

# The Importance of Complete Response in Outcomes in Myeloma

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**Abstract:** Outcomes for patients with multiple myeloma have dramatically improved during the past 20 years as a result of improved therapeutic options and a better understanding of malignant plasma cell biology. Until the past 10 years, the major limitations on improving outcomes were related to the minimal efficacy of existing agents and balancing the toxicity of therapy in an older patient population. However, despite these limitations, there have been advances that have resulted in improvements in progression-free survival and overall survival (OS). High-dose therapy and autologous transplant were the first among therapies to demonstrate an improvement in OS; but more recent analyses have demonstrated that there can be improvement in OS, which is also associated with improvement in the complete response (CR) rate, even among nontransplant patients as well. Thus, achieving CR has been associated with improved OS and has become a therapeutic goal. In the current era of new agents, such as thalidomide, bortezomib, and lenalidomide, the fraction of patients who achieve a CR is now greater than before, and the data regarding the importance of achieving this benchmark of response have never been more benefit.

**Key Words:** myeloma, complete response

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It is clear that perhaps not all patients who achieve complete response (CR) are the same, just as not all patients with myeloma are the same with regard to disease biology and host factors that may influence the clinical benefit of any given therapy. It is also clear that CR, as currently defined, does not represent eradication of all malignant plasma cells, and thus for most patients does not represent cure. Finally, in this era of “cure versus control” where does achievement of CR fall as a therapeutic goal and can it be a uniform approach that is suitable for all patients, or only applied to selected subsets of patients? To better address the issues surrounding this controversial endpoint, it is important that we first review how CR has been measured, in which contexts it has been shown to be relevant, and where future approaches in therapy may lead with regards to targeting the optimal endpoints for patients.

## DEFINITION OF CR

The Chronic Leukemia and Myeloma Task Force first defined objective response as at least a 50% reduction in the serum paraprotein.<sup>1</sup> Southwest Oncology Group (SWOG) subsequently redefined objective response as either a 75% reduction of the serum paraprotein and to a value  $\leq 2.5$  g/100 mL or 90% reduction of Bence-Jones protein excretion and to a value  $\leq 200$  mg/d or both.<sup>2</sup> Neither the Chronic Leukemia and Myeloma Task Force nor the

SWOG response criteria included a definition of CR as few therapies achieved this endpoint. The next response criteria came from the European Group for Blood and Marrow Transplantation (EBMT) where CR was defined as absence of M-protein by immunofixation (IFX) and  $<5\%$  plasma cells in bone marrow.<sup>3</sup> The definition of CR including IFX negativity is more sensitive than routine electrophoresis but also has its reliability issues. Patients in CR by electrophoresis as well as IFX had an overall 5-year survival rate of 72%, which was significantly different from 48% for the patients who achieved IFX-positive CR.<sup>4</sup> Subsequently, a new endpoint was defined for patients with no detectable protein by electrophoresis, but IFX positive was defined as a “near CR” (nCR).<sup>3</sup> However, because of the variability in IFX as a qualitative test, its reproducibility has often been limited.<sup>5</sup> Subsequently, the IFM identified the category of very good partial response (VGPR) that represents a 90% or greater reduction in the serum M-protein level along with urine paraprotein of  $<100$  mg/24 h. The VGPR criterion does not depend on the vagaries of IFX interpretation, and data from the Francophone Myeloma Inter-group (IFM) suggest that achieving a VGPR results in similar progression-free survival (PFS) and overall survival (OS) to CR.

Most recently, the uniform response criteria was described by the International Myeloma Working Group (IMWG), resulting in proposal of the new response category “stringent CR” (sCR), which requires normalization of the free light-chain ratio and the absence of clonality by immunohistochemistry or IFX.<sup>6,7</sup> nCR and VGPR are considered as a single entity in the revised IMWG uniform criteria.

