Response Adapted Induction Treatment Improves Outcomes for Myeloma Patients: Results of the Phase III Myeloma XI Study

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On behalf of the UK NCRI Haemato-oncology Clinical Studies Group

Disclosures

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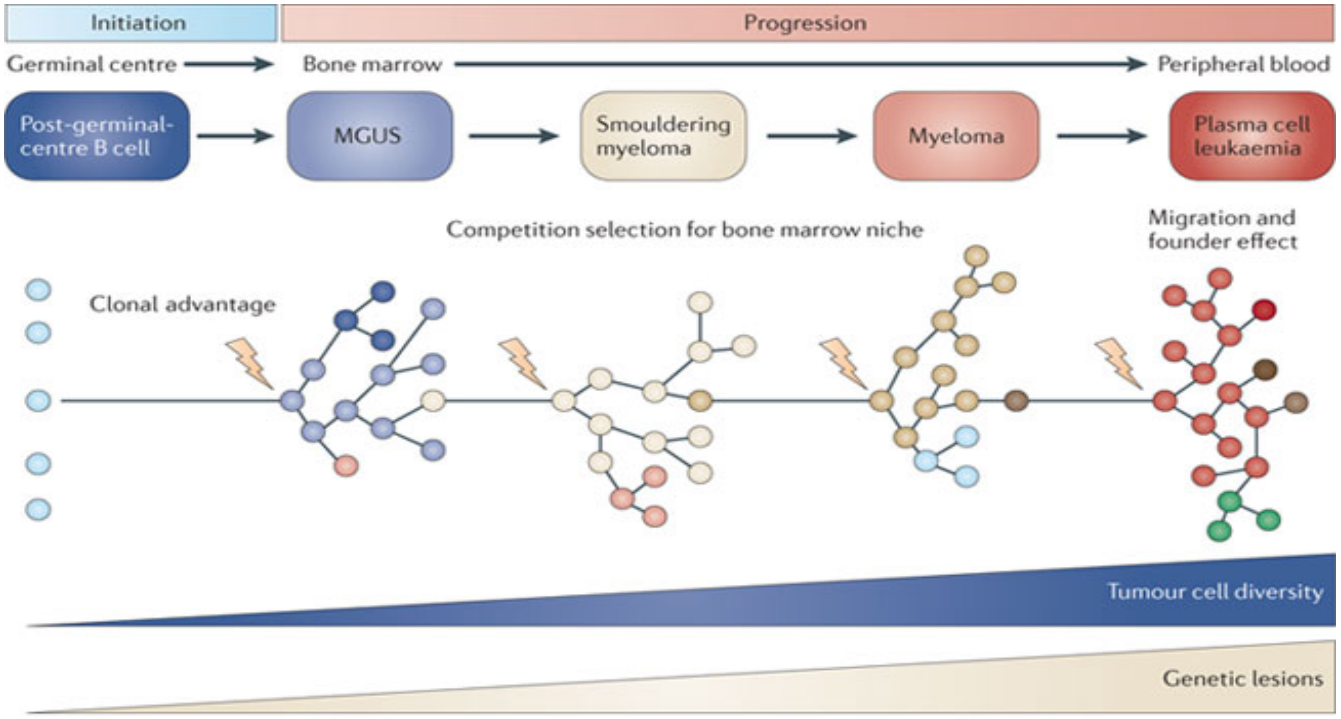
GHJ has received honoraria for speaking from Celgene, Takeda, Roche, J and J, and Amgen. He is a director of myeloma UK. He has attended advisory boards for Takeda, Roche, Amgen, J and J, and Celgene.

Introduction

- Darwinian evolution drives myeloma development:

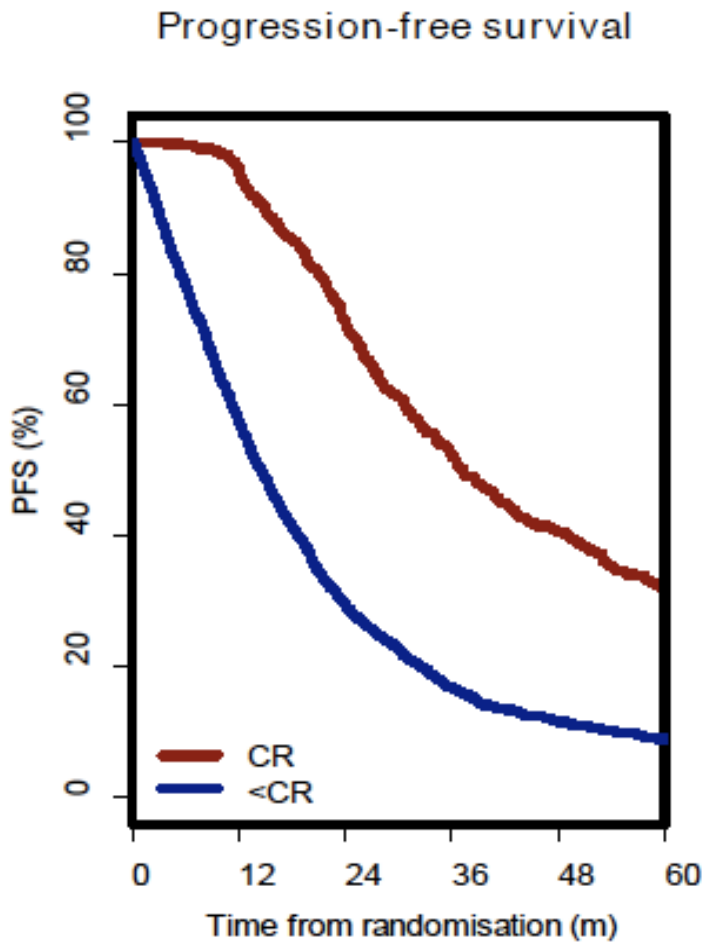


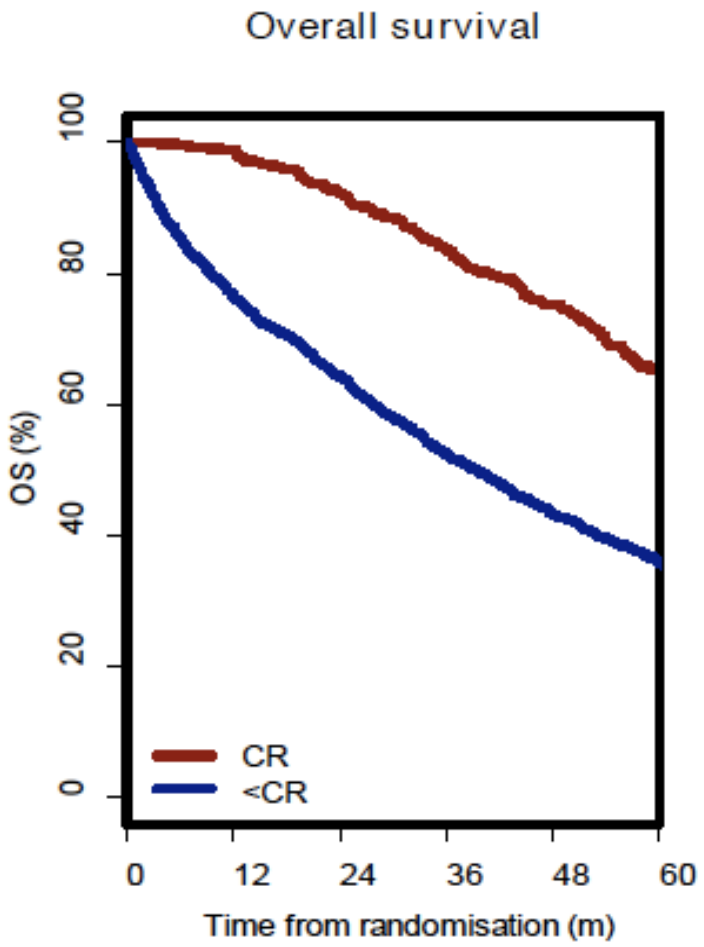
- Diversity both within and between patients suggests that if we can customise therapy to the features of the patient and the cancer that we will improve outcomes.

Morgan GJ, Walker BA & Davies FE *Nat Rev Cancer* 2012

Depth of response impacts outcomes

Results from our previous UK MRC IX study





Morgan GJ et al *Haematologica*. 2012
Morgan GJ et al *Blood*. 2011
Morgan GJ et al *Clin Can Res*. 2013

Introduction

- Maximising depth of response is one of the key aims of modern myeloma therapy.
- Combining myeloma therapies with different modes of action can eliminate resistant sub-clones.
- Response adapted therapy based on rapidly changing to an alternate therapy in the face of a lack of response to initial therapy offers the potential to personalise therapy and improve outcomes.

Trial Questions

Myeloma XI is the first randomised study to investigate a response-adapted approach to induction therapy for newly diagnosed myeloma (NDMM).

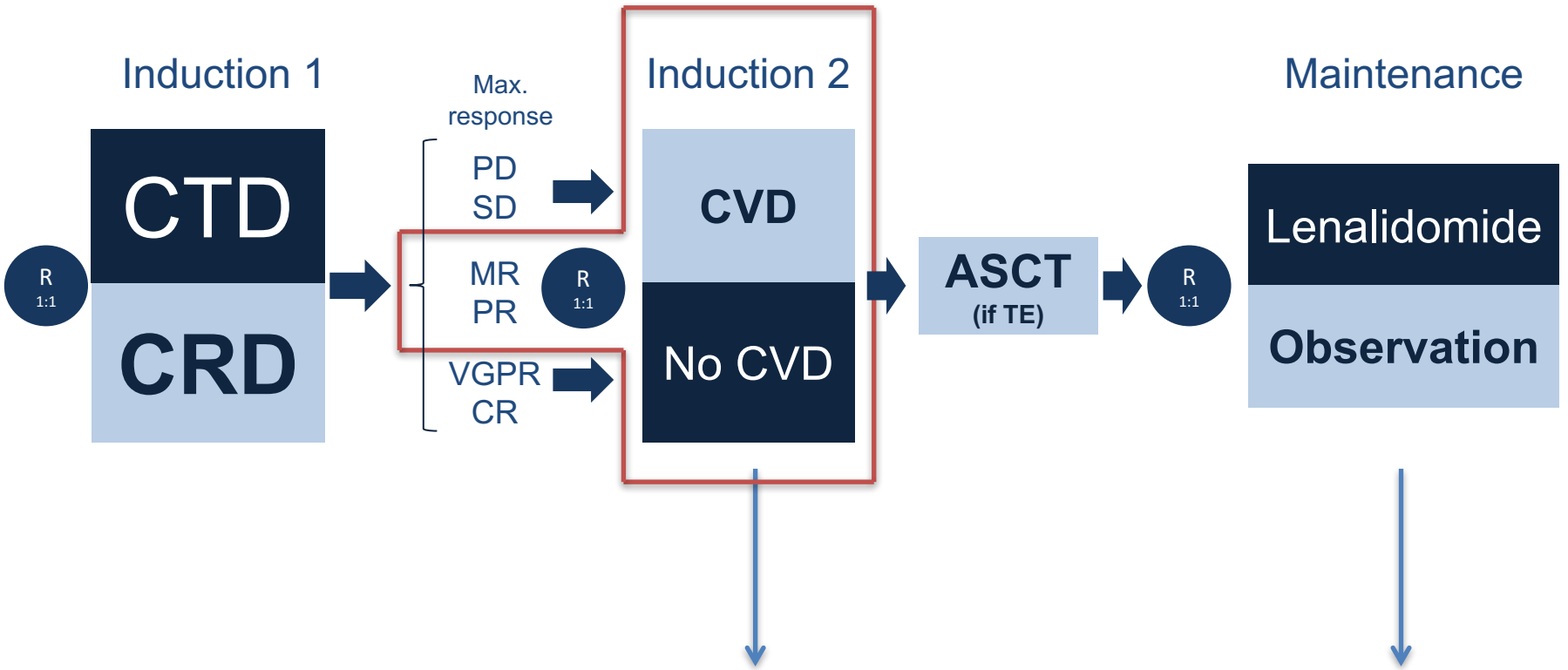
Myeloma XI addresses whether, for patients with a suboptimal response to a triplet IMiD containing induction regimen whether treatment with a proteasome inhibitor based triplet can improve depth of response, PFS and OS.

