Clinical Trials: Targeted Therapy

Clinical Cancer Research

Phase II Study of the ALK5 Inhibitor Galunisertib in Very Low-, Low-, and Intermediate-Risk Myelodysplastic Syndromes

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Abstract

Purpose: Overactivation of TGF-β signaling is observed in myelodysplastic syndromes (MDS) and is associated with dysplastic hematopoietic differentiation. Galunisertib, a first-in-class oral inhibitor of the TGF-β receptor type 1 kinase (ALK5) has shown effectiveness in preclinical models of MDS and acceptable toxicity in phase I studies of solid malignancies.

Patients and Methods: A phase II multicenter study of galunisertib was conducted in patients with very low-, low-, or intermediate-risk MDS by the Revised International Prognostic Scoring System criteria with hemoglobin $\leq$ 10.0 g/dL. Patients received oral galunisertib 150 mg twice daily for 14 days on/14 days off.

Results: Ten of 41 evaluable patients (24.4%; 95% confidence interval, 12.4–40.3) achieved hematologic improvement erythroid response by International Working Group (IWG) 2006 criteria. A total of 18 of 41 patients (43.9%) achieved erythroid response as per IWG 2000 criteria. Nine of 28 (32.1%) of transfusion-dependent patients had hematologic improvement. A total of 18 of 41 (44%) patients had a significant reduction in fatigue. Overall median duration of response was 90 days in all patients. Rigorous stem and progenitor flow cytometry showed that patients with an early stem cell differentiation block were more likely to respond to galunisertib. The most common treatment-emergent adverse events were grade 1 or 2 in 20 (49%) of 41 patients, including any-grade fatigue (8/41, 20%), diarrhea (7/41, 17%), pyrexia (5/41, 12%), and vomiting (5/41, 12%).

Conclusions: In summary, galunisertib treatment has an acceptable safety profile and was associated with hematologic improvements in lower- and intermediate-risk MDS, with responses in heavily transfusion-dependent patients and in those with signs of an early stem cell differentiation block.

Introduction

Myelodysplastic syndromes (MDS) are a group of hematopoietic stem cell neoplasms that occur predominantly in elderly adults; these patients present with bone marrow failure and resultant cytopenias, and may progress to acute leukemia (1). Optimal evaluation of patients involves integration of morphologic [e.g., according to World Health Organization (WHO) criteria; ref. 2)], cytogenetic, and molecular characterization to facilitate diagnosis and prognostic stratification via the Revised International Prognostic Scoring System (IPSS-R) for MDS. Patients with MDS in higher-risk IPSS-R categories have shorter overall survival (3) and those in lower-risk categories, although endowed with longer life expectancy, will suffer cytopenia-related events, including fatigue, bleeding, and infection (4).

Symptomatic anemia, which is the most frequent cytopenia exhibited by patients with lower-risk MDS, may be reduced via red

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Translational Relevance

Galunisertib is a first-in-class oral inhibitor of the TGF-β receptor type 1 kinase (ALK5) that has shown effectiveness in preclinical models of myelodysplastic syndromes (MDS). Galunisertib was tested in a phase II multicenter study in patients with very low-, low-, or intermediate-risk MDS and led to erythroid hematologic improvements, specifically in transfusion-dependent patients without any major toxicities. Rigorous stem and progenitor flow cytometry showed that patients with an early stem cell differentiation block were more likely to respond to galunisertib. These studies show clinical activity of TGF-β pathway inhibitors in MDS and can potentially lead to further studies with newer dosing regimens as well as other inhibitors of this pathway.

blood cell transfusions or erythropoiesis-stimulating agents (ESA; ref. 5). Chronic red blood cell transfusions, however, are associated with fluctuating levels of hemoglobin, iron overload, and dependence on hospitals and caregivers (5). Among ESAs, erythropoietin alpha has been recently approved for treatment of symptomatic anemia and yields a response in up to 50% of cases. Although ESAs are a first-line therapeutic option, response is usually transient (20–24 months) and is less likely for patients with transfusion dependency, very high serum erythropoietin levels (e.g., >500 U/L), and long duration of disease (5, 6). Lenalidomide is approved to treat patients with lower-risk MDS with chromosome 5q deletion, which is present in 16%–28% of patients, and has been shown to provide transfusion independence in 56%–67% (7, 8) of this group, whereas it has lower efficacy in patients without 5q deletion (6). For these reasons, a number of agents have been investigated for the treatment of patients with low- to intermediate-risk MDS and clinically significant anemia.

