FINAL RESULTS OF THE OBSERVATIONAL STUDY FIRST-NIS

FIRST-LINE THERAPY WITH LENALIDOMIDE AND DEXAMETHASONE IN TRANSPLANT-INELIGIBLE PATIENTS WITH MULTIPLE MYELOMA

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Abbreviations:
AE - Treatment-emergent Adverse Event | CR - Complete response | DOR - Duration of Response | ECOG - Eastern Cooperative Oncology Group | FAS - Full Analysis Set | LDH - Lactate dehydrogenase | LPI - Last patient in | MPT - Melphalan-Prednisone-Thalidomide | NDMM - Newly diagnosed multiple myeloma | ORR - Overall Response Rate | OS - Overall Survival | PD - Progressive Disease | PFS - Progression-Free Survival | PR - Partial Response | QoL - Quality of Life | Rd - Lenalidomide-dexamethasone | sCR - stringent Complete Response | SD - Stable Disease | SAF - Safety Set | SPM - Secondary Primary Malignancy | VGPR - Very Good Partial Response

References:
1. Facon, T. et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood 131, 301–310 (2018).

2. Benboubker, L. et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N. Engl. J. Med. 371, 906–917 (2014).

Conflicts of Interest:
Nückel, H: Honoraria: AMGEN GmbH, Bristol-Myers Squibb Gmbh & Co. KGaA, Celgene GmbH, Janssen-Cilag GmbH, Roche Pharma AG

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INTRODUCTION

Lenalidomide plus low-dose dexamethasone (Rd) is an established standard of care for transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). Approval was based on the results of the pivotal phase III FIRST trial showing a significantly prolonged progression-free (PFS) and overall survival (OS) in patients treated with Rd compared with melphalan-prednisone-thalidomide (MPT).[1] Since MM is predominantly a disease of advanced age (median age of >65 years at diagnosis) and only 35% of patients were >75 years in the FIRST trial, the results are difficult to extrapolate to a real-world setting. Besides, real-world data of this commonly used regimen are still scarce.

METHODS

Study design and participants

The prospective, multicenter, non-interventional, observational FIRST-NIS study was designed to collect data on 167 patients with multiple myeloma receiving Rd as first-line therapy from about 50 sites across Germany.

Objectives

Primary objective was to evaluate effectiveness of Rd assessed by 24-month PFS rate. Secondary endpoints include OS, PFS, overall response rate (ORR), duration of response (DOR), safety and quality of life (QoL).

Final analysis

For the final analysis of the primary endpoint (final analysis part one), the database cut was 24 months after last patient in (LPI). The primary analysis population (full analysis set (FAS)), relevant for effectiveness evaluation as well as patient and disease characteristics at baseline, comprised all patients who received at least one dose of lenalidomide. Patients with identified off-label treatment were excluded from the FAS. The Safety Set (SAF) comprised all patients having received at least one dose of lenalidomide and for whom at least one further (post-baseline) information under treatment was available. Descriptive statistics were used to analyze the data. Time-to-event analyses were performed using the Kaplan-Meier method. Final survival analysis (final analysis part two) will be performed 60 months after LPI in 2023.

RESULTS

Patients

At final analysis part one (cut-off, November 4th 2020), 172 patients had been enrolled across 41 sites in Germany. Thereof, 164 patients qualified for effectiveness and 168 patients for safety analysis. Baseline characteristics of all patients and patients stratified by age (≤75 years, >75 years) are presented in **Table 1**. Comorbidities associated with an increased risk of cardiovascular disease were of specific interest. Hypertension was diagnosed in 104 patients (63.4%), diabetes mellitus in 23 patients (14.0%), and coronary artery disorder in 14 patients (8.5%). Overall, 137 patients (83.5%) suffered from cardiovascular comorbidities (**Figure 1**).