Myeloma XI

Study design:

- Phase III, multicenter, open label, parallel group, randomised controlled trial.
- Newly diagnosed symptomatic myeloma patients of all ages.
- Patients received initial induction with cyclophosphamide lenalidomide dexamethasone or cyclophosphamide thalidomide and dexamethasone (CRD vs CTD).
- Cases with a suboptimal response defined as MR/PR were randomised to further induction therapy with a bortezomib based triplet.
- Primary endpoints: PFS and OS.

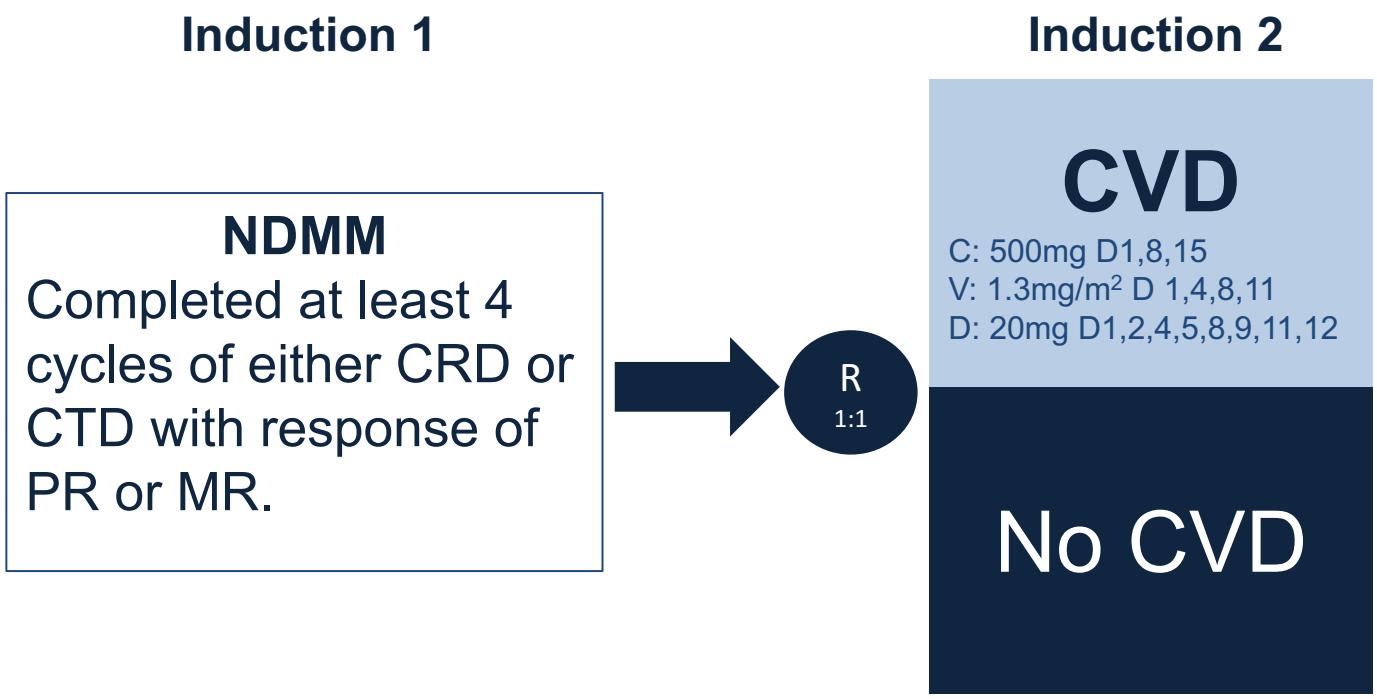
Myeloma XI – trial outline



Charlotte Pawlyn
Monday Dec 5th
5:15pm Seaport Ballroom

Gareth Morgan
Monday Dec 5th
5:00pm Seaport Ballroom

Myeloma XI



N = 583 (**TE** = 367, **TNE** = 216)

Median follow up: 30 months (IQR 17-46)

Exclusion criteria:

Patients were ineligible for the CVD randomisation if they achieved a **CR** or **VGPR** or had **PD** or **SD** to induction (all primary refractory patients received CVD).

Myeloma XI

Definitions of risk:

- **Clinical risk**
  - ISS I, II, III

- **Genetic risk**
  - SR: absence of any adverse lesion
  - HR: presence of at least one adverse lesion: translocation (t(4;14), t(14;16)) gain 1q or del 17p
  - UHR: more than one adverse lesion

Baseline characteristics

		No CVD (n=294)	CVD (n=289)
Pathway	TE TNE	63% (184) 37% (110)	63% (183) 37% (106)
Sex	Male % (n) Female % (n)	54% (158) 46% (136)	61% (175) 39% (114)
Age	Mean (SD) Median (range)	64 (10.48) 66 (39-90)	65 (10.38) 66 (34-87)
ISS	I II III unknown	31% (90) 43% (126) 20% (60) 6% (18)	33% (95) 45% (129) 18% (51) 5% (14)
Genetic risk Available 184/583 (32%) % given is of those known	SR HR/UHR UHR	53% 47% 10%	61% 39% 13%

