

Impact of Chromosome 1 Abnormalities on Newly Diagnosed Multiple Myeloma treated with Proteasome Inhibitor, Immunomodulatory Drug, and Dexamethasone: Analysis from the ENDURANCE ECOG-ACRIN, E1A11 trial

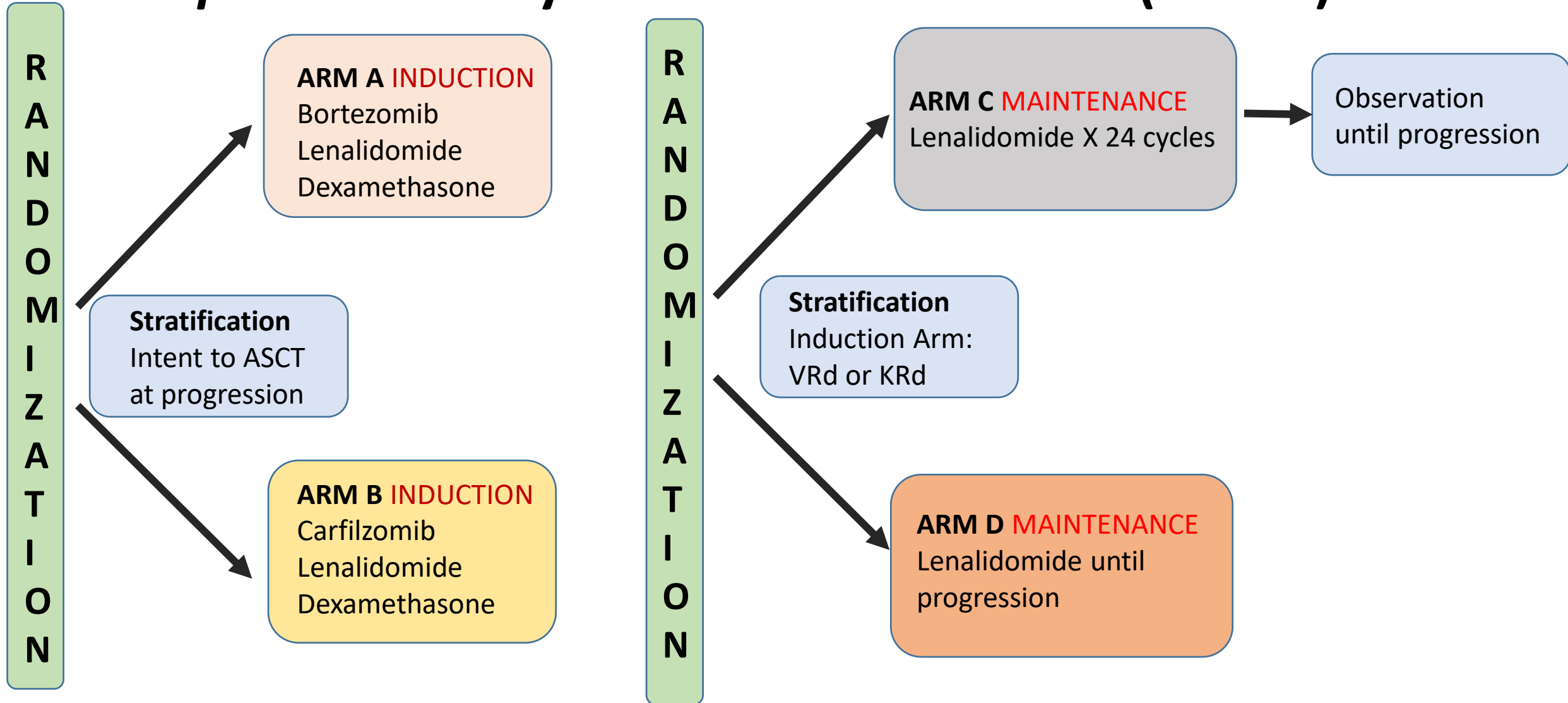
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***Co-first Authors**

Introduction

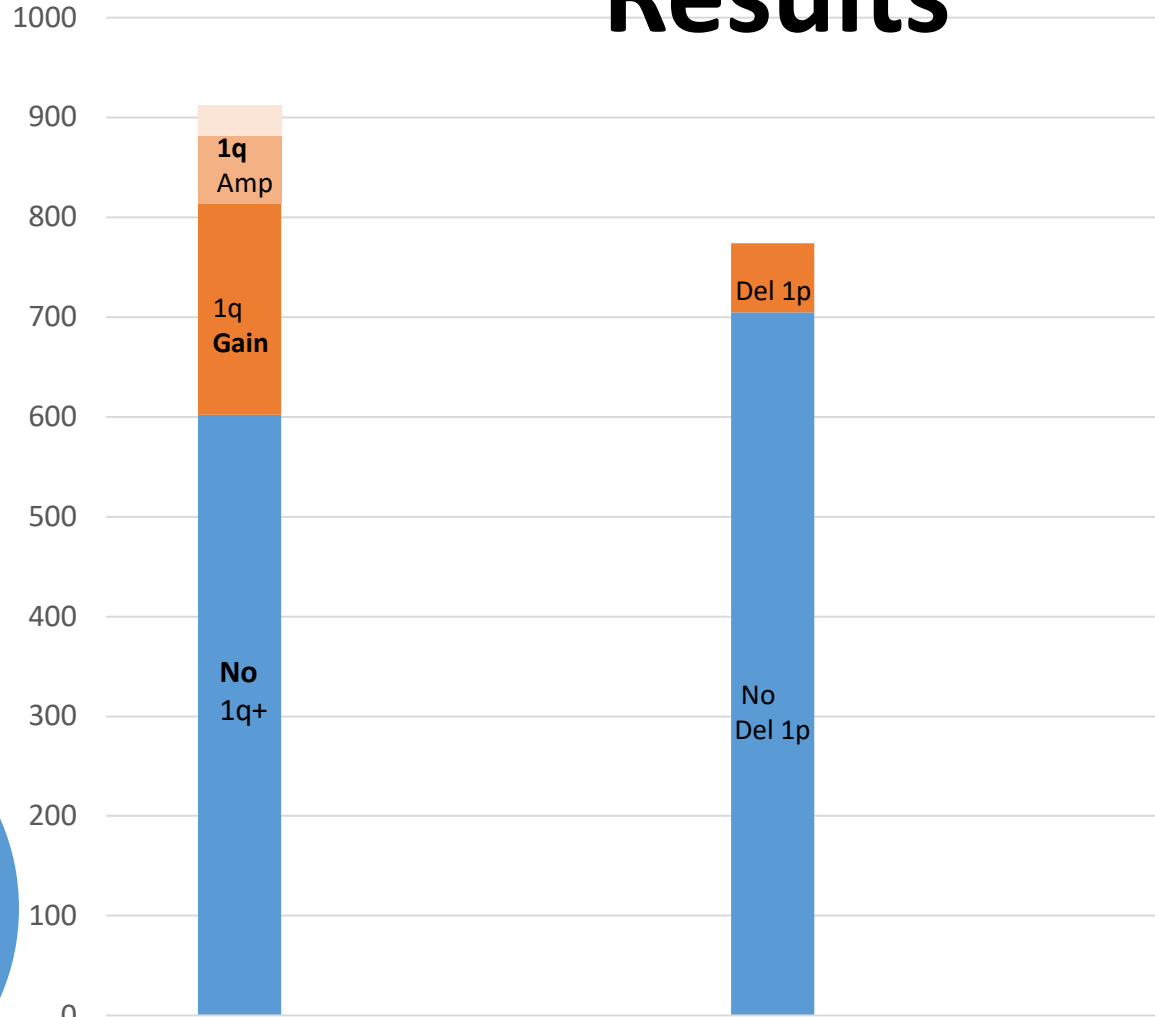
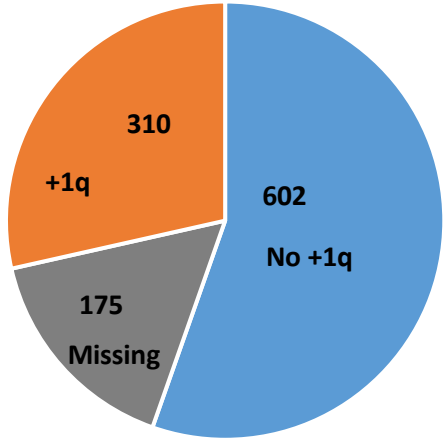
- Chromosome 1 Abnormalities (C1A) are among common recurrent chromosomal aberrations in multiple myeloma.
- Extra copies of chromosome 1 long arm (+1q21) & deletion of its short arm [del(1p32)] associated with high-risk features.
- Genes on chromosome 1 have been associated with early progression/resistance to therapy
- Unclear whether carfilzomib (K) is more effective than bortezomib (V), in combination with lenalidomide (R) and dexamethasone (d) for pts with C1A.
- E1A11 included pts without the following high-risk features: [t(14;20), t(14;16), del(17p), LDH > 2 X upper limit of normal and plasma cell leukemia].