In all likelihood, the present definition of CR represents a threshold to the limits of current detection. Use of techniques such as quantitative polymerase chain reaction (qPCR) and multiplex flow cytometry (MFC) to detect minimal residual disease (MRD) below the limits of current detection is necessary if we seek to eradicate evidence of all disease. Molecular CR can be attained in higher proportion of patients who have achieved CR after undergoing allogeneic transplant ( $\approx 50\%$ )<sup>8,9</sup> compared with a smaller fraction of patients after autologous transplant ( $<10\%$ ). However, allogeneic transplants are associated with high risk of early mortality and morbidity; and patients continue to relapse at 4, 5, and 6 years after transplant. The use of bortezomib, thalidomide, and dexamethasone (VTD) consolidation after autologous transplant has been shown to induce molecular remission in a higher proportion of patients with myeloma.<sup>10</sup> Among a group of 40 patients who received autologous transplantation, 94% were noted to have a PCR-positive bone marrow posttransplant. After treatment with 4 cycles of VTD, 36% of patients converted from VGPR to CR and 12% from nCR to CR. Overall, 22% of the patients transformed from PCR positivity to PCR negativity, suggesting that combinations of newer agents may be able to induce molecular responses, whereas conventional agents failed to achieve similar responses. Seven relapses occurred on the updated analysis, all in PCR-positive patients. Another prospective analysis demonstrating the benefit of achieving lower levels of MRD detection by MFC at day 100 after autologous transplant was reported by Paiva et al.<sup>11</sup> Persistent plasma cells were detected by MFC in 170 of 295 (58%) patients after autologous transplant. Median PFS (71 vs. 37 months;  $P <$

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0.001) and OS (median not reached vs. 89 months;  $P < 0.002$ ) were significantly longer in patients who were MRD negative versus MRD positive, using MFC as a measure of CR. With the development of standardized flow cytometric approaches and a defined specificity and sensitivity, MFC could be a potential method for monitoring and establishing even lower levels of MRD and thus better predictive value of long-term remission.<sup>12</sup>

### CR AND OUTCOMES AMONG NONTRANSPLANT CANDIDATES

Although much has been made of the improvement in OS among younger patients with myeloma, there has been little tangible evidence that these improvements in OS have translated to older patients.<sup>13</sup> In the Eastern Cooperative Oncology Group (ECOG) trial E9486, 653 patients were randomized to 1 of the 3 treatment arms—vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (VBMCP); VBMCP and recombinant interferon alfa-2 ( $INF\alpha$ -2); or VBMCP and high-dose cyclophosphamide. Objective response was achieved in 420 of the 628 (67%) eligible patients, and 85 of the 628 (14%) achieved a CR. Among them, the patients who achieved a CR had a 61 months median OS when compared with patients with less than CR with 44 months median survival ( $P < 0.0001$ ). This study is an important landmark, because it helps to establish that CR is critical even when transplant is not the primary therapeutic modality.<sup>14</sup> Five randomized studies have assessed the combination of melphalan and prednisone (MP) plus thalidomide in patients with newly diagnosed multiple myeloma. The CR + VGPR rate was significantly higher in all the studies with addition of thalidomide yet only two of the studies demonstrated an improvement in OS.<sup>15</sup> The reason for this discrepancy may be methodology related (different more toxic doses of thalidomide in some studies), but may also relate to the fact that the CR difference with the addition of thalidomide is not high enough to consistently demonstrate a survival benefit.

In the absence of alkylation-based therapies, few studies have compared MP-based combinations with non-MP-based treatments among older nontransplant patients. A comparison of thalidomide and dexamethasone (TD) versus dexamethasone demonstrated a significant improvement in overall response rate (ORR) using TD, which did translate into improved time to progression (TTP) and PFS<sup>16</sup>; but when TD was compared with MP in elderly patients,<sup>17</sup> while the ORR favored TD, PFS was the same and OS favored the use of MP (41.5 vs. 49.4 months). In the E4A03 trial comparing lenalidomide with low-dose dexamethasone (Rd) versus lenalidomide with high-dose dexamethasone (RD) in newly diagnosed patients, 2-year OS rates clearly favored the Rd arm, a difference most marked among older patients. The 1- and 2-year OS rates for the Rd arm does compare favorably with other trials for nontransplant eligible patients and thus should be considered a reasonable treatment option for these patients. Notably, the VGPR and CR rates for the Rd arm improved with longer duration of therapy but were still inferior to the RD arm.<sup>18</sup>