Baseline characteristics

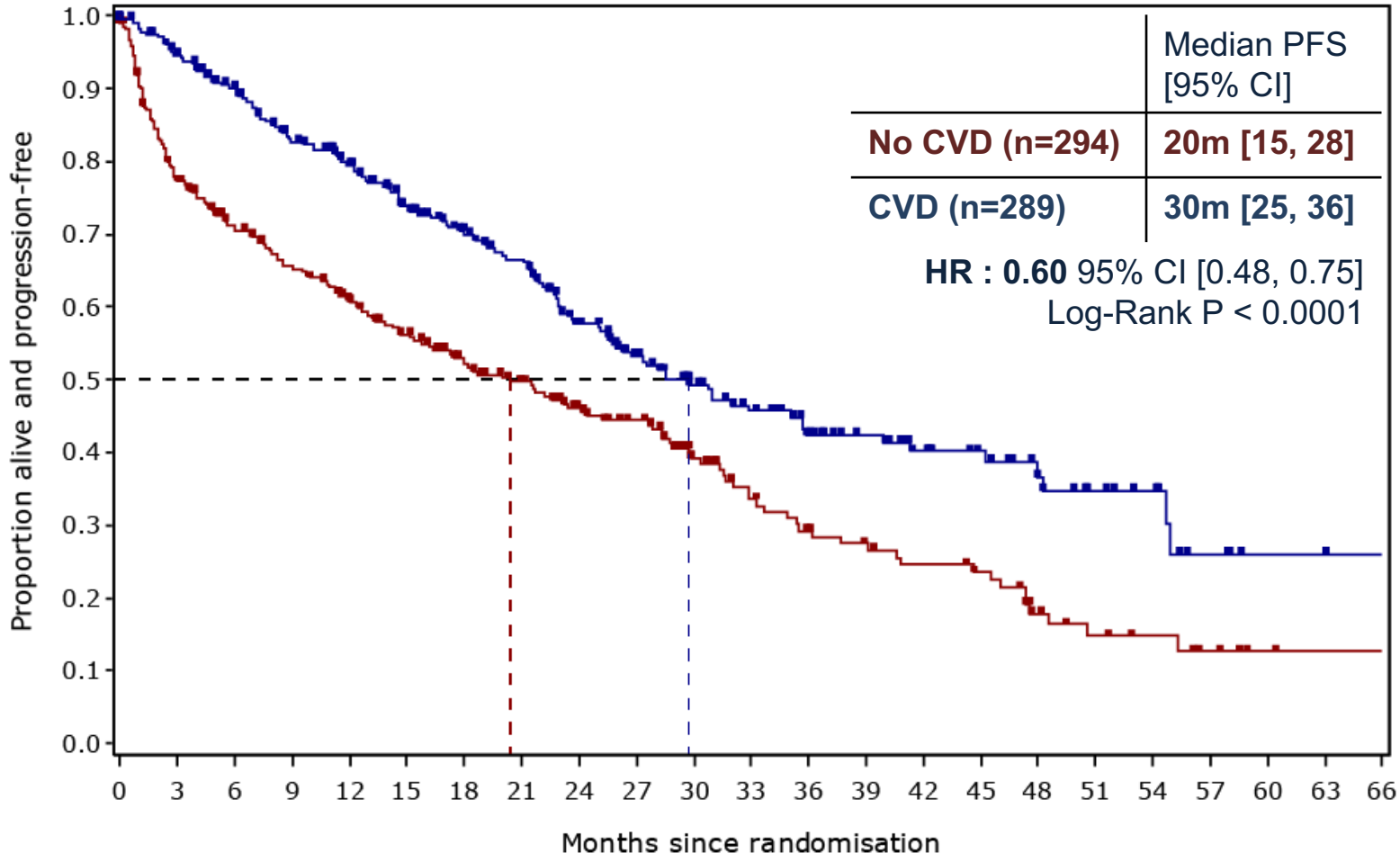
		No CVD (n=294)	CVD (n=289)
Induction 1 therapy	CTD CRD CTDa CRDa	35% (102) 28% (82) 21% (61) 17% (49)	34% (98) 29% (85) 20% (57) 17% (49)
Time initial to CVD randomisation	Mean (SD) Median (range)	5.9 (1.68) 5.8 (2.8-12.9)	5.9 (1.78) 5.7 (2.7-14.1)

Response rates

		Response to initial induction triplet	Response at end of CVD	% of patients with improved response to VGPR/CR
CVD (n=289)	CR VGPR **PR** **MR** SD/PD	0.3% 4.2% **84%** **8.3%** 1.0%	3.5% 39% 39% 1.4% 3.8%	38%
No CVD (n=291)	CR VGPR **PR** **MR** SD/PD	0% 4.1% **84%** **7.5%** 4.0%	n/a	n/a