A *post-hoc* analysis of the ENDURANCE (E1A11) trial



Results

1q Status



Chr 1q Status

- Add1q
- 1q Amp/ >=4 copies
- 1q Gain/ 3 copies
- Normal 1q

Chr 1p Status

- Of 1087 pts, 912 examined for +1q (gain1q or amp1q)
- 310 /912 (34%) had +1q.
- Gain 1q21 noted in 212 (23%)
- Amp 1q21 in 68 pts (8 %)
- Del(1p32) was noted in 69 pts (9.2%) of 774 who were evaluated for del1p.

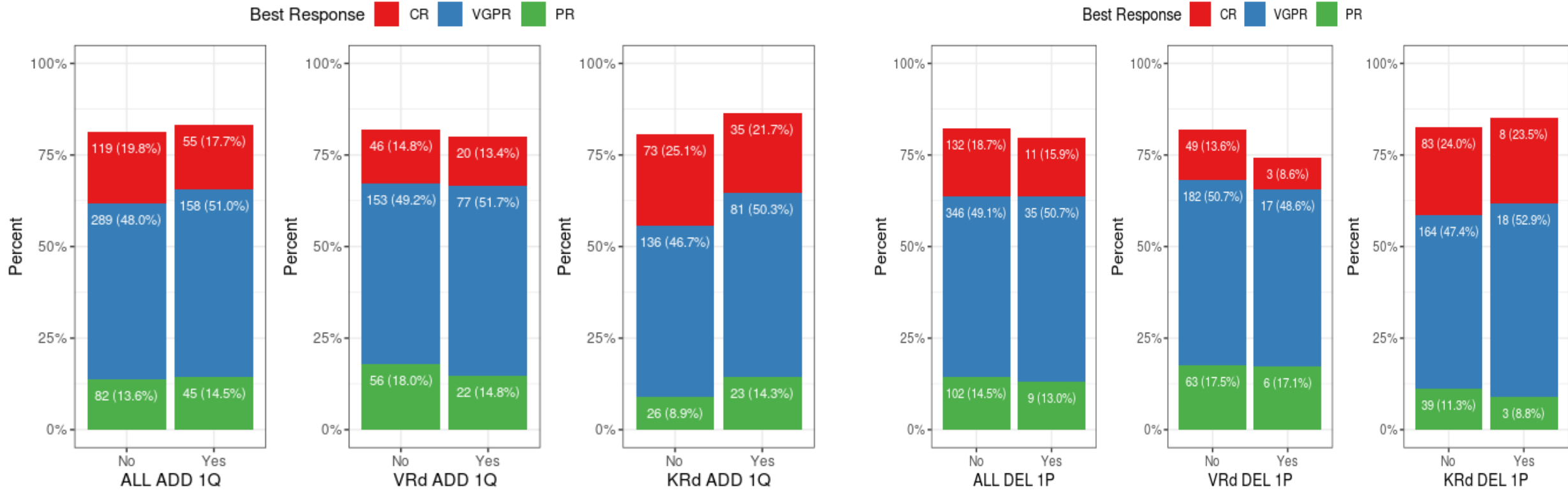
Results

	+1q (310)	No +1q (602)	P Value
VRd	149(48%)	311 (52%)	0.3
KRd	161 (52%)	291 (48%)	
Female	140 (45%)	227 (38%)	0.035
ISS 3	98 (32%)	145 (24%)	0.016
Hb <10 g/dL	111 (36%)	161 (27%)	0.006
Abnormal karyotype	90 (35%)	124 (24%)	0.002
Monosomy 13/Del 13	154 (51%)	131 (29%)	<0.001
t(4;14)	46(15%)	27 (06%)	<0.001
t(11;14)	30 (10%)	107 (24%)	<0.001

	Del1p (69)	No Del 1p (705)	P value
VRd	35 (51%)	359 (51%)	>0.9
KRd	34 (49%)	380 (49%)	
ISS 3	28 (41%)	185 (26%)	0.013
ECOG PS >0	49 (71%)	397 (56%)	0.026
t(11;14)	2 (2.9%)	120 (21%)	<0.001

No differences in treatment arm allocation noted between groups

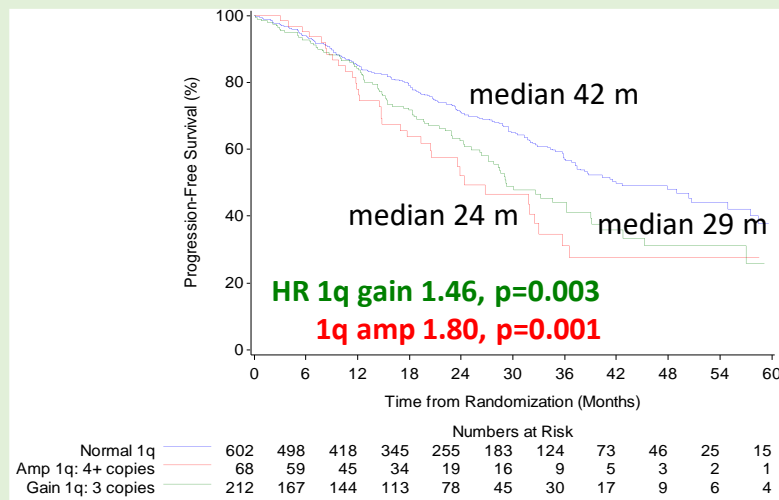
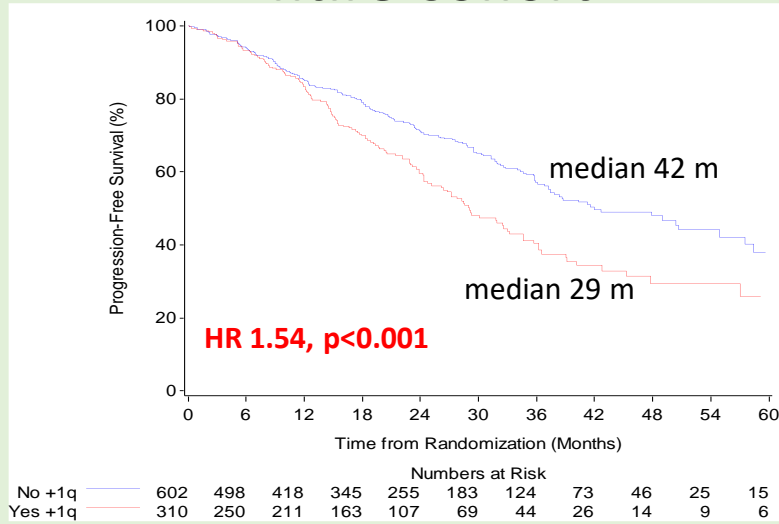
Response



