Lenalidomide and low-dose dexamethasone (Ld) is equivalent to Ld plus autologous stem cell transplantation in newly diagnosed multiple myeloma: results of a randomized, phase III trial

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BACKGROUND

- High-dose chemotherapy combined with autologous stem cell transplantation (ASCT) is the current standard of care for patients aged ≤75 years who are newly diagnosed with multiple myeloma (MM)
- The role of ASCT has come into question in recent years with the emergence of novel agents such as lenalidomide and bortezomib, which are associated with significant improvements in outcomes in MM patients, regardless of whether they are eligible for transplantation[1–3]
  - As a result, whether upfront ASCT should remain the standard treatment for patients with newly diagnosed MM (NDMM) is currently under debate[4,5]
  - A recent phase III study indicated that survival is longer with high-dose therapy/ASCT than with melphalan-prednisone-lenalidomide consolidation.[6] However, the findings of an earlier study suggested that ASCT can be omitted from frontline treatment without deleterious effects on survival[7]
- This randomized, phase III clinical trial investigated the efficacy and safety of upfront ASCT versus a lenalidomide-based consolidation regimen without ASCT in patients with NDMM
- Here, we present the efficacy results

OBJECTIVES

Primary objective

- To compare complete response rate in patients with NDMM treated with lenalidomide plus low-dose dexamethasone (Ld) followed by ASCT (Arm A; Ld+ASCT) versus Ld alone (Arm B)

Secondary objectives

- To compare objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety between the two treatment arms

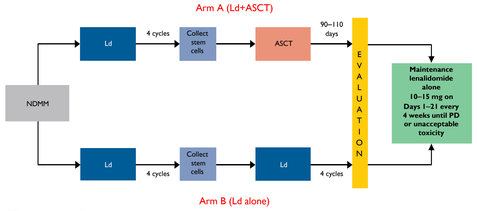
METHODS

Patients and trial design

- Eligible patients were aged 18–75 years, with previously untreated, transplant-eligible, NDMM
- Patients were randomized to receive four 28-day cycles of lenalidomide (25 mg on Days 1–21) plus low-dose dexamethasone (40 mg on Days 1, 8, 15, and 22) followed by stem cell mobilization and
  - ASCT conditioned with 200 mg/m^2 melphalan (Arm A; Ld+ASCT)

  or
  - A further four cycles of Ld (Arm B; Ld alone; Figure 1)

Figure 1. Trial design



PD, progressive disease

- In both treatment arms, stem cells were collected from patients after four cycles of Ld if at least a partial response (PR) was achieved
- Patients in both arms received maintenance therapy comprising lenalidomide 10–15 mg on Days 1–21 of 28-day cycles for up to 2 years or until disease progression
  - To be eligible for maintenance therapy, patients in Arm B had to achieve ≥PR after eight cycles of Ld
- All patients received thromboprophylaxis with aspirin, enoxaparin, or warfarin
- Patients with stable disease (SD) prior to stem cell collection (cycle 4), or with progressive disease at any time, went off study
- Follow-up of all patients continued either for up to 5 years from randomization or until death, whichever came first

Response and data analyses

- Responses were evaluated using the 2011 International Myeloma Workshop Consensus Panel 1 guidelines and the SWOG Oncology Research Professional Manual[8,9]
- Response and survival data were subject to an intention-to-treat analysis
- PFS, OS, and DOR curves were estimated using the Kaplan–Meier method
- Between-treatment differences in response rates were assessed using a Chi-square test. Differences in PFS, OS, and DOR were assessed using a log-rank test

RESULTS

Patients

- Sixty patients were randomized between January 30, 2008, and August 12, 2014 (Arm A [Ld+ASCT]: n=31; Arm B [Ld alone]; n=29)
- Baseline characteristics were similar in the two arms (Table 1)
- One-third of patients (20/60) had intermediate or high-risk cytogenetics at trial entry

