Final Results of a Frontline Phase 1/2 Study of Carfilzomib, Lenalidomide, and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM)

Introduction

In relapsed and/or refractory MM, the combination of carfilzomib (CFZ) with lenalidomide (Len), and low-dose dexamethasone (Dex) (CRd) has shown very promising efficacy (78% ≥partial response [PR], 40% ≥very good partial response [VGPR], and 24% CR/nCR) and good tolerability including a low rate of peripheral neuropathy (Wang et al, ASCO, 2011). In a Phase I/II study of newly diagnosed MM, the regimen was well tolerated in the Phase I portion of the study up to a maximum dose of CFZ 36 mg/m², Len 25 mg, and Dex 40 mg, and very active with 96% ≥PR, 70% ≥VGPR, and 55% CR/nCR (Jakubowiak et al, ASH 2010). The lack of overlapping toxicities has allowed these agents to be used at full doses and for extended periods. Here we report the results for all patients (pts) enrolled in both phases of this first prospective trial of CFZ combination in new MM.

Methods

In the initial eight 28-day cycles, pts were treated with CFZ at 20 mg/m², 27 mg/m² (Phase I), and 36 mg/m² (Phase I and II), given IV on days 1, 2, 8, 9, 15 and 16, Len at 25 mg PO (days 1–21), and Dex at 40/20 mg PO weekly (cycles 1–4/5–8). Pts achieving ≥PR could proceed to stem cell collection (SCC) using growth factors alone (protocol recommendation) and autologous stem cell transplant (ASCT) after 4 cycles. Per protocol, ASCT candidates were offered the option to continue CRd treatment after SCC. After 8 cycles, pts received 28-day maintenance cycles of CFZ (days 1, 2, 15, 16), Len days 1–21, and Dex weekly at the doses tolerated at the end of 8 cycles. Responses were assessed by IMWG criteria with the addition of nCR.

Results

Enrollment was completed (53 pts): 4 pts at CFZ 20 mg/m², 13 at CFZ 27 mg/m² and 36 at CFZ 36 mg/m² (18 in Phase I and 18 in Phase II). Median age was 59 years (range 35–81; 23 pts ≥65), 60% had ISS stage II/III, and 33% (of 49 with available data) had unfavorable cytogenetics: del 13 or hypodiploidy by metaphase, or t(4;14), t (14;16), del 17p by FISH. As of June 30, 2011, toxicity data (cycles 1–8) were available for 51 pts. Hematologic toxicities were reversible and included Grade (G) 3/4: anemia (18%), neutropenia (12%), and thrombocytopenia (10%). The most common non-hematologic toxicities (all G) were hyperglycemia (76%), hypophosphatemia (61%), and infection (53%). G3/4 non-hematologic AEs included hyperglycemia (24%), DVT/PE while on ASA prophylaxis (10%), infection (6%), and mood alteration (2%). PN was limited to G1/2 sensory (24%). Forty-five pts continue treatment with 22 pts in the maintenance phase. Six pts discontinued treatment: 2 proceeded to ASCT, 1 due to toxicity, and 3 due to events unrelated to treatment or per pt wish. The majority of pts did not require dose modifications, either
in the initial (31%) or in the maintenance (25%) phase. After a median of 8 cycles (range 1–20), the best responses per IMWG criteria for 49 response-evaluable pts (all pts who completed 1+ cycle) are shown in the Table. Responses were rapid with 46/49 pts achieving at least PR after 1 cycle, and improved with the duration of treatment reaching 100% ≥PR after 4 cycles and 100% ≥VGPR, 79% CR/nCR after 12 cycles. Responses were deep even at the 2 lower dose levels with the majority of pts at 36 mg/m² still early in treatment. Responses in pts with unfavorable cytogenetics were similar to response rates in all remaining pts and included a 100% ≥PR in 6 pts with del 17p. Twenty-four pts proceeded to SCC after a median of 5 cycles of CRd (range 4–9); using growth factors only in 23 pts and cyclophosphamide and growth factors in 1 pt, with a median 6.55 x 10⁶ CD34+ cells/kg collected (range 3.75–9.6); all resumed CRd treatment. After a median of 9.5 months of follow-up, only 1 pt has progressed, and all are alive. 

**Conclusions**

CRd is highly active and well-tolerated allowing the use of full doses for an extended time in newly-diagnosed MM pts with limited need for dose modification. Responses are rapid and improve over time reaching 100% ≥VGPR and early time-to-event data are very encouraging. These results compare favorably to the best frontline regimens in MM.