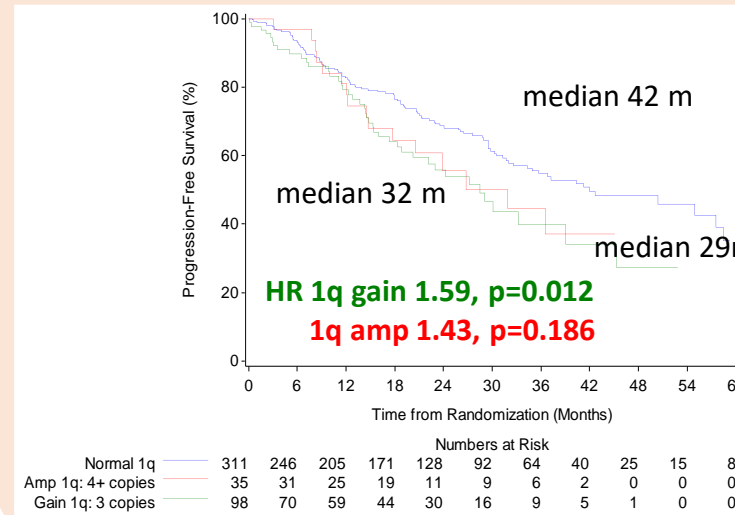
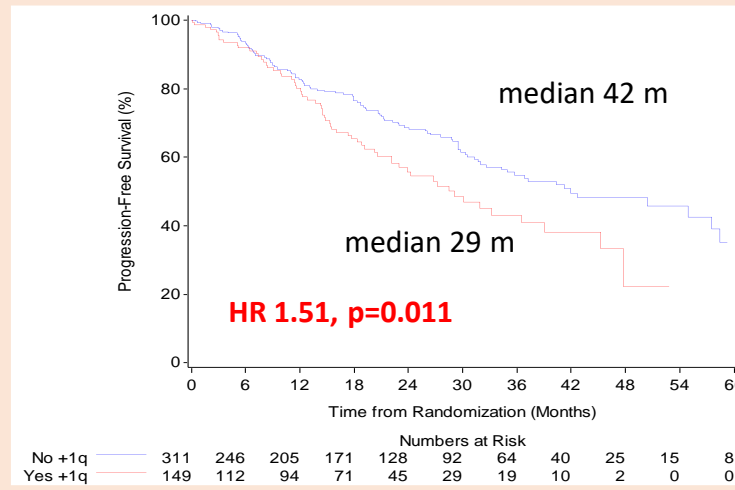
Best response rates to VRd or KRd within each response category, including ORR, \geq VGPR, and \geq CR similar for pts with and without +1q, and with and without del1p.

+1q21 associated with significantly worse PFS

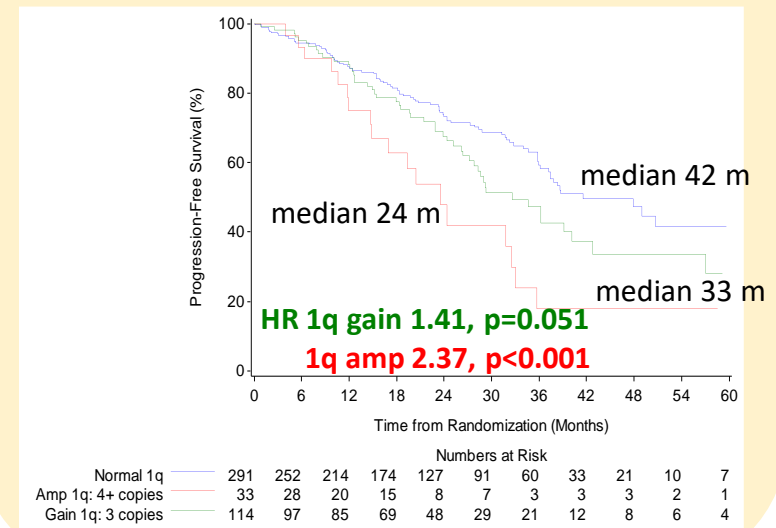
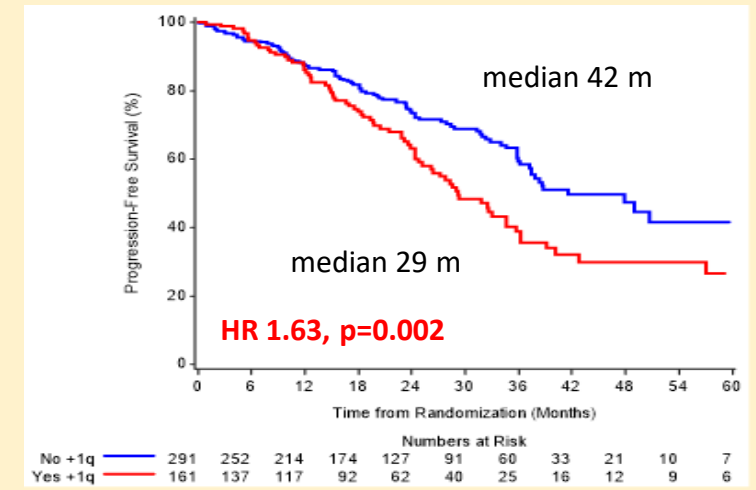
Entire Cohort