Effectiveness and safety

With a median follow-up of 18.7 months at data base cut, the 24-month PFS rate of all patients was 48.0% [95%-CI; 39.1, 56.4], 65.5% [48.6, 78.0] for patients ≤75 years and 40.1% [29.8, 50.3] for patients >75 years. The median PFS of all patients was 22.9 months [19.3, 28.1], 31.5 months [22.0, NA] for patients ≤75 years and 19.3 months [14.2, 25.0] for those >75 years (**Figure 2 a, b**). The preliminary median OS was 48.0 months [51.5, 66.4] for the total population, 48.0 months [56.7, 81.8] for patients ≤75 years and 43.5 months [45.3, 63.1] for patients >75 years (**Figure 3 a, b**). The ORR was 59.1% in all patients, 70.8% in patients ≤75 years and 54.3% in patients >75 years. 26.2% of all patients were documented with stable disease (SD) and 1.8% with progressive disease (PD) as best response, while for 12.8% results are missing. Details on best responses are depicted in **Table 2**. Treatment-emergent adverse events (AEs) of any grade were experienced by 165 of 168 patients (98.2%). For details refer to **Table 3**. Grade 3/4 AEs were reported in 106 patients (63.1%) of which the most common were anemia (8.3%), thrombocytopenia (4.8%), dyspnea (4.8%), pneumonia (4.8%) and neutropenia (3.6%). Lenalidomide-related AEs occurred in 123 of 168 patients (73.2%). For details refer to **Table 4**. Grade 3/4 lenalidomide-related AEs occurred in 45 patients (26.8%) of which the most common were anemia (4.2%), thrombocytopenia (3.6%) and neutropenia (2.4%). Secondary primary malignancies (SPMs) were assessed during and after lenalidomide administration. At the database cut, <5% (n=8, 4.8%) of patients had a documented SPM.

DISCUSSION

Despite a high proportion of elderly patients and patients with comorbidities in the FIRST-NIS the effectiveness and safety data of Rd as first-line treatment in real-world is favorable. This real-world patient population clearly differs in terms of patient characteristics compared to the pivotal phase III FIRST trial, with differences in the proportion of patients >75 years (70.7% vs 35%), ECOG ≥2 (17.7% vs 23%), and elevated LDH level of ≥200 U/liter (43.3% vs 16%).[2] Differences seen with regard to effectiveness between our real-world patients (median PFS 22.9 months, median OS 48.0 months, ORR 59.1%, with median PFS 31.5 months, median OS 48.0 months and ORR 70.8% for patients ≤75 years) and the FIRST trial population (median PFS 26.0 months, median OS 59.1 months and ORR 81% for continuous Rd) might be attributed to the high proportion of elderly patients with a more advanced diseased and potentially also to the shorter median follow-up among surviving patients (18.7 vs 67 months) as compared to the FIRST trial.[1] The safety results were consistent with the known safety profile of the Rd regimen.

Figure 1

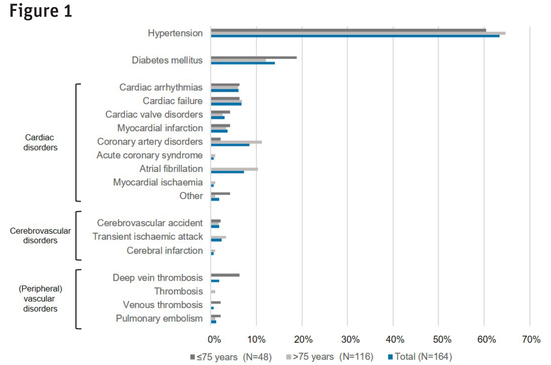

Figure 1 – Comorbidities associated with an increased risk of cardiovascular disease in the total population

CONCLUSION

Although the FIRST-NIS represents an elderly real-world patient population with approximately 70% of patients aged >75 years, the results revealed a favorable risk-benefit profile for Rd in NDMM patients. In elderly patients >75 years, however, PFS results were lower compared to younger patients ≤75 years. Reasons might be the higher rates of advanced-stage disease and renal impairment observed in the elderly patients. Overall, the Rd combination seems to be a reasonable, alkylator-free and orally available treatment option also for elderly patients with NDMM in the real-world setting. Final survival analysis will be presented after 5 years follow-up after LPI.

Table 1

	All (N=164)	≤75 years (N=48, 29.3%)	>75 years (N=116, 70.7%)
Age, years			
Median, range	77.7, 53.6-91.3		
Sex, n (%)			
Female	91 (55.5)	22 (45.8)	69 (59.5)
Male	73 (44.5)	26 (54.2)	47 (40.5)
ECOG Performance Status, n (%)			
0-1	126 (76.8)	39 (81.3)	87 (75.0)
≥2	29 (17.7)	7 (14.6)	22 (19.0)
Missing	9 (5.5)	2 (4.2)	7 (6.0)
International Staging System Stage, n (%)			
I	38 (23.2)	14 (29.2)	24 (20.7)
II	60 (36.6)	23 (47.9)	37 (31.9)
III	40 (24.4)	8 (16.7)	32 (27.6)
Unknown	26 (15.9)	3 (6.3)	23 (19.8)
Lactate dehydrogenase (LDH), n (%)			
<200 U/l	67 (40.9)	19 (39.6)	48 (41.4)
≥200 U/l	71 (43.3)	18 (37.5)	53 (45.7)
Missing	26 (15.9)	11 (22.9)	15 (12.9)
Creatinine clearance, n (%)			
<30 ml/min	16 (9.8)	2 (4.2)	14 (12.1)
<60 ml/min	87 (53.0)	12 (25.0)	75 (64.7)
≥60 ml/min	77 (47.0)	36 (75.0)	41 (35.3)
High-risk cytogenetic profile (t(4;14) or t(14;16) or del17p), n (%)			
Yes	12 (7.3)	3 (6.3)	9 (7.8)
No	97 (59.1)	28 (58.3)	69 (59.5)
Unknown	52 (31.7)	17 (35.4)	35 (30.2)
Missing	3 (1.8)	0 (0.0)	3 (2.6)