**Randomized, Open Label Phase 1/2 Study of Pomalidomide (POM) Alone or in Combination with Low-Dose Dexamethasone (LoDex) in Patients (Pts) with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide (LEN) and Bortezomib (BORT): Phase 2 Results**

**Background**

Pts with relapsed/refractory multiple myeloma (RRMM), resistant to LEN and BORT, have poor outcomes. POM (2 or 4 mg/d for 28 d of each 28-d cycle) is an immunomodulatory compound with activity in pts refractory to both LEN and BORT (Lacy MQ et al. Blood 2011;doi:10.1182). This multicenter phase 1/2 study investigated the safety and efficacy of POM alone or in combination with LoDex (POM+LoDex) for treatment of pts with RRMM who had received both BORT and LEN. Phase 1 identified 4 mg/d of POM as the recommended dose for phase 2 (Richardson PG et al. Blood 2010;116:Abs 864). Phase 2 results are presented.

**Methods**
Pts with RRMM after ≥ 2 prior regimens, including ≥ 2 cycles of LEN and BORT separately or in combination, were eligible. Pts had to have progressed ≤ 60 d of their last treatment prior to study entry (refractory disease). This analysis evaluated the efficacy and safety of POM+LoDex (POM 4 mg/d 1–21 d of each 28-d cycle; Dex 40 mg/wk) and POM alone in a randomized open-label study. Results presented here were based on investigator assessed responses for the intent-to-treat population. Responses were independently adjudicated. The primary endpoint was progression-free survival (PFS). Secondary endpoints were objective response (partial response [PR] or ≥ PR), duration of response (DOR), overall survival (OS), and safety. All pts received daily low-dose aspirin thromboprophylaxis.

**Results**

A total of 221 pts were enrolled in phase 2 (POM+LoDex n = 113; POM n = 108); 219 received ≥ 1 cycle of study treatment and 191 pts were evaluable for response. Baseline characteristics were comparable between the two arms with a median of 5 (range 2–13) prior therapies in both arms; 74% of pts in POM+LoDex and 76% of pts in POM alone had prior autologous stem-cell transplantation (ASCT). The remaining pts were elderly (aged > 75 yrs) or ineligible for ASCT; all pts were exposed to corticosteroids and 84% in the POM+LoDex and 95% in POM alone arms were exposed to alkylators. Pts were refractory to LEN (POM+LoDex 77% and POM alone 79%), BORT (73% and 69%), or both drugs (61% and 59%). Among pts who were randomized to receive POM alone, 61 (56%) subsequently went on to receive POM+LoDex due to progressive disease (PD) per protocol.

A median of 5 (range 1–17) treatment cycles were received by pts in both arms. Median treatment duration was 5.0 mos.

Response of ≥ PR was seen in 34% of pts in the POM+LoDex arm and 13% in the POM alone arm, including 1% complete response (CR) in each arm; ≥ minor response (MR) was 45% vs 29%, respectively. Median DOR was 7.7 mos with POM+LoDex and 8.3 mos with POM alone, and median PFS was 4.6 mos and 2.6 mos, respectively (Fig 1). Median OS was comparable for both arms (14.4 and 13.6 mos). Results from independent adjudication were similar, with ≥ PR in 30% of pts in the POM+LoDex arm and 9% in the POM alone arm, including 1% and 0% CR, respectively, in each arm. ≥ MR was achieved with POM+LoDex in 45% and with POM alone in 25%; PFS was 3.8 mos and 2.5 mos, respectively.

In the subgroup of pts refractory to both LEN and BORT, 30% and 16% of pts treated with POM+LoDex or POM alone, respectively, achieved ≥ PR; ≥ MR was 45% and 30%, respectively. Median PFS was 3.8 mos for POM+LoDex and 2.0 mos for POM alone; median OS showed a similar trend (13.5 and 10.8 mos, respectively).

The main reason for treatment discontinuation was PD in both arms (POM+LoDex 51%; POM alone 44%); discontinuations due to adverse events (AEs) were 7% and
12%, respectively. Grade 3/4 AEs in POM+LoDex vs POM alone, respectively, were: neutropenia 38% and 47%; febrile neutropenia 2% and 2%; thrombocytopenia 19% and 21%; anemia 21% and 17%; pneumonia 19% and 8%; and fatigue 10% and 8%. All grades of peripheral neuropathy, deep vein thrombosis, and renal failure occurred in 7% and 10%, 2% and 1%, and 2% and 1% of pts for POM+LoDex vs POM alone, respectively.