VRd

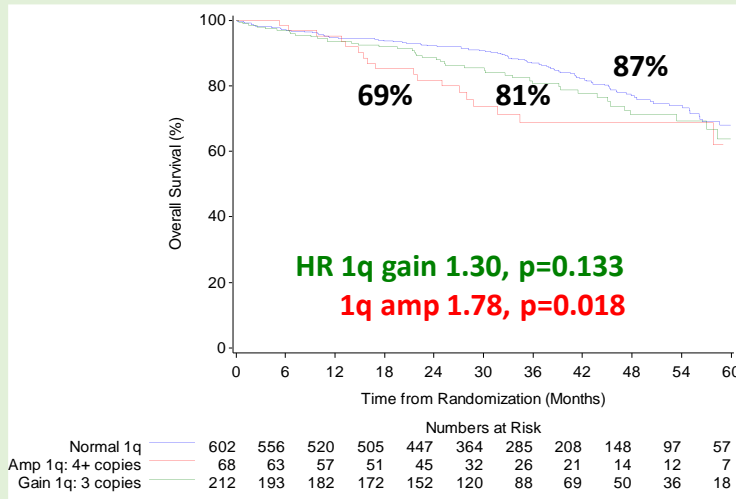
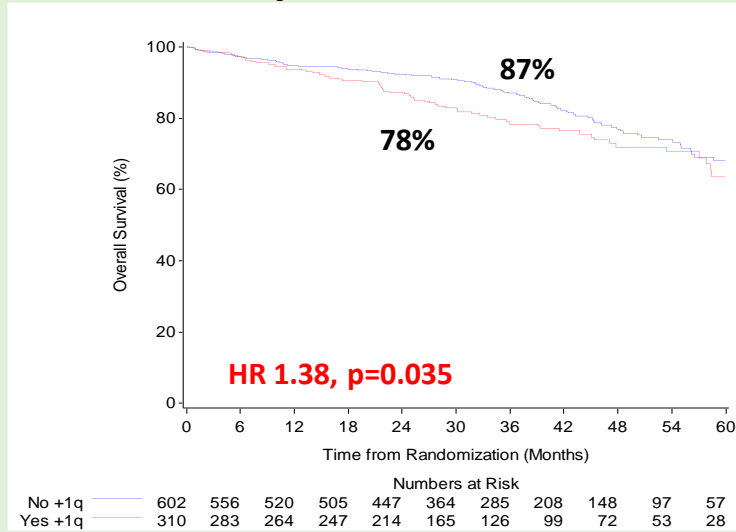


KRd

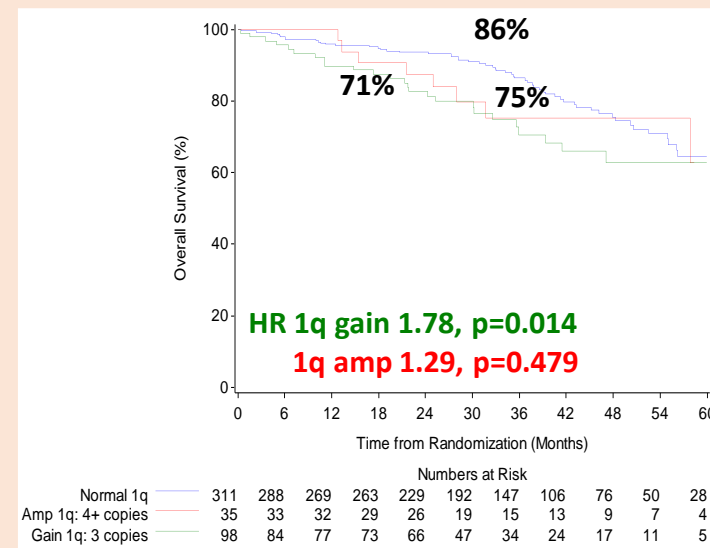
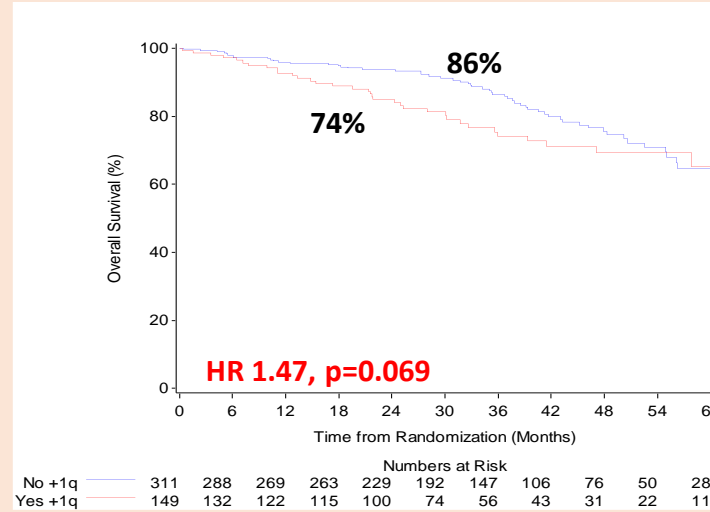


+1q21 Entire Cohort: Worse OS

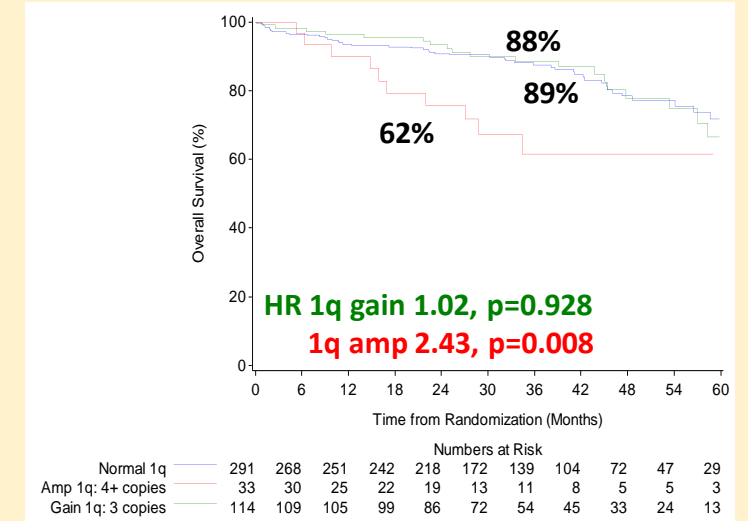
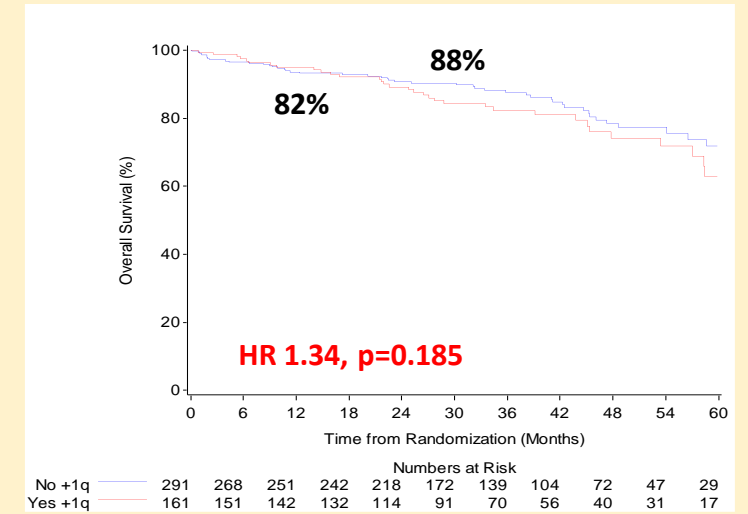
3-yr OS: Entire Cohort