Preclinical studies have shown that the TGF-β pathway is activated in MDS stem and progenitor cells, and causes a block in differentiation of stem cells into committed progenitors (9). SMAD7, a negative regulator of TGF-β signaling, is decreased in MDS stem and progenitor cells, resulting in upregulation of TGF-β signaling and subsequent suppression of hematopoiesis (10). Galunisertib is a first-in-class oral selective inhibitor of TGF-β receptor I kinase (ALK5) that inhibits SMAD2/3 activation and stimulates hematopoiesis in primary MDS cell cultures and in murine models of MDS, and has an acceptable safety profile in phase I studies (10–12). Furthermore, galunisertib is hypothesized to relieve the early stem cell differentiation block seen in some cases of MDS. In contrast, ALK1 inhibitors like luspatercept and sotatercept target a different TGF-β signaling pathway mediated by GDF and activin ligands and restore late stages of hematopoiesis (13, 14). The primary aim of this study was to estimate the rate of hematologic improvement (15) in patients with IPSS-R very low-, low-, and intermediate-risk MDS treated with galunisertib.

Patients and Methods

Study design and participants

This study was designed as a prospective, multicenter, global, phase II/III study of galunisertib in patients with IPSS-R very low-, low-, and intermediate-risk MDS. Phase II was conducted at six centers in Germany, three centers in Italy, and five centers in Spain. Provided galunisertib showed hematologic improvement in at least 50% of treated patients, the study design (Supplementary Fig. S1) anticipated initiation of a randomized phase III study after approval from regulatory authorities.

A sample size of 40 was calculated for the phase II portion to provide 96.5% power and to control type I error at a one-sided 0.025 level of significance for a null hypothesis of a hematologic improvement rate with galunisertib of no higher than 20% and an alternative hypothesis that the rate would be at least 50%.

The study population consisted of patients with a confirmed MDS diagnosis (WHO criteria; ref. 16) aged at least 18 years in the IPSS-R very low- to intermediate-risk groups at screening, and who had anemia with baseline hemoglobin of 10.0 g/dL or less (average of two baseline measurements and transfusion free for at least 1 week) with or without red blood cell transfusion dependence (at least four units administered within 8 weeks before enrollment), according to International Working Group (IWG) definition. Patients with a WHO diagnosis of nonproliferative MDS/myeloproliferative neoplasms (white blood cells < 13,000/μL) also were eligible. Patients with MDS with 5q deletions were only allowed if lenalidomide treatment did not produce a response or was not tolerated.

An Eastern Cooperative Oncology Group (ECOG) scale score of two or less and adequate liver and kidney function were required, and participants must have discontinued all disease-modifying MDS therapy for 28 days prior to treatment initiation with the exception of transfusions and supportive care measures. Patients who presented with moderate or severe cardiovascular disease, received ESAs within 28 days of enrollment, or had a history of acute myeloid leukemia were excluded.

This study was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, and ethical approval was obtained from the ethics review board at each study site. All participants provided written informed consent prior to enrollment.

Procedures

Phase II participants received oral open-label galunisertib 150 mg (Eli Lilly and Company) twice daily (Supplementary Fig. S1) for 14 days in a 28-day cycle. A cohort of three patients was planned to receive 80 mg twice daily according to the same intermittent dosing regimen for comparative pharmacokinetic analysis. All patients were to receive six treatment cycles or fewer unless they met one or more discontinuation criteria prior to completing six cycles. Assessments included hematologic tests (weekly), plasma cytokine/chemokine and TGF-β1 (day 1 and 15 of each cycle) measurements, and bone marrow biopsy, and aspirate (baseline and every three cycles). All patients were followed for 12 months.

Outcomes

The phase II primary endpoint was the rate of hematologic improvement according to IWG 2006 criteria (15). Erythroid response was defined by reduction of red blood cell transfusions by at least four units or a hemoglobin increase (in patients with less than four units in the previous 8 weeks) of at least 1.5 g/dL, with either lasting at least 8 weeks. Key secondary objectives included progression-free survival (PFS), change in bone marrow

fibrosis, time to best hematologic improvement, and duration of best hematologic improvement. Additional assessments included safety and pharmacokinetics. The exploratory objectives were to identify biomarker subsets in bone marrow cells and associated responses and to evaluate relationships between genetic molecular markers and RNA expression as predictors of response. In an *ad hoc* analysis, estimated rate of hematologic improvement was calculated according to IWG 2000 criteria, which provides two levels of erythroid response, either of which must be sustained for at least 8 weeks: major (transfusion independence or hemoglobin increase of >2 g/dL) and minor (≥50% transfusion reduction or hemoglobin increase of 1–2 g/dL; ref. 17).