In the VISTA trial comparing bortezomib, melphalan, and prednisone (VMP) versus MP,<sup>19</sup> CR rates were 30% versus 4% by EBMT criteria, and 33% versus 4% CR and 8% versus 4% VGPR, by IMWG criteria. CR by EBMT criteria was associated with significantly longer TTP, time to next therapy, treatment-free interval, and OS versus PR further supporting the benefit of CR in a nontransplant setting. The median duration of response among patients with CR was 24 versus 12.8 months without CR suggesting that patients who achieve CR stay in remission longer, despite the CR penalty that was present in the older response criteria.<sup>5</sup>

In the nontransplant population, achieving a CR in elderly patients is associated with improved outcomes and this benefit is more evident with the introduction of newer agents. However, in the

TABLE 1. Survival and Response Rates With HDT vs. CT

Study (N)	Median Follow-Up (mo)	CT					HDT						
		Regimen	CR (%)	VGPR (%)	PR (%)	mEFS (mo)	mOS (mo)	CT + Regimen	CR (%)	VGPR (%)	PR (%)	mEFS (mo)	mOS (mo)
Ahtal et al <sup>20</sup> IFM-90 1996 (200)	84	Alt VMCP and BVAP	5	9	43	18	44	MEL140, TBI, IFN- $\alpha$	22	16	43	27	56
Child et al <sup>21</sup> MRC VII 2003 (407)	42	BCAM	8	81	19.6	42.3	MEL140	44		42	31.6	54.1	
Fernand et al <sup>44</sup> GMA 2005 (190)	10	VMCP	4.1	15.6	38.5	18.7	MEL140 vs. MEL200 vs. MEL140 + Bu16	8.4	39.4	26	25.3	47.8	
Barolgie et al <sup>22</sup> S9321 2006 (516)	76	VBMCP	15	NR	NR	14	38	MEL140 + TBI	17	NR	NR	17	38
Blade et al <sup>45</sup> PETHEMA(164)	44	VBMCP and VBAD	11	NR	NR	33	61	MEL200 vs. MEL140 + TBI	30	NR	NR	42	66
Palumbo et al <sup>46</sup> (142)	39	MP	5	44	17.7	48	MEL100	47	41	41	34	56+	
Lenhoff et al <sup>47</sup> (548)	32	VAD	NR	NR	NR	44	44	MEL200	41	48	32	NRe	
Barolgie et al <sup>48</sup> (232)	31	VMCP/VBAP	NR	52	22	48	VAD, Cy EDAP, MEL200	25	85	85	49	62+	

VMCP indicates vincristine, melphalan, cyclophosphamide, and prednisone; BVAP, BCNU, vincristine, doxorubicin, and prednisone; BCNU, melphalan, cyclophosphamide, and prednisone; VBAD, vincristine, BCNU, doxorubicin, dexamethasone; BCAM, BCNU, cyclophosphamide, doxorubicin and melphalan; EDAP, etoposide, dexamethasone, cytarabine, cisplatin; HDT, high-dose chemotherapy; TBI, total body irradiation; mEFS, median event-free survival; mOS, median overall survival; MEL100, melphalan 100 mg/m<sup>2</sup>; MEL140, melphalan 140 mg/m<sup>2</sup>; MEL200, Melphalan 200 mg/m<sup>2</sup>; MEL140 + Bu16, Melphalan 140 mg/m<sup>2</sup> + Busulfan 16 mg/m<sup>2</sup>; Cy, high-dose cyclophosphamide; IFN- $\alpha$ , interferon- $\alpha$ ; NRe, not reached; and NR, not reported.

older patient population, additional attention must be paid to toxicities. The ECOG trial suggests that not just rapid responses, but longer duration of therapy may be equally important in the older population and should be balanced with the drive to CR. Additional studies are clearly needed, but it is clear that we should not abandon aggressive therapy in suitable patients, because clearly, there can be improvements in OS associated with achieving CR even in the older patient population.