3-yr OS: Arm A VRd

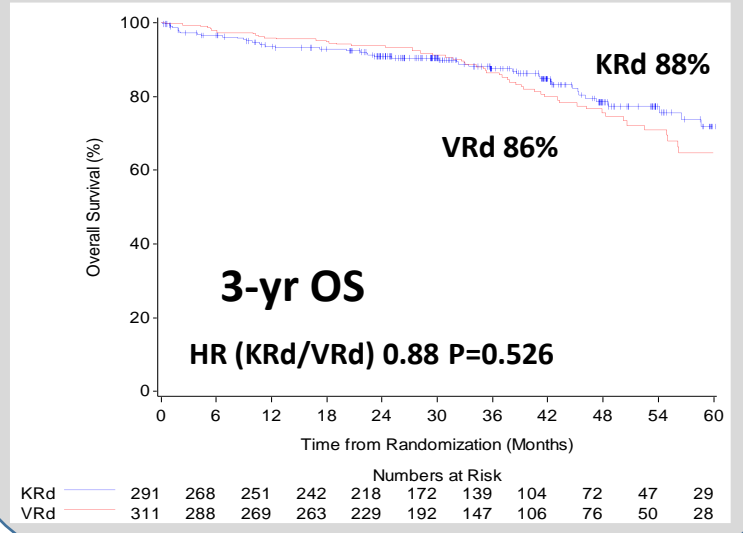
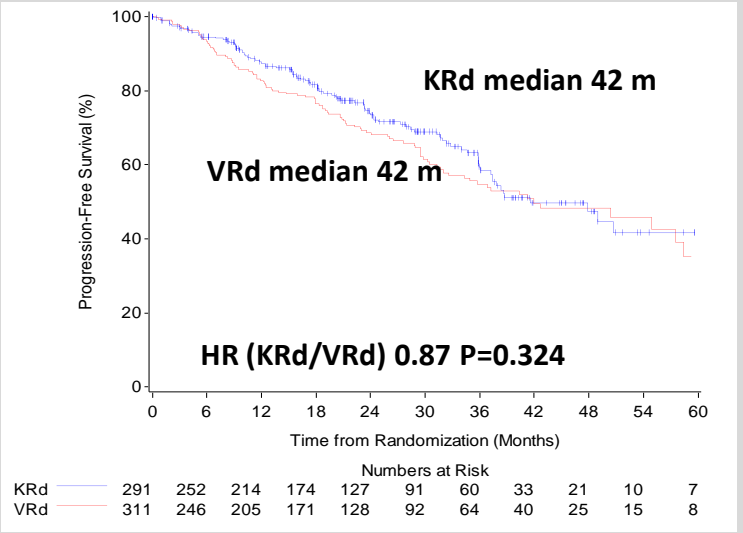


3-yr OS: Arm B KRd

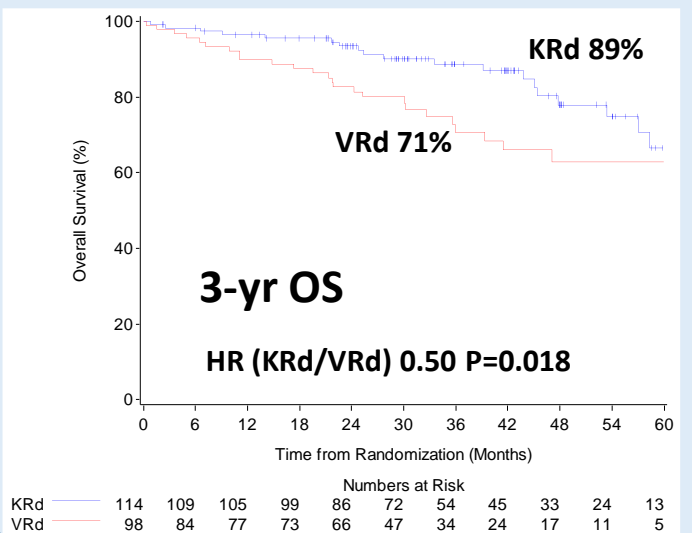
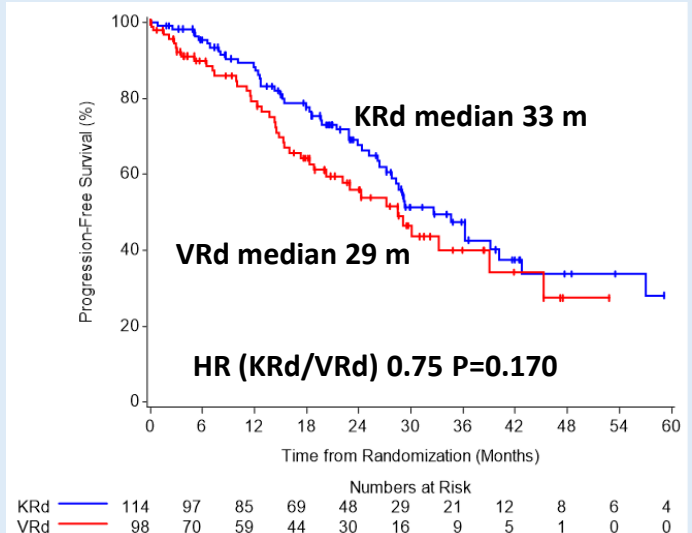


Gain1q and Amp 1q: Outcomes Affected by Treatment Arm

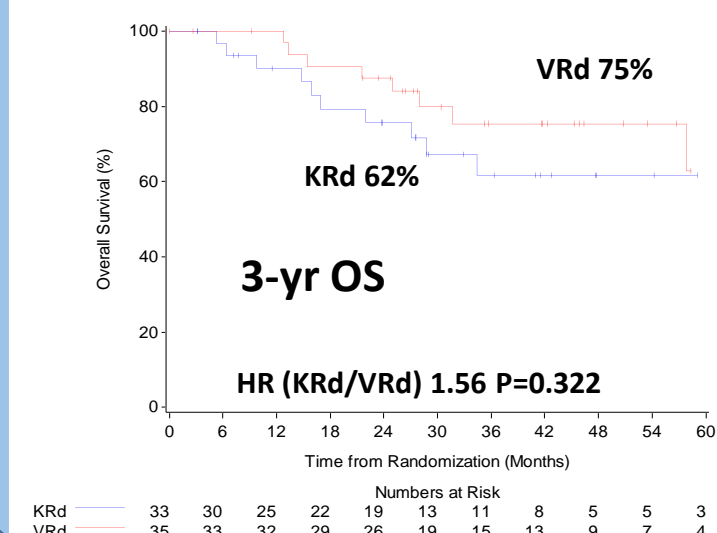
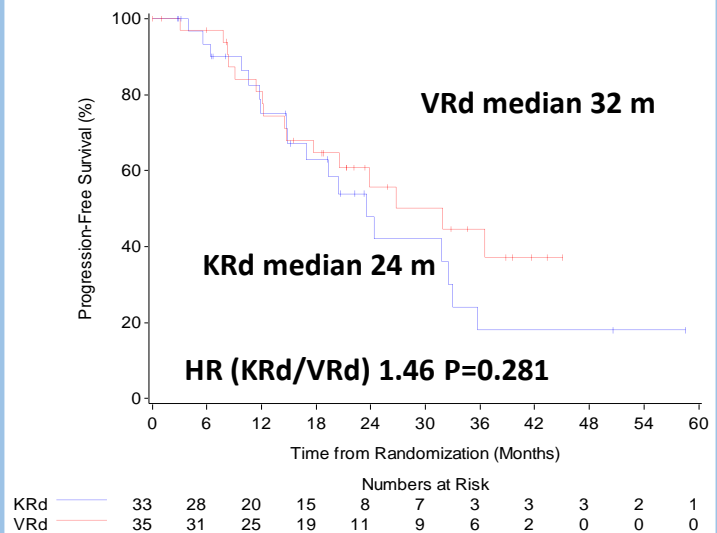
No +1q