Safety measurements included treatment-emergent adverse events, laboratory analyses, vital signs and physical examinations, hospitalizations, and blood transfusions. Cardiac safety was assessed by echocardiography/Doppler and serial measurements of brain natriuretic peptide (BNP) and troponin I. Treatment-emergent adverse events were measured using the NCI Common Terminology Criteria for Adverse Events (18).

The Brief Fatigue Inventory is a nine-item patient-reported instrument developed to assess severity of fatigue and its impact on quality of life with scale ratings of 0–10 (19). A fatigue response was prespecified as a 30% reduction from baseline. The inventory was administered at the screening visit, on day 1 of each cycle, and at the final visit.

To evaluate the goal of decreased bone marrow fibrosis with treatment, change in bone marrow fibrosis from baseline was assessed on day 15 of every third cycle through 12 months, and then every 6 months as long as the patient remained in active follow-up.

Statistical analysis

All patients who received at least one dose of galunisertib were included in the efficacy and safety analyses, and in the pharmacokinetic analyses provided they had evaluable samples. The hematologic improvement rate was calculated as the proportion of all patients who received treatment and achieved hematologic improvement for at least 8 weeks.

Data on dosing, plasma concentration versus time, and patient characteristics were pooled and analyzed using a population pharmacokinetics analysis approach, and nonlinear mixed-effect modeling was used to estimate the population pharmacokinetics parameters of galunisertib. Change in bone marrow fibrosis was assessed using a mixed-effect model repeated measures analysis.

Biomarker analysis

Mutational analysis. Patient bone marrow or blood samples were used for targeted sequencing of 40 recurrently mutated genes at 500 × coverage (Genoptix). Clinically significant mutations were identified and variant allele frequency was calculated as described previously (20).

Stem and progenitor analysis. Mononuclear cells were isolated from peripheral blood samples by density gradient centrifugation at baseline and up to cycle 3, and subjected to immunomagnetic enrichment of $CD34^+$ cells (Miltenyi Biotec). When samples were available, later cycles were also assessed to determine changes in lineages. $CD34^+$ cells were stained with PE-Cy5 (Tricolor)-conjugated mAbs against lineage antigens (CD2, CD3, CD4, CD7, CD10, CD11b, CD14, CD15, CD19, CD20, CD56, and glycophorin A; BD Biosciences) and fluorochrome-conjugated antibodies against CD34, CD38, CD90, CD45RA, and CD123 (eBioscience). Cells were analyzed and sorted on a Becton Dickinson FACSAria II equipped with four lasers (407, 488, 561/568, and 633/647-nm). We distinguished and sorted hematopoietic stem cells (HSC; Lin^-, $CD34^+$, and $CD38^-$) and progenitors (Lin^-, $CD34^+$, and $CD38^+$), as performed previously (21).

This study is registered with ClinicalTrials.gov, number NCT02008318.

Role of the funding source

The funder provided the study drug and collaborated with investigators on the study design, protocol, data collection, analysis, interpretation, and writing and preparation of this article. V. Santini prepared the first draft in collaboration with the study funder and other coauthors. Authors had access to the study data and all authors approved submission for publication.

Data sharing statement

The study protocol (redacted) may be found in a Supplementary Data available with the online version of this article. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank, or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

Results

Study participants and efficacy measures

From January 9, 2014, to September 3, 2015, 41 participants were enrolled in the 150-mg twice-daily cohort and two in the 80-mg twice-daily cohort; all received at least one dose and were available for evaluation (Supplementary Fig. S2). The median age and gender distribution of the participants (Table 1) were representative of MDS patient population demographics.