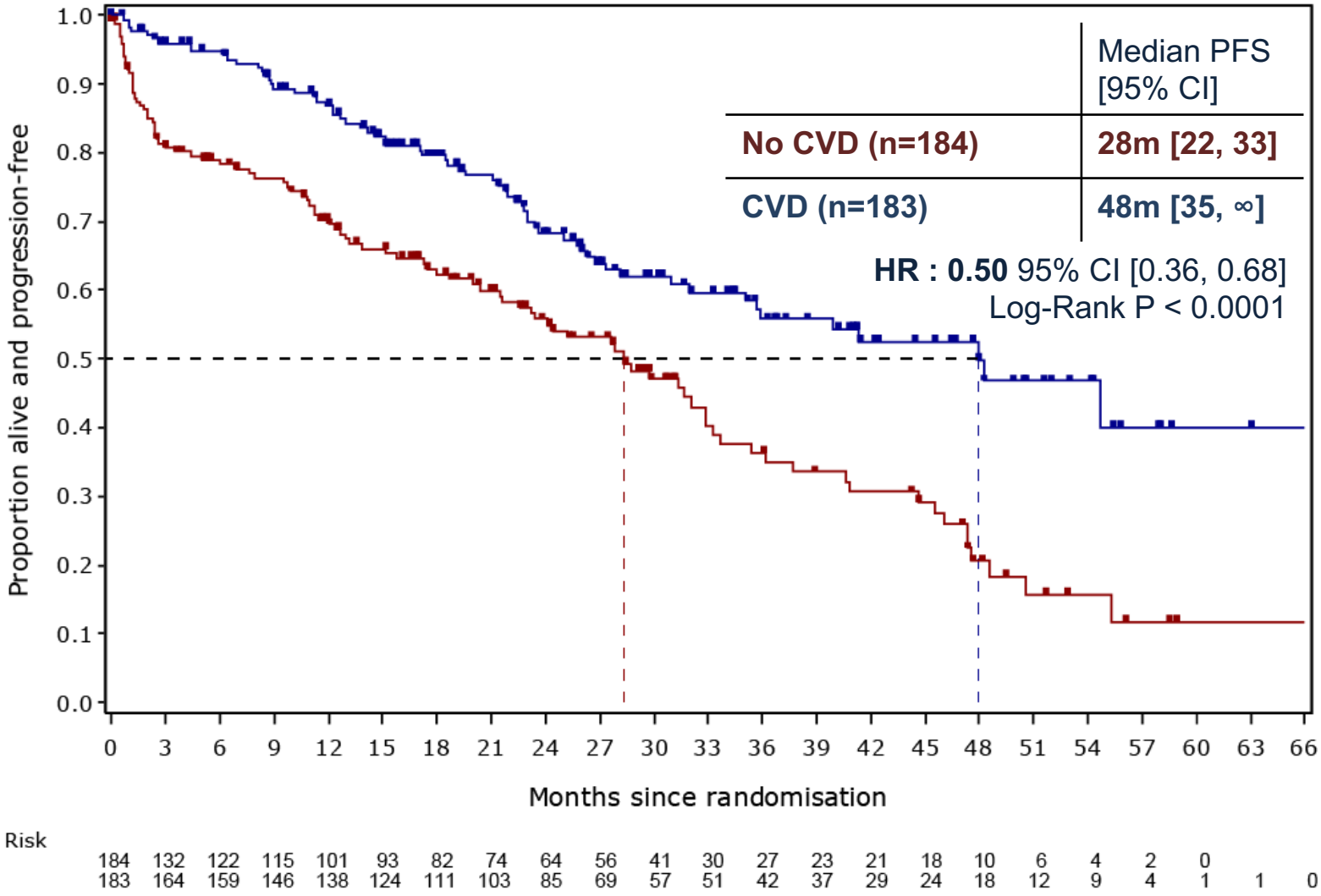
Progression Free Survival

Significant improvement in PFS from 20 to 30 months for patients receiving CVD, HR 0.60



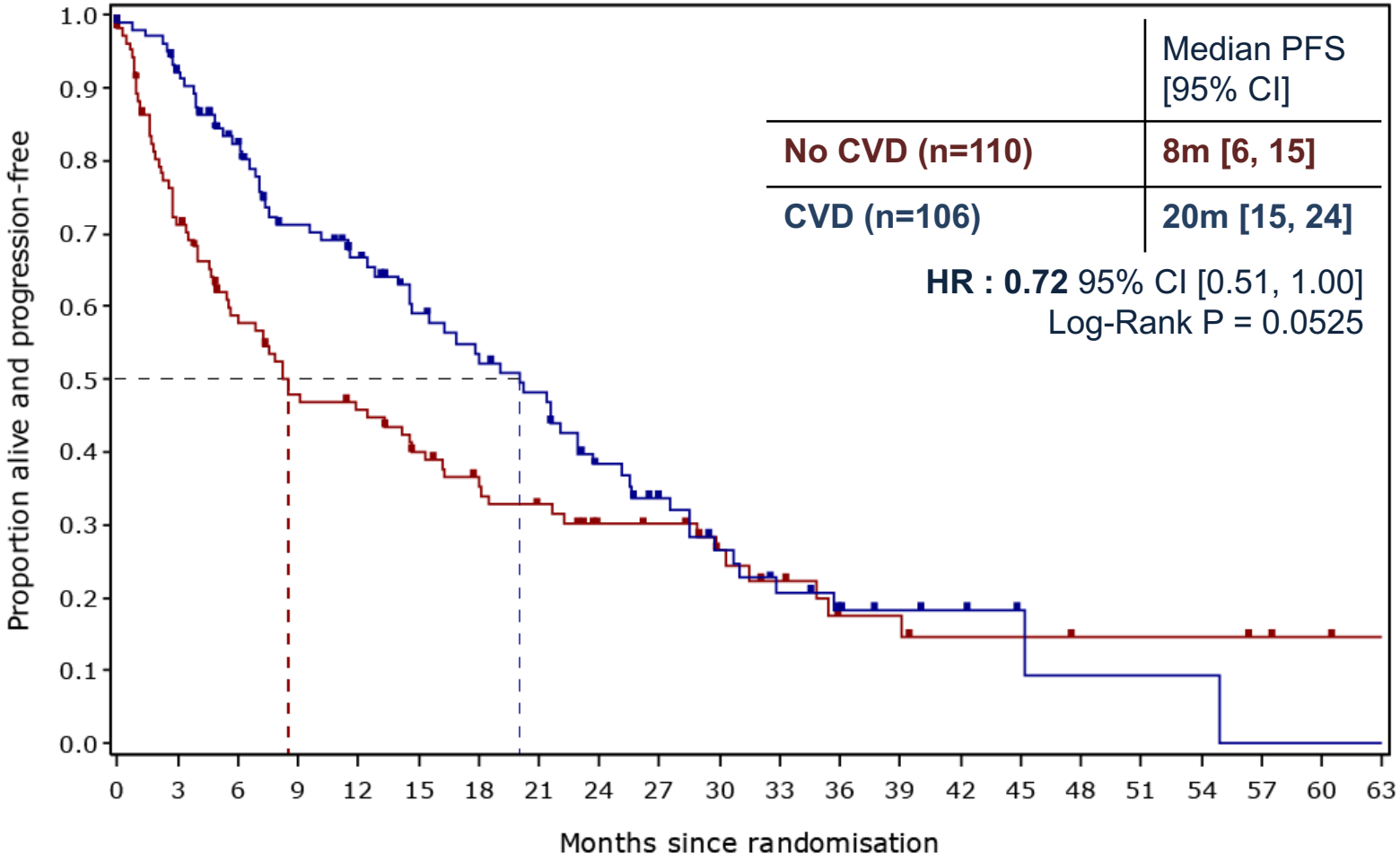
Transplant eligible pathway

Significant improvement in PFS from 28 to 48 months for patients receiving CVD, HR 0.50

