PREDICTORS OF TREATMENT OUTCOME WITH THE COMBINATION OF CARFILZOMIB, LENALIDOMIDE, AND LOW-DOSE DEXAMETHASONE IN NEWLY DIAGNOSED MULTIPLE MYELOMA

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INTRODUCTION

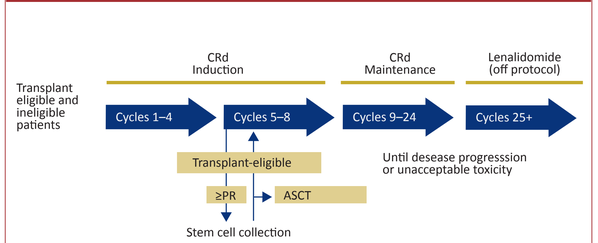
- We previously have shown that patients with newly diagnosed multiple myeloma (NDMM) treated with CRd (carfilzomib [CFZ], lenalidomide [LEN], low-dose dexamethasone) in a phase 1/2 trial (NCT01029054) demonstrated high rates of complete response (CR, 64%) and stringent complete response (sCR, 55%) that correlated with excellent estimated 2-year progression-free survival (PFS; 94%) and overall survival (OS; 98%)[1,2]
  - A correlation between risk factors or response rates and long-term treatment outcomes could not be demonstrated at that time, owing to the limited number of events
- In this analysis, we provide updated overall response rates (ORR), PFS, and OS, along with an evaluation of outcomes based on pretreatment characteristics (including cytogenetics and gene expression profiling [GEP]) and depth of response, including minimal residual disease (MRD) status

PATIENTS and METHODS

Treatment

- Patients received 28-day cycles of CFZ 20–36 mg/m^2 intravenously (days [d]1, 2, 8, 9, 15, 16), LEN 25 mg orally (PO; d1–21), and dexamethasone 40/20 mg PO weekly (cycles 1–4/5–8)[1]
  - For cycles 9–24, CRd was given with a modified CFZ schedule (d1, 2, 15, 16), and single-agent LEN at the last tolerated dose was administered after cycle 24
- Patients had the option to receive stem cell transplantation after cycle 4

Figure 1. Treatment Schema



ASCT, autologous stem cell transplant; CRd, carfilzomib, lenalidomide, and low-dose dexamethasone; PR, partial response.

Key Eligibility Criteria

- Transplant and nontransplant candidates with NDMM
- Measurable disease per International Myeloma Working Group (IMWG) criteria
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2
- Absolute neutrophil count (ANC) >1.0 × 10^9/L, hemoglobin >8.0 g/dL, platelets >75,000/μL
- Creatinine clearance >50 mL/min or serum creatinine ≥2 g/dL
- No serious comorbidities
- Additional details regarding eligibility criteria can be found in Jakubowiak et al[1]

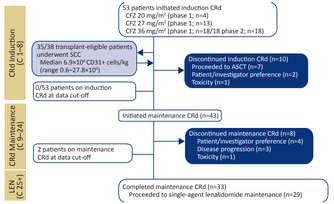
Assessments

- Response was assessed on d1 and d15 of cycle 1, and on d1 of all other cycles by IMWG criteria, with the addition of near complete response (nCR)
- MRD was measured with 10-color flow cytometry as described previously[1]
- Cytogenetic high-risk disease was assessed by IMWG criteria
- GEP was performed in a subset of patients with available high-quality RNA (n=15) by SkylineDx (Rotterdam, The Netherlands), using gene expression microarrays (GeneChip Human Genome U133 Plus 2.0; Affymetrix, Santa Clara, CA), and a prognostic 92-gene signature (SKY92; SkylineDx, Rotterdam, The Netherlands)[3]
- Analyses were conducted using a data cutoff date of May 31, 2013

RESULTS

- As of May 31, 2013, a total of 53 patients had received a median of 24 cycles of CRd (range, 2–24)
- Of these, 24 patients continued LEN maintenance for a median of 12 months (range, 3–15) **(Figure 2)**
- Median follow-up time was 31 months (range, 16–43)
- Patient characteristics at baseline are shown in **Table 1**

Figure 2. Patient Flow and Disposition



ASCT, autologous stem cell transplant; CFZ, carfilzomib; CRd, CFZ, LEN, and low-dose dexamethasone; LEN, lenalidomide; SCC, stem cell collection.