Conclusions

POM (4 mg/d 1–21 d of each 28-d cycle) with or without LoDex demonstrates clinical activity and is generally well tolerated in pts with advanced MM who have received multiple prior therapies and are refractory to both LEN and BORT. Prospective comparison indicates that POM+LoDex is associated with greater clinical benefit and no increased toxicity vs POM alone. This is supported by high response rates, long DOR, and PFS benefit achieved with POM+LoDex. The regimen is now being investigated both in phase 3 trials, and as part of combination treatment including with BORT.

Phase 1/2 Study of Oral MLN9708, A Novel, Investigational Proteasome Inhibitor, in Combination with Lenalidomide and Dexamethasone in Patients with Previously Untreated Multiple Myeloma (MM)

Background

MLN9708 is an investigational, oral, potent, reversible, and specific 20S proteasome inhibitor, which immediately hydrolyzes to MLN2238, the biologically active dipeptidyl leucine boronic acid. In preclinical studies, MLN2238 has shown faster proteasome dissociation and greater tissue penetration than bortezomib. Current phase 1 data indicate that oral administration of single-agent MLN9708 was generally well tolerated, with no grade 3 peripheral neuropathy, and showed signs of antitumor activity in some patients with relapsed and/or refractory MM. Bortezomib in combination with lenalidomide and dexamethasone demonstrated a 100% partial response or better (≥PR) rate in patients with previously untreated MM, providing the rationale for evaluating oral MLN9708 in place of bortezomib in this combination. Here we report phase 1 data from the first combination study of MLN9708 (ClinicalTrials.gov: NCT01217957).

Methods

Primary phase 1 objectives were to determine the safety, tolerability, and maximum tolerated dose (MTD) of weekly MLN9708 in combination with lenalidomide and dexamethasone; secondary objectives included characterization of the pharmacokinetic (PK)/pharmacodynamic (PD) profile of MLN9708, assessment of PK interaction and response. Adults aged ≥18 years with ECOG performance status of 0 to 2, and adequate renal, hepatic, and hematologic function were eligible. Patients
with grade ≥2 peripheral neuropathy or prior/concurrent deep vein thrombosis (DVT)/pulmonary embolism were excluded. Patients received oral MLN9708 weekly on days 1, 8, and 15, lenalidomide 25 mg on days 1–21, and dexamethasone 40 mg on days 1, 8, 15, and 22, for up to twelve 28-day cycles. Patients received thromboprophylaxis with aspirin or low molecular weight heparin. Transplant-eligible patients could undergo stem cell transplant after six cycles. MLN9708 dose escalation, from a starting dose of 1.68 mg/m², followed a 3+3 scheme based on the occurrence of dose-limiting toxicities (DLTs) in cycle 1. Adverse events (AEs) were evaluated according to NCI-CTCAE v4.0. Response was assessed according to modified EBMT criteria.

Results

At data cut-off (June 29, 2011), 10 patients have been enrolled and treated: three each at 1.68, 2.23, and 2.97 mg/m² and one at 3.95 mg/m²; median age was 66 years (range 59–77). Patients completed a median of 3 cycles (range 1–6), with three having received 6 cycles; treatment is ongoing in six patients. A DLT of grade 3 fainting was observed in a patient treated at 3.95 mg/m². The MTD has not yet been reached; the current cohort is receiving 3.95 mg/m². Drug-related AEs included rash in four patients (two maculopapular, two erythematous); vomiting and fatigue in three patients each; and diarrhea, constipation, and nausea in two patients each. Grade 1 treatment-related peripheral neuropathy was reported in one patient. Serious AEs were seen in four patients: one at 3.95 mg/m² (DLT of grade 3 fainting), one at 2.23 mg/m² (grade 3 DVT) unrelated to MLN9708, and two unrelated at 1.68 mg/m² (grade 3 hypotension; grade 3 gastrointestinal hemorrhage resulting in discontinuation). Two patients required lenalidomide dose reductions to 15 mg due to erythematous rash; no dose reductions were required for MLN9708 or dexamethasone. There were no on-study deaths. Of nine response-evaluable patients, all nine achieved ≥PR, including three very good PR (VGPR) and one complete response. Time to response was rapid; all responders achieved a ≥50% decrease in M-protein in cycle 1, and best response was reached by the end of cycle 4. No patient has progressed to date. One patient with confirmed VGPR discontinued at cycle 6 to undergo stem cell transplant.