For the efficacy analyses, 28 of 41 (68.3%) patients were transfusion dependent at baseline, needing at least four units in the 8 weeks prior to study initiation (Table 2; Fig. 1A). Nine (32.1%) of these patients achieved a clinically significant transfusion reduction of ≥4 units of packed red blood cells over 8 or more weeks. Among patients who obtained significant transfusion reduction, one also achieved platelet response (average platelet count of $<100 \times 10^9$/L over 8 weeks at baseline, and an increase of $\geq 30 \times 10^9$/L lasting at least 8 weeks during the study). Erythroid response (HI-E) was observed in 10 of 41 patients (24.4%; Table 2). The median duration of galunisertib treatment for erythroid responders ($n = 10$) was 22 weeks. Figure 1A demonstrates the maximum change in transfusion requirements in previously transfused patients. Figure 1B shows the distribution of change in hemoglobin levels from baseline. One patient who

Table 1. Patient characteristics

Characteristics	Galunisertib 150 mg twice daily ($N = 41$)	Galunisertib 80 mg twice daily ($N = 2$)
Age, years, median (IQR)	71 (66–76)	63 (55–70)
Sex		
Male	26 (63%)	1 (50%)
ECOG performance status		
0	22 (54%)	0
1	19 (46%)	2 (100%)
IPSS-R prognostic risk		
Very low (≤1.5)	2 (5%)	0
Low (>1.5–3)	30 (73%)	1 (50%)
Intermediate (>3–4.5)	9 (22%)	1 (50%)
Classification of MDS, WHO 2008		
Unclassified	3 (7%)	1 (50%)
RARS	8 (20%)	0
RCMD	28 (68%)	0
Refractory cytopenia with unilineage dysplasia	2 (5%)	1 (50%)
Cytogenetic		
Normal	23 (56%)	0
Abnormal	7 (17%)	2 (100%)
NA	11 (27%)	0
Bone marrow ringed sideroblasts (by central laboratory)[a]		
Available bone marrow, n	27 (66%)	1 (50%)
0%	11/27 (41%)	0
>5%	16/27 (59%)	1/1 (100%)
NA	14 (34%)	1 (50%)
SFB31 gene mutation (by central laboratory)		
Evaluable samples	28 (68%)	1 (50%)
SF3B1	17/28 (61%)	1/1 (100%)
No SF3B1 mutation	11/28 (39%)	0
NA	13 (32%)	0
Erythropoietin		
<200 U/L	23 (56%)	2 (100%)
≥200–≤500 U/L	7 (17%)	0
>500 U/L	10 (24%)	0
NA	1 (2%)	0
Prior therapies – class[b]		
≥1 prior systemic therapy	27 (66%)	NA
ESA	22 (54%)	
Immunomodulatory (e.g., lenalidomide and thalidomide)	11 (27%)	
Experimental drugs	5 (12%)	
Growth stimulating agents (e.g., G-CSF)	4 (10%)	
Chemotherapy	3 (7%)	
Differentiating factor	3 (7%)	
Hypomethylating agents	2 (5%)	
Steroids	2 (5%)	
Iron chelator	1 (2%)	

NOTE: Data are *n* (%) except where indicated otherwise. Where baseline values are missing, the percentage is of the patients with baseline values.

Abbreviation: NA, not available.

[a]Prussian Blue stain.

[b]Patients may be included in more than one category.

was transfusion independent at baseline achieved erythroid hematologic improvement measured by an increase in hemoglobin of at least 1.5 g/dL from baseline for more than 8 weeks, had a durable response of 462 days at time of data cutoff, and did not require transfusions pre- and posttreatment. The hemoglobin level for this patient at baseline was 9.7 g/dL and rose to a peak of 14.1 g/dL on day 547 (Supplementary Fig. S3). No patients achieved neutrophil response.

The HI-E was paralleled by improvement of fatigue as determined by the change in score of the Brief Fatigue Inventory (Fig. 1C). Results from the Brief Fatigue Inventory analysis revealed the two patients who received galunisertib 80 mg twice daily achieved no change in fatigue compared with baseline. However, in patients who received galunisertib 150 mg twice daily for six cycles, 18 of the 41 patients (44%) were observed to have a 30% reduction from baseline in the Brief Fatigue Inventory mean score at cycle 6 (Fig. 1C). Of the 10 patients with HI-E, six patients also had an improvement in the Brief Fatigue Inventory score.