Table 1. Baseline patient characteristics

	Arm A (Ld+ASCT)	Arm B (Ld alone)	All patients
Number of patients	31	29	60
Mean age, years (range)	62 (48–75)	62 (50–75)	62 (48–75)
Male, n (%)	16 (51.6)	17 (58.6)	33 (55.0)
Race, n (%)			
White	23 (74.1)	20 (68.9)	43 (71.6)
African–American	4 (12.9)	6 (20.6)	10 (16.6)
Other	4 (12.9)	3 (10.3)*	7 (11.7)*
ECOG performance status, n (%)			
0	13 (41.9)	15 (51.7)	28 (46.6)
1	18 (58.0)	13 (44.8)	31 (51.6)
2	0	1 (3.4)	1 (1.6)
ISS stage, n (%)			
0	8 (25.8)	7 (24.1)	15 (25.0)
I	13 (41.9)	14 (48.2)	27 (45.0)
II	8 (25.8)	5 (17.2)	13 (21.6)
III	2 (6.4)	3 (10.3)	5 (8.3)
Cytogenetics, n (%)			
None	13 (41.9)	11 (37.9)	24 (40.0)
Standard	10 (32.2)	6 (20.6)	16 (26.6)
Intermediate	6 (19.3)	12 (41.3)	18 (30.0)
High	2 (6.4)	0	2 (3.3)

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System
*Includes 1 patient whose race was not recorded

Efficacy

- The median follow-up time was 53.6 months (95% confidence interval [CI], 49.5–58.3) for the total patient population, 55.7 months (95% CI, 45.8–59.8) for Arm A (Ld+ASCT), and 53.1 months (95% CI, 42.9–61.2) for Arm B (Ld alone)
- There were no significant differences in ORR or ≥ complete response (CR) rates (Table 2), or in OS, PFS, or DOR between the two treatment arms (Table 3, and Figures 2–4)
- There were no significant differences in OS, PFS, or DOR between the two treatment arms when analyzed by cytogenetic risk profile (standard, intermediate, or high risk)

Table 2. Best response to therapy

Best response*	Arm A (Ld+ASCT) (n=31)	Arm B (Ld alone) (n=29)	p value
ORR, n (%)†	26 (83.8)	21 (72.4)	0.35
≥CR, n (%)	7 (22.5)	7 (24.1)	1.00

*Confirmed and unconfirmed responses are combined; †≥PR

Figure 2. OS

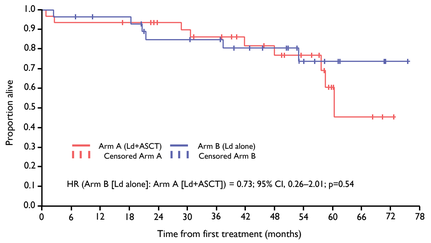


Figure 3. PFS

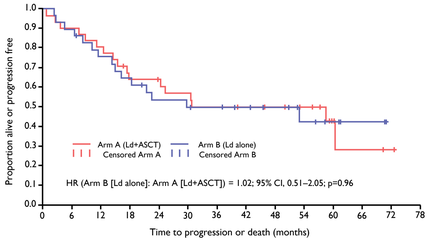


Figure 4. DOR

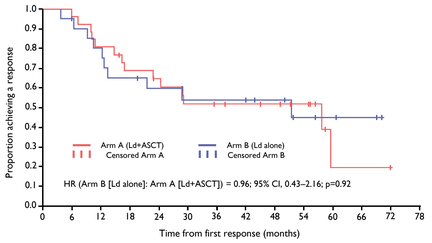


Table 3. 4-year OS, PFS, and DOR (Kaplan–Meier estimates)

	Arm A (Ld+ASCT) (n=31)	Arm B (Ld alone) (n=29)	p value
4-year OS, %	81.5	80.5	0.54
(95% CI)	(60.8–92.0)	(59.0–91.4)	
4-year PFS, %	49.9	49.6	0.96
(95% CI)	(31.1–66.2)	(30.1–66.4)	
4-year DOR,* %	51.8	53.8	0.92
	(30.8, 69.3)	(29.6, 72.8)	

*Response: ≥PR

DISCUSSION AND CONCLUSIONS

- Eight cycles of lenalidomide without upfront ASCT (Ld alone) conferred similar response rates (ORR and ≥CR rate), OS, PFS, and DOR to four cycles of lenalidomide followed by ASCT (Ld+ASCT)
- These findings are similar to those reported recently by Weltz et al[10]
  - In transplant-eligible patients who had responded to Ld induction, PFS and OS were comparable regardless of whether patients received continuous Ld or underwent ASCT followed by Ld maintenance
- Due to the small numbers of patients and relatively short follow-up, our findings require confirmation in larger studies, and should be interpreted with caution
  - However, our results suggest that, in patients with NDMM, Ld alone may provide comparable outcomes to those achieved with Ld plus upfront ASCT

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