/299 (43)	156/317 (49)	284/616 (46)
t(11;14)	46/304 (15)	46/313 (15)	92/617 (15)
del22q	30/250 (12)	26/242 (11)	56/492 (11)
t(6;14)	3/299 (1)	2/307 (1)	5/606 (1)

iFISH, interphase FISH.

Boyd KD, et al. Leukemia. In press 2011.

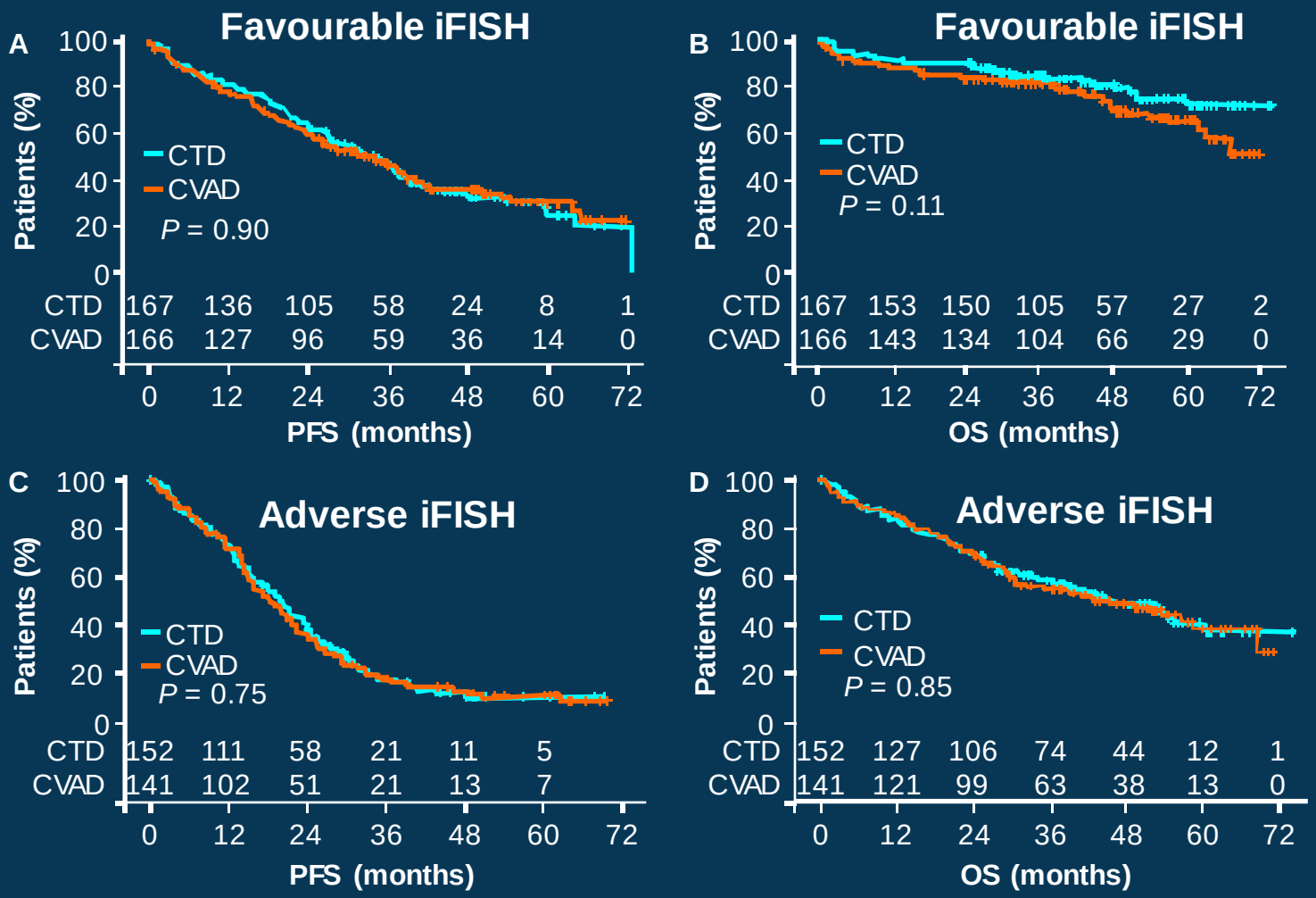
Impact of cytogenetics on survival in patients with a CR following induction therapy





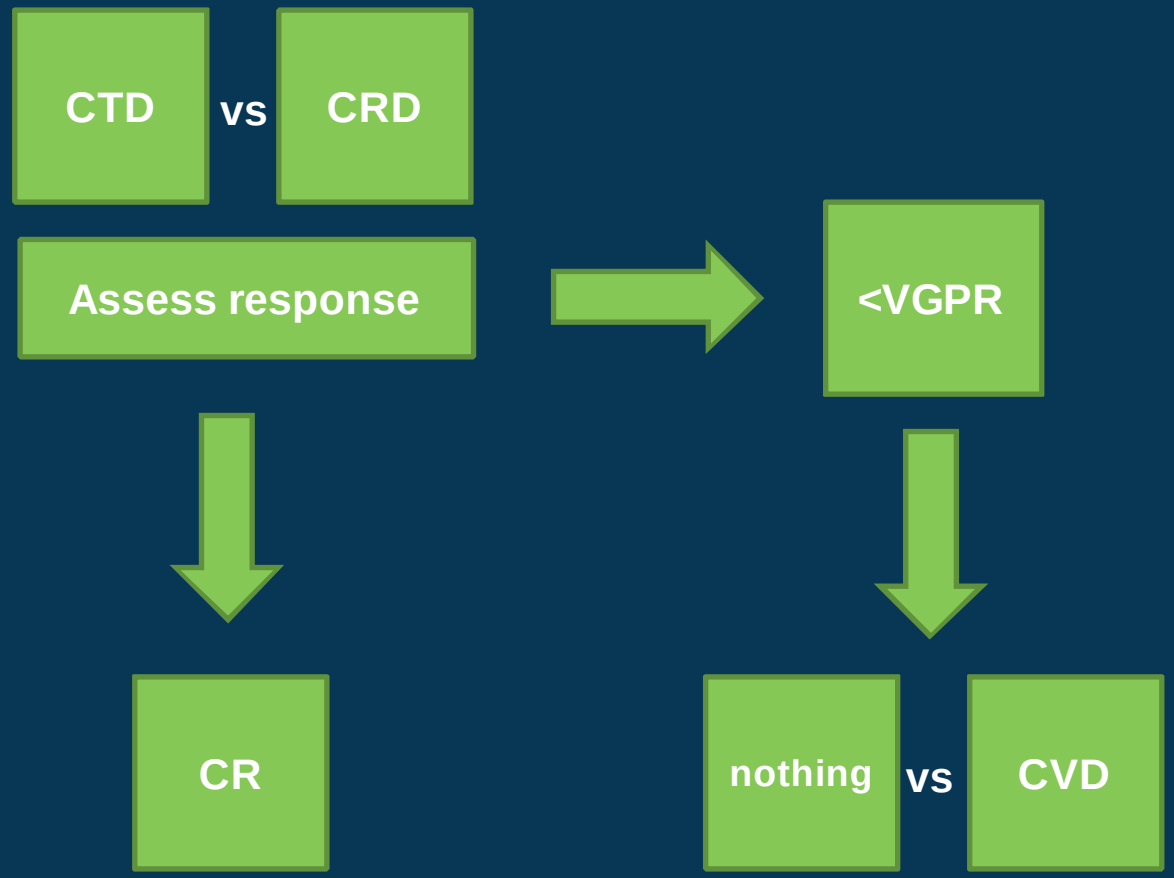
- Among patients who achieved CR, adverse iFISH remains a predictor of poor PFS and OS.

