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MYELODYSPLASTIC SYNDROMES (M SAVONA, SECTION EDITOR)

# Activin Receptor II Ligand Traps: New Treatment Paradigm for Low-Risk MDS

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**Abstract**

**Purpose of Review** Alleviating cytopenias, namely anemia, is the main goal of therapy in lower-risk myelodysplastic syndromes (MDS). Current available treatment options remain limited. We review the role of TGF-B pathway in MDS, the current available data on luspatercept and sotatercept development.

**Recent Findings** TGF-B pathway is overactivated in MDS contributing to observed myelosuppression. SMADs, the downstream proteins of TGF-B pathway, are upregulated. GDF-11 is a negative regulator of terminal erythroid differentiation and an activin receptor ligand. Sotatercept and luspatercept are fusion ligand trap novel agents for activin II receptors A and B, respectively. Early promising results have been reported with those novel agents for treating anemia in lower-risk MDS patients, and higher responses were observed among patients with ring sideroblasts and SF3B1 mutation. A phase III randomized clinical trial with luspatercept was recently conducted.

**Summary** Activin receptor II ligand traps may represent a new paradigm for anemia treatment in MDS.

**Keywords** MDS · TGFB Pathway · Erythroid Maturation Agents

## Introduction

Myelodysplastic syndromes are heterogeneous neoplastic hematopoietic stem cell disorders characterized by clonal hematopoiesis, dysplastic morphology, clinical bone marrow failure with resultant cytopenias, namely macrocytic anemia, and tendency to progress to acute myeloid leukemia (AML) [1]. Patients are risk stratified using the International Prognostic Scoring System (IPSS) or its revised version (R-IPSS) into lower-risk (LR-MDS) or higher-risk (HR-MDS) disease [2, 3]. Two-thirds of myelodysplastic syndromes (MDS) patients are classified as LR-MDS by IPSS. MDS with ring sideroblasts (MDS-RS) represents a unique subset of MDS with favorable outcomes and less frequent AML transformation [4]. The splicing mutation *SF3B1* is observed in 70–80% of patients with RS subtypes and associated with favorable outcome [4, 5]. The new WHO 2016 classification incorporates presence of SF3B1 mutation in diagnosis where patients with RS > 5% and SF3B1 mutation are classified as RS subtype compared with the 15% RS required threshold without the presence of the mutation [6•].

The majority of MDS patients present with anemia and become red blood cell transfusion dependent (RBC-TD) during course of their disease. Treatment of anemia in LR-MDS remains an unmet challenge with few options currently available [7]. Erythroid-stimulating agents (ESAs) represent often the first step of management with overall response rates of 20–40% and 18–24-month duration of response [7]. Lenalidomide is the standard of care for patients with deletion 5q MDS patients, and 67% of patients treated with lenalidomide become RBC transfusion independent (TI) with 3 years median duration of response [8]. However, in non-del5q, lenalidomide RBC-TI rates are 25% with less than a year median duration of response [9]. Hypomethylating agents are used for treatment of anemia in LR-MDS with 20–40% response rates reported [10]. Finally, immunosuppressive therapy is recommended only for small subset of young MDS patients who are not heavily RBC-TD [11].

In this article, we review the emerging evidence for the role of TGF-B pathway overactivation in MDS and the novel activin receptor II ligand trap fusion proteins, sotatercept and

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luspatercept, which showed early promising results in clinical studies for treatment of anemia in LR-MDS.

## TGF-B Pathway

The TGF-B receptors are superfamily of serine/threonine kinase receptors. TGFβ superfamily receptors are grouped into three types: type I, type II, and type III. There are seven type I receptors, termed the activin like receptors (ALK1–7), five type II receptors, and one type III receptor. TGF-B signaling pathway involves ligand binding to type II receptor which recruits and phosphorylates the type I receptor. Activin type II A and B receptors are members of the type II family receptors [12••, 13, 14].

The TGF-B receptor ligands are polypeptide growth factors, including TGF-B, activins, bone morphogenetic proteins (BMPs), and growth differentiation factor (GDF-11). Those cytokines regulate several cellular processes during development and in adults including hematopoiesis and regulating hematopoietic stem cells. Activin and GDF-11 exhibit inhibitory effect on terminal erythropoiesis distinct from the erythropoietin early regulatory role.

Following ligand binding and receptor phosphorylation, the SMAD signaling pathway becomes activated including SMAD-2 and SMAD-4. SMAD-6 and SMAD-7 serve as regulatory inhibitory proteins [12••] (Fig. 1).

## TGF-B Pathway in MDS

TGF-B pathway is overactivated in MDS which contributes to myelosuppression and cytopenias. SMAD-2 downstream mediator is overexpressed in MDS CD34+ cells. Lentiviral mediated downregulation or pharmacological inhibition improves hematopoiesis in vitro and murine models [15•]. The increased TGF-B signaling in MDS patients is related to decreased expression of SMAD-7 which is a negative regulatory protein [16]. The overexpression of miRNA-21 in MDS patients leads to its binding to 3′UTR of the SMAD-7 gene reducing it [17]. GDF-11 levels, a negative regulator of terminal erythrocyte differentiation, are elevated in MDS patients and in wild-type mice model, GDF-11 exposure led to mild anemia and erythroid hyperplasia [18].

## Activin Receptor II Ligand Traps

Two activin receptor (ActR) fusion ligand trap novel agents, sotatercept and luspatercept, have been tested for the treatment of anemia in LR-MDS (Table 1). The molecules consist of the extracellular domain of those TGF-B receptors linked to the human $IgG_1$ Fc domain. Those agents will neutralize the ligands before binding the receptor and thus inhibit signaling through the receptor [19].

Sotatercept (ACE-011) is an ActRIIA ligand trap protein with a bone remodeling effect as well [20]. RAP-011, the

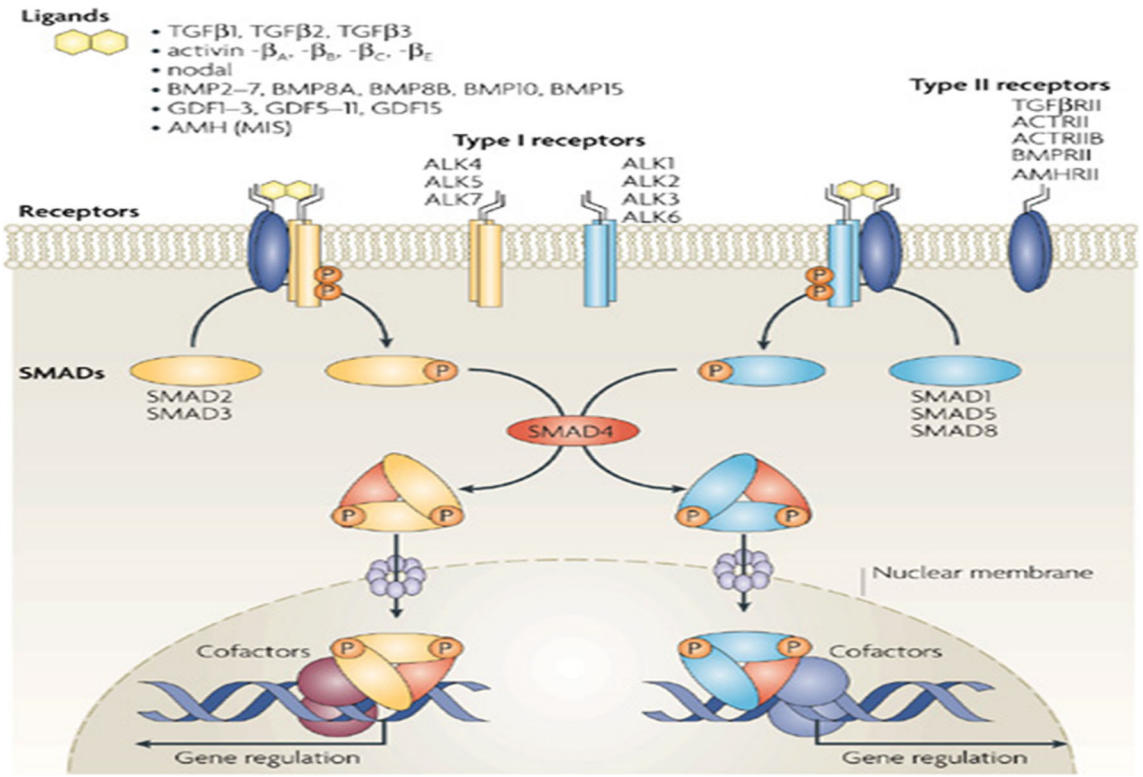


**Fig. 1** TGF-B-SMAD pathway (Reprinted with permission from Schmierer et al. (2007) [32])

**Table 1** Activin receptor ligand traps

| | Sotatercept | Luspatercept |
|---|---|---|
| Fusion protein ligand activity |  Extracellular domain of ActRIIA |  Extracellular domain of ActRIIB |
| Receptor ligand interaction | GDF11, activin A | GDF 11, GDF 8, activin B, BMP 6, BMP10 |
| Heme effect | + | + |
| Bone effect | + | – |

sotatercept murine analog, was tested for the reduction of osteoporosis in mice and later for the treatment of chemotherapy-related anemia and B-thalassemia [21]. In humans, it was first tested in single and multiple doses in post-menopausal healthy women volunteers where it increased bone mineral density and biomarkers of bone formation, but the dose-limiting effect was erythrocytosis and increased hemoglobin (Hgb) [22, 23]. In a small study for multiple myeloma, patients were randomized 4:1 to receive 4 doses of sotatercept ($n = 24$) (at 0.1, 0.3, 0.5 mg/Kg doses) versus placebo ($n = 6$) along with melphalan, thalidomide, and prednisone. Among sotatercept-treated patients, 71% had at least one dose interruption due to Hgb increase. The Hgb increased levels when compared with baseline and the duration of the increases were higher in the sotatercept-treated patients [24]. Sotatercept was tested also for treatment of chemotherapy-induced anemia among breast and lung cancer patients; the studies were terminated early because of slow accrual, but patients treated with sotatercept achieved Hgb increase of more than 1 g/dl, while no patients in the placebo arm did [25].

Luspatercept (ACE-536) is an ActRIIB ligand trap fusion protein [26••]. RAP-536, the murine analog, demonstrated robust increase in erythrocyte numbers and reduced or prevented anemia in mice models [18]. Co-treatment with RAP-536 and erythropoietin produced a synergistic response. RAP-536 bounds GDF-11 and potently inhibited its mediated Smad2/3 signaling. In humans, the first study included 34 post-menopausal female healthy volunteers. The dose was escalated where a dose-dependent increases in Hgb concentration were observed, beginning 7 days after the initiation of treatment and maintained for several weeks following treatment [27].

## Sotatercept MDS Clinical Data

A phase II dose finding study was conducted with sotatercept for treatment of anemia in LR-MDS patients [28••]. Eligible patients had low- or intermediate-1-risk disease by IPSS and had transfusion-dependent anemia defined as requiring ≥ 2 RBC units within 84 days of enrolment for a Hgb level ≤ 9.0 g/dl. Patients also had no response or loss of response to prior treatment with ESA, or had a low chance of response to ESAs. Patients were classified as low transfusion burden (LTB; < 4 red blood cell [RBC] units transfused in 56 days prior to enrolment) and those with high transfusion burden (HTB; ≥ 4 RBC units in 56 days). Sotatercept at 0.1, 0.3, 0.5, 1.0, or 2.0 mg/kg was administered once every 3 weeks. The primary efficacy endpoint was rate of hematological improvement-erythroid (HI-E), according to International Working Group 2006 criteria (IWG 2006) [29]. The study enrolled 74 patients, and preliminary data was presented for 59 patients. The median age was 71 years, average time from MDS diagnosis was 4 years, and 50 patients were classified as HTB and 9 as LTB. The median RBC transfusion burden was 6 (0–16) units/8 weeks. Two-thirds of the patients were int-1 risk IPSS. The majority received prior ESA treatment, and almost half received hypomethylating agents and lenalidomide. Of 54 evaluable patients, 24 (44%) achieved HI-E. Among HTB patients, 40% achieved HI-E, and 6 patients became RBC transfusion independence (TI). Among patients with LTB, 63% became RBC TI with mean an Hgb increase of more than 1.5 g/dl sustained for 8 weeks or more. HI-E was achieved in 56% of RS-positive and 20% of RS-negative patients in the sotatercept 1.0 mg/kg dose group. Treatment was well tolerated and only 4 patients discontinued treatment due to suspected drug grade 2–related events (hemolytic anemia, myalgia, and hypertension).

In a pilot study for treatment of anemia in myelofibrosis, 5 out 14 patients achieved a response [30].

## Luspatercept MDS Clinical Data

In a phase II multicenter, dose finding study, luspatercept was tested in LR-MDS patients [26••]. The PACE-MDS study enrolled low- and intermediate-risk IPSS MDS patients with anemia. Patients were stratified as LTB or HTB similar to the sotatercept study. Luspatercept was given subcutaneous every 3 weeks with dose ranging from 0.125 to 1.75 mg/kg for 5 doses in escalation/expansion phase and up to 5 years in the extension study. The primary endpoint was HI-E by IWG 2006. Fifty eight patients were enrolled, including 27 in the escalation phase (0.125–1.75 mg/kg), 31 in the expansion phase (1–1.75 mg/kg), and 32 patients in the extension study.

**Table 2** Phase I/II clinical trials with sotatercept and luspatercept in lower-risk MDS for treatment of anemia

| | Sotatercept | Luspatercept |
|---|---|---|
| *n* | 74 (data presented on 59) | 58 |
| Baseline characteristics | •Median age 74<br>•2/3 Int-1 IPSS risk<br>•Prior therapy HMA 53% and lenalidomide in 46% of patients<br>•50 HTB and 9 LTB | •Median age 72<br>•Half Int-1 IPSS risk<br>•Prior therapy lenalidomide in 17% of patients<br>•39 HTB and 19 LTB |
| Dose and schedule | •0.1, 0.3, 0.5, 1.0, or 2.0 mg/kg q 3 weeks SC<br>•1.5 mg/kg dose for expansion | •0.125–1.75 mg/kg q 3 weeks SC in dose escalation phase<br>•1–1.75 mg/kg in expansion and extension phase |
| Response | 54 patients evaluable for efficacy<br>•Overall HI-E 44%<br>•LTB: RBC TI and Hgb > 1.5 g/dl 63%<br>•HTB: HI-E 41%, RBC-TI 13%<br>•RS+: HI-E 56% | Response reported at 0.75 mg/kg or higher dose ($n = 51$)<br>•Overall HI-E 63%<br>•RBC TI 38%<br>•LTB: HI-E 65%, RBC TI 75%<br>•HTB: HI-E 62%, RBC TI 29%<br>•RS+: HI-E 69%, RBC-TI 42%<br>•SF3B1+: HI-E 77%, RBC-TI 44% |
| Adverse events | Grade 2 adverse events: hemolytic anemia, myalgia, and hypertension | Grade 3 adverse events: myalgia, general health deterioration, and increased myeloblasts |

Of the 58 patients in the base study, 19 had low LTB and 39 had HTB. Of the 32 patients in the extension study, 13 had LTB and 19 had HTB.

All over, 32 (63%) of 51 patients receiving higher-dose luspatercept concentrations (0.75–1.75 mg/kg) achieved HI-E versus two (22%) of nine patients receiving lower-dose concentrations (0.125–0.5 mg/kg). Among LTB patients treated with higher-dose luspatercept, 11 out of 17 patients (65%) achieved HI-E where 6 out of 8 patients who were requiring RBC transfusion became TI. Among HTB patients treated with higher-dose luspatercept, 21 out 34 patients (62%) achieved HI-E including 29% RBC TI.

No difference in response was noted based on prior ESA use or lenalidomide use. Higher response rates were observed among patients with lower endogenous serum erythropoietin level. Among patients treated with higher-dose concentrations of luspatercept, 29 (69%) of 42 ring sideroblast–positive patients achieved HI-E versus three (43%) of seven ring sideroblast–negative patients. Among *SF3B1* mutation–positive patients, 24 (77%) of 31 achieved HI-E compared with 6 (40%) of 15 *SF3B1* mutation–negative patients who achieved HI-E.

Treatment was well tolerated in general. Only three grade 3 adverse events were reported (myalgia, general health deterioration, and one patient had increased myeloblasts).

A phase III placebo randomized clinical study using luspatercept (MEDALIST) for anemic MDS patients who are RBC TD with lower-risk MDS and ring sideroblasts subtypes after ESA failure or low chance of ESA response was presented recently at the plenary session of the American Society of Hematology 2018 meeting. The study randomized 153 patients to luspatercept and 76 patients to placebo. The baseline characteristics were similar with majority of patients classified as RCMD-RS by the WHO 2018 classification and harbored SF3B1 somatic mutation. The rate of RBC transfusion independence for ≥ 8 weeks between 1 and 24 weeks was 37.9% on luspatercept compared with 13.2% on placebo ($P$ value < 0.0001). Around 40% of responders on luspatercept remained RBC-TI at 1 year. There was no difference in response rate to luspatercept based on baseline endogenous serum erythropoietin. The rate of reduction of 4 units or more was 48.6% compared with 14.3% for luspatercept and placebo, respectively ($P$ value < 0.0001). In patients with baseline transfusion burden less than 4 units/8 weeks, the rate of Hgb increase of 1.5 g/dl or more was 63% with luspatercept compared with 5% with placebo ($P$ value < 0.0001). The most common adverse events were fatigue, diarrhea, nausea, asthenia, dizziness, and back pain.

Table 2 summarizes the phase I/II data for sotatercept and luspatercept clinical trials in treating anemia in LR-MDS patients.

## Conclusions

Treatment of anemia in LR-MDS is an unmet need. TGF-B pathway overactivation in MDS contributes to the observed myelosuppression, and sotatercept and luspatercept are novel ligand trap proteins targeting ActRII within this pathway which restore terminal erythroid differentiation. A phase III randomized study of luspatercept treating LR-MDS with ring sideroblasts has been completed; results of which if positive can lead to the next drug approval in MDS. Other small molecules targeting the TGF-B pathway are being evaluated [31].

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Komrokji reports personal fees from Celgene, personal fees from Novartis, personal fees from Incyte, and personal fees from Pfizer, outside the submitted work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance


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