Outcome at first relapse after frontline RVD regimen plus lenalidomide maintenance in transplant eligible MM patients

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Abstract

Background: The IFM 2009 trial recruited 700 MM pts between 2010-2012. Pts were randomly assigned to received RVD (5-8 cycles) and 1-yr Len maintenance +/- upfront ASCT. More than 250 pts relapsed. We aimed to analyze response rates (RR) and survival outcomes after salvage therapy. **Methods:** Pts who relapsed during RVD cycles or first 2 months of maintenance (group 1) were considered Relapsed and Double Refractory and were likely to receive CVAD or DCEP regimen. Pts who relapsed during or early after maintenance (Group 2) were considered Relapsed and Len Refractory and were likely to receive VCD, CPAD or pomalidomide based regimen (PCD). Pts who relapsed during FU (Group 3) were standard Relapsed. Eligible pts could receive SCT (auto and/or allo). **Results:** 83 pts were retrospectively analyzed. Median age was 56 years (28-65), ISS 2/3=37/22. 27 pts had High Risk (HR) cytogenetics. Group 1 comprised 15 pts (10 relapsed during RVD induction/consolidation). Eight pts received CVAD, 3 DCEP and 1 PD. Three pts died before any tx. Group 2 comprised 40 pts; 14 received VCD, 8 CPAD, 4 DCEP and 11 PCD. Group 3 comprised 28 pts; 12 received VCD, 3 CPAD and 11 PCD. RR and survival outcomes are listed in table 1. ORR was 40, 67.5 and 75% in groups 1,2,3, respectively. 46 pts proceeded to SCT (allo, n = 5). Median FU is 42 months from initial therapy: 64% pts relapsed again and 29% died. Median PFS2 is 11 months and 3-year OS 74%. Pts from group 1 had the poorest prognosis with 60% death, median OS 11.7 months. Median PFS2 was 3.5 months. **Conclusions:** Relapsed pts within 1 year after RVD induction/consolidation have impaired prognosis after salvage therapy.

Updated data are presented here with data cut-off May 1st.

Materials & Methods

The IFM/DFCI 2009 trial recruited in France 700 de novo MM patients (pts) between 11/2010 and 11/2012. Patients were randomly assigned to received lenalidomide, bortezomib , and dexamethasone = RVD (5 to 8 cycles) followed by 1-year lenalidomide (Len) maintenance with or without upfront ASCT.

To date, more than 300 pts relapsed. As the outcome at first relapse after frontline RVD and len maintenance could be a matter of concern, we aimed to analyze response rates and survival outcomes after salvage therapy in relapsing patients. IFM/DFCI 2009 trial is ongoing and the second intermediate analysis has not been yet performed, we therefore DID NOT use extracted data.

We retrospectively studied relapsed patients issued from 10 IFM centers. Relapsed patients not requiring therapy or with a follow-up less than 6 months after relapse were not included into that analysis. Patients were recruited until Q4 2014

There was no mandatory salvage therapy within the trial but recommendations of the PI were as followed:
•Patients who relapsed during RVD induction/consolidation or during the first 2 cycles of maintenance (**group 1**) were considered **Relapsed and Double Refractory patients** and were likely to receive C-VAD or DCEP based regimen.
•Patients who relapsed during maintenance or within the first 2 months of follow-up (**group 2**) were considered **Relapsed and Len Refractory patients** and were likely to receive CyborD or equivalent, C-PAD or pomalidomide based regimen (PD or PCD).
•Patients who relapsed during follow-up (**group 3**) were standard **Relapsed patients** and were likely to receive CyborD or equivalent, C-PAD or pomalidomide based regimen (PCD).
Non-progressive eligible patients could receive ASCT and/or allogeneic SCT at time of relapse.

Patients: 116 patients relapsed before end of 2014, 27 did not need salvage therapy yet or had a too short Follow-up
89 patients were included into that retrospective analysis. Median age was **55 years** (28-65), ISS 1/2/3 in 25/40/24 patients, respectively (**ISS2/3 =72%**).
Overall, 27 (**35%**) on 78 evaluable patients were classified as **High Risk (HR) cytogenetics** with t(4;14), del 17p or HR molecular caryotype.

Group 1 comprised 16 patients: 11 relapsed during RVD induction/consolidation and 5 during early lenalidomide maintenance.
Group 2 comprised 40 patients: 13 relapsed within 6 months of Len maintenance.
Group 3 comprised 33 patients.