Impact of induction therapy on PFS in favourable and adverse iFISH



- In patients with favourable iFISH receiving CTD induction, there is a trend for an emerging survival benefit compared with CVAD.
- This effect is not seen in patients with adverse iFISH.

Myeloma XI
Can response and outcome be improved by using a "sequential approach"

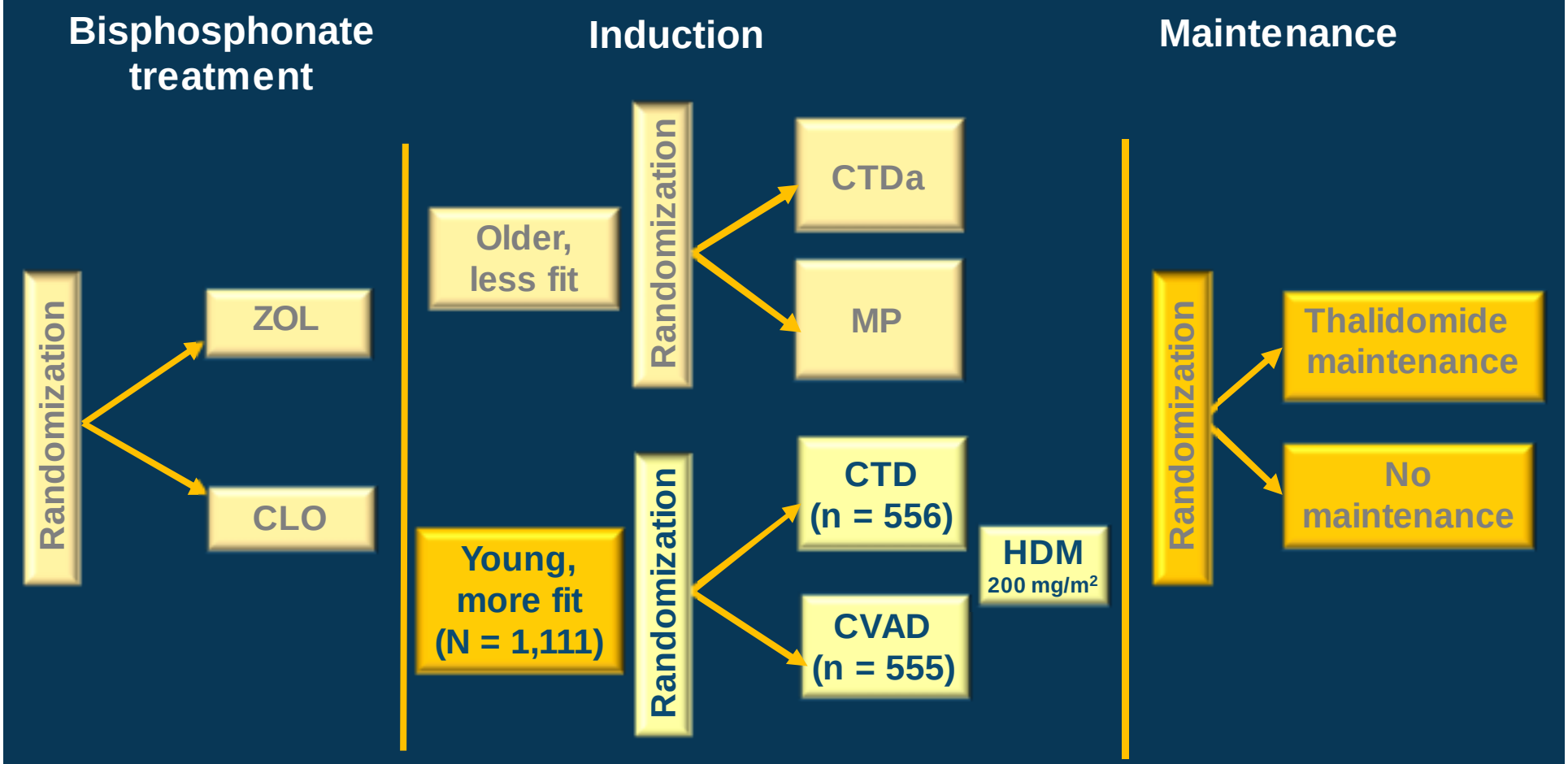


Endpoints response rates (pre and post transplant), PFS, OS, impact by genetic risk status.

Maintenance of responses is an approach that can improve outcomes

Hypothesis 2.
Thalidomide maintenance superior to no maintenance (OS)

MRC Myeloma IX study – factorial design



Morgan GJ, et al. Lancet 2010; 376: 1989–99.
Morgan GJ, et al. Lancet Oncol. 2011;in press.
Morgan GJ, et al. Haematologica 2011;in press.