Gain 1q



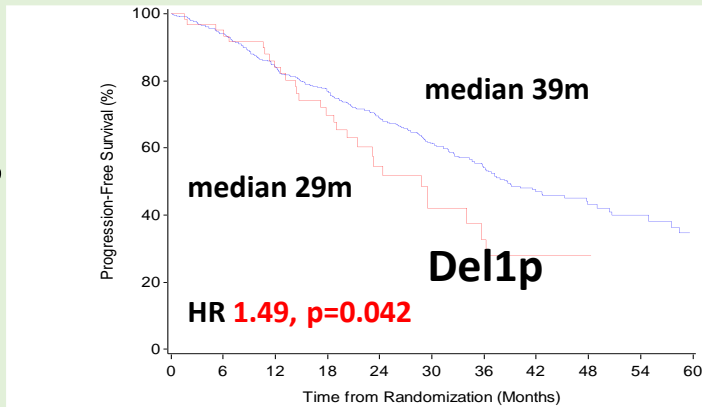
Amp 1q



Deletion 1p is associated with inferior outcomes, except OS with KRd

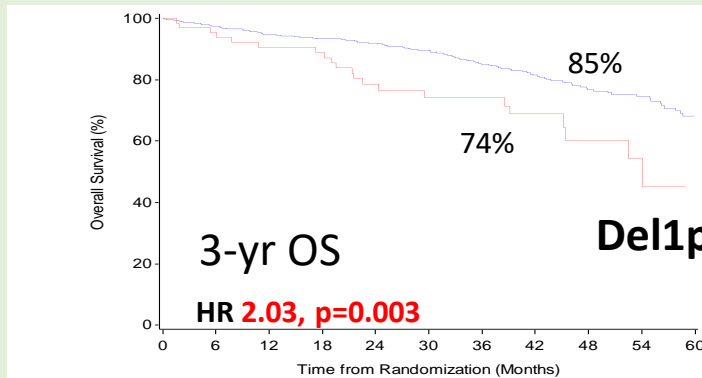
Entire Cohort

PFS



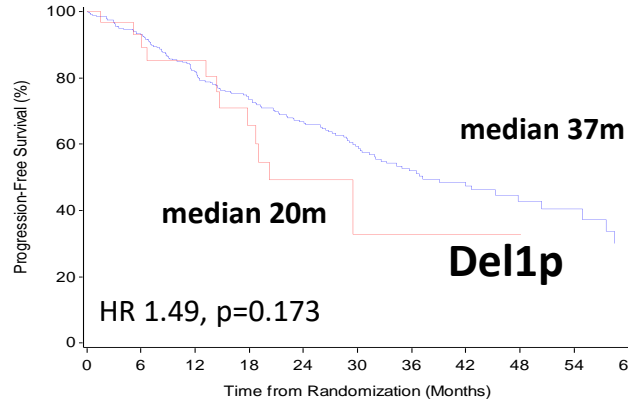
		Numbers at Risk										
		705	580	489	410	294	205	136	81	47	25	16
No -1p		705	580	489	410	294	205	136	81	47	25	16
Yes -1P		69	54	45	32	19	12	7	3	2	0	0

OS

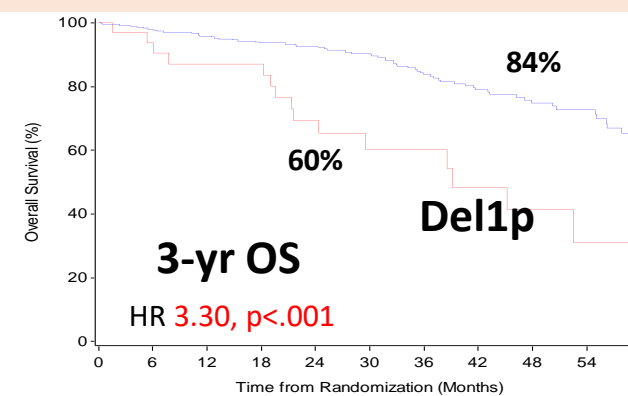


		Numbers at Risk										
		705	647	609	586	516	413	314	237	165	111	62
No -1p		705	647	609	586	516	413	314	237	165	111	62
Yes -1P		69	59	55	53	40	31	28	20	12	6	3

VRd

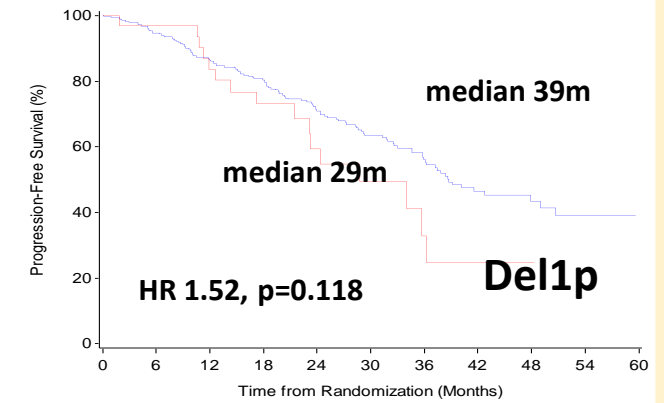


		Numbers at Risk										
		359	283	236	195	145	99	65	40	22	13	8
No -1p		359	283	236	195	145	99	65	40	22	13	8
Yes -1P		35	24	20	12	6	5	3	1	1	0	0

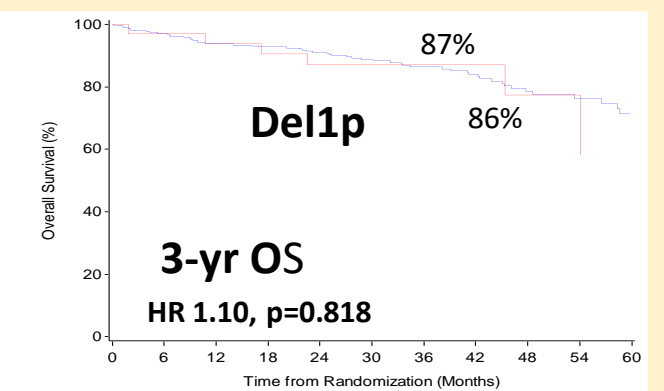


		Numbers at Risk										
		359	326	308	297	261	212	155	113	80	55	31
No -1p		359	326	308	297	261	212	155	113	80	55	31
Yes -1P		35	29	26	25	17	12	10	8	5	2	0

KRd



		Numbers at Risk										
		346	296	253	214	149	106	71	40	25	12	8
No -1p		346	296	253	214	149	106	71	40	25	12	8
Yes -1P		34	30	25	20	13	8	4	2	1	0	0

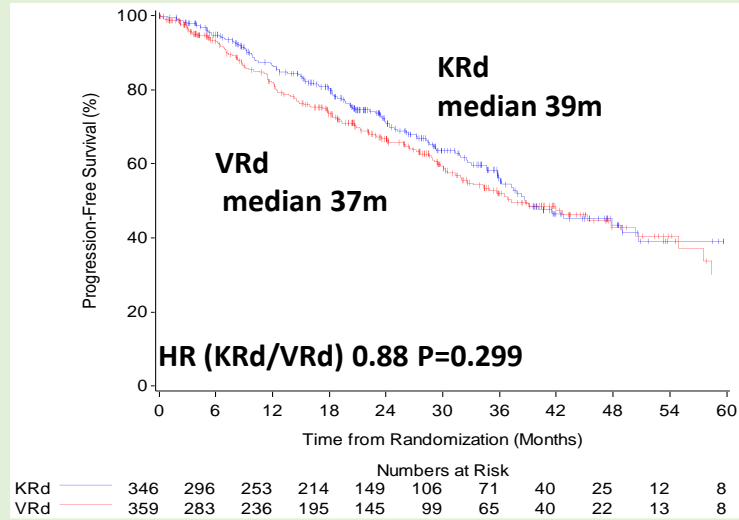


		Numbers at Risk										
		346	321	301	288	255	201	158	123	85	56	31
No -1p		346	321	301	288	255	201	158	123	85	56	31
Yes -1P		34	30	29	28	23	19	18	12	7	4	3

