Lenalidomide induction and maintenance maximizes outcome for newly diagnosed transplant eligible myeloma patients irrespective of risk status: Long-term follow-up of the Myeloma XI trial

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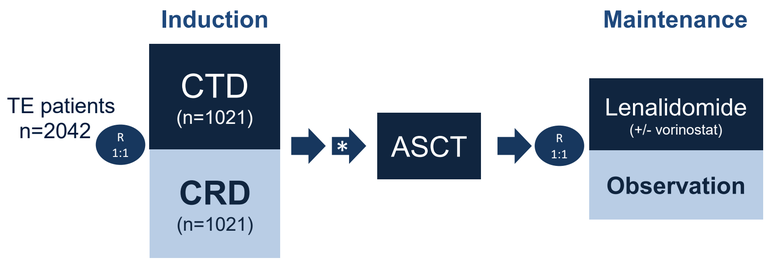
Background

- Immunomodulatory (IMiD) compounds are effective therapies for multiple myeloma (MM) acting via modulation of the CUL4 E3-ubiquitin ligase cereblon.
- Based on their structure, individual IMiD compounds have different substrate specificities altering both their efficacy and side effect profile. These mechanistic differences impact the optimum sequencing of these agents as induction and maintenance.
- Within the UK NCRI Myeloma XI trial we compared triplet induction regimens containing Lenalidomide (Len) or Thalidomide (Thal) and maintenance treatment with Len or observation.
- With extensive long term follow up data we have explored the interaction of the induction and maintenance use of Thal and Len before and after autologous stem cell transplant (ASCT).

Myeloma XI

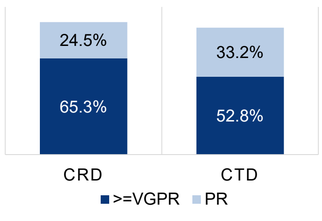
- Myeloma XI is a phase III trial with pathways for transplant eligible (TE) and transplant ineligible (TNE) newly diagnosed myeloma patients. The transplant eligible pathway is presented in this analysis.

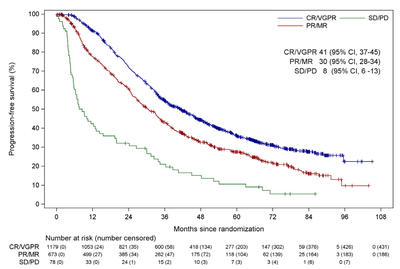


CTD, cyclophosphamide, thalidomide, dexamethasone; CRD, cyclophosphamide, lenaldidomide, dexamethasone. *Patients with a suboptimal response to induction (<VGPR) were eligible for intensification. Patients with PR/MR were randomised to CVD (cyclophosphamide, bortezomib and dexamethasone) or no further therapy prior to ASCT. Patients with SD/PD all received CVD.

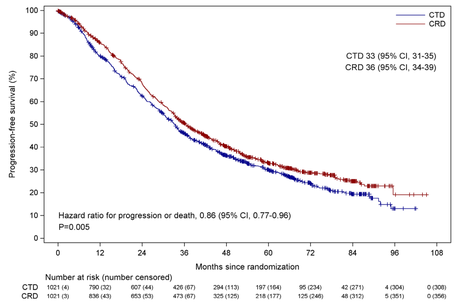
- The study was powered for the primary endpoints PFS and OS.
- Analyses by molecular risk strata were pre-specified. Adverse molecular risk lesions were defined as gain(1q), t(4;14), t(14;16), t(14;20), or del(17p): standard risk (SR, no adverse risk lesions), high risk (HiR, one adverse risk lesion), or ultra-high risk (UHiR, two or more adverse risk lesions).
- The median follow up for this analysis is 67 months (interquartile range 52-82) for the induction randomization and 45 months (interquartile range 32-63) for the maintenance randomization.