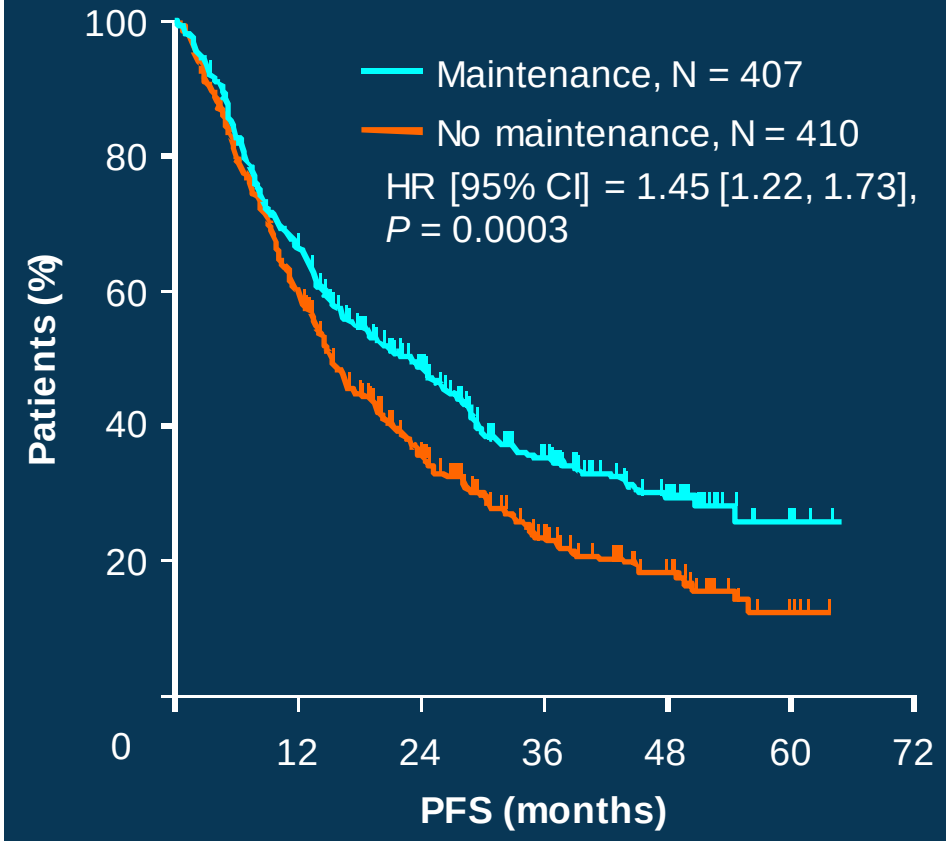
Baseline characteristics at maintenance randomization

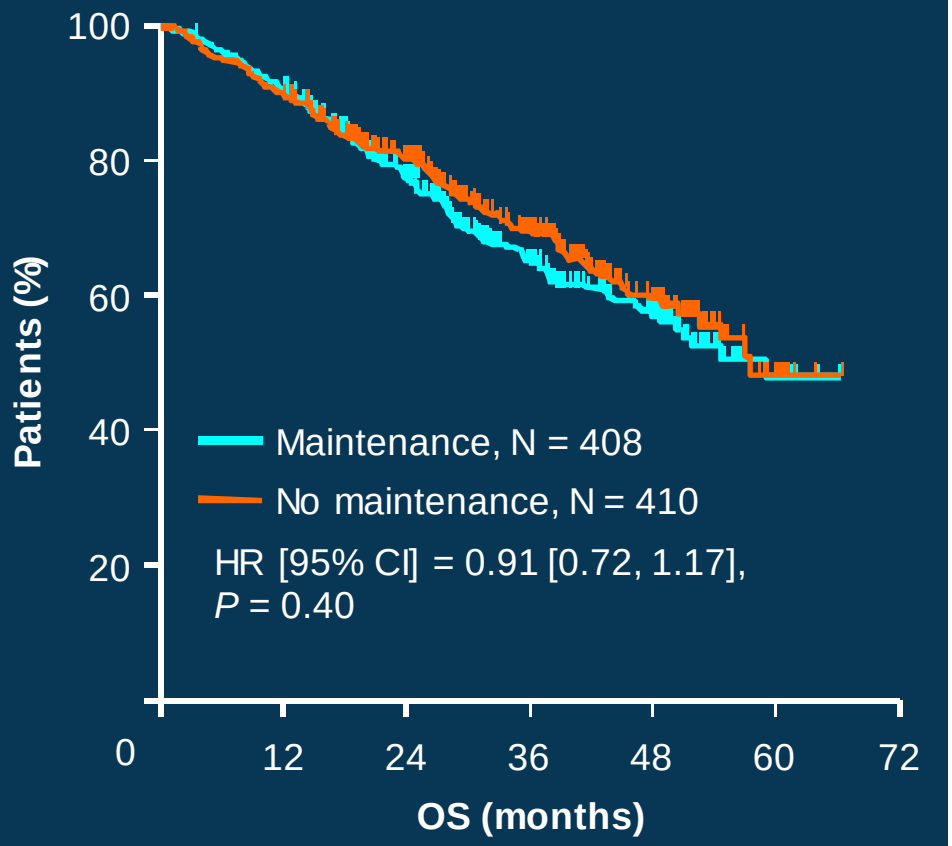
	Maintenance (N = 408)	No maintenance (N = 410)
Median time between initial and maintenance randomization, months (range)	8.3 (3.5–21.7)	8.2 (3.9–18.6)
Randomized induction chemotherapy regimen, n (%)		
CVAD	121 (29.7)	120 (29.3)
CTD	124 (30.4)	127 (31.0)
MP	79 (19.4)	82 (20.0)
CTDa	84 (20.6)	81 (19.8)
Response at maintenance randomization*, n (%)		
CR	158 (38.7)	139 (33.9)
VGPR	65 (15.9)	79 (19.3)
PR	125 (30.6)	119 (29.0)
Minimal response	17 (4.2)	23 (5.6)
No change	10 (2.5)	24 (5.9)
Progressive disease	9 (2.2)	14 (3.4)
Missing data	24 (5.9)	12 (2.9)

*After induction/high-dose therapy and therefore preceding maintenance randomization.

PFS and OS according to maintenance randomization

Median follow-up from maintenance randomization: 38 months (range, 12–66)