Characteristics of patients according to groups are summarized in table 1;

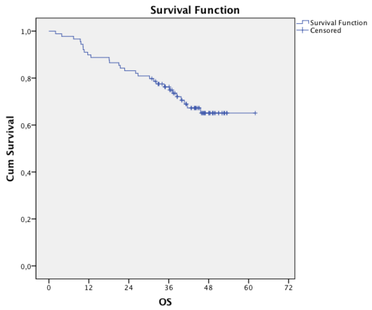
Table 1	Group 1 Double Refractory	Group 2 Len Refractory	Group 3 standard Relapse
n	16	40	33
median age	51 (37-64)	56 (28-65)	59 (44-65)
HR cytogenetics	3/13=23%	14/37=38%	10/28 =36%
ISS at dg 1/2/3 (n)	6/4/6	9/21/10	10/15/8
Isotype	G 9/ A 4/ D 1/ FLC 2	G 22/ A 11/ D 1/ FLC 6	G 18/ A 11/ FLC 4
BRA to frontline	CR2/ VGPR2/ PR5	CR10/ VGPR 14/ PR 12	CR 15/ VGPR 12/ PR 6
time to relapse	VRD 11/ Len M 5	Len M <6 13/ Len M >6 11/FU 7	FU
median PFS 1	6.7 mos	15.2 mos	30.0 mos

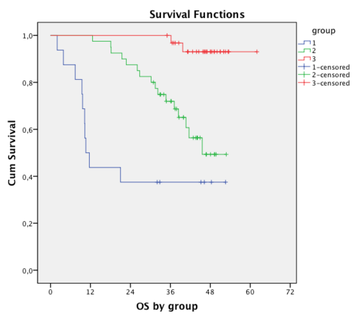
Results

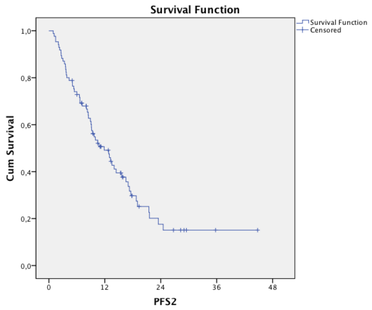
Responses rates and survival outcomes according to relapsing categories are summarized in table 2. ORR was 65% in the whole cohort with 50% in group 1, 67.5% in group 2 and 75% in group 3. 47 non-progressive patients proceeded to ASCT and/or allogeneic SCT (n=5).

With a median follow-up of 46 months from initial therapy and 19 months from start of salvage therapy, 58 (68%) pts relapsed and 28 (31.5%) died during or after salvage therapy. Estimated 4-year OS is 65% and 3-year OS is 76%. As expected, pts from group 1 had the poorest prognosis with 62.5% death and a median OS at 10.6 mos.

Median Second PFS was 11.9 months for the whole cohort. Estimated 1-year and 2-year PFS2 was 49% and 18%, respectively.







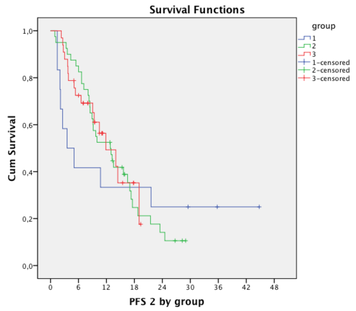
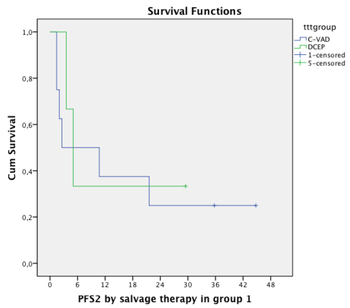
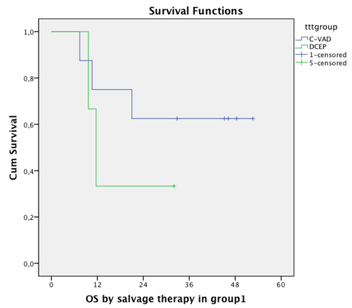