Response at the end of induction was associated with outcome



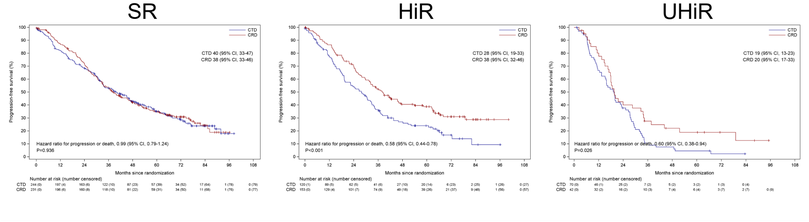


CRD was associated with significantly longer PFS than CTD: HR 0.86

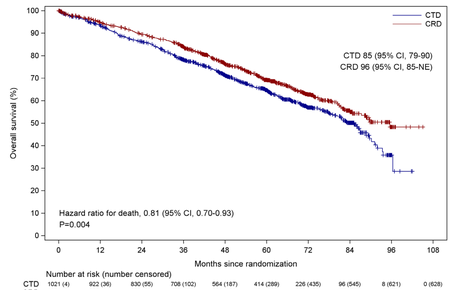


Subgroup	Category	CRD n/N	CTD n/N	HR (95%CI)	P. (het)
Sex	Male	439/611	394/610	0.84 (0.73, 0.97)	0.579
	Female	274/410	271/411	0.89 (0.75, 1.05)	
Age	<=65 years	509/754	484/772	0.85 (0.75, 0.96)	0.489
	>65 years	204/267	181/249	0.91 (0.75, 1.12)	
WHO PS	0	295/441	258/424	0.85 (0.72, 1.01)	0.434
	1	263/368	251/364	0.93 (0.78, 1.10)	
	>=2	127/171	120/174	0.76 (0.59, 0.98)	
ISS	Stage I	189/307	177/304	0.93 (0.75, 1.14)	0.078
	Stage II	278/389	274/393	0.91 (0.77, 1.08)	
	Stage III	200/254	164/247	0.70 (0.57, 0.86)	
t(4,14)	Present	65/71	42/58	0.63 (0.42, 0.96)	0.144
	Absent	259/363	241/368	0.82 (0.69, 0.98)	
t(14,16)	Present	11/12	6/8	0.84 (0.30, 2.39)	0.356
	Absent	313/422	277/418	0.79 (0.67, 0.93)	
t(14,20)	Present	1/2	0/3		0.963
	Absent	323/432	283/423	0.78 (0.66, 0.92)	
del(17p)	Present	36/43	25/32	0.69 (0.40, 1.18)	0.549
	Absent	288/391	258/394	0.79 (0.67, 0.94)	
gain(1q)	Present	118/139	91/138	0.55 (0.41, 0.72)	0.003
	Absent	206/295	192/288	0.92 (0.75, 1.12)	
Cytogenetic Risk	SR	165/244	154/231	0.99 (0.79, 1.24)	0.011
	HiR	93/120	96/153	0.58 (0.44, 0.78)	
	UHiR	66/70	33/42	0.60 (0.38, 0.94)	
Overall		**713/1021**	**665/1021**	**0.86 (0.77, 0.96)**	

- Significant heterogeneity in PFS outcome was identified between molecular risk groups; patients with HiR and UHiR benefitted the most from induction with CRD rather than CTD

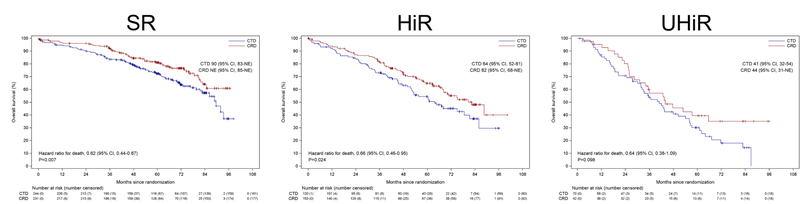


CRD was associated with significantly longer OS than CTD: HR 0.81

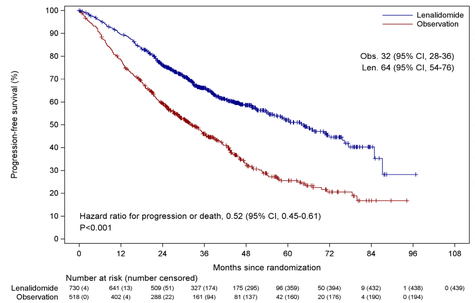


Subgroup	Category	CRD n/N	CTD n/N	HR (95%CI)	P. (het)
Sex	Male	249/611	192/610	0.74 (0.62, 0.90)	0.22
	Female	144/410	143/411	0.90 (0.71, 1.13)	
Age	<=65 years	278/754	241/772	0.78 (0.65, 0.93)	0.374
	>65 years	115/267	94/249	0.85 (0.64, 1.13)	
WHO PS	0	129/441	112/424	0.84 (0.65, 1.09)	0.557
	1	167/368	139/364	0.85 (0.68, 1.06)	
	>=2	82/171	71/174	0.70 (0.51, 0.97)	
ISS	Stage I	82/307	75/304	0.87 (0.64, 1.19)	0.596
	Stage II	153/389	130/393	0.79 (0.63, 1.00)	
	Stage III	137/254	106/247	0.74 (0.57, 0.95)	
t(4,14)	Present	45/71	25/58	0.59 (0.35, 0.98)	0.955
	Absent	150/363	114/368	0.65 (0.51, 0.83)	
t(14,16)	Present	9/12	5/8	0.46 (0.13, 1.64)	0.883
	Absent	186/422	134/418	0.65 (0.52, 0.81)	
t(14,20)	Present	1/2	0/3		0.965
	Absent	194/432	139/423	0.65 (0.52, 0.81)	
del(17p)	Present	32/43	22/32	0.87 (0.48, 1.56)	0.78
	Absent	163/391	117/394	0.64 (0.51, 0.81)	
gain(1q)	Present	83/139	59/138	0.57 (0.41, 0.80)	0.484
	Absent	112/295	80/288	0.67 (0.50, 0.90)	
Cytogenetic Risk	SR	83/244	54/231	0.62 (0.44, 0.87)	0.982
	HiR	60/120	61/153	0.66 (0.46, 0.95)	
	UHiR	52/70	24/42	0.64 (0.38, 1.09)	
Overall		**393/1021**	**335/1021**	**0.81 (0.70, 0.93)**	