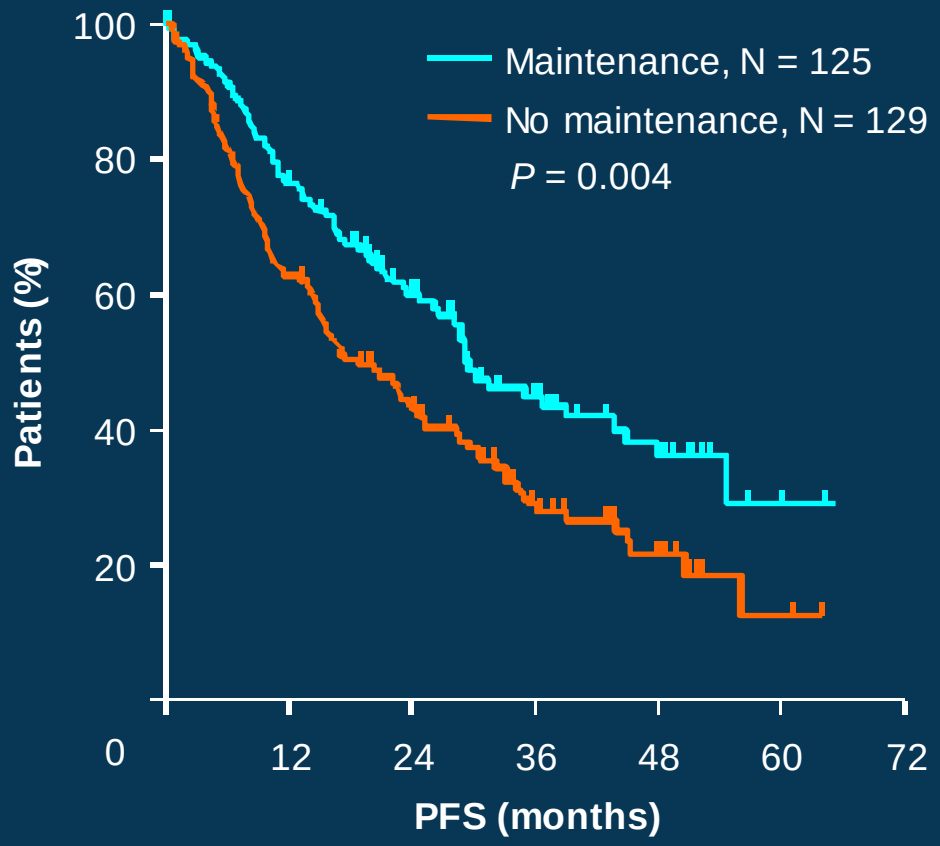


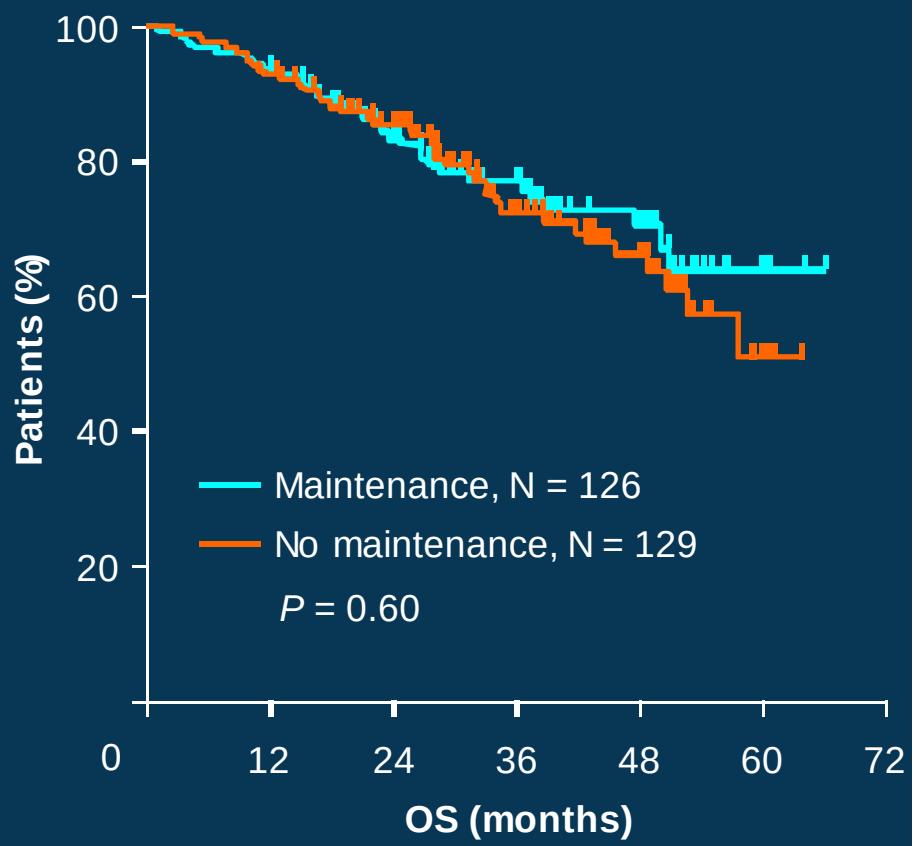


- Thalidomide maintenance improves PFS but no OS benefit could be demonstrated.

CI, confidence interval; HR, hazard ratio.

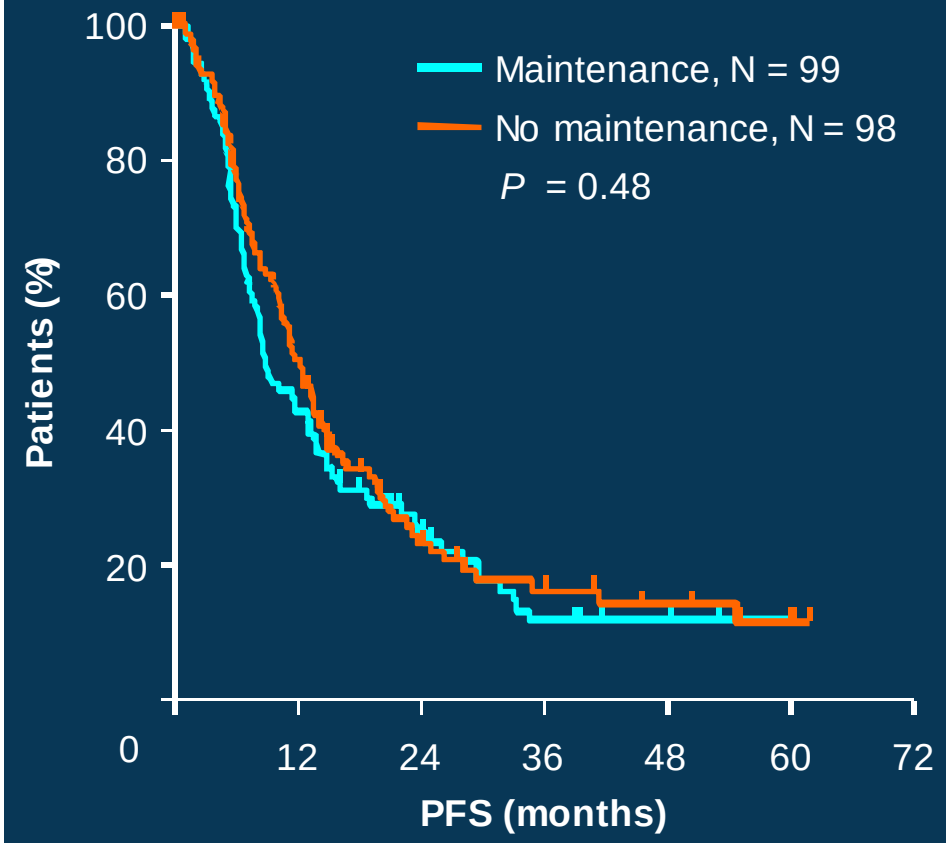
PFS and OS according to maintenance randomization: favourable iFISH