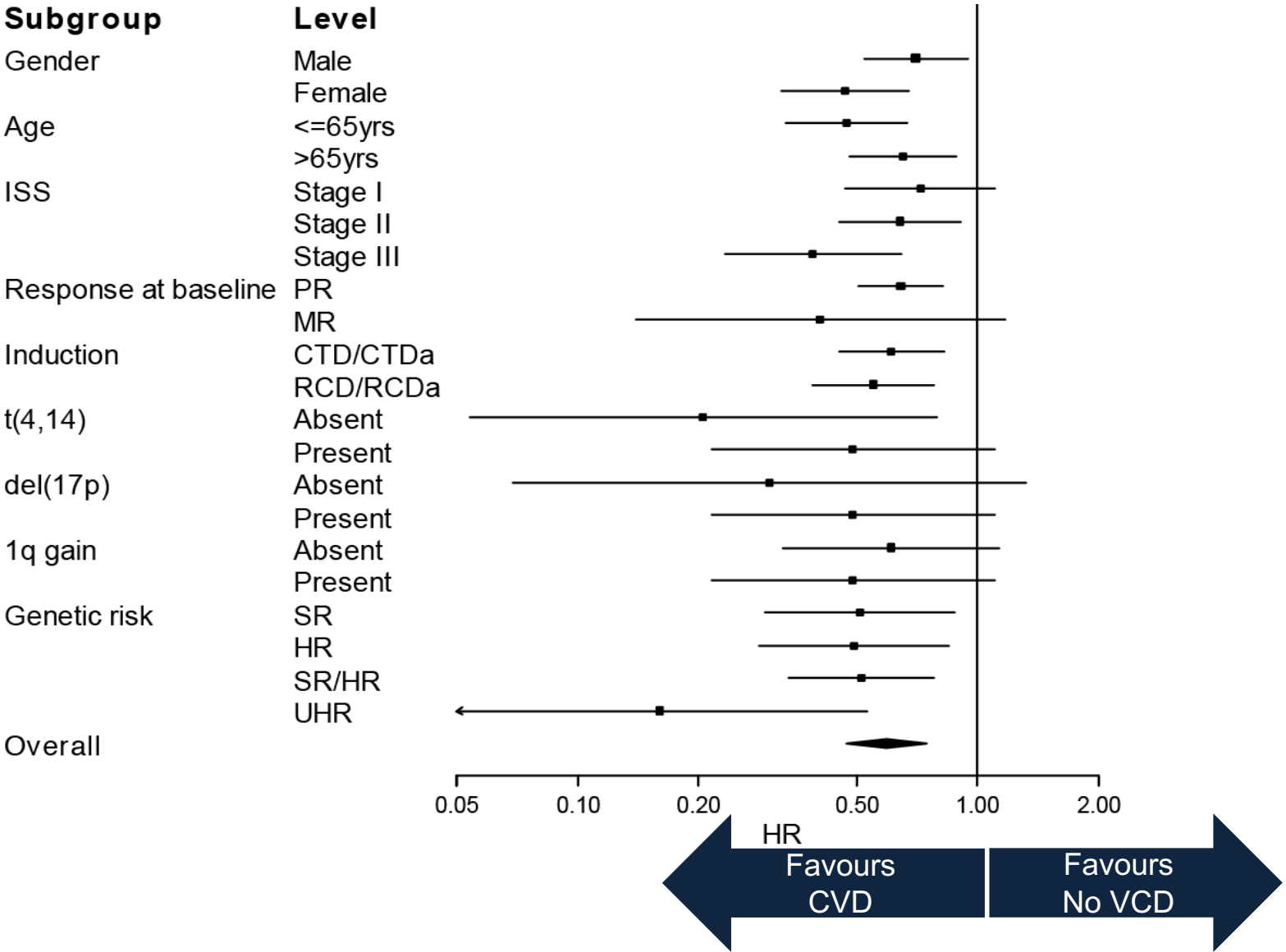


Transplant non-eligible pathway

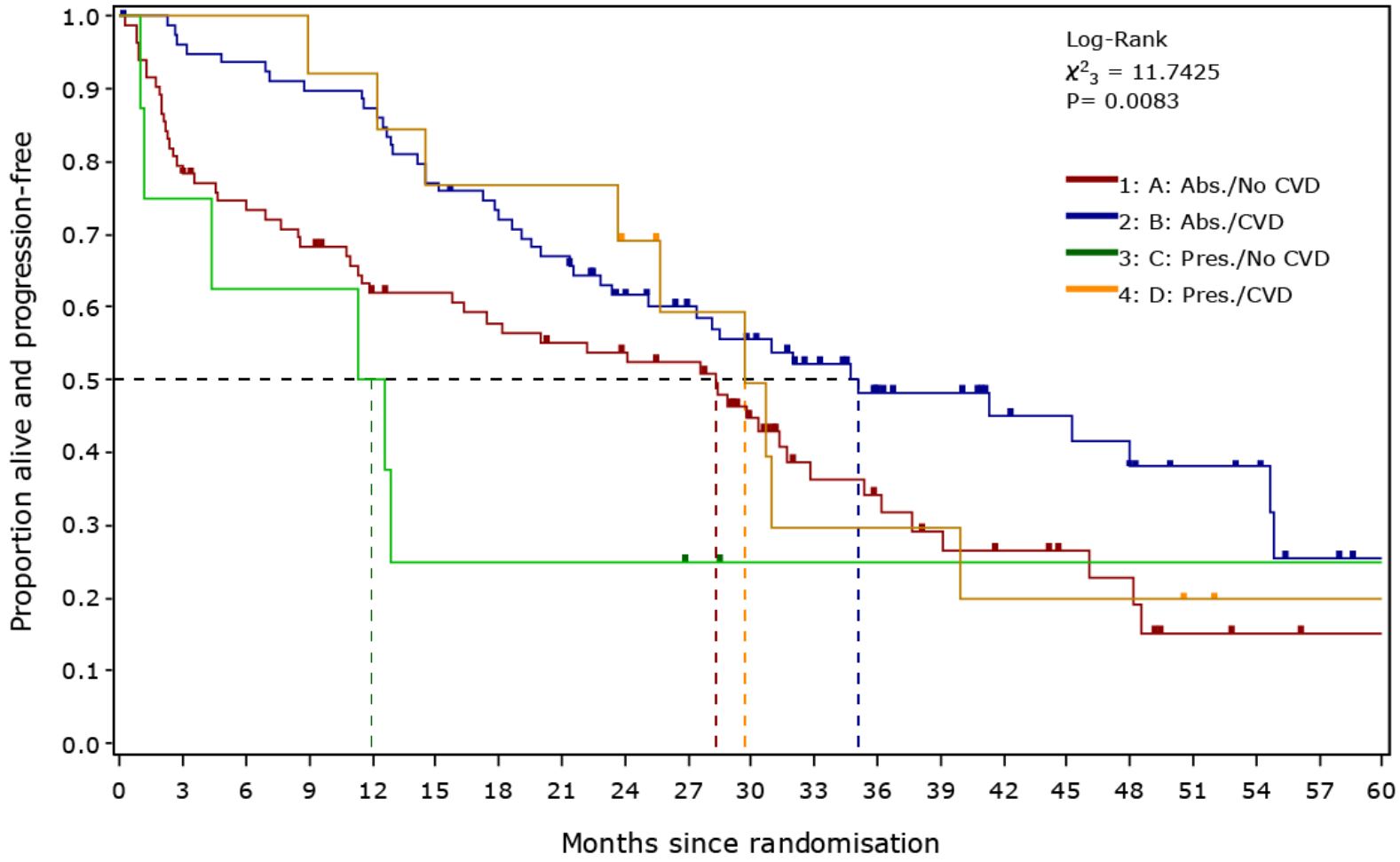
Significant improvement in PFS from 8 to 20 months for patients receiving CVD, HR 0.72



Subgroup analysis (PFS)



Impact on t(4;14)



Number at Risk

1: A: Abs./No CVD	83	64	60	55	47	46	43	40	38	36	25	16	14	11	9	7	6	2	1	0	
