**FIRST Clinical Trial**

**FIRST Overview**

The FIRST trial, also known as MM-020/IFM 07-01, is one of the largest phase III, randomised, international studies ever conducted in newly diagnosed multiple myeloma.¹

**What is Multiple Myeloma?**

Multiple myeloma is a blood cancer in which plasma cells—important components of the immune system—replicate uncontrollably and accumulate in the bone marrow. More than 114,000 new cases are diagnosed annually worldwide², with over 38,000 diagnosed in Europe.³

**Trial Design**

Phase III, randomised, open-label, international study¹

- 1,623 patients with previously untreated, symptomatic and measurable multiple myeloma who were either 65 years or older, or younger than 65 and ineligible for autologous stem cell transplantation
- Patients were stratified by age (75 years or younger vs. older than 75), stage of disease (ISS stage 1 & 2 vs. 3), and country
- Conducted at 246 centres in 18 countries on 4 continents

Patients were randomised into three study arms and received the following:¹

- **Arm A (Rd)**, n=535: Continuous oral REVLIMID® plus low-dose dexamethasone (dex) in 28-day cycles until disease progression
- **Arm B (Rd18)**, n=541: REVLIMID® plus low-dose dex for eighteen 28-day cycles (72 weeks)
- **Arm C (MPT)**, n=547: Melphalan, prednisone and thalidomide (MPT) for twelve 42-day cycles (72 weeks)

**FIRST Trial: Study Design**

<table>
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<tr>
<th>Screening</th>
<th>Active Treatment + PFS Follow-up Phase</th>
<th>LT Follow-Up</th>
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<tbody>
<tr>
<td><strong>Arm A</strong> Continuous Rd</td>
<td>LEN + LoDEX: Continuously</td>
<td>PD or Unacceptable Toxicity</td>
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<tr>
<td>Lenalidomide 25 mg D1-21/28</td>
<td>LoDEX 40 mg D1,8,15, and 22/28</td>
<td>PD, OS, and Subsequent anti-MM Tx</td>
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<tr>
<td><strong>Arm B</strong> Rd18</td>
<td>LEN + LoDEX: 18 Cycles (72 wks)</td>
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<tr>
<td>Lenalidomide 25 mg D1-21/28</td>
<td>LoDEX 40 mg D1,8,15, and 22/28</td>
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<td><strong>Arm C</strong> MPT</td>
<td>MEL + PRED + THAL: 12 Cycles (72 wks)</td>
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<td>Melphalan 0.25 mg/kg D1-4/42</td>
<td>Prednisone 2 mg/kg D1-4/42</td>
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<td>Thalidomide 200 mg D1-42/42</td>
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**Notes**

ISS, International Staging System; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; LEN, lenalidomide; LoDEX, low-dose dexamethasone; LT, long-term; MEL, melphalan; MM, multiple myeloma; MPT, melphalan, prednisone, thalidomide; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Pred, prednisone; pt, patient; THAL, thalidomide; Tx, treatment.

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For additional information about the study refer to clinicaltrials.gov NCT00689936.

Date of Preparation: February 2015 INT-REV150001
Results

Primary endpoint: Comparison between Rd and MPT of the time until death or disease worsening while on treatment, also known as progression-free survival (PFS)\(^1\)

- The median PFS at the data cut-off on 3 March 2014, was 26.0 months with Rd, 21.0 months with Rd18 and 21.9 months with MPT. Rd was associated with a significant improvement in PFS, as compared with MPT (hazard ratio [HR] for progression or death 0.69; 95% confidence interval [CI], 0.59 to 0.80, P<0.001), and also when compared with Rd18 (HR 0.71; 95% CI 0.61 to 0.83, P<0.001)\(^4\)

Secondary endpoints

- Overall survival rate

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<th>Rd</th>
<th>Rd18</th>
<th>MPT</th>
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<tr>
<td>3 years</td>
<td>70%</td>
<td>66%</td>
<td>62%</td>
</tr>
<tr>
<td>4 years</td>
<td>60%</td>
<td>57%</td>
<td>51%</td>
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Although not indicative of superiority at the time of the interim analysis, Rd did show a reduced risk of death compared with MPT (HR 0.78; 95% CI 0.64 to 0.96; P=0.02)*\(^1\)

- Response rates were higher with Rd (75.1%) and with Rd18 (73.4%) than with MPT (62.3%; P<0.001 for both comparisons)*\(^4\)
  - Response rate: how well the disease responds to treatment as defined by the International Uniform Response Criteria for Multiple Myeloma\(^5,6\)
- The median duration of response with Rd was significantly longer with Rd18 (35.0 months) than with Rd18 (22.1 months, P<0.001) or MPT (22.3 months, P<0.001)*\(^4\)
- The median time to response (assessed in patients who had a partial response or better) was shorter with Rd (1.8 months) than MPT (2.8 months, P<0.001)*\(^1\)
- The median time to second-line anti-myeloma therapy was significantly longer with Rd (39.1 months), than with Rd18 (28.5 months, P<0.001) or with MPT (26.7 months, P<0.001)*\(^1\)
- The serious adverse events observed more frequently (≥5%) with Rd and Rd18 than with MPT were pneumonia (9.8%) and renal failure (including acute) (6.3%)\(^4\)
- The adverse events observed more frequently with Rd or Rd18 than MPT were diarrhea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%)\(^4\)

Exploratory endpoint: Time from randomisation to second progression event, or death (PFS2)

The median PFS2 benefit observed with Rd was maintained with the next line of therapy. The median PFS2 was 42.9 months with Rd, 40.0 with Rd18 (HR 0.92; P=0.316) and 35.0 with MPT (HR 0.74; P<0.001)*\(^4\)

- PFS2 is defined as per EMA guidance\(^7\) as time from randomisation to:
  - objective tumour progression on next-line treatment, or
  - death from any cause
- In some cases, time on next line therapy may be used as proxy for PFS
- PFS2 is based on intention to treat population

*For Rd to show superiority in terms of overall survival to MPT, the comparison would need to achieve a pre-specified P-value of <0.0096.