In an *ad hoc* assessment of responses by IWG response criteria 2000, 18 of 41 patients (43.9%) achieved erythroid response, with nine (22.0%) of 41 patients each meeting major and minor response thresholds (Supplementary Table S1). Eight of the 18 patients qualified for response under IWG 2000 but not for IWG 2006, including two patients who achieved major response by transfusion independence for at least 8 weeks, three who achieved minor response by transfusion reduction ≥50% for at least 8 weeks, and three who achieved minor response by hemoglobin increase.

Biomarker studies (plasma TGF-β1 levels, cytogenetics, mutational status, stem cell and bone marrow studies, and lymphocyte subsets)

In addition to the clinical response assessments, we observed that plasma TGF-β1 levels were reduced by more than 20% from baseline in the first six cycles in 14 of 15 patients (93.3%) who had baseline levels of more than 2,000 ng/L. We noted that seven patients with HI-E per IWG 2006 also had a significant decrease in plasma TGF-β1 levels. This reduction occurred about 90–100 days after starting galunisertib therapy (Supplementary Fig. S4).

We also investigated whether specific baseline biological characteristics could help identify patients who may benefit from receiving an ALK5 inhibitor. This investigation was done based on available samples and the analysis was performed on both in relationship to all available samples and based on the IWG 2006 and 2000 response criteria. We observed that six patients with normal cytogenetics and one patient with multiple cytogenetic abnormalities experienced HI-E (Table 3). Analyses of HI-E per WHO MDS subtype showed that nine of the 10 responders had refractory cytopenia with multilineage dysplasia (RCMD) and one had refractory anemia with ringed sideroblasts (RARS; Table 3). There was no correlation between response and endogenous erythropoietin levels, and endogenous EPO levels were less than or equal to 500 U/L in 73% (30/41) of the cases (Table 3).

Because MDS is characterized by differentiation arrest, and to determine whether galunisertib had an effect on stem cell modulation, we performed analysis of stem and progenitor cells in a subset (15/41) of patient samples. Patients with HI-E had a pronounced stem cell differentiation arrest with a higher baseline proportion of stem cells [Lineage$^-$ (Lin$^-$) and CD33$^-$/CD34$^+$/CD38$^-$ cells] in peripheral blood ($n = 5$) when compared with nonresponders ($n = 10$; Fig. 2A). Furthermore, serial samples available in one responder patient showed an increase in differentiation of stem cells to progenitors with treatment (Fig. 2B and C).

We further evaluated the mutational status of 28 MDS cases with available DNA by targeted deep sequencing of MDS recurrently mutated genes. In the 150-mg twice-daily group, the most

Table 2. Hematologic improvement in patients treated with galunisertib, 150 mg twice daily, IWG 2006 criteria (prespecified assessment)

Baseline transfusion need	Number of patients	HI (Tf or Hb increase) during any 8 weeks	Median duration of response, days (IQR)	TI during any 8 weeks
≥4 units	28	9/28 (32.1%)	89 (75–95)	6/28 (21.4%)
1–3 units	2	0		2/2 (100%)
0 units	11	1/11 (9.1%)	462[a]	10/11 (90.9%)[b]
Total	41	10/41 (24.4%)	90 (75–103)	18/41 (43.9%)

NOTE: Data are *n* (%) except where indicated otherwise.
Abbreviations: Hb, hemoglobin; HI, hematologic improvement; Tf, transfusion; TI, transfusion independent.
[a]Duration of response in only one patient no range available.
[b]Remained transfusion free.