2: B: Abs./CVD	80	76	74	71	69	61	57	52	44	39	35	29	22	19	14	13	11	8	7	3	1
3: C: Pres./No CVD	8	6	5	5	4	2	2	2	2	1	0										
4: D: Pres./CVD	13	13	13	12	12	10	10	10	8	6	5	3	3	3	2	2	2	1	0		

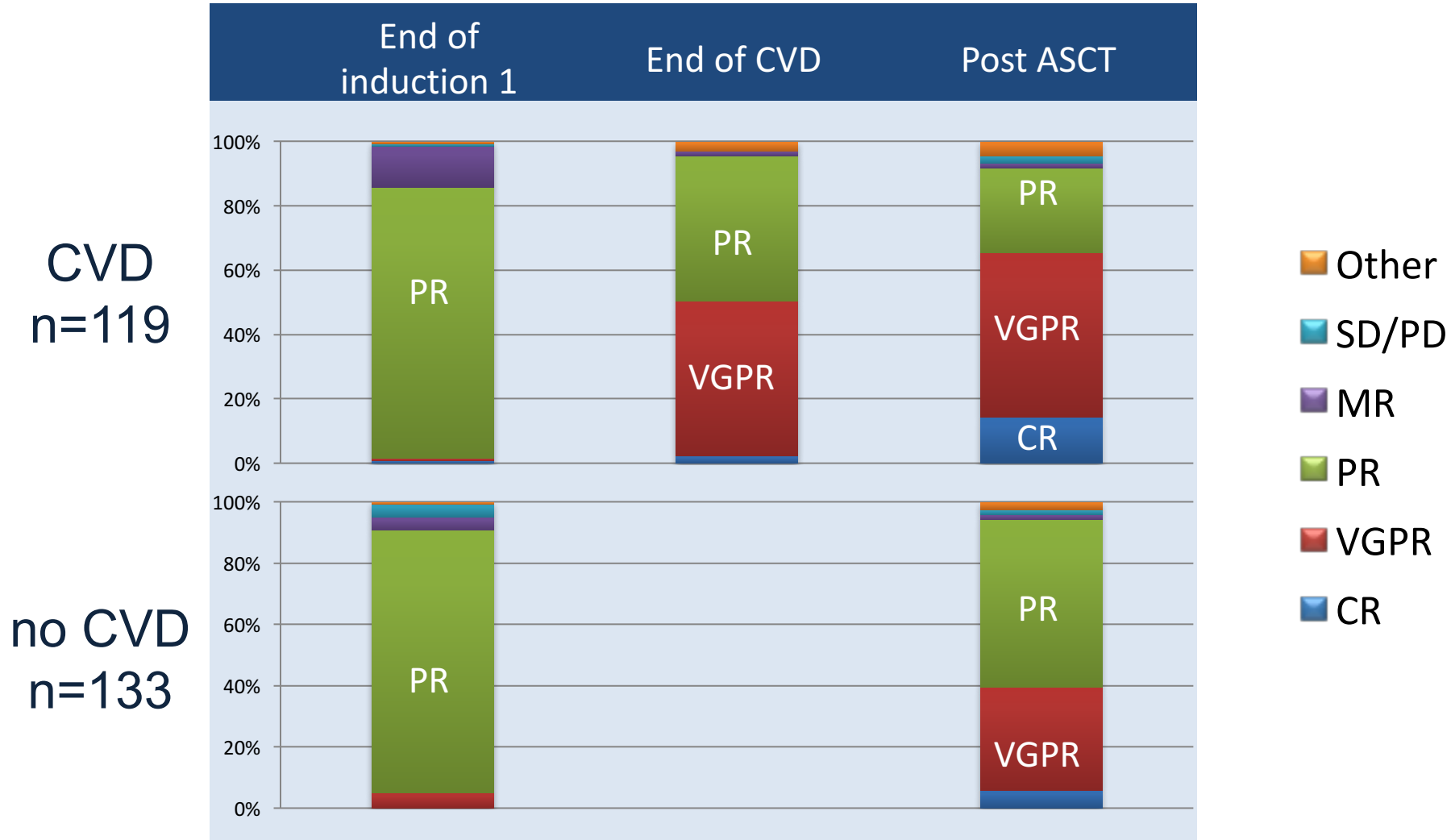
Post ASCT response

Reponses after ASCT improved across both arms but remained deeper for those randomised to receive CVD