All values are depicted in n (%)

Table 1 – Patient demographics and clinical characteristics at baseline

Table 2

	All (N=164)	≤ 75 years (N=48, 29.3%)	> 75 years (N=116, 70.7%)
Overall Response Rate (ORR)	97 (59.1)	34 (70.8)	63 (54.3)
Stringent complete response (sCR)	2 (1.2)	0 (0.0)	2 (1.7)
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)
Very good partial response (VGPR)	29 (17.7)	11 (22.9)	18 (15.5)
Partial response (PR)	66 (40.2)	23 (47.9)	43 (37.1)
Stable disease (SD)	43 (26.2)	9 (18.8)	34 (29.3)
Progressive disease (PD)	3 (1.8)	0 (0.0)	3 (2.6)
Missing	21 (12.8)	5 (10.4)	16 (13.8)

All values are depicted in n (%)

Table 2 – Best response and overall response rate

Figure 2a

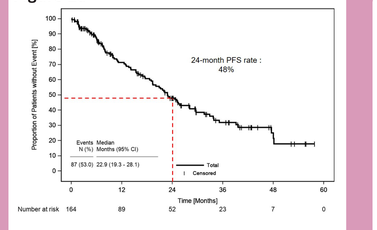

Figure 2a - Progression-free survival in the total population.

Figure 2b

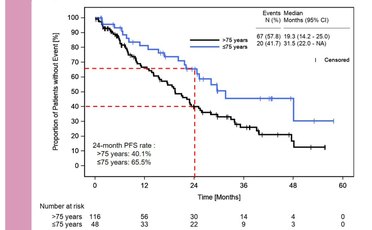

Figure 2b - Progression-free survival stratified by age (>75 years; ≤75 years)

Figure 3a

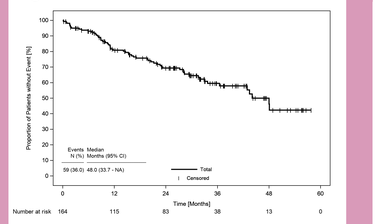

Figure 3a - Preliminary Overall survival in the total population

Figure 3b

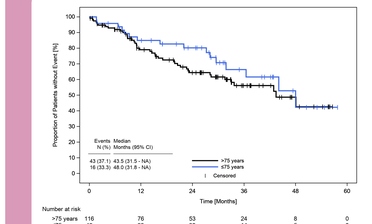

Figure 3b - Preliminary Overall survival stratified by age (>75 years; ≤75 years)

Table 3

Adverse Event	All patients (N=159)	
	Any grade n (%)	Grade 3/4 n (%)
Patients with any event	165 (98.2)	106 (63.1)
Haematologic AE		
Anemia	50 (29.8)	14 (8.3)
Thrombocytopenia	21 (12.5)	8 (4.8)
Nonhaematologic AE		
Infection	69 (41.1)	27 (16.1)
Diarrhoea	34 (20.2)	4 (2.4)
Fatigue	31 (18.5)	2 (1.2)
Back pain	25 (14.9)	6 (3.6)
Dyspnea	19 (11.3)	8 (4.8)
Constipation	17 (10.1)	1 (0.6)

Adverse events were coded using MedDRA version 21.0. Time range: from first administration of lenalidomide until 30 days after lenalidomide discontinuation.
Infection is defined as any event having a preferred term of the system organ class infections and infestations.

Table 3 – Treatment-emergent adverse events that occured in at least 10% of patients

Table 4

Adverse Event	All patients (N=168)	
	Any grade, n (%)	Grade 3/4, n (%)
Patients with any event	123 (73.2)	45 (26.8)
Hematologic AE		
Anemia	19 (11.3)	7 (4.2)
Thrombocytopenia	18 (10.7)	6 (3.6)
Nonhaematologic AE		
Diarrhoea	22 (13.1)	2 (1.2)
Fatigue	19 (11.3)	2 (1.2)

Adverse events were coded using MedDRA version 21.0. Time range: from first administration of lenalidomide until 30 days after lenalidomide discontinuation.
Infection is defined as any event having a preferred term of the system organ class infections and infestations

Table 4 - Treatment-emergent adverse events related to lenalidomide that occured in at least 10% of patients