Phase 1 Dose Escalation Study of Sotatercept (ACE-011) in Combination with Lenalidomide and Dexamethasone in Patients with Relapsed and/or Refractory Multiple Myeloma

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Background

Anemia and bone disease are hallmarks of multiple myeloma

Activin A may mediate some of the bone disease in multiple myeloma

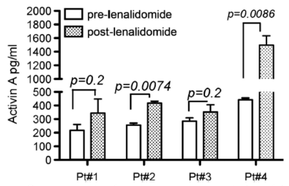
- Activin A is a member of the TGFβ superfamily (see also Vallet et al., *PNAS* 2010)
- Activin A levels are increased in bone marrow plasma of myeloma patients
- Activin A is produced by bone marrow stromal cells and osteoclasts
- Activin A stimulates osteoclasts and inhibits osteoblasts.

Bone marrow plasma levels of activin A correlate with bone disease in myeloma

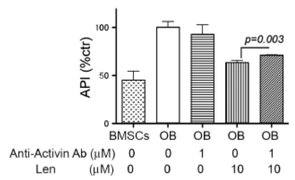
Presence of osteolytic lesions	Activin A (mean ± SE)
MM pts with 0-1 osteolytic lesion	28.62 ± 6.2 pg/mL
MM pts with >1 lesion	112.07 ± 30.4 pg/mL
Control patients	30.6 ± 7.9 pg/mL

Vallet S, et al. *Proc Natl Acad Sci USA* 2010;107:5124-5129

Lenalidomide may adversely affect bone dynamics



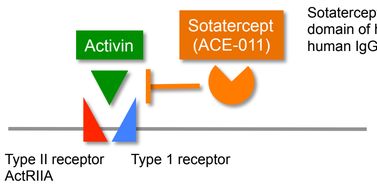
Serum samples from bone marrow aspirates of 4 MM patients undergoing lenalidomide treatment



Lenalidomide increases activin A secretion by bone marrow stromal cells and inhibits osteoblastogenesis (Scullen et al, *Leukemia* 2013)

Anti-activin antibody can overcome lenalidomide inhibition of osteoblastogenesis

Sotatercept (ACE-011) is a receptor fusion protein that sequesters activin



Sotatercept is a receptor fusion protein with the extracellular domain of human ActRIIA receptor fused to the Fc domain of human IgG1 that sequesters activin

Sotatercept simulates erythropoiesis

- Sotatercept stimulates erythropoiesis through an erythropoietin-independent mechanism
- Binds GDF11, which is associated with ineffective erythropoiesis in β thalassemia (Dussiot et al., *Nature Medicine* 2014)
- Sotatercept has shown promising activity in clinical trials for anemia in myelodysplastic syndromes (Komrokji et al., ASH 2014) and in thalassemia (Cappellini et al., EHA 2015)

Small randomized study of sotatercept in multiple myeloma (MPT ± sotatercept) (Abdulkadyrov et al., *Br. J Haematol* 2014)

- Associated with increase in hemoglobin
- Associated with decrease in bone turnover markers
- Trend towards improvement in osteolytic lesions (though bisphosphonates were permitted in this trial)

Based on these findings, we hypothesized that sotatercept will attenuate the negative effects on bone metabolism by lenalidomide as well as improve anemia, and therefore improve the overall outcomes of patients with relapsed/refractory multiple myeloma treated with lenalidomide and dexamethasone.

Eligibility and trial design

- Relapsed and/or refractory multiple myeloma with at least one prior line of therapy
- Hemoglobin ≤13 g/dL
- Adequate organ function
- FDG PET-CT and DEXA scan at screening and end of cycle 4 and/or end of study
- Phase I trial with 3 + 3 dose escalation scheme to determine MTD
- Sotatercept held if hemoglobin ≥13 g/dL
- Sotatercept held for grade ≥3 hypertension
- Bisphosphonates ***not*** allowed while on study (prior bisphosphonate permitted)
- Trial registered as NCT01562405

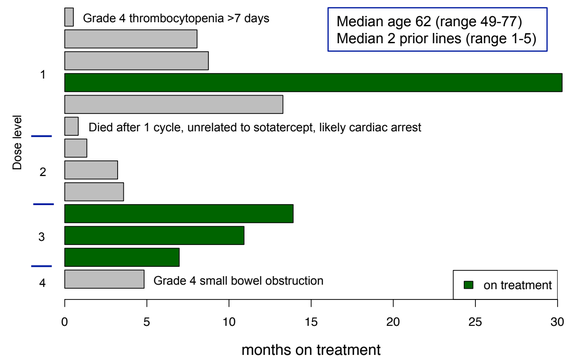
Treatment cycle, 28 days

Dose level	Sotatercept (s.c.)	Lenalidomide (p.o.)	Dexamethasone (p.o.)
1*	15 mg day 1	15 mg days 1-21	40 mg on days 1, 8, 15, 22
2	30 mg day 1	15 mg days 1-21	40 mg on days 1, 8, 15, 22
3	45 mg day 1	15 mg days 1-21	40 mg on days 1, 8, 15, 22
4	45 mg day 1	25 mg days 1-21	40 mg on days 1, 8, 15, 22

*First 3 patients on dose level 1 received sotatercept 10 mg

Results

13 patients enrolled; 4 continue on treatment

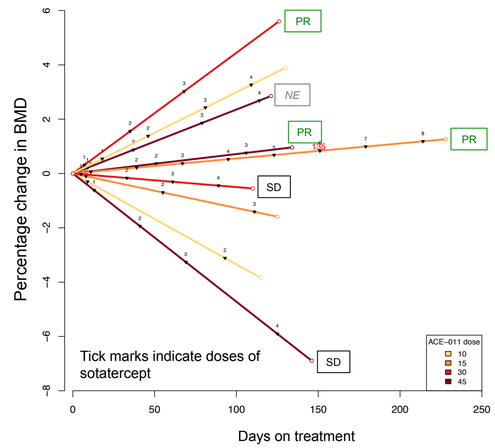


Adverse events (related or unrelated), grade 3-4

Term	Grade 3	Grade 4
Anemia	4	1
Febrile neutropenia	1	0
Neutropenia	2	0
Thrombocytopenia	2	1
Diarrhea	2	0
Fatigue	2	0
Headache	1	0
Hyperglycemia	1	0
Hypertension	2	0
Hypophosphatemia	2	0
INR increased	1	0
Lipase increased	1	0
Peripheral neuropathy	1	0
Colonic obstruction*	0	1
Small intestinal anastomotic leak*	1	0

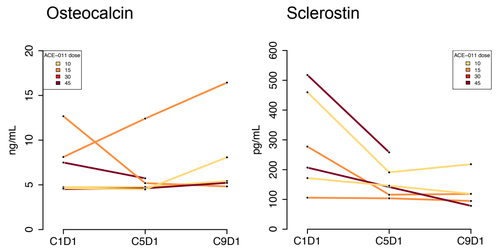
*Grade 4 small bowel obstruction due to incarcerated hernia (unrelated to drug) requiring small bowel resection on C3D26. Grade 3 abdominal pain and hospitalization C4D25 likely to due to small bowel anastomosis leak. Drain placed with complete recovery.

Increase in lumbar spine BMD in patients who achieved a response



No significant effect on total *hip* bone mineral density (data not shown)

Change in bone biomarkers



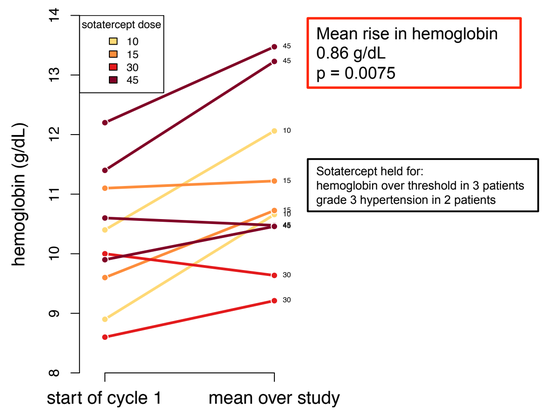
Serum osteocalcin, Immunodiagnostic Systems N-MID osteocalcin ELISA assay
Serum sclerostin, R&D ELISA assay

IMWG overall response rate 60%

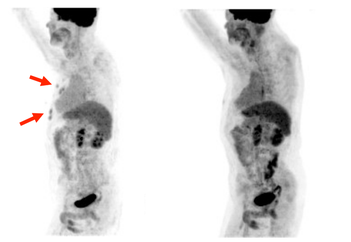
Best response	N
CR	1
VGPR	1
PR	4
SD	4

10 of 13 patients assessable for response

Significant increase in hemoglobin in patients who received at least two cycles



FDG PET-CT responses may correlate with paraprotein disease response



Patient at screening

After 4 cycles, resolution of bone lesions

Conclusions and future directions

- Sotatercept in combination with lenalidomide and dexamethasone was well tolerated
- Sotatercept significantly improved anemia, with an increase in hemoglobin of 0.86 g/dL
- Sotatercept was associated with an increase in lumbar spine BMD in patients who received an adequate dose and responded to treatment, in the absence of bisphosphonates
- Overall response rate was 60%, similar to the combination of lenalidomide and dexamethasone alone
- Interruptions in dosing due to hemoglobin thresholds may affect response; adjustments in dosing may improve continued exposure to sotatercept
- Change in bone biomarkers osteocalcin and sclerostin may reflect favorable effects on bone metabolism
- FDG PET-CT response may correlate with disease response
- Current dosing level is level 4, sotatercept 45 mg with lenalidomide 25 mg and weekly dexamethasone
- Sotatercept is a novel drug with a unique mechanism of action that may address both anemia and bone disease—major causes of morbidity in patients with multiple myeloma

Acknowledgments

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