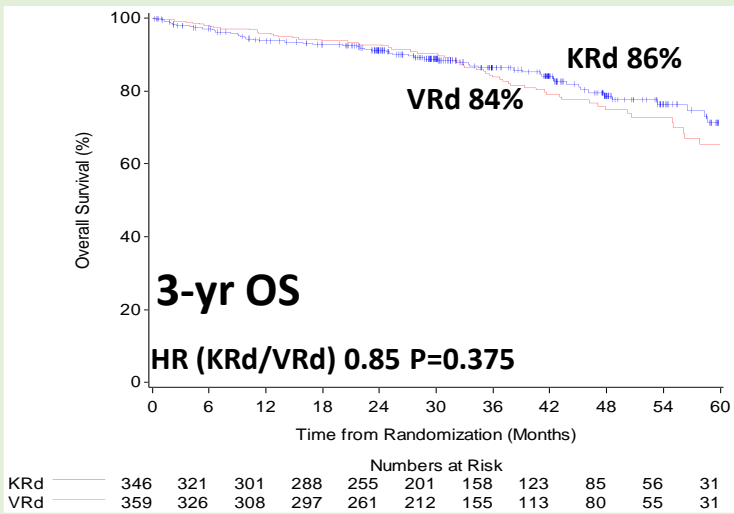
Del 1p Outcomes Affected by Treatment Arm: KRd/VRd