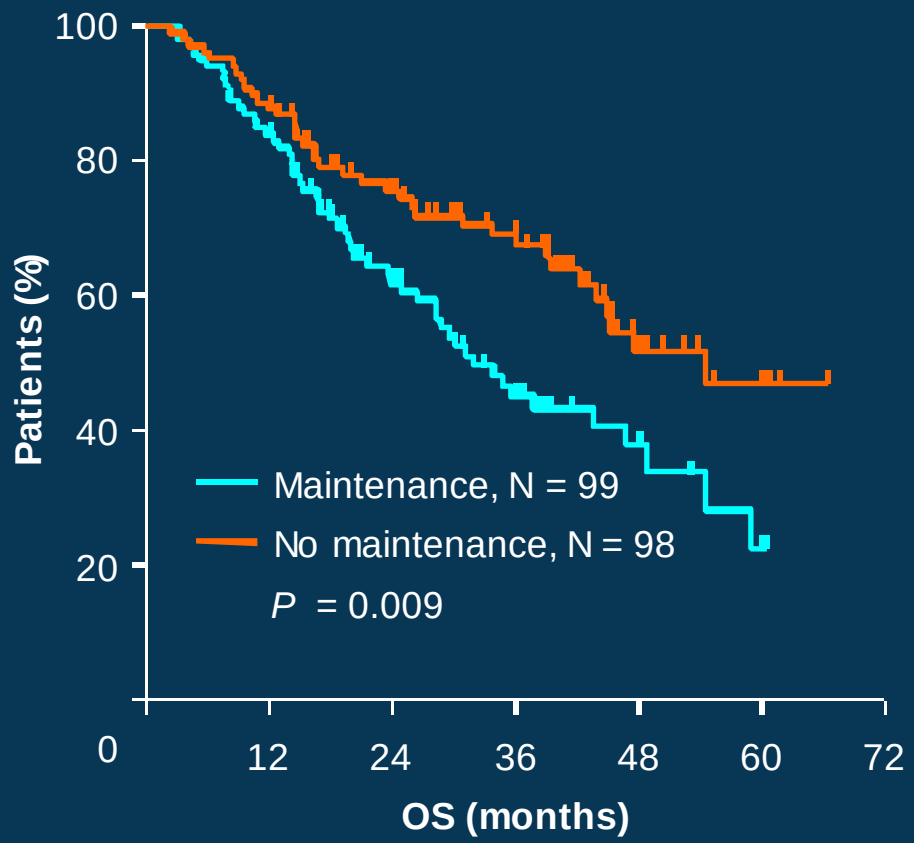




- Among patients with favourable iFISH, thalidomide maintenance significantly prolongs PFS with emergent OS benefit.

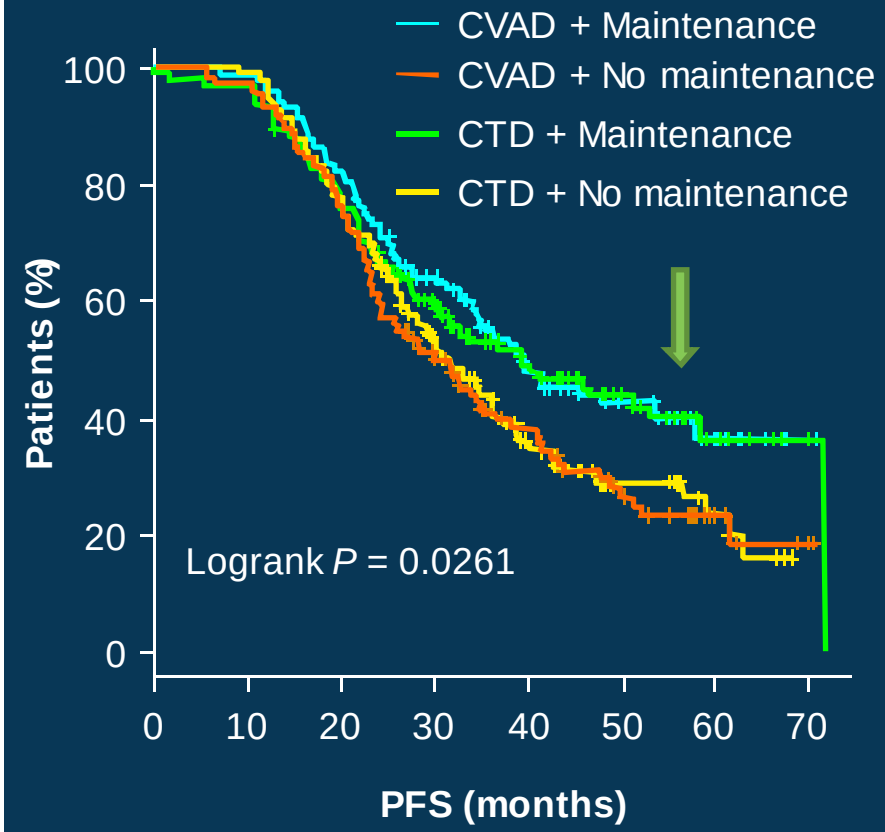
PFS and OS according to maintenance randomization: adverse iFISH

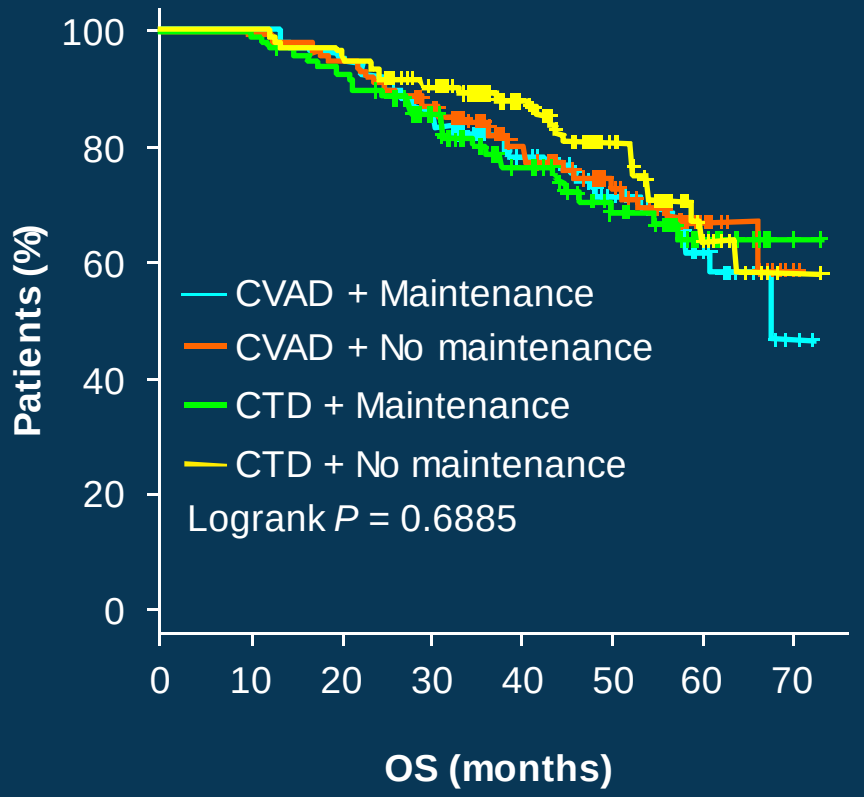




- Among patients with adverse iFISH, thalidomide maintenance had no effect on PFS and adverse effect on OS.