Table 1. Patient Demographics and Disease Characteristics

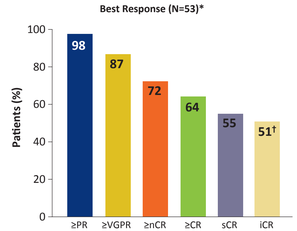
Characteristic	Overall (N=53)
Median age, years (range)	59 (35–81)[a]
Male sex, n (%)	39 (74)
ISS stage II/III, n (%)	32 (60)
Durie-Salmon stage II/III, n (%)	46 (87)
High-risk cytogenetics[b]	17/51 (33)
del 13 /Hyperploidy	10/50 (20)
t(4;14)	5/49 (10)
t(14;16)	0/48 (0)
del 17p	7/48 (15)

IMWG, International Myeloma Working Group; ISS, International Staging System.
[a]A total of 43% of patients were >65 years of age.
[b]Per IMWG criteria, ≥1 of the abnormalities listed.
[c]del 13 by metaphase only.

Primary Efficacy Results

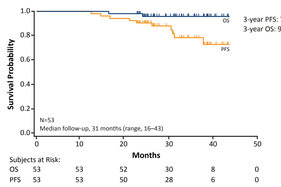
- Thirty-four patients (64%) achieved at least a CR, and 29 patients (55%) achieved an sCR **(Figure 3)**
- The estimated 3-year PFS and OS rates for all patients were 79% and 96%, respectively **(Figure 4)**

Figure 3. Best Overall Response (N=53)



*ITT, including patients who discontinued treatment early (eg, proceed to transplant)
†iCR is an estimate of MRD-negative disease (10 color flow), based on percentage of patients in sCR evaluated for MRD at 24 months (range, 2–24)

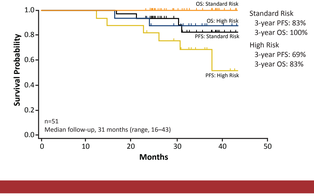
Figure 4. Kaplan-Meier Estimates of PFS and OS in the Overall Study Population



Cytogenetics

- Cytogenetic data were available for all but 2 patients
  - A total of 33% of patients had high-risk disease; of these, 47% had del p53
- There was a trend toward lower 3-year PFS rates in patients with high-risk cytogenetics compared with standard-risk cytogenetics (69% vs 83%, *P*=.081) **(Figure 5)**
  - Ten patients had disease progression
- Among patients with high-risk cytogenetics, similar 3-year PFS rates were observed in patients with p53 mutation (70%) and those without p53 mutation (67%)
- Estimated 3-year OS rates were also lower in patients with high- vs standard-risk cytogenetics (83% vs 100%; **Figure 5**), although the number of events observed was very low (only 2 patients had died)
  - The observed difference in OS was statistically significant (*P*=.041)
- There was a trend in the high- vs standard-risk groups toward a lower CR rate (53% vs 71%, respectively) and sCR rate (41% vs 62%), although the differences did not reach statistical significance (*P*=.223 and *P*=.234, respectively, using Fisher's exact test)

Figure 5. Kaplan-Meier Estimates of PFS and OS in Patients With High- and Standard-Risk Cytogenetics



Gene Expression Profiling

- A subset of 15 patients was analyzed by GEP, including 7 of 10 patients with disease progression
- Based on GEP, 4 of 15 patients (27%) had SKY92 high-risk disease[3]
  - All 4 patients relapsed, and 2 of these patients also had high-risk cytogenetics
- Of the 11 patients with SKY92 standard-risk disease, 3 patients relapsed, all of whom had high-risk cytogenetics[3]

Minimal Residual Disease

- Twenty-six patients with nCR, or sCR (including 7 patients [28%] with high-risk cytogenetics) were evaluated for MRD
  - Of these, 23 patients (88%) were MRD-negative
- Patients who achieved sCR at any time during CRd treatment showed a trend toward longer estimated 3-year PFS and OS rates compared with those who did not achieve sCR **(Figure 6)**
  - PFS, 87% vs 68% (log-rank *P*=.222); OS, 100% vs 91% (log-rank *P*=.107)
- Among the 22 patients with MRD-negative disease, the estimated 3-year PFS was 89% and OS was 100% **(Figure 7)**

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3. Kuiper R, Broyl A, de Knegt Y, et al. Leukemia. 2012;26:2406–2413.