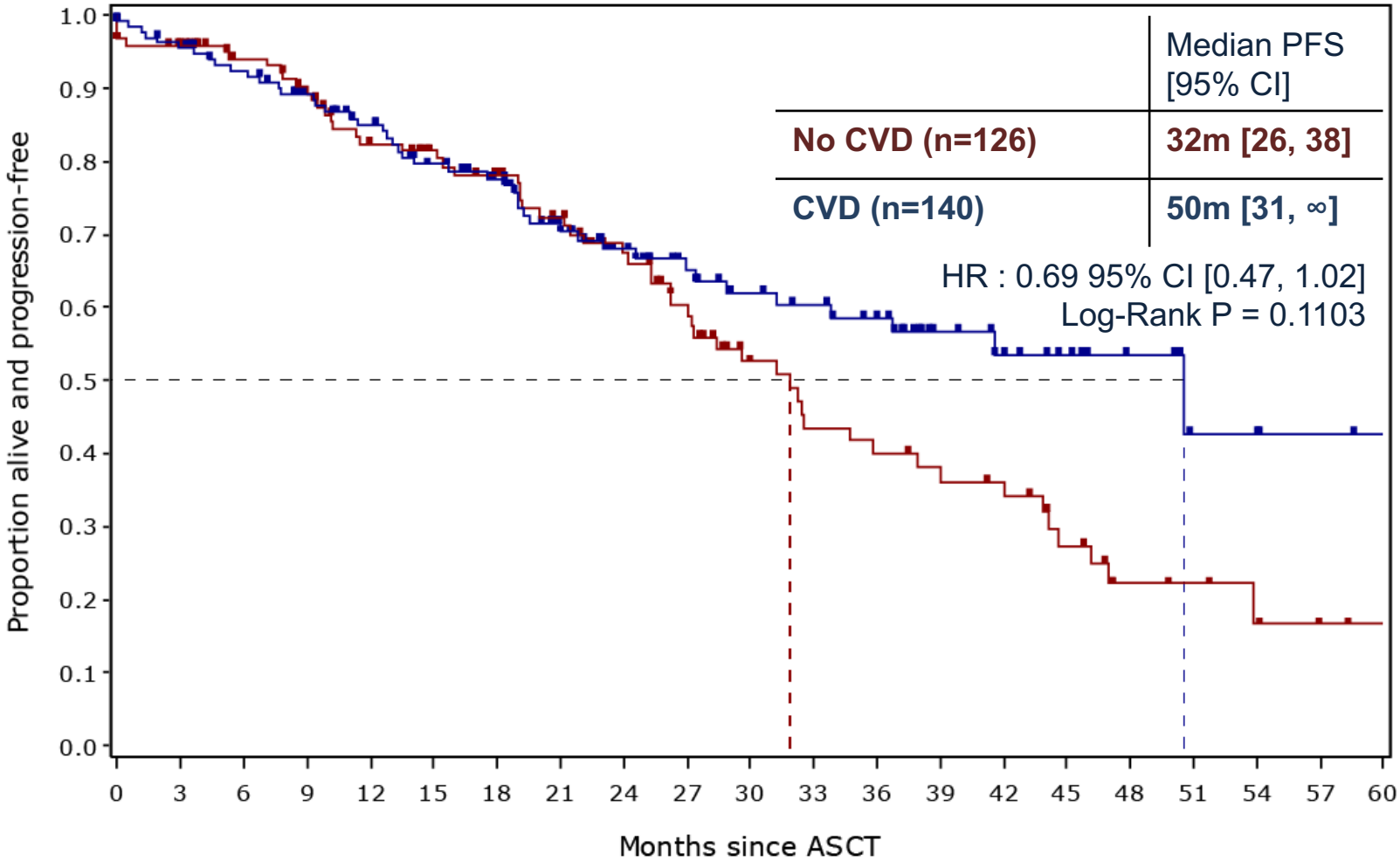
		Response to initial induction triplet	Response at end of CVD	Response after ASCT (3/12)
CVD (n=119)	CR VGPR **PR** **MR** SD/PD	0.8% 0.8% **84%** **13%** 0.8%	2.3% 48% 45% 1.5% 0%	14% 51% 26% 1.5% 2.3%
No CVD (n=133)	CR VGPR **PR** **MR** SD/PD	0.0% 5.0% **86%** **4.2%** 4.2%	n/a	5.9% 34% 55% 1.7% 1.7%

Post ASCT response

Reponses after ASCT improved across both arms and remained deeper for those randomised to receive CVD



Post ASCT PFS (CVD vs no CVD)



Conclusions

- Response adapted therapy based on the use of chemotherapeutic agents with a different mode of action improves response rates and prolongs PFS.
- In this study 38% of patients upgraded their depth of response to VGPR or better. In the TE population post transplant 65% achieved VGPR/CR in the VCD arm v 39.9% in the no VCD arm
- PFS improved by 12 months (HR 0.72) in transplant ineligible and by 20 months (HR 0.5) in transplant eligible patients.
- This effect is seen across all patient subgroups and persists both pre and post ASCT.
- This data supports exploring four drug induction regimens.

Myeloma XI

NCRI National Cancer Research Institute

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CANCER RESEARCH UK

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