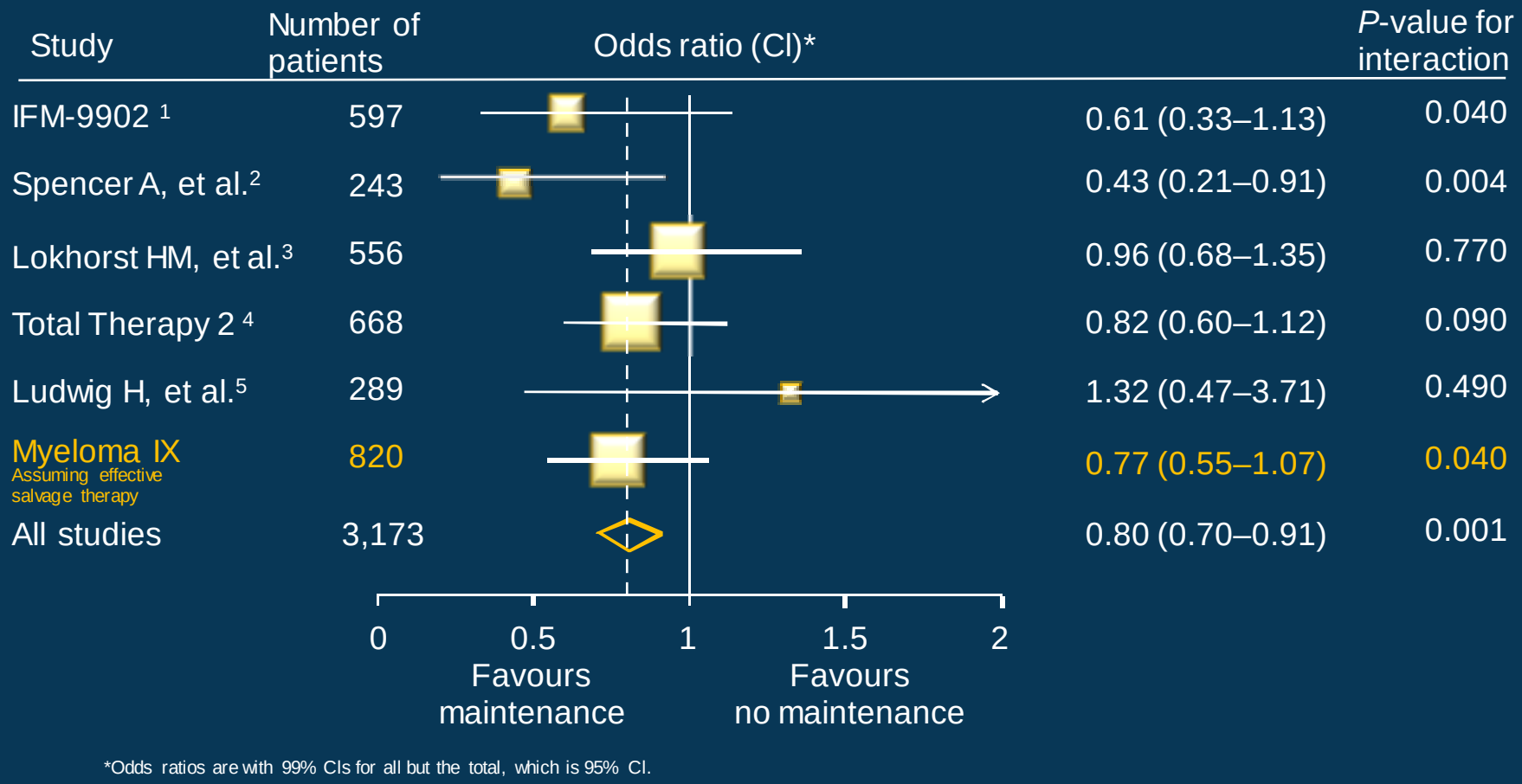
Impact of induction and maintenance on outcome following HDT





- Thalidomide maintenance prolongs PFS regardless of induction treatment.
- Consistent with overall study results.

Meta-analysis of all studies including a thalidomide maintenance arm

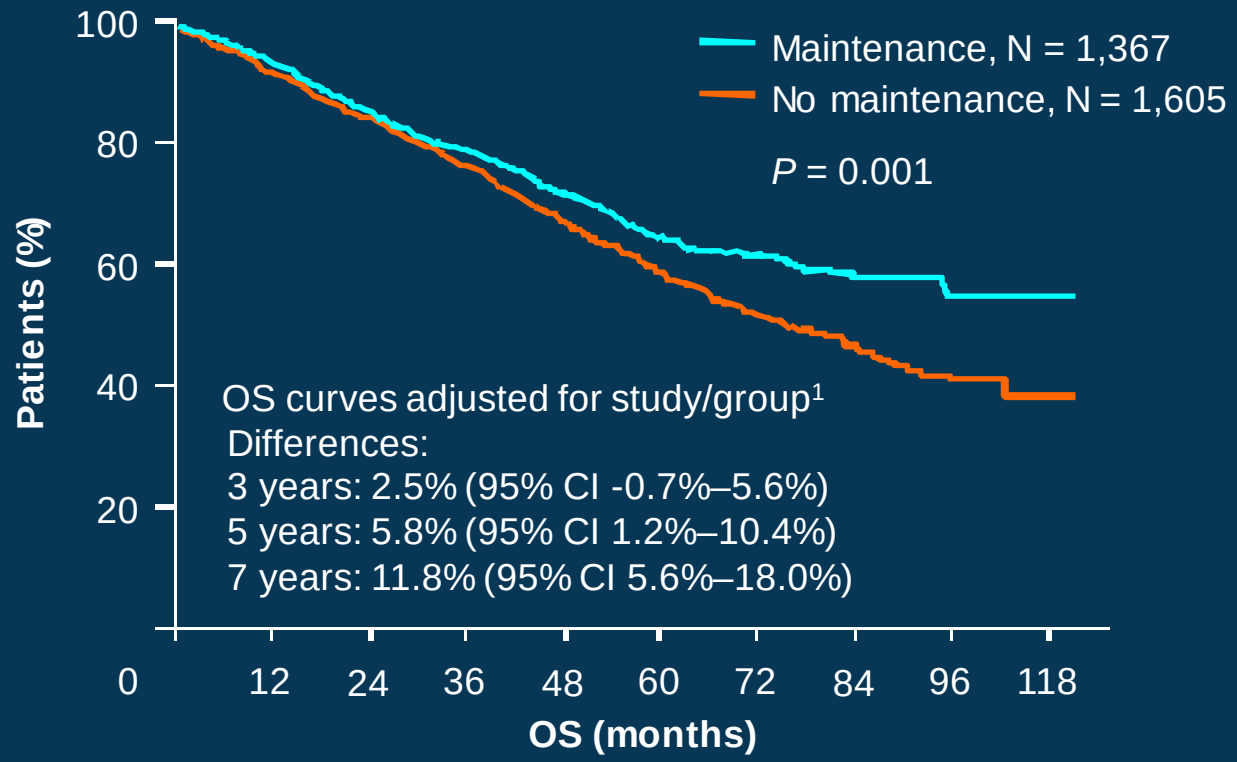


*Odds ratios are with 99% CIs for all but the total, which is 95% CI.

- Thalidomide maintenance offers an OS advantage.

1. Attal M, et al. Blood. 2006;108:3289-94.
2. Spencer A, et al. J Clin Oncol. 2009;27:1788-93. 3. Lockhorst HM, et al. Blood. 2010;115:1113-20.
4. Barlogie B, et al. Blood. 2009;112:3115-21. 5. Ludwig H, et al. Blood. 2009;113:3435-42.

Composite OS curve in a pooled analysis of thalidomide maintenance studies



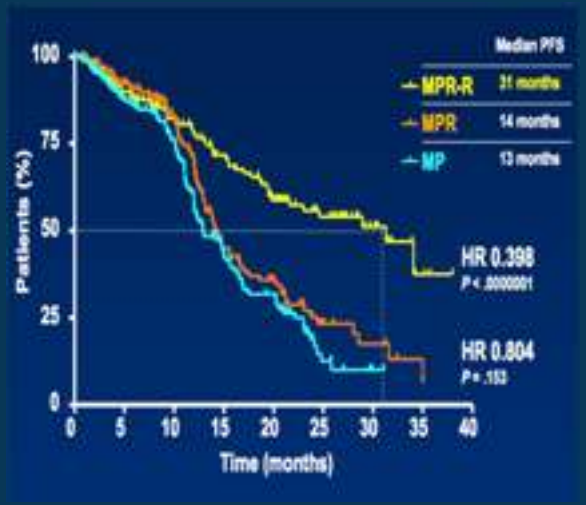
Numbers at risk										
Maintenance	1,367	1,246	1,023	786	503	298	168	88	48	12
No maintenance	1,605	1,451	1,235	903	472	248	139	88	46	9

- Thalidomide maintenance offers a significant OS benefit across trials.

1. Gregory WM. Br J Cancer 1988; 58:202-4.

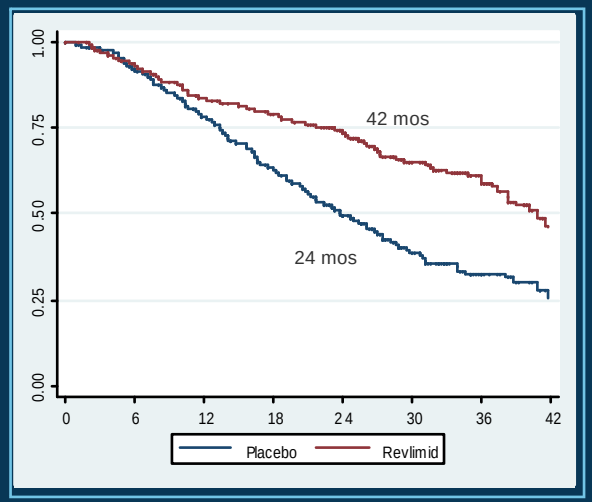
Lenalidomide maintenance significantly improves PFS

MM-015[1]
NDMM/Continuous Therapy



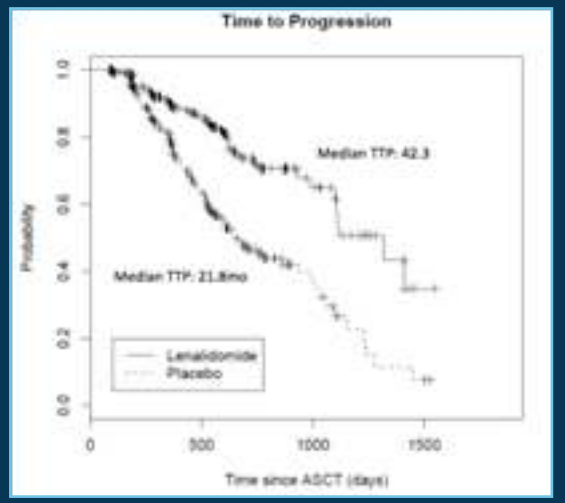
HR 0.40, *P* < 0.001

IFM 2005-02[2]
Maintenance Therapy Post-SCT



HR 0.50, *P* < 0.0001

CALGB 100104[3]
Maintenance Therapy Post-SCT

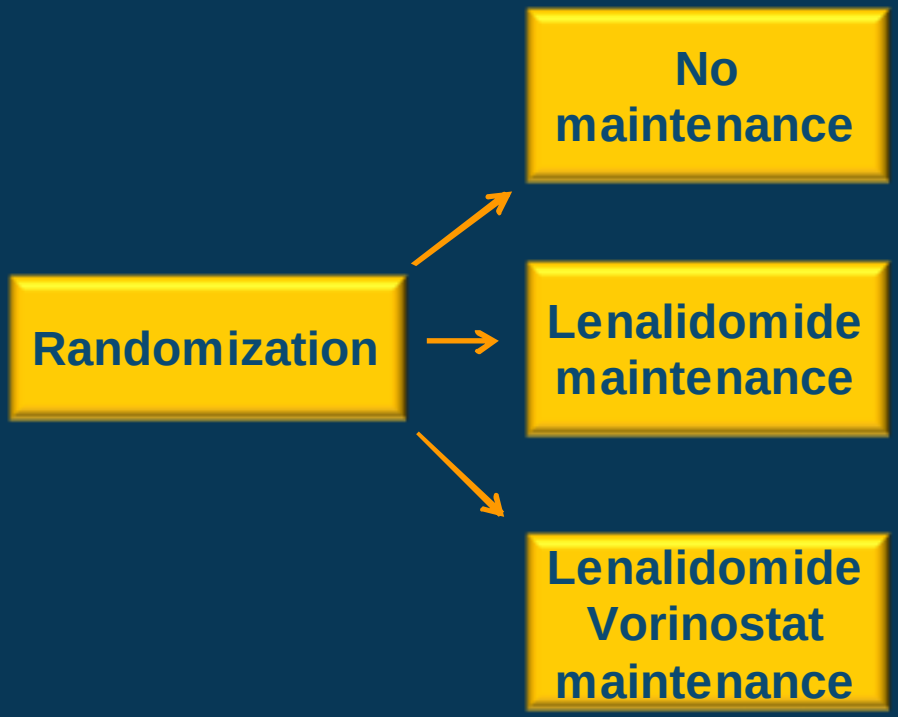


HR 0.40, *P* < 0.0001

SCT, stem-cell transplantation

1. Palumbo A, et al. Blood. 2010; 116: Abstract 622
2. Attal M, et al. Blood. 2010; 116: Abstract 310
3. McCarthy P, et al. Blood; 2010; 116: Abstract 37

How can lenalidomide maintenance be improved further?