Conclusions

MLN9708 administered weekly in combination with lenalidomide and dexamethasone appears to be generally well tolerated in previously untreated MM patients at the MLN9708 dose levels studied, with evidence of antitumor activity in the dose-escalation cohorts. Evaluation continues to determine the MTD of MLN9708 in this combination. Updated results, PK data, assessment of PK interaction, and PD data will be presented.
Randomized, Open Label Phase 1/2 Study of Pomalidomide (POM) Alone or in Combination with Low-Dose Dexamethasone (LoDex) in Patients (Pts) with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Treatment That Includes Lenalidomide (LEN) and Bortezomib (BORT): Phase 2 Results

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Smoldering Multiple Myeloma (SMM) At High-Risk of Progression to Symptomatic Disease: A Phase III, Randomized, Multicenter Trial Based On Lenalidomide-Dexamethasone (Len-Dex) As Induction Therapy Followed by Maintenance Therapy with Len Alone Vs No Treatment
In this phase III trial, SMM patients at high-risk of progression were randomized to receive Len-dex as induction followed by Len alone as maintenance vs no treatment in order to evaluate whether the early treatment prolongs the time to progression (TTP) to symptomatic disease. The high-risk population was defined by the presence of both >PC 10% and MC >30g/L or if only one criterion was present, patients must have a proportion of aberrant PCs within the total PCsBM compartment by immunophenotyping of 95% plus immunoparesis.

Len-dex arm received an induction treatment consisting on nine four-weeks cycles of lenalidomide at dose of 25 mg daily on days 1-21 plus dexamethasone at dose of 20 mg daily on days 1-4 and 12-15 (total dose: 160mg), followed by maintenance until progression disease with Lenalidomide at dose of 10 mg on days 1-21 every two months (amended in May 2010 into monthly).

The 124 planned patients were already recruited, and 118 were evaluable (six patients didn’t meet inclusion criteria).

According to baseline characteristics, both groups were well balanced. On an ITT analysis (n=57), based on IMWG criteria, the overall response rate during induction therapy was 81%, including 56% PR, 11% VGPR, 7% CR and 7% sCR. 51 patients have completed the nine induction cycles, and the ORR was 87%, including 12% VGPR, 8% CR and 8% sCR. After a median of 7 cycles of maintenance therapy (1-21), the sCR increased to 12%.

After a median follow-up of 22 months (range: 5-42), six patients progressed to symptomatic disease in the Len-dex arm: four of them during maintenance therapy and the other two progressed 3 and 8 months after early discontinuation of the trial due to personal reasons. In addition, twelve patients have developed biological progression during maintenance, and dex was added according to the protocol. In nine of them, the addition of dex was able to control again the disease without CRAB symptoms (median of 11 months). In the therapeutic abstention arm, 28 out of 61 patients (46%) progressed to active MM. The estimated hazard ratio was 6·2 (95%CI= 2·6 -15), corresponding to a median TTP from inclusion of 25 months for the not treatment arm vs median not reached in the treatment arm (p<0.0001). It should be noted that 13 out of these 28 patients developed bone lesions as a symptom of active MM. Deaths in the Len-dex and no treatment arms were 1 and 2, respectively (p=0·6). Estimated 3-years overall survival (OS) from the inclusion in the trial was 98% for Len-dex arm and 82% for no treatment arm (p=0·05) and this difference was more evident if we evaluate the OS from the moment of diagnosis (HR: 6.7; 95% IC (0.7–57); p=0.03).

As far as toxicity is concerned, during induction therapy, no G4 adverse events (AEs) were reported with Len-dex; 1 pt developed G3 anemia, 4 patients G3 asthenia 2 patients G3 diarrhea and 1 patient G3 skin rash; 3 patients developed G2 DVT. During maintenance, no G4 AEs were reported and only 1 patient developed G3
infection. Two patients in the Len-dex arm developed second primary malignancies (SPM): one developed polycythemia vera JAK2+, but the analysis of a frozen DNA sample obtained at the moment of inclusion in the trial demonstrated that JAK2 was already positive. The second-one was a prostate cancer in a patient with previous history of prostate enlargement plus elevated prostate specific antigen (PSA) who was closely followed by the urologist.

In conclusion, this analysis shows that in high-risk SMM patients, delayed treatment resulted in early progression to symptomatic disease (median 25 months), while Len-dex as induction followed by Len as maintenance significantly prolonged the TTP (HR: 6.2), with a trend to improve the overall survival; in addition, tolerability is acceptable and concerning SPM, no safety warnings are at the present time. Moreover, biological progressions occurring under maintenance have remained controlled over a prolonged period of time.