**CR AND OUTCOMES AMONG TRANSPLANT CANDIDATES**

Three prospective randomized trials comparing conventional chemotherapy and high-dose therapy (HDT) provided evidence that achieving CR correlates with improved EFS and OS (Table 1). The IFM-90 study demonstrated CR rate of 22% versus 5% and OS benefit of 12 months with HDT.<sup>20</sup> When the results of a second study Medical Research Council VII<sup>21</sup> were combined with the others, the estimated treatment effect was consistent with a significant survival benefit with HDT compared with conventional therapy (OR 0.70; 95% CI 0.53–0.93; *P* = 0.01). In addition, it conferred an increase in median survival of approximately 1 year among patients in the HDT group. Although the US Intergroup Trial S9321<sup>22</sup> did not demonstrate a survival benefit for HDT, the conditioning was found

to be toxic and the length of the time to enroll this trial was so prolonged that its results cannot be easily generalized.

Several meta-analysis reviewed the association between CR, PFS, and OS after HDT/autologous stem-cell transplantation (ASCT) in newly diagnosed<sup>23</sup> as well as relapsed patients.<sup>24</sup> A majority of studies reviewing the single (Table 2) or double ASCT (Table 3) demonstrated that achieving CR or at least VGPR was associated with a longer PFS and usually a longer OS.

In a large analysis from the IFM, Attal et al<sup>20</sup> evaluated the probability of extended event-free survival (EFS) and OS after HDT. In this analysis, the 5-year probability of survival after diagnosis was 72% among patients who achieved CR/VGPR, 39% among patients who achieved PR, and 0% among patients who achieved less PR after HDT. In the studies evaluating<sup>25</sup> double ASCT versus single ASCT, EFS was significantly higher for double-transplant group while lacked significance for improvement in OS. The absence of a survival benefit for patients in the double-ASCT arm, despite their significantly higher CR or nCR rate and superior EFS, may be due to the long OS of patients assigned to the single-transplantation arm attributed to second salvage ASCT and usage of novel agents as salvage therapies.

Studies from University of Arkansas evaluating tandem transplants have demonstrated the importance of obtaining a CR or nCR.

**TABLE 2.** Survival Outcomes With High Dose Chemotherapy (HDT) and Autologous Stem Cell Transplant (ASCT), by Response

Study (N)	RR (Postinduction)			RR1 (Post-ASCT1)			Survival			
	CR (%)	VGPR (%)	PR (%)	CR1 (%)	VGPR1 (%)	PR1 (%)	Median EFS (mo)	Median OS (mo)	5 yr EFS (%)	5 yr OS (%)
Bjorkstrand et al <sup>49</sup> (130)	12		56	47		47				
Attal et al <sup>20</sup> (100)	22	16	43	30	22	43				CR1/VGPR1 72 PR1 39 <PR1 0
Majolino et al <sup>50</sup> (290)	19.7		66.2	40		50				
Lahuerta et al <sup>4</sup> (344)				24 + 19 nCR1	16	33			CR1 35 nCR1 21 VGPR1 27 PR1 15	CR1 72 nCR1 48 VGPR1 42 PR1 41
Davies et al <sup>51</sup> (96)	18		70	53		47	CR1 49.4 PR1 41.4			CR1 58 PR1 64
Alexanian et al <sup>52</sup> (68)	6		37				PR → CR1 49.2 PR → PR1 27.6	PR → CR1 99.6 PR → PR1 60		
Terpos et al <sup>53</sup> (127)	6		73	15		81	CR1 31 PR1 16.3	CR/PR 50.2 <PR1 58.9		*CR1 77 PR1 69
Child et al <sup>21</sup> (201)				44		42		CR1 88.6 PR1 39.8 <PR1 25.6		
Alvares et al <sup>54</sup> (383)	15			50		10	CR1 45.6 <PR1 22.4	CR1 71 <PR1 64		
Fermand et al <sup>44</sup> (94)				36	26		CR1/VGPR1 59 < CR1/VGPR1 40			
O'Shea et al <sup>55</sup> (211)	5.2		71.2	16		68	CR1 59 <PR1 22	CR1 NR PR1 47		
Lenhoff et al <sup>56</sup> (247)	13		60	43		47	CR1 40 <CR1 27	CR1 71 <CR1 64		
Lahuerta et al <sup>30</sup> (632)	16	15	55	44	20	28	CR1 61 nCR1 40 PR 34			CR1 74 nCR1 63 PR 50

\*3 yr overall survival.