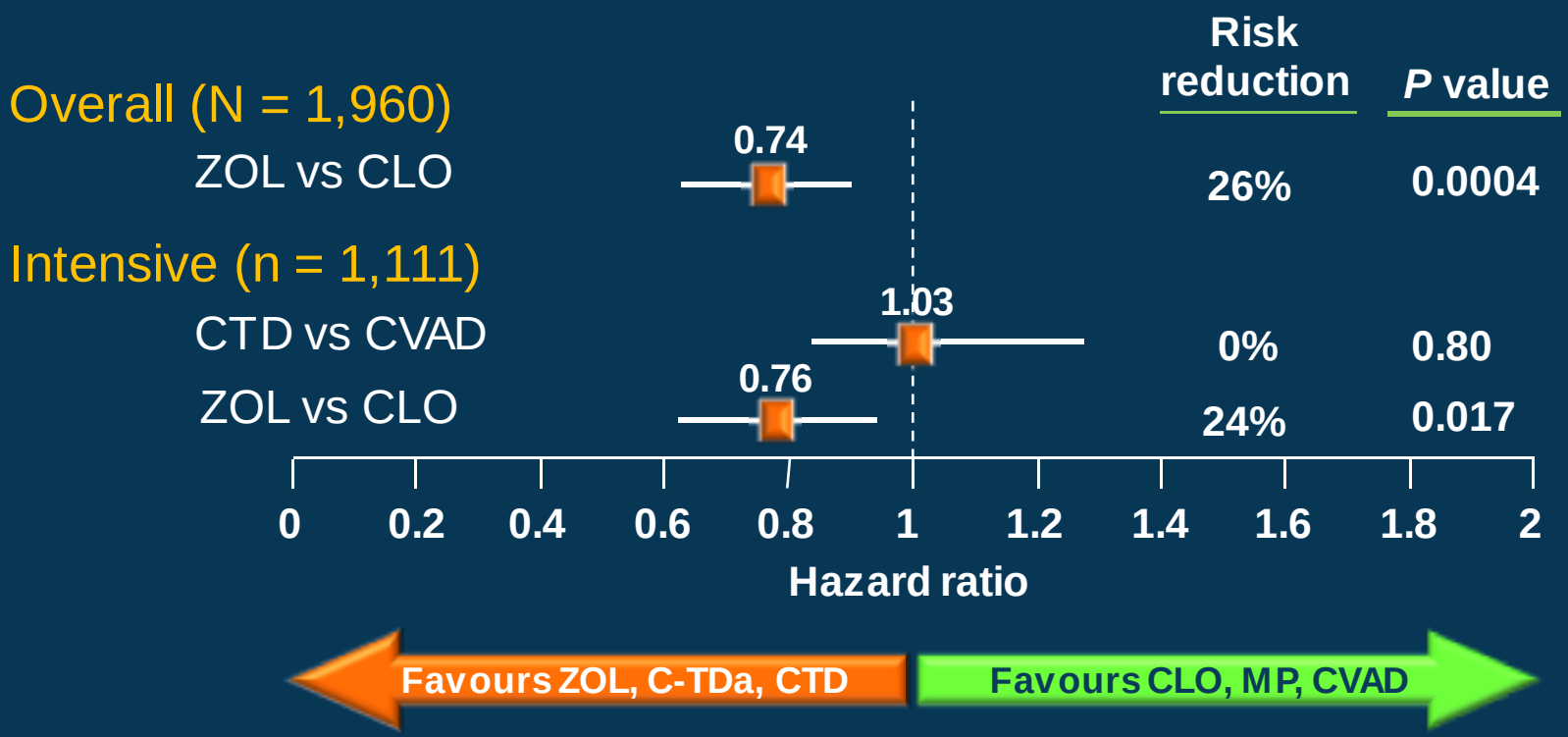
Vorinostat characteristics

- Inhibits IL6
- Turns on tumour-suppressor genes
- Inhibits HSP90
- Ideal companion for lenalidomide

Targeting bone is important to reduce SRE and may improve survival

Hypothesis 3.
ZOL superior to CLO
(improve survival, reduction in SREs)

Relative risk of SREs by treatment*



* SREs were defined as vertebral fractures, other fractures, spinal cord compression, and the requirement of radiation or surgery for bone lesions or the appearance of new osteolytic bone lesions.

- ZOL treatment significantly reduces the risk of SREs compared with CLO.

Morgan G, et al. Blood; 2010; 116: abstract 311.

Conclusions (1)

- CTD should be considered a standard induction therapy for patients with NDMM undergoing HDT/ASCT.
  - Significant difference in CR rates maintained post-HDT ($p = 0.0001$)
    - ✓ This effect is independent of bias introduced by investigator assessment as the response was predominantly assessed centrally
    - ✓ This observation illustrates the importance of high-dose melphalan in improving response rates even when the induction is given to maximum effect
  - Patients with a CR who had favourable iFISH show the greatest benefit
  - After 2 years there is an emerging OS benefit with CTD
- ZOL decreases the SREs vs CLO in both study arms.
- This large data set analysis shows that CTD is an alternative option to current triplet drug combinations such as VTD, PAD, and CVD.

Conclusions (2)

- Thalidomide maintenance therapy improves PFS significantly without a significant survival benefit.
  - With effective treatment at progression, thalidomide maintenance results in improved OS
  - Patients with favourable iFISH benefit the most from maintenance treatment
- The clinical impact would be improved if patients could remain on maintenance therapy for longer.
- The use of novel agents as maintenance is important.
  - Is this relevant for all patients?
  - Subsequent analysis will aim to identify the optimal sequence of agents to use

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B Walker
D Johnson
D Gonzalez
N Dickens
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A Avridromou

MRC Leukaemia Trial Steering Committee

MRC Leukaemia Data Monitoring and Ethics Committee

NCRI Haematological Oncology Clinical Studies Group

NIHR, through the National Cancer Research Network

UK Myeloma Forum Clinical Trials Committee

Myeloma UK

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