Name of Sponsor/Company: Celgene	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Revlimid® Capsules		
Name of Active Ingredient: Lenalidomide		

Title of Study: A Phase III, Randomized, Open-Label, 3-Arm Study to Determine the Efficacy and Safety of Lenalidomide (Revlimid®) Plus Low-Dose Dexamethasone When Given Until Progressive Disease or for 18 Four-Week Cycles Versus the Combination of Melphalan, Prednisone, and Thalidomide Given for 12 Six-Week Cycles in Patients With Previously Untreated Multiple Myeloma Who Are Either 65 Years of Age or Older or Not Candidates for Stem Cell Transplantation (IFM 07-01)

Coordinating Principal Investigator:

Study center(s): 246 sites (165 in Europe, 39 in North America, 23 in Asia, and 19 in the Pacific region)

Publications (references):

Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014 Sep 4;371(10):906-17.

Delforge M, Minuk L, Eisenmann JC, Arnulf B, Canepa L, Fragasso A, et al. Health-related quality-of-life in patients with newly diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. Haematologica. 2015 Jun;100(6):826-33.

Dimopoulos MA, Cheung MC, Roussel M, Liu T, Gamberi B, Kolb B, et al. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. Haematologica. 2016 Mar;101(3):363-70.

Facon T, Dimopoulos M, Dispenzieri A, Catalano JV, Belch A, Cavo M, et al. Final analysis of overall survival from the First Trial. Abstract presented at: 58th Annual Meeting and Exposition of the American Society of Hematology (ASH). 2016 Dec 3-6; San Diego, CA; USA: Abstract 241.

Studied period (years): Date first subject randomized: 29 Aug 2008 Date last subject last visit: 14 Jul 2016	Phase of development: Phase 3

Objectives:

Primary: To compare the efficacy of lenalidomide plus low-dose dexamethasone (Rd) given until progressive disease (PD) to that of melphalan, prednisone, and thalidomide (MPT) given for twelve 42-day cycles

Secondary: (1) To compare the efficacy of Rd given for eighteen 28-day cycles (Rd18) to that of MPT given for twelve 42-day cycles; (2) to assess the safety of Rd versus that of MPT; and (3) to assess the safety and efficacy of Rd therapy given until PD versus the safety and efficacy of Rd given for eighteen 28-day cycles.

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Methodology:

CC-5013-MM-020/IFM 07-01 (hereafter referred to as MM-020) was a Phase 3, multicenter, randomized, open-label, 3-arm study that compared the efficacy and safety of Rd given for 2 different durations of time (ie, until PD or for up to eighteen 28-day cycles [72 weeks]) to that of MPT given for a maximum of twelve 42-day cycles (72 weeks). Key eligibility criteria included subjects with newly diagnosed symptomatic multiple myeloma (MM) who had measurable monoclonal protein (M-protein) by protein electrophoresis analyses and who were aged ≥ 65 years or who were not candidates for stem cell transplantation (SCT). Subjects with poor performance status (Eastern Cooperative Oncology Group [ECOG] status of 3 or 4) or serious coexistent medical conditions were excluded.

Eligible subjects were randomized (1:1:1) to 1 of the 3 treatment arms. Subjects were stratified at randomization by age (≤ 75 versus > 75 years); stage (International Staging System [ISS] Stages I or II versus Stage III); and country. Study treatment began the same day the subject was randomized. Study visits and serial measurements of safety and efficacy were performed as outlined in the protocol. Response, including PD, was assessed according to the International Myeloma Working Group (IMWG) criteria based on central laboratory values. Guidelines for study drug dose reduction for dose-limiting toxicity (DLT) were followed. Subjects continued their prescribed therapy until the documentation of PD or intolerable toxicity. All subjects were to receive antithrombotic prophylaxis.

This study consisted of an active treatment phase; progression-free survival (PFS) follow-up phase; and long-term follow-up phase. The active treatment phase ended when study treatment was discontinued permanently because of documented occurrence of PD, completion of study treatment per protocol, or intolerable toxicity or any reason other than PD. Subjects in Arm Rd18 or Arm MPT who completed 18 or 12 cycles, respectively, entered the PFS follow-up phase to be followed until PD. Regularly scheduled response and PD assessments continued for these subjects every 28 days. No antimyeloma therapy (AMT) was to be started during the PFS follow-up phase until development of PD.