- Patients in all risk groups had an OS benefit with CRD vs CTD

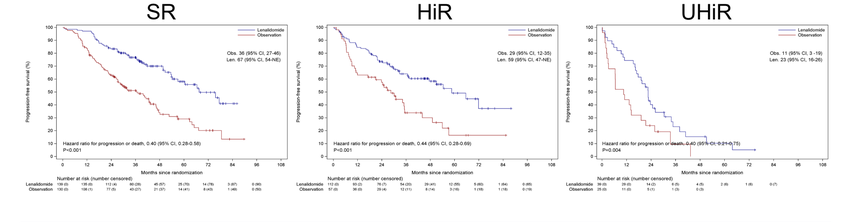


Lenalidomide maintenance was associated with improved PFS vs observation

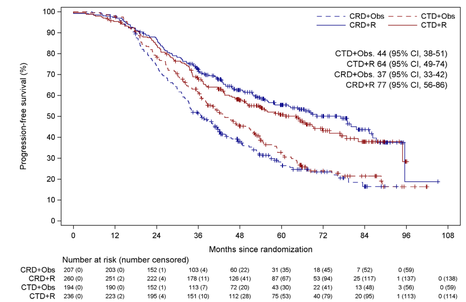


Subgroup	Category	Observation n/N	Lenalidomide n/N	HR (95%CI)	P. (het)
Sex	Male	204/327	197/459	0.56 (0.46, 0.68)	0.222
	Female	120/191	94/271	0.45 (0.34, 0.59)	
Age	<=65 years	250/406	226/577	0.54 (0.45, 0.64)	0.522
	>65 years	74/112	65/153	0.50 (0.36, 0.71)	
t(4,14)	Present	25/27	26/45	0.36 (0.20, 0.64)	0.124
	Absent	115/185	102/245	0.51 (0.39, 0.67)	
t(14,16)	Present	5/6	4/8	0.17 (0.02, 1.17)	0.339
	Absent	135/206	124/282	0.51 (0.40, 0.65)	
t(14,20)	Present	0/1	1/3	1.00 (1.00, 1.00)	0.972
	Absent	140/211	127/287	0.51 (0.40, 0.65)	
del(17p)	Present	10/13	19/26	0.48 (0.19, 1.20)	0.905
	Absent	130/199	109/264	0.48 (0.37, 0.62)	
gain(1q)	Present	42/60	64/112	0.60 (0.40, 0.90)	0.104
	Absent	98/152	64/178	0.39 (0.29, 0.54)	
Cytogenetic Risk	SR	80/130	49/139	0.40 (0.28, 0.58)	0.908
	HiR	38/57	47/112	0.44 (0.28, 0.69)	
	UHiR	22/25	32/39	0.40 (0.21, 0.75)	
Randomised treatment	CTD	134/194	115/236	0.60 (0.47, 0.77)	0.326
	CRD	147/207	117/260	0.46 (0.36, 0.59)	
	KCRD	43/117	59/234	0.55 (0.37, 0.82)	
Response (Induction)	CR / VGPR	234/400	213/581	0.53 (0.44, 0.64)	0.884
	PR / MR	79/101	73/136	0.46 (0.34, 0.64)	
	SD / PD	3/4	4/5		
Overall		**324/518**	**291/730**	**0.52 (0.45, 0.61)**	

- The benefit of Lenalidomide maintenance over observation was consistent across all risk groups



Optimum outcomes were seen in those receiving Len as both induction and maintenance therapy



Conclusions

- With long term follow up CRD induction for newly diagnosed transplant eligible myeloma patients was associated with both a PFS and OS benefit compared to CTD and was better tolerated.
- The PFS impact of CRD was particularly notable in patients with high and ultra-high risk disease. The OS benefit was consistent across all risk groups.
- Lenalidomide maintenance was associated with significantly longer PFS than observation across all risk groups.
- The use of Lenalidomide as both induction and maintenance was associated with the best outcomes.

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Conflicts

GHJ has received honoraria from Celgene, Amgen, Roche, Janssen, Sanofi.
For full details of other authors please see abstract book.