Figure 6. Kaplan-Meier Estimates of PFS and OS in Patients With and Without sCR

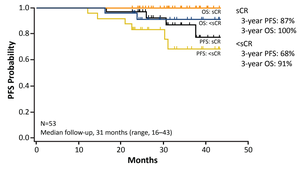
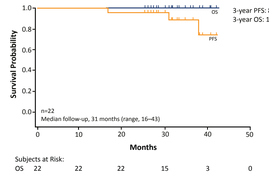


Figure 7. Kaplan-Meier Estimates of PFS and OS in Patients In sCR With MRD-Negative Disease



CONCLUSIONS

- After extended follow-up (median 31 months), CRd treatment continues to show excellent outcomes, with estimated 3-year PFS rate of 79% and 3-year OS rate of 96% for all patients with NDMM, 33% of whom had high-risk cytogenetics
- This is one of the first reports correlating prognostic factors with outcomes with carfilzomib-based treatment
- Patients with high-risk cytogenetics by IMWG criteria or with SKY92 high-risk disease demonstrated a trend toward inferior PFS and OS compared with patients with standard-risk cytogenetics or SKY92 standard-risk disease, indicating that CRd treatment may not completely overcome the effect of high-risk disease characteristics on survival outcomes
  - However, differences in PFS were not statistically significant between high- and standard-risk groups
  - While there were a low number of events, the long OS observed in patients poor prognostic factors was notable
    - Specifically, approximately 15% of enrolled patients had del p53, and yet, the OS rate at 3 years was 96% in the overall study population and 83% in patients with high-risk cytogenetics
- Additionally, these results suggest that achievement of sCR and having MRD-negative disease may be associated with superior PFS and OS
- Follow-up analyses of MRD disease using the LymphoSIGHT deep sequencing platform in patients with sCR are ongoing
  - Results compare favorably with historical results for both standard- and high-risk patients

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CONFLICTS of INTEREST DISCLOSURE

Kathryn McDonnell is employed by the University of Chicago Medical Center (Myeloma Program Coordinator); David H. Vesole has been a member of advisory committees for Celgene and Onyx, and has participated in speakers bureaus for Celgene, Onyx, and Millennium; Sundar Jagannath has received honoraria from Millennium, Celgene, Onyx, and Merck, and has been a member of advisory committees for Ortho Biotech, Imedex, Medicom Worldwide, OptumHealth Worldwide, and PER group; Ravi Vij has received research funding from Onyx and Celgene, has received honoraria from Eli Lilly and BMS, and has participated in speakers bureaus for Onyx, Celgene, and Millennium; Malek Faham is an employee of, holds equity ownership of, and is a member of the Board of Directors of Sequenta, Inc.; Liana Lee is an employee of, and holds equity ownership of Sequenta, Inc.; Erik H. van Beers and Martin H. Van Vliet are employees of Skyline Diagnostics; Andrzej J. Jakubowiak has served as a consultant for, and has received honoraria and research funding from BMS, Celgene, and Janssen-Cilag, has served as a consultant for, has received honoraria and research funding from, has been a member of advisory committees of, and has participated in speakers bureaus of Onyx and Millennium, and has received research funding from Novartis; and authors Jagoda Jasielec, Dominik Dytfeld, Kent A. Griffith, Daniel Lebovic, Malathi Kandarpa, Melissa Mietzel, Joan Levy, Mattina Alonge, Shaun Rosebeck, and Mark Kaminski have no relevant financial relationships to disclose.

PLACEHOLDER CODE

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