No Deletion 1p

PFS

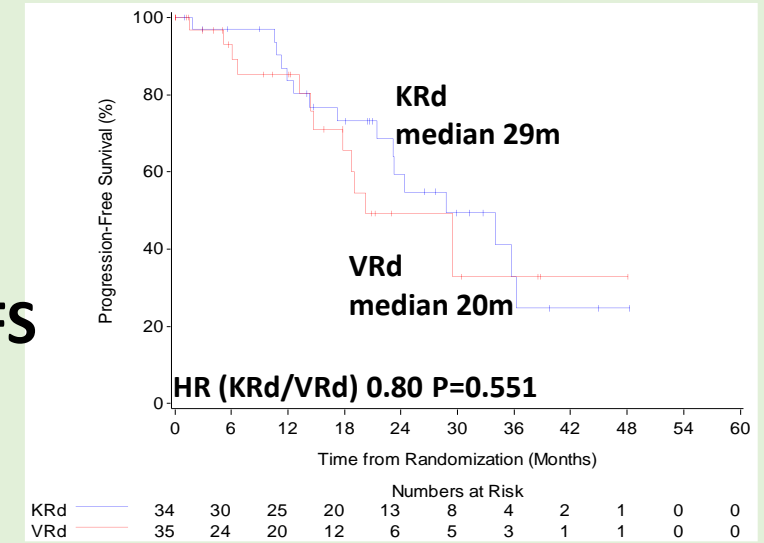


OS

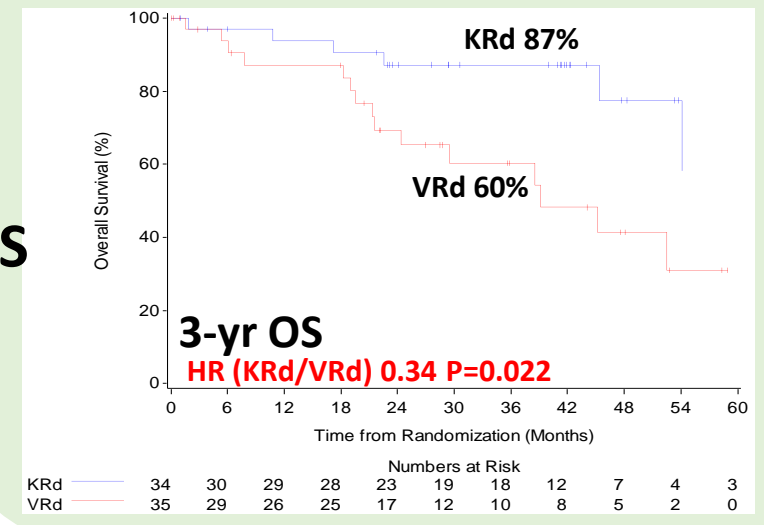


Deletion 1p

PFS

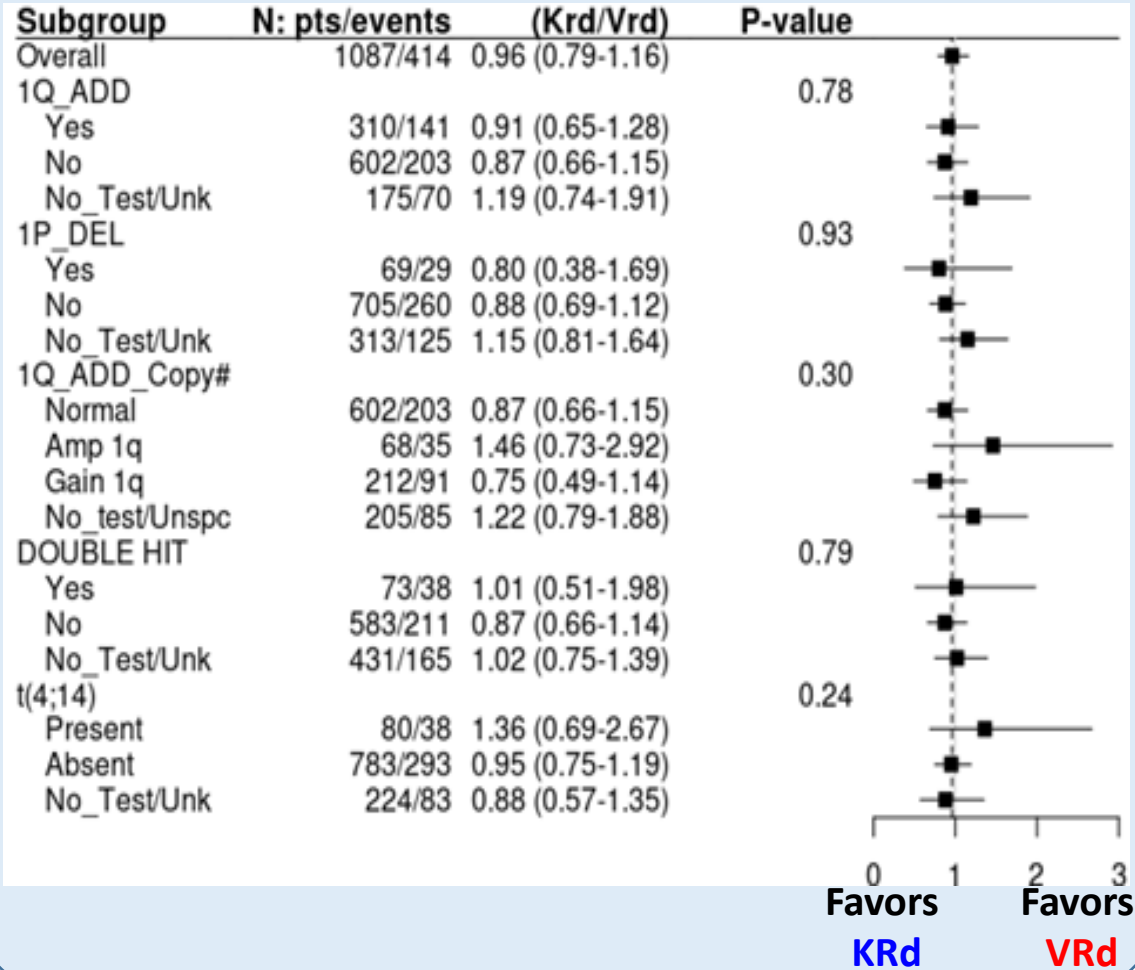


OS

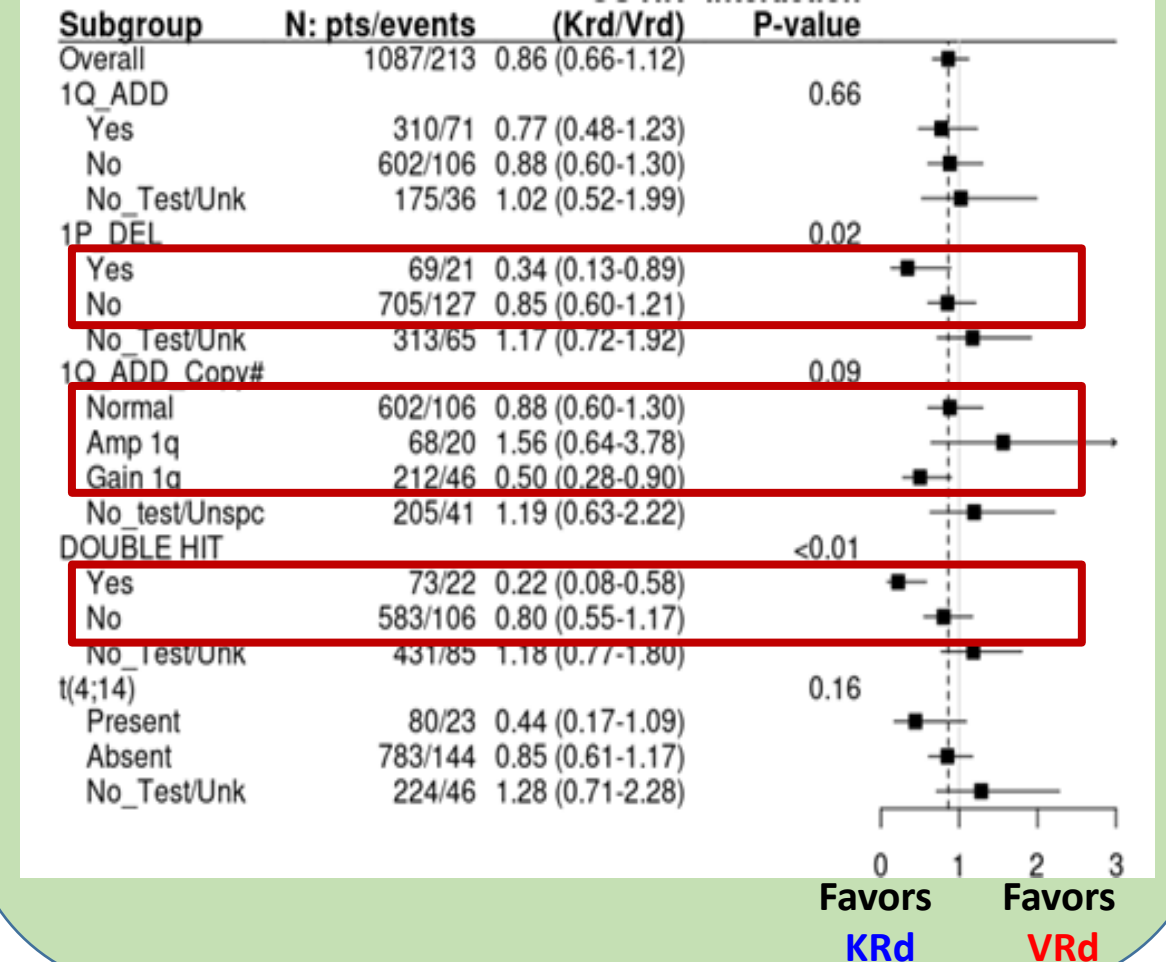


Summary Treatment Hazard Ratios within Subgroups

PFS HR Interaction



OS HR Interaction



Conclusions

Chromosome 1 abnormalities (C1A) observed in ~40% of pts with NDMM.

Shorter PFS with +1q (*vs those without +1q*) and with del1p (*vs those without del1p*). PFS analyses by +1q /del1p status within both treatment arms showed the same trends as overall.

On KRd, OS is similar with gain1q (*vs. those without*) or with *del1p* (*vs. those without*). Pts with amp1q as a sole HR abnormality have distinctly poor outcome with KRd.

With gain1q or del1p, OS superior in KRd vs. VRd arm. Similar observations for a select group of ultra-HR MM, with ≥ 1 HR features involving C1A.

Given limitations of post hoc analyses, small subgroup sample sizes, and lack of data on salvage therapy, confirmatory studies are warranted for definitive conclusions.

Acknowledgments

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- We thank the patients who volunteered to participate in this trial, their families, and the staff members at the trial sites who cared for them.
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- This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health



Back-up Slides

Summary MV Models

+1q

	Overall				VRd				KRd			
	N_event/ N	HR	95%CI	P-value	N_event/ N	HR	95%CI	P-value	N_event/ N	HR	95%CI	P-value
PFS Uni	344/912	1.54	1.24, 1.91	<0.001	173/460	1.51	1.10, 2.06	0.011	171/452	1.63	1.21, 2.20	0.002
PFS MV*	344/912	1.65	1.30, 2.10	<0.001	173/460	1.69	1.19, 2.40	0.004	171/452	1.63	1.16, 2.28	0.004
OS Uni	177/912	1.38	1.02, 1.87	0.035	95/460	1.47	0.97, 2.23	0.069	82/452	1.34	0.87, 2.08	0.185
OS MV*	177/912	1.26	0.90, 1.76	0.181	95/460	1.34	0.85, 2.11	0.213	82/452	1.37	0.82, 2.28	0.231
	Overall				VRd				KRd			
	N_event/ N	HR	95%CI	P-value	N_event/ N	HR	95%CI	P-value	N_event/ N	HR	95%CI	P-value
PFS Uni	289/774	1.49	1.01, 2.19	0.042	148/394	1.49	0.84, 2.64	0.173	141/380	1.52	0.90, 2.56	0.118
PFS MV*	289/774	1.49	1.00, 2.23	0.051	148/394	1.60	0.88, 2.90	0.121	141/380	1.45	0.82, 2.56	0.201
OS Uni	148/774	2.03	1.28, 3.22	0.003	84/394	3.30	1.88, 5.81	<0.001	64/380	1.10	0.48, 2.56	0.818
OS MV*	148/774	1.70	1.05, 2.76	0.032	84/394	2.93	1.62, 5.29	<0.001	64/380	0.73	0.28, 1.88	0.516

Del1p

MV model for +1q includes all variables with p<0.1 in the baseline association table: Gender, Race, ISS Stage III, Risk CRP, Risk BM Plasma Cells, Risk Hemoglobin, Cytogenetics, Monosomy 13_Del 13q, t(11_14), t(4_14) and for del(1p)