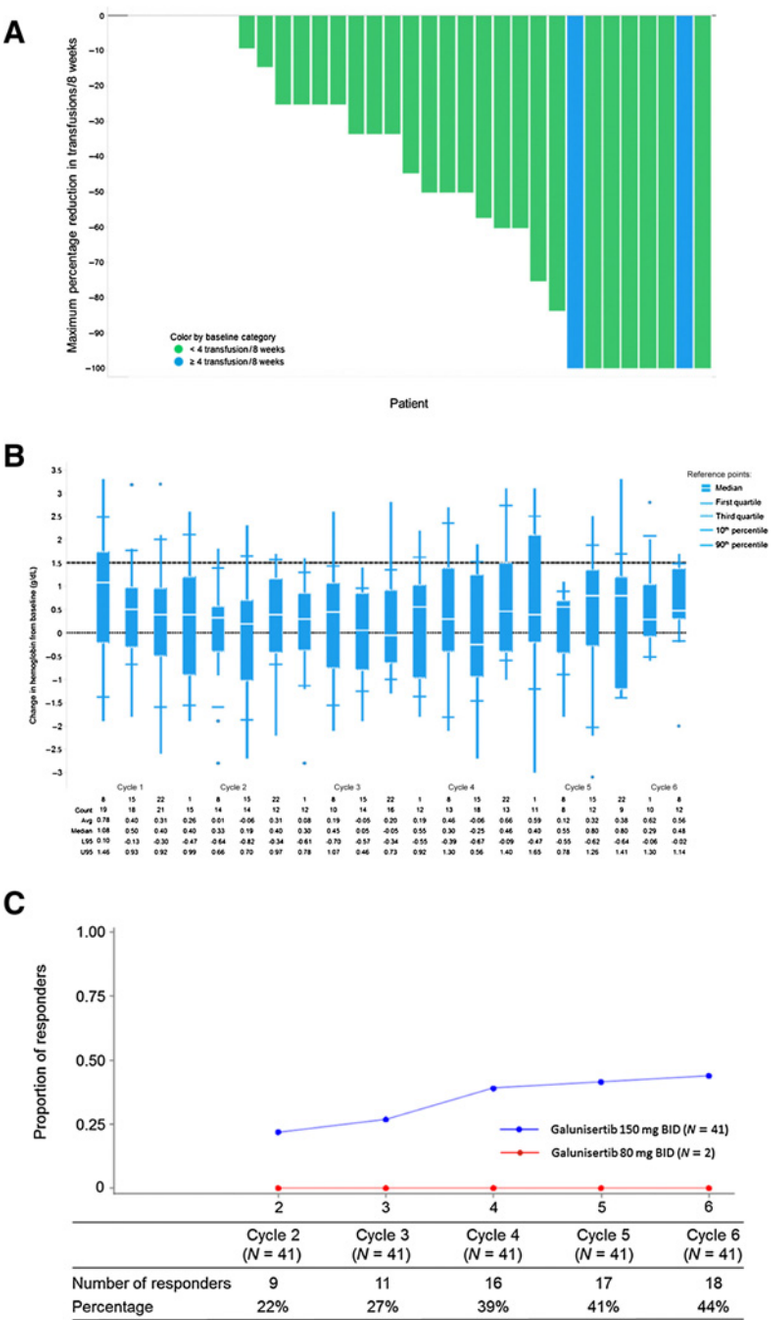

Figure 1.
Response assessments for patients receiving galunisertib. Changes in transfusion burden (**A**), in hemoglobin levels (**B**), and by achieving prespecified response on the Brief Fatigue Inventory (**C**). **A,** Maximum percentage change in red blood cell transfusion burden in previously transfused patients ($N = 32$). Patients are differentiated by baseline transfusion requirements of <4 units in any 8-week period (blue) or ≥4 units in any 8-week period (green) before treatment initiation. Note: two patients who were transfusion dependent at baseline had no change in transfusion requirements. Four patients that were transfusion dependent at baseline had no postbaseline records and are represented on the graph as no change in transfusion burden. Eleven patients not shown on this graph were transfusion independent at baseline (three patients who were transfusion independent at baseline received transfusions posttreatment and the minimum in any 8-week period for two of these was zero transfusions; the other patient required ongoing transfusions). **B,** Distribution of change in hemoglobin from baseline for patients. Number of patients with available measurements at each timepoint is shown under the graph. $N = 35$ (all patients who received transfusions). **C,** Percentage of patients achieving prespecified response on the Brief Fatigue Inventory (improvement of 30% reduction from baseline score). Data were available from all patients at baseline and in each of the first six cycles. BID, twice daily.

Table 3. Hematologic improvement (IWG 2006 and IWG 2000) by available baseline disease characteristics (150-mg twice-daily group) and adjusted for available samples