HDT indicates high-dose chemotherapy; ASCT, autologous stem cell transplant; CR, complete response; nCR, near CR; PR, partial response; OS, overall survival; and VGPR, very good partial response.

**TABLE 3. Survival Outcomes With High Dose Chemotherapy (HDT) and Double Autologous Stem Cell Transplant (ASCT2), by Response**

Study Yr (N)*	RR (Post-HDT/Pre-ASCT)				RRI (Post-ASCT1/Pre-ASCT2)				RR2 (Post-ASCT2)				Survival	
	Regimen	CR%	VGPR%	PR%	Transplant Regimen 1	CR1%	VGPR1%	PR1%	Transplant Regimen 2	CR2%	VGPR2%	PR2%	EFS	OS
Barlogie et al <sup>26</sup> TT (231)	VAD Cy EDAP	15	12	50	MEL200	26	49	49	MEL200 vs. MEL200 + TBI/Cy	41	42	42	CR1 78 + m PR1 52 m	CR1 80 + m PR1 68 m
Attal et al <sup>32</sup> (399)	VAD	15	12	57	MEL140 /TBI	39	42	42	MEL140/TBI	46	50 (NS)	38	30 m	58 m
Galli et al <sup>57</sup> (110)	VAD	15	11	57	MEL200	39	28	20	MEL200 v MEL140/TBI	46	15	10	†CR 65% PR 24%	‡CR 63% PR 47%
Cavo et al <sup>25</sup> (321)	VAD Cy				MEL200	33			MEL120 + Bu12	47			CR1 30% 35 m	PR1 58% 71 m (NS)
Barlogie et al <sup>27</sup> TT2 (668)	VAD EDAP	16	19	19	MEL200 vs. MEL200 + EAP	30	28	20	MEL200	56	24	12	§PR → nCR/ CR1 70%	¶CR → CR1 70%
Harousseau et al <sup>28</sup> (849)	VAD	4	12	49	MEL140/200vs. MEL140/200 + Thalidomid				Allogeneic SCT vs. MEL220	32	22.5	37	CR 42 m VGPR 38 m	5y CR 77% 5y VGPR 63%
Sonneveld et al <sup>58</sup> (155)	VAD	2			MEL140 Cy	19			Cy/TBI	32			22 m	50 m

\*All the studies are prospective except by Galli et al, which is a retrospective study.

†5-yr event-free survival.

‡5-yr overall survival.

§4-yr event-free survival.

¶4-yr overall survival.

VAD indicates vincristine, doxorubicin, and dexamethasone; Cy, high-dose Cyclophosphamide; EAP, etoposide, cytarabine, and cisplatin; VBMCP, melphalan, cyclophosphamide, and prednisone; VBAD, vincristine, BCNU, doxorubicin, dexamethasone EDAP, etoposide, dexamethasone, cytarabine, and cisplatin; TBI, total body irradiation; MEL140 Melphalan 140 mg/m<sup>2</sup>; MEL200, Melphalan 200 mg/m<sup>2</sup>; and MEL140 + Bu16, Melphalan 140 mg/m<sup>2</sup> + Busulfan 16 mg/m<sup>2</sup>.