The primary efficacy endpoint, PFS, was calculated as the time from randomization to the first documented PD (confirmed by the blinded Independent Response Adjudication Committee [IRAC]) or death due to any cause during the study, whichever occurred first. All subjects were followed for response and PD during the active treatment phase and the PFS follow-up phase.

The following subjects entered the long-term follow-up phase: subjects who developed disease progression (PD) in either the active treatment phase and/or the PFS follow-up phase; subjects who declined further participation in the active treatment or PFS follow-up phases before documented occurrence of PD; and subjects who did not complete 6 cycles of treatment and who discontinued for reasons other than PD.

Subjects who entered the long-term follow-up phase initially had assessments every 4 months and then every 2 months from Amendment 3 (dated 01 Apr 2011) onward. Subjects who progressed were assessed for subsequent AMTs (best response to the first AMT regimen used after study discontinuation), potential development of second primary malignancies (SPMs), subsequent PD after second-line therapy, and overall survival.

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Number of patients (planned and analyzed):

Planned: 1590 (530 per treatment arm)

Analyzed: 1623 (randomized/intent-to-treat population); 1613 (safety population)

Diagnosis and main criteria for inclusion:

Previously untreated symptomatic MM as defined by 3 diagnostic criteria, including monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma, monoclonal protein (M-protein) present in the serum and/or urine, and myeloma-related organ dysfunction (all 3 required); and had measurable disease by protein electrophoresis analyses; and were at least 65 years of age or older or, if younger than 65 years of age, were not candidates for SCT.

Test product, dose and mode of administration:

Celgene supplied lenalidomide 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules in bottles and commercial supplies of dexamethasone (4-mg tablets) for oral administration.

Duration of treatment:

Arm Rd: treatment until PD; Arm Rd18: treatment for up to eighteen 4-week cycles (72 weeks); and Arm MPT: treatment for up to twelve 6-week cycles (72 weeks)

Reference therapy, dose and mode of administration:

Commercial supplies of melphalan (2-mg tablets), prednisone (5-, 10-, 20-, and 50-mg tablets), and thalidomide (50-, 100-, and 200-mg capsules) were provided by Celgene for oral administration.

Criteria for evaluation (for this synoptic report):

Efficacy: No efficacy analyses were performed. Safety: Adverse events (AEs), deaths, and SPMs

Statistical methods:

Descriptive analyses were performed to summarize subject disposition, treatment duration, and dose exposure.

Adverse events were categorized according to the Medical Dictionary for Drug Regulatory Activities (MedDRA®), Version 15.1. Severity of AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

Absolute differences in the number of subjects with AEs occurring between the final database lock date of 07 Oct 2016 and the previous data cutoff of 21 Jan 2016 were provided for Arm Rd.

Deaths during the entire study (the active treatment and follow-up phases) were tabulated by the primary cause of death.

The frequency of subjects who were diagnosed with SPMs during the entire study was summarized by SPM category. Incidence rate per person-years as well as the number and percentage of subjects who died and who remained alive were provided by SPM category. Person-years were calculated.

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SUMMARY – CONCLUSIONS

This synoptic report presents data on treatment duration, dose exposure, AEs, and deaths (both during and after treatment) from 21 Jan 2016 to the date of the last subject last visit (14 Jul 2016) as well as on SPMs during the entire study and represents the final closeout report for this study. Additional data were collected up to the final database lock date of 07 Oct 2016.

Subject Disposition

As of the 21 Jan 2016 data cutoff date, 52 subjects (9.7%) were still receiving treatment in Arm Rd while 20 subjects (3.7%) and 130 subjects (24.3%) were still being followed in the PFS and long-term follow-up phases, respectively. All subjects in Arm Rd18 and Arm MPT had either discontinued or completed 18 (Rd18) or 12 (MPT) cycles of study treatment. In Arm Rd18, 4.8% and 36.6% of subjects were still being followed in the PFS and long-term follow-up phases, respectively, while in Arm MPT, 4.4% and 26.9% of subjects were still being followed in these phases. The last subject last visit was 14 Jul 2016.

EFFICACY RESULTS:

No efficacy analyses are presented in this synoptic report.

SAFETY RESULTS:

Treatment Duration

Per study design which stipulated that treatment in Arm Rd continue until PD, the mean duration of treatment was longer in Arm Rd than that in the other 2 treatment arms: 111.6 weeks or approximately double that of Arm Rd18 (54.8 weeks) or of Arm MPT (51.9 weeks). In comparison with the mean duration of treatment of 110.6 weeks in Arm Rd reported at the time of the 21 Jan 2016 cutoff, the mean duration of treatment of 111.6 weeks in this arm at the final visit was only 1 week longer.