Table 2	n	Salvage Therapy	HR cytogenetics (n)	Median PFS 1	SCT (done)	BRA to salvage	Relapse 2	Median PFS 2	Death	3-y OS	Median OS
Group 1 Double Refractory	**16**	**all**	**3/13**	**6.7 mos**	**8 (57%)**	**CR2/VGPR1/PR3**	**9/12 (60%)**	**3.5 mos**	**10 (62.5%)**	**37.5%**	**10.6 mos**
	8	C-VAD	1	7.2	6 (75%)	CR 1/PR 3	6 (75%)	2.6	3 (37.5%)	62,5%	NR*ALLO
	3	DCEP	1	3.0	2 (67%)	CR 1/VGPR 1	2 (67%)	5.0	2 (67%)	-	11.7
Group 2 Len Refractory	**40**	**all**	**14/37**	**15.2 mos**	**25 (62.5%)**	**CR 10/VGPR 9/ PR 8**	**32 (80%)**	**12.8 mos**	**16 (40%)**	**72%**	**45.6 mos**
	14	CyBord	4	13	9 (64%)	CR 3/VGPR 3/PR 2	12 (86%)	15.6	7 (50%)	78.5%	45.6
	8	C-PAD	3	16	7 (87.5%)	CR 3/VGPR 3/PR 2	5 (62.5%)	13.5	1 (12.5%)	87.5%	NR
	4	DCEP	0	9.7	3 (75%)	CR 2/PR 1	3 (75%)	8.3	2 (50%)	50%	26.0
	11	PCD	6	19	4 (36%)	CR 1/VGPR 3/PR 3	9 (82%)	9.1	4 (36%)	72%	NR
Group 3 Relapsed	**33**	**all**	**10/28**	**30.1 mos**	**17 (51.5%)**	**CR 6/VGPR 8/PR 8**	**17 (51.5%)**	**11.9 mos**	**2 (6%)**	**100%**	**NR**
	13	CyBord	5	26.0	7 (54%)	CR 2/VGPR 3/PR 3	8 (61.5%)	9.4	2 (15%)	100%	NR
	4	C-PAD	1	25.0	3 (75%)	CR 2	3 (75%)	10.5	0	100%	NR
	13	PCD	3	30.9	7 (54%)	CR 2/VGPR 4/PR 4	4 (31%)	14	0	100%	NR

Group 1: double refractory

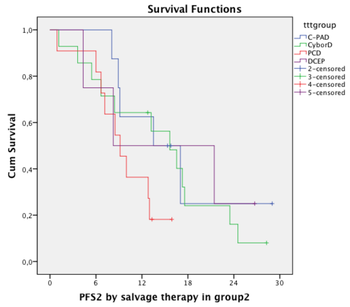
8 patients received C-VAD, 3 DCEP and 1 pomalidomide treatment at time of relapse. 4 patients died before any treatment.
Median PFS 2 was 3.5 mos. 9 patients relapsed and 10 patients died. Median OS was 10.6 mos.

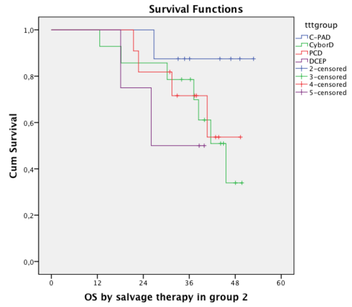




Group 2: Len refractory

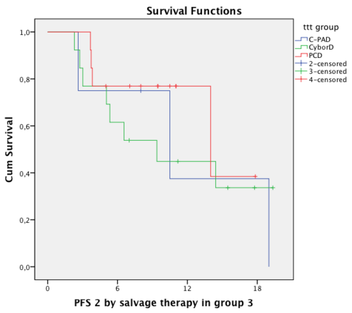
14 patients received CyborD, 8 C-PAD, 4 DCEP and 11 PD/PCD regimen at time of relapse. Median PFS 2 was 12.8 mos. 16 patients died.
Median OS was 45.6 mos. Bortezomib-based regimen may be the salvage therapy of choice for these patients.

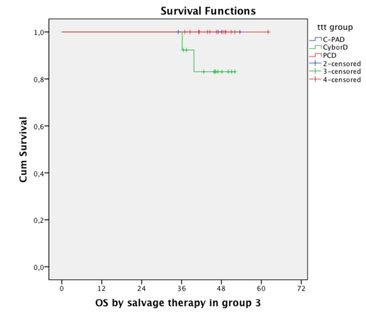




Group 3: standard relapse

13 patients received CyborD, 4 C-PAD and 13 PCD at time of relapse. Median PFS 2 was 11.9 mos. Only 2 patients died. Median OS was not reached. Pomalidomide could be the drug of choice for these patients.





Conclusions

Salvage therapy after frontline RVD regimen +/_ ASCT followed by len maintenance is difficult with short second response duration even in patients with standard relapse.
Early Relapse on frontline RVD regimen confers HR features with poor response duration and a median OS less than 1 year. There is an unmet need for these double refractory patients.
Relapse after frontline RVD regimen, during lenalidomide maintenance or early follow-up impairs response duration, mainly in standard relapsed patients.
Bortezomib-based regimen should be of value for len refractory patients, even compared to pomalidomide.
Conversely, pomalidomide could be the salvage therapy for non refractory patients.

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