**TABLE 4. RR, PFS, OS From Various Studies With Novel Agents**

Study (N)	Median Age (yr)	Regimen	Median Follow-Up (mo)	RR			Median OS (mo)	Comments	
				CR %	VGPR%	PR %			
Palumbo et al <sup>59</sup> GIMEMA (331)	72	MPT vs. MP	38.4	16 vs. 4	29 vs. 11	24 vs. 33	45 vs. 47.6	↑ $\beta$ 2-m treated with MPT HR = 0.70 95% CI, 0.45–1.08) $P = 0.05$	
Facon et al <sup>60</sup> IFM 99-06 (447)	<70	MPT vs. MP	51.5	13 vs. 2	47 vs. 7	16 vs. 27	51.6 vs. 33.2	Third arm is MEL100; OS MEL100 vs. MP; $P =$ 0×32 (NS)	
Hulin et al <sup>61</sup> IFM 01/01 (232)	>75	MPT vs. MP- PLACEBO	47.5	7 vs. 1	21 vs. 7	33 vs. 23	45.3 vs. 27.7		
Waage et al <sup>62</sup> (362)	75	MPT vs. MP- PLACEBO	NR	13 vs. 4	44 vs. 36		30 vs. 30	Interim analysis- better RR and TTP in MPT group ( $P = 0.03$ ). No improvement in PFS/OS.	
Wijermans et al <sup>15</sup> HOVON 49 (344)	>65	MPT vs. MP	NR	2 vs. 2	28 vs. 8	36 vs. 37	37 vs. 30	PFS after 2 yr, 33% vs. 19%	
Richardson et al <sup>15</sup> APEX (669)	61	Vel vs. Dex	15.8	9 vs. <1	7 vs. 1	34 vs. 17	25.4 vs. NR	1-yr. survival rate is 80% vs. 66% ( $P =$ 0.003)- updated	
Kyle et al <sup>14</sup> E9486 (653)	63	BCNU vs. VBMCP vs. VBMCP-IFN $\alpha$ vs. VBMCP-CY	157	14%	53%		CR 61 vs. PR 40	VBMCP-IFN $\alpha$ had higher CR (18%) than VBMCP alone (10%) CR rate VBMCP-CY-12% 13% vs. 22% deaths	
San Miguel et al <sup>19</sup> VISTA (682)	71	VMP vs. MP	16.3	30 vs. 4	41 vs. 31		NRe		
Palumbo et al <sup>63</sup> (511)	71	VMPT vs. VMP	36	35 vs. 21	16 vs. 21		NRe		
Rajkumar et al <sup>16</sup> (470)	64	TD vs. D	>17	7.7 vs. 2.6	55.3 vs. 43.4		NR	24.3% vs. 28.9% deaths	
Ludwig et al <sup>17</sup> (289)	72	TD vs. MP	28.1	2 vs. 2	24 vs. 11	42 vs. 37	41.5 vs. 49.4		
Wang et al <sup>64</sup> (704) n = 430	64	RD vs. D (No prior Thal exposure)	74	19 vs. 2.5	19.5 vs. 4.4	26.1 vs. 20.6	36.1 vs. 32	39% of patients previously exposed to thalidomide; OS statistically NS	
n = 274	63	RD vs. D (prior Thal exposure)		7.9 vs. 1.4	13.4 vs. 0.7	32.3 vs. 12.2	33.3 vs. 28.7		
Rajkumar et al <sup>18</sup> E4A03(445)	65	RD vs. Rd	24	52 vs. 42		30 vs. 26	NRe	2 yr OS rates 87% (Rd) vs. 75% (RD).	
Anderson et al <sup>39</sup> (64)		RVD	NR	21	47		30	NRe	

NR indicates not reported; NRe, not reached.

Among the patients treated with Total Therapy I,<sup>26</sup> patients with CR after the first transplant had longer EFS and OS when compared with patients with only a PR. The trend continued in Total Therapy II,<sup>27</sup> EFS and OS were significantly longer for those who had a CR than for those who had a PR or no response. The duration of CR was significantly longer in patients with early onset of CR.<sup>28</sup> Early onset CR before transplant<sup>29,30</sup> as well as sustained CR<sup>31</sup> are the other critical prognostic factors for improved OS; and in particular, CR duration is important among patients with high-risk disease.

Early intensification of therapy in patients already in CR was of no further benefit.<sup>32,33</sup> In the IFM study, patients who did not have at least a VGPR after the first transplant had a significant benefit from the second transplantation. The rates of survival at 7 years were 11% versus 43% for single versus double transplantation ( $P < 0.001$ ). Patients who had at least a VGPR did not benefit significantly from the second transplantation ( $P = 0.70$ ). Similar results were noted in the retrospective evaluation of response and survival of 758 patients by Wang et al<sup>34</sup> and Dingli et al.<sup>33</sup>

### CR AND OUTCOMES WITH NOVEL AGENTS AS INDUCTION REGIMENS

Encouraging results are being seen with novel agents as induction regimens (Table 4). CR rates in the range of >30% and VGPR >70% with induction therapy alone before even receiving HDT/ASCT raise the hope that curability is in reach. In the IFM phase 3 randomized trial, CR + nCR/≥VGPR response of 78% were seen with the randomized trial of bortezomib and dexamethasone (VD) compared with the vincristine, doxorubicin, and dexamethasone (VAD) arm.<sup>35</sup> After autologous transplant, VD arm continued to show superior results as given in Table 5. We reviewed results with VTD induction at our institution.<sup>36</sup> Of the 44 patients who were treated with VTD, we had ORR of 91% (increased to 94% in treatment naive patients). CR/VGPR rate of 57% was reported postinduction. After ASCT in 34 patients, the ORR is 100% and VGPR ≥76% (sCR/CR 53%). Median PFS was 27.4 months, and 2-year OS rate is 82%. Similar results were seen with Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) trial that compared VTD with TD in 480 patients: ORR was 92%, of which 61% had CR + nCR/≥VGPR postinduction, and 76% achieved VGPR or better after HDT.<sup>37</sup> Results with three drug regimens have demonstrated superior results that were deemed impossible a decade earlier. The combination of bortezomib with lenalidomide has been treated in the relapsed and upfront setting with impressive results. Lenalidomide, bortezomib, and dexamethasone (RVD) as induction therapy resulted in ≥PR in 100% patients, ≥VGPR in 74% patients, and CR/nCR in 44% patients.<sup>38</sup> RVD in refractory setting, at the time of presentation at ASCO 2009, achieved a response rate of 94% and PFS was reached at 30 months.<sup>39</sup> It seems that the combination of proteasome inhibition and immunomodulatory drugs would form the frontline therapy in the upcoming years. Although RVD is being tested in two ongoing phase III trials (ECOG evaluating RVD vs. VD and SWOG evaluating RVD vs. RD), the clinical benefit of the CR achieved with RVD is still to be validated.

### CORRELATION BETWEEN CR AND OUTCOMES IN MAINTENANCE THERAPY

By offering maintenance therapy, the primary goal is to prolong CR by decreasing the burden of residual tumor cells. Two randomized trials have been published demonstrating that post-ASCT treatment with thalidomide increases the rate of CR + VGPR, PFS, and OS.<sup>40,41</sup> From the Australian study that compared thalidomide and prednisone versus prednisone,<sup>41</sup> after a median follow-up of 3 years, the postrandomization 3-year PFS rates for thalidomide and control group were 42% and 23% (HR 0.5; 95% CI

TABLE 5. Novel Agents as Induction Regimens

Study (N)	Median Age (yr)	Regimen	Median f/u (m)	RR			Median OS (mo)	Comments
				CR %	VGPR %	PR %		
Lokhorst et al <sup>65</sup> HOVON-50 2007 (402)	56	TAD vs. VAD	NR	4 vs. 2	29 vs. 13	39 vs. 39	NR	Post-HDT-76% vs. 79% ORR (NS)
Sonneveld et al <sup>66</sup> HOVON-65	NR	PAD vs. VAD	NR	5 vs. 1 (CR + nCR)	37 vs. 14	41 vs. 44	NR	Post-ASCT responses of CR + nCR/≥VGPR/≥PR are 23%/80%/93% vs. 9%/50%/80% for PAD vs. VAD
Cavo et al <sup>37</sup> GIMEMA (480)	<65	VTD vs. TD	15	33 vs. 12 (CR + nCR)	28 vs. 18	31 vs. 48.5 93% vs. 86%, $P = 0.04$	20 mo estimate 93% both arms	ITT basis-VTD vs. TD- CR (41% vs. 20%, $P < 0.001$ ), CR + nCR (54% vs. 29%, $P < 0.001$ ) and ≥VGPR (75% vs. 53%, $P < 0.001$ )
Harousseau et al <sup>35</sup> IFM (482)	<65	VD vs. VAD	NR	21.3 vs. 8.3 (CR + nCR)	46.7 vs. 18.6	NR	NRe	CR + nCR/≥VGPR Vd- post-ASCT, in pts → ASCT (40.8%/71.8% vs. 28.8%/51%, $P = 0.0089$ ) and in the ITT population (35%/61.7% vs. 23.6%/41.7%, $P = 0.0056$ ) <0.0001
Kaufman et al <sup>36</sup> (44)	58	VTD	NR	20	37	34	27.4 2-yr OS rate 82%	ORR post-ASCT in 34 patients-100%; 76% ≥ VGPR (53% sCR/CR)

VAD indicates vincristine, doxorubicin, dexamethasone; TAD, thalidomide, doxorubicin, dexamethasone; PAD, bortezomib, doxorubicin, dexamethasone; VD, bortezomib, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone; NR, not reached; and NRe, not reported.

0.35–0.71;  $P < 0.001$ ) and the OS rates were 86% and 75% (HR, 0.41; 95% CI, 0.22–0.76;  $P = 0.004$ ), respectively. The findings differed with IFM study comparing thalidomide versus placebo, where benefit was only evident in the patients not achieving CR or VGPR after HDT, and patients who did not have deletion of chromosome 13 [del (13)] by cytogenetics.

## CR AND OUTCOMES AMONG HIGH-RISK PATIENTS

In the era of novel agents, studies suggest that innovative combinations may overcome the unfavorable prognosis conferred by the high-risk features by improving RR and prolong the PFS and OS. In the IFM 2005 trial, where VAD was compared with VD, achievement of CR was independent of elevated  $\beta_2$ -microglobulin (International Staging System stage III).<sup>35</sup> In the GIMEMA trial of VTD versus TD, CR + nCR rates of 43% versus 4% were seen for patients with del (13) and 47% versus 8% for t(4;14).<sup>37</sup> Data from Richardson et al<sup>38</sup> evaluating RVD as induction therapy also showed efficacy independent of baseline cytogenetics or stage. Although these 3 trials show encouraging ORRs and high CR rates, durability of this response remains unknown.<sup>42</sup> From the VISTA trial, any high-risk chromosomal abnormality did not impact the efficacy of VMP ( $\geq$ PR of 81% vs. 82% for high risk vs. standard risk) or in terms of TTP or OS.<sup>19</sup> From UAMS data, CR correlates with OS in high-risk patients, suggesting that novel agents improve ORR and CR rate and overcome the unfavorable prognosis conferred by the high-risk features.<sup>43</sup> Because OS in high-risk patients is associated with CR, and higher CR rates were associated with VD, VTD than VAD or TD, newer combination RVD, whose efficacy is independent of baseline cytogenetics, may have better outcome with regards to OS. Overall, combination therapies resulted in improved OS for high-risk patients.

## CONCLUSION

The past 10 years have represented a time of unprecedented growth and improvements in therapeutic outcomes for patients with myeloma. As we have improved treatments, the measures of our success are changing as well. The definition of CR has been revised to include sCR; however, the current definition represents a threshold to the limits of current detection. To evaluate the disease below the limits of current detection to eradicate evidence of all disease, new techniques for assessing MRD with quantitative PCR or multiparameter flow cytometry to detect molecular remissions need to be validated and used. Specially, in the context of novel agents achieving molecular CRs, and the evidence that molecular CR represents translation to improved PFS and OS is essential if we are to eventually cure myeloma.

CR has been demonstrated as a relevant and meaningful endpoint among nontransplant eligible older patients; however, it must be balanced with safety and toxicity in this group of patients. Among younger transplant eligible patients, the data are much clearer. Achievement of CR or at least VGPR is generally associated with prolonged PFS and OS. Achieving CR or at least VGPR before transplant and sustained CR remained important prognostic factors for PFS and OS.

The future for our patients with current therapeutic tools and new technology to risk stratify has never looked better. As we further refine our treatment regimens and strive toward individualized therapy, it has never been more important to push measurable disease to lower limits. CR as currently defined is one of those limits that help us to improve outcomes and survival for patients.

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