For additional information about the study refer to clinicaltrials.gov NCT00689936.
Contraindications

REVLIMID® (lenalidomide) is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients in the formulation.

REVLIMID® (lenalidomide) is contraindicated during pregnancy, and also in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

Warnings and precautions

Pregnancy: the conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Cardiovascular disorders: patients with known risk factors for myocardial infarction or thromboembolism should be closely monitored.

Neutropenia and thrombocytopenia: complete blood cell counts should be performed every week for the first 8 weeks of treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required.

Infection with or without neutropenia: all patients should be advised to seek medical attention promptly at the first sign of infection.

Renal impairment: monitoring of renal function is advised in patients with renal impairment.

Thyroid disorders: optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Tumour lysis syndrome: patients with high tumour burden prior to treatment should be monitored closely and appropriate precautions taken.

Allergic reactions: patients who had previous allergic reactions while treated with thalidomide should be monitored closely.

Severe skin reactions: REVLIMID® (lenalidomide) must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Lactose intolerance: patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Second primary malignancies (SPM): the risk of occurrence of hematologic SPM must be taken into account before initiating treatment with REVLIMID® (lenalidomide) either in combination with melphalan or immediately following high-dose melphalan and autologous stem cell transplant (ASCT). Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated.

Hepatic disorders: abnormal liver function is generally reversible on dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered. It is important to dose-adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended.

Newly diagnosed multiple myeloma patients: patients should be carefully assessed for their ability to tolerate REVLIMID® (lenalidomide) in combination, with consideration to age, ISS stage III, ECOG PS≤2 or CLcr<60 mL/min.

Cataract: regular monitoring of visual ability is recommended.
Summary of the safety profile in multiple myeloma

Newly diagnosed multiple myeloma in patients treated with REVLIMID® (lenalidomide) in combination with low dose dexamethasone:

- The serious adverse reactions observed more frequently (≥5%) with REVLIMID® (lenalidomide) in combination with low dose dexamethasone (Rd and Rd18) than with melphalan, prednisone and thalidomide (MPT) were pneumonia (9.8%) and renal failure (including acute) (6.3%)

- The adverse reactions observed more frequently with Rd or Rd18 than MPT were: diarrhoea (45.5%), fatigue (32.8%), back pain (32.0%), asthenia (28.2%), insomnia (27.6%), rash (24.3%), decreased appetite (23.1%), cough (22.7%), pyrexia (21.4%), and muscle spasms (20.5%).

Newly diagnosed multiple myeloma patients treated with REVLIMID® (lenalidomide) in combination with melphalan and prednisone:

- The serious adverse reactions observed more frequently (≥5%) with melphalan prednisone, and REVLIMID® (lenalidomide) followed by REVLIMID® (lenalidomide) maintenance (MPR+R) or melphalan prednisone, and REVLIMID® (lenalidomide) followed by placebo (MPR+p) than melphalan, prednisone and placebo followed by placebo (MPp+p) were febrile neutropenia (6.0%) and anaemia (5.3%)

- The adverse reactions observed more frequently with MPR+R or MPR+ p than MPp+p were: neutropenia (83.3%), anaemia (70.7%), thrombocytopenia (70.0%), leukopenia (38.8%), constipation (34.0%), diarrhoea (33.3%), rash (28.9%), pyrexia (27.0%), peripheral oedema (25.0%), cough (24.0%), decreased appetite (23.7%), and asthenia (22.0%).

Patients with multiple myeloma who have received at least one prior therapy:

- The most serious adverse reactions observed more frequently with REVLIMID® (lenalidomide) and dexamethasone than with placebo and dexamethasone in combination were venous thromboembolism (deep vein thrombosis, pulmonary embolism) and grade 4 neutropenia

- The observed adverse reactions which occurred more frequently with REVLIMID® (lenalidomide) and dexamethasone than placebo and dexamethasone in pooled multiple myeloma clinical trials (MM-009 and MM-010) were fatigue (43.9%), neutropenia (42.2%), constipation (40.5%), diarrhoea (38.5%), muscle cramp (33.4%), anaemia (31.4%), thrombocytopenia (21.5%), and rash (21.2%).

Special populations

Paediatric population: REVLIMID® (lenalidomide) should not be used in children and adolescents from birth to less than 18 years.

Older people with newly diagnosed multiple myeloma: for patients older than 75 years of age treated with REVLIMID® (lenalidomide) in combination with dexamethasone, the starting dose of dexamethasone is 20 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle. No dose adjustment is proposed for patients older than 75 years who are treated with REVLIMID® (lenalidomide) in combination with melphalan and prednisone.

Older people with multiple myeloma who have received at least one prior therapy: care should be taken in dose selection and it would be prudent to monitor renal function.

Patients with renal impairment: care should be taken in dose selection and monitoring of renal function is advised. No dose adjustments are required for patients with mild renal impairment and multiple myeloma. Dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impaired renal function or end stage renal disease.

Patients with hepatic impairment: REVLIMID® (lenalidomide) has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Please click here for full Prescribing Information (EU Summary of Product Characteristics)

References:
4. REVLIMID® Summary of Product Characteristics