The total number of person-years on study treatment in each treatment arm was 1137 in Arm Rd, 587 in Arm Rd18, and 549 in Arm MPT.

Dose Exposure

Final lenalidomide and dexamethasone dose information for Arm Rd was very similar to the dose information reported at the 21 Jan 2016 data cutoff. Maximum values for cumulative dose, dose exposure, and duration of dose increased with the final data—a finding which was expected—but the median values for each parameter reported remained the same.

Adverse Events

An overview of AEs that occurred during the entire study as of the final data (07 Oct 2016) shows that the change in the number of subjects for which TEAEs were reported was relatively small (absolute differences ranged from 0 to 4) across all categories. When compared with the prior data cutoff of 21 Jan 2016, there were no changes in the percentage of subjects who had at least 1 TEAE (99.4%), at least 1 Grade 3 or 4 TEAE (86.3%), at least 1 Grade 5 TEAE (10.3%), or at least 1 treatment-emergent serious adverse event (SAE) (71.1%).

In the final data, 2 additional subjects each experienced Grade 3 or 4 AEs and SAEs considered related to lenalidomide or to lenalidomide/dexamethasone. Otherwise; no other subjects experienced

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AEs that were considered related to lenalidomide. Four additional subjects experienced an AE leading to withdrawal of lenalidomide.

Deaths

Overall, 928 (57.5%) subjects died during the entire study (during the active treatment and follow-up phases). The overall percentage of deaths was lower in Arm Rd (55.3%, 294/532) than that in Arm MPT (63.0%, 341/541). In Arm Rd18, the overall percentage of deaths was similar to that in Arm Rd: 54.3%, 293/540. From the 21 Jan 2016 data cutoff date to the final data (07 Oct 2016), 25 deaths occurred: 10 in Arm Rd, 10 in Arm Rd18, and 5 in Arm MPT. All of these deaths occurred during follow-up after study treatment had been discontinued.

The final data (07 Oct 2016) show that multiple myeloma (preferred term) was specifically selected by the investigators as the most frequent primary cause of death: 20.3% in Arm Rd, 23.5% in Arm Rd18, and 28.5% in Arm MPT. Other common primary causes of death included infections (system organ class [SOC] of Infections and Infestations) (9.6%, 5.9%, and 8.5% of subjects, respectively) and cardiac disorders (SOC) (5.8%, 5.6%, and 3.7%, respectively).

Second Primary Malignancies

A total of 194 (12.0%) of the 1613 subjects in all 3 treatment arms experienced at least 1 SPM as of the final data of 07 Oct 2016. The frequencies of subjects with invasive SPMs (hematologic and solid tumor SPMs) were similar for Arms Rd and Rd18 (7.1% and 7.0%, respectively). A higher frequency of invasive SPMs was observed in Arm MPT (8.7%). The incidence rates of developing an invasive SPM were 1.85, 1.87, and 2.47 per 100 person-years in Arms Rd, Rd18, and MPT, respectively. Of the subjects with invasive SPMs, 7 of the 21 subjects with hematologic SPMs, the majority of which were acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), were in the lenalidomide/dexamethasone-containing arms (5 subjects in Arm Rd and 2 subjects in Arm Rd18), while 14 subjects were in Arm MPT. One subject in Arm Rd was diagnosed with a B-cell malignancy (acute lymphocytic leukemia [ALL]) and 1 subject in Arm Rd had an "other" hematologic malignancy (chronic myelomonocytic leukemia [CMML]). Overall, the frequencies of subjects with solid tumor SPMs were similar for all 3 treatment arms (Arm Rd [6.2%], Arm Rd18 [6.9%], and Arm MPT [6.1%]).

Overall, the 95% confidence intervals for the incidence rates of all SPM categories overlap across all 3 treatment arms with the exception of the hematologic malignancies. The observed increase in frequency of hematologic SPMs in MPT-treated subjects represents the greatest difference for any SPM category.

As of the final data of 07 Oct 2016, the overall median time to diagnosis of an invasive SPM was 31.6 months (range: 0.5 to 81.1 months). The median time to onset of an invasive SPM was longer for Arm Rd (48.2 months) compared with Arm Rd18 and Arm MPT (19.1 and 33.9 months, respectively).