Disease characteristic	Number of available samples	IWG 2006 (see Table 2)		IWG 2000[a] (see Table 2)	
Cytogenetic abnormalities (where more than 20 metaphases analyzed)	$N_1 = 30$	Responder $N = 10$	Nonresponder $N = 31$	Responder $N = 18$	Nonresponder $N = 23$
Normal	23/30 (77%)	6/23 (26%)	17/23 (74%)	13/23 (57%)	10/23 (43%)
[% by response]		[6/10 (60%)]	[17/31 (55%)]	[13/18 (72%)]	[10/23 (43%)]
Abnormal	7/30 (23%)	1/7 (14%)	6/7 (86%)	1/7 (14%)	6/7 (86%)
[% by response]		[1/10 (10%)]	[6/31 (19%)]	[1/18 (6%)]	[6/23 (26%)]
		Responder	Nonresponder	Responder	Nonresponder
MDS subtypes	$N_1 = 41$	$N = 10$	$N = 31$	$N = 18$	$N = 23$
UN	3/41 (7%)	0/3 (0%)	3/3 (100%)	0/3 (0%)	3/3 (100%)
[% by response]		[0/10 (0%)]	[3/31 (10%)]	[0/18 (0%)]	[3/23 (13%)]
RARS	8/41 (20%)	1/8 (13%)	7/8 (88%)	2/8 (25%)	6/8 (75%)
[% by response]		[1/10 (10%)]	[7/31 (26%)]	[2/18 (11%)]	[6/23 (26%)]
RCMD	28/41 (68%)	9/28 (32%)	19/28 (68%)	15/28 (54%)	13/28 (46%)
[% by response]		[9/10 (90%)]	[19/31 (61%)]	[15/18 (83%)]	[13/23 (57%)]
RCUD	2/41 (5%)	0/2 (0%)	2/2 (100%)	1/2 (50%)	1/2 (50%)
[% by response]		[0/10 (0%)]	[2/31 (6%)]	[1/18 (6%)]	[1/23 (4%)]
		Responder	Nonresponder	Responder	Nonresponder
Gene mutation	$N_1 = 28$	$N = 10$	$N = 31$	$N = 18$	$N = 23$
SF3B1	17/28 (61%)	6/17 (35%)	11/17 (65%)	11/17 (65%)	6/17 (35%)
[% by response]		[6/10 (60%)]	[11/31 (35%)]	[11/18 (61%)]	[6/23 (26%)]
No SF3B1	11/28 (39%)	3/11 (27%)	8/11 (73%)	4/11 (36%)	7/11 (64%)
[% by response]		[3/10 (30%)]	[8/31 (26%)]	[4/18 (22%)]	[7/23 (30%)]
		Responder	Nonresponder	Responder	Nonresponder
Bone marrow ringed- sideroblasts[b]	$N_1 = 27$	$N = 10$	$N = 31$	$N = 18$	$N = 23$
0%	11/27 (41%)	2/11 (18%)	9/11 (82%)	5/11 (45%)	6/11 (55%)
[% by response]		[2/10 (20%)]	[9/31 (29%)]	[5/18 (28%)]	[6/23 (26%)]
>5%	16/27 (59%)	4/16 (25%)	12/16 (75%)	5/16 (31%)	11/16 (69%)
[% by response]		[4/10 (40%)]	[12/31 (39%)]	[5/18 (28%)]	[11/23 (48%)]
		Responder	Nonresponder	Responder	Nonresponder
Serum erythropoietin (U/L)	$N_1 = 41$	$N = 10$	$N = 31$	$N = 18$	$N = 23$
NA	1/41 (2%)	1/1 (100%)	0/1 (0%)	1 (100%)	0/1 (0%)
[% by response]		[1/10 (10%)]	[0/31 (0%)]	[1/18 (6%)]	[0/23 (0%)]
<200	23/41 (56%)	6/23 (26%)	17/23 (74%)	13/23 (57%)	10/23 (43%)
[% by response]		[6/10 (60%)]	[17/31 (55%)]	[13/18 (72%)]	[10/23 (43%)]
≥200–≤500	7/41 (17%)	1/7 (14%)	6/7 (86%)	2/7 (29%)	5/7 (71%)
[% by response]		[1/10 (10%)]	[6/31 (19%)]	[2/18 (11%)]	[5/23 (22%)]
>500	10/41 (24%)	2/10 (20%)	8/10 (80%)	2/10 (20%)	8/10 (80%)
[% by response]		[2/10 (20%)]	[8/31 (26%)]	[2/18 (11%)]	[8/23 (35%)]

NOTE: Data are *n* (%) except where indicated otherwise. Percentages are calculated on the basis of number of nonmissing values in each disease category. Where responders do not total 10 for IWG 2006 or 18 for IWG 2000 criteria, patients are missing baseline values.

Abbreviations: *N*, number of patients dosed; N_1, number of patients with sample; *n*, number of patients in category; NA, not available; UN, unclassified; RCUD, refractory cytopenia with unilineage dysