Updated results from the CALGB (Alliance) 100104 clinical trial to assess efficacy of lenalidomide maintenance treatment post-ASCT

For newly diagnosed Multiple Myeloma (NDMM) patients aged 70 years or younger and eligible for transplant, autologous stem cell transplantation (ASCT) followed by lenalidomide maintenance, has become a fairly standard first regimen. In the CALGB (Alliance) 100104 study, maintenance treatment with a course of lenalidomide was compared with placebo after ASCT, and initially assessed at a median follow-up of 34 months. In August 2017, the findings of this randomized, double-blind, placebo-controlled, phase III trial, with a longer median follow-up of 91 months, were published in The Lancet Haematology. The study was led by Sarah A. Holstein from The University of Nebraska Medical Center, Omaha, USA, and Philip L. McCarthy, from the Roswell Park Cancer Institute, Buffalo, USA, along with a team of researchers throughout the USA. The primary endpoint was time to progression (TTP), with intention-to-treat (ITT) analysis.

Key Highlights:

All data is given as lenalidomide vs placebo:

- Patients (pts) (n = 460) were recruited between April 14th 2005, and July 2nd 2009, aged 18-70 years
- Eligibility: Pts were symptomatic and requiring treatment; had received ≤ 2 induction regimens and had achieved stable disease or better in the first 100 days after ASCT
- Pts were divided into two groups to receive either lenalidomide (n=231) or placebo (n=229)
- Starting dose = two capsules (10 mg) per day, with three capsules (15 mg) per day given after 3 months
- At a median follow-up of 18 months and 3 interim studies, the trial was unblinded
- Pts in the placebo group without progressive disease (PD) moved into the lenalidomide group = 86/128 (67%)
- Median duration of treatment: 31 months (95% CI, 24.8-35.8) vs 18.1 months (95% CI 17.1-22.6)
- Median duration of treatment within placebo group: crossover group = 30.7 months (95% CI 12.5-17.3); non-crossover pts = 14.5 months (95% CI 12.5-17.3)
- Median follow-up for updated survival analysis = 91 months (IQR 83.6–103.1)
- Pts with progressive disease (PD) or death = 146/231 (63%) vs 176/229 (77%)
- Median OS = 113.8 months (95% CI 100.4–not reached) vs 84.1 months (73.8–106.0); HR = 0.61, (95% CI 0.46–0.80; p= 0.00040).
- OS at 5-years = 76% (95% CI 70–81) vs 64% (95% CI 58–70)
- Median TTP: 57.3 months (95% CI 44.2–73.3) vs 28.9 months (23.0–36.3); HR = 0.57 (95% CI 0.46–0.71); p<0.0001
- TTP benefits observed regardless of prior lenalidomide or thalidomide exposure
- Most common grade 3–4 adverse events (AEs):
  - Neutropenia = 116 pts (50%) vs 41 pts (18%)
  - Thrombocytopenia = 34 pts (15%) vs 12 pts (5%)
  - Haematological malignancies = 18 pts (8%) vs 3 pts (1%)
  - Solid tumour = 14 pts (6%) vs 9pts (4%)
  - Non-invasive second primary malignancies = 11 pts (5%) vs 6 pts (3%)
Conclusion:
This long-term study strengthens the case for ASCT followed by lenalidomide maintenance as a standard of care for transplant eligible patients. Despite the higher occurrence of SPMs in the lenalidomide group, the benefit with regards to TTP and OS outweighs the risk. This is encouraging for physicians in the USA that are using this in routine practice, but it has yet to be licensed in Europe for the treatment of NDMM patients. Currently, the European Medicines Agency licenses (EMA) only allow treatment of newly diagnosed patients that are not eligible for transplant, and in combination with dexamethasone for patients that have received at least one prior therapy.

In a Comment by Mario Boccadoro from the Division of Haematology, University of Turin, also published in The Lancet Hematology, the uncertainties surrounding maintenance therapy were outlined. Firstly, Boccadoro discussed the need to identify the patient subset that will benefit the most from maintenance therapy, and pointed out that this study did not evaluate data for patients with cytogenetic abnormalities. This is important in light of the results from the FIRST clinical trial, where no benefit was observed from treatment with continuous lenalidomide in this subset. Secondly, the optimum schedule and duration of treatment needs to be addressed, in order to limit toxicity while maximising benefits. Two European trials with lenalidomide did not replicate the benefits observed in this study, and it was suggested that differences in treatment schedules and duration could be the reason. However, it was noted that the authors did recognize these limitations themselves, and hoped that long-term studies already underway would provide clarity. The problem with this is that the longer patient survival times will mean a greater wait until endpoints can be effectively evaluated. As a solution, it was noted that since minimal residual disease (MRD) strongly correlates with survival and a good prognosis, this could be a more useful endpoint for evaluating maintenance in such long-term studies and should be incorporated into future trials.

Summary
Background: In the CALGB (Alliance) 100104 study, lenalidomide versus placebo after autologous stem-cell transplantation (ASCT) was investigated for patients with newly diagnosed myeloma. That study showed improved time to progression and overall survival and an increase in second primary malignancies for lenalidomide at a
median follow-up of 34 months. Here we report an updated intention-to-treat analysis of CALGB (Alliance) 100104 at a median follow-up of 91 months. **Methods:** Patients were eligible for this randomised, double-blind, placebo-controlled, phase 3 trial if they had symptomatic disease requiring treatment; had received, at most, two induction regimens; and had achieved stable disease or better in the first 100 days after ASCT. We randomly assigned patients to either lenalidomide or placebo groups using permuted block randomisation, with a fixed block size of six. Randomisation was stratified by three factors: normal or elevated $\beta_2$ microglobulin concentration at registration ($\leq 2.5$ mg/L vs $>2.5$ mg/L), previous use or non-use of thalidomide during induction therapy, and previous use or non-use of lenalidomide during induction therapy. The starting dose was two capsules (10 mg) per day, escalated to three capsules (15 mg) per day after 3 months. The primary endpoint was time to progression (time of progressive disease or death from any cause), with intention-to-treat analysis. This study is registered with ClinicalTrials.gov, identifier NCT00114101. New patients are no longer being recruited, but some patients remain on treatment and in follow-up. **Findings:** Between April 14, 2005, and July 2, 2009, 460 patients were randomly assigned to receive either lenalidomide (n=231) or placebo (n=229). After three interim analyses, the study was unblinded at a median follow-up of 18 months, at which point 86 (67%) of 128 patients without progressive disease in the placebo group chose to cross over to the lenalidomide group. The median follow-up for the updated survival analysis, as of Oct 19, 2016, was 91 months (IQR 83.6–103.1). The median time to progression was 57.3 months (95% CI 44.2–73.3) for the lenalidomide group and 28.9 months (23.0–36.3) for the placebo group (hazard ratio 0.57, 95% CI 0.46–0.71; p<0.0001). The most common grade 3–4 adverse events were neutropenia (116 [50%] patients in the lenalidomide group and 41 [18%] patients in the placebo group) and thrombocytopenia (34 [15%] patients in the lenalidomide group and 12 [5%] patients in the placebo group). 18 (8%) haematological and 14 (6%) solid tumour second primary malignancies were diagnosed after randomisation and before disease progression in the lenalidomide group, compared with three (1%) haematological and nine (4%) solid tumour second primary malignancies in the placebo group. Three haematological and five solid tumour second primary malignancies in the placebo group were in the crossover subgroup. **Interpretation:** Despite an increase in haematological adverse events and second primary malignancies, lenalidomide maintenance therapy after ASCT significantly improved time to progression and could be considered a standard of care.
References:


2. Boccadoro M. Updated analysis of CALGB (Alliance) 100104. Published online: 17 August 2017. DOI:http://dx.doi.org/10.1016/S2352-3026(17)30148-5