Of the 194 subjects who experienced an SPM, 86 remain alive (26 subjects in Arm Rd, 30 subjects in Arm Rd18, and 30 subjects in the Arm MPT), while 108 died (36 subjects in Arm Rd, 30 subjects in Arm Rd18, and 42 subjects in the Arm MPT). Of the 108 subjects who died, 44 subjects died due to their SPM or a complication of their SPM (13 subjects in Arm Rd, 15 subjects in Arm Rd18, and

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16 subjects in Arm MPT), 29 subjects died due to progression of multiple myeloma or a complication of their multiple myeloma (7 subjects in Arm Rd, 5 subjects in Arm Rd18, and 17 subjects in Arm MPT), 21 subjects died due to other causes (10 subjects in Arm Rd, 5 subjects in Arm Rd18, and 6 subjects in Arm MPT), and 14 subjects died due to unknown causes (6 subjects in Arm Rd, 5 subjects in Arm Rd18, and 3 subjects in Arm MPT).

Of the 21 subjects who had hematologic SPMs, 3 subjects remain alive (1 subject each in Arms Rd, Rd18, and MPT), while 18 died (4 subjects in Arm Rd, 1 subject in Arm Rd18, and 13 subjects in Arm MPT). Nineteen of the 21 subjects with hematologic SPMs were diagnosed with AML/MDS, of whom 2 subjects remain alive and 17 subjects died. Of the 17 subjects with AML/MDS who died, 12 died due to their hematologic SPM or a complication of their SPM, 3 died due to progression of multiple myeloma or a complication of their multiple myeloma, 1 subject died due to other causes (severe sepsis), and 1 subject died due to unknown causes. One subject in Arm Rd was diagnosed with an "other" hematologic malignancy (CMML) and remains alive, and 1 subject in Arm Rd was diagnosed with a B-cell malignancy (ALL) and died due to ALL.

Of the 103 subjects who had solid tumor SPMs, 38 remain alive (11 subjects in Arm Rd, 13 subjects in Arm Rd18, and 14 subjects in the Arm MPT) and 65 died (22 subjects in Arm Rd, 24 subjects in Arm Rd18, and 19 subjects in the Arm MPT). Of the 65 subjects who died, 31 died due to their solid tumor SPM or a complication of their SPM, 16 died due to progression of multiple myeloma or a complication of their multiple myeloma, 11 died due to other causes (sepsis [2 subjects], and complete heart block, heart failure, respiratory failure, respiratory distress, pneumonia, pneumonitis, multi-organ failure, cerebrovascular disease, and suicide [1 subject each]), and 7 died due to unknown causes.

Fifty-six of the 89 subjects who had at least 1 non-melanoma skin cancer remain alive (18 subjects in Arm Rd, 20 subjects in Arm Rd18, and 18 subjects in Arm MPT), while 33 died (14 subjects in Arm Rd, 7 subjects in Arm Rd18, and 12 subjects in Arm MPT) due to causes other than their non-melanoma skin cancer. Of the 33 subjects with at least 1 non-melanoma skin cancer who died, 14 died due to progression of multiple myeloma or a complication of their multiple myeloma, 9 died due to other causes (end-stage renal failure, chronic renal failure, cardiac failure, pulmonary embolism, hemorrhagic cerebrovascular stroke, arteritis of right lower limb, influenza A pneumonia, left hip fracture, and accident [1 subject each]), 7 died due to unknown causes, and 3 died due to their invasive SPM (MDS, ALL, and malignant neoplasm of unknown primary [1 subject each]).

CONCLUSIONS

Treatment with Rd was generally well tolerated. For the final data of 07 Oct 2016, there were no increases in the frequency of AEs in subjects who had at least 1 TEAE, at least 1 Grade 3 or 4 TEAE, at least 1 Grade 5 TEAE, or at least 1 treatment-emergent SAE compared with the findings reported for the data cutoff date of 21 Jan 2016 in the updated CSR. The overall percentage of deaths was lower in Arm Rd than that in Arm MPT, while in Arm Rd18 the overall percentage of deaths was similar to that in Arm Rd.

There was no apparent increased risk of invasive SPMs with continuing treatment of Rd until PD compared with that for Rd18. The frequency of hematologic SPMs in Arm Rd and Arm Rd18 was < 1%.

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In summary, the results of Study MM-020, which compared the efficacy and safety of continuous treatment with Rd with the standard control of MPT and with Rd given for up to eighteen 28-day cycles (Rd18), showed that the safety profile of the Rd regimen continued to be consistent with the known safety profile of lenalidomide with low-dose dexamethasone. Results of the efficacy analyses were presented in previous reports. Date of the report: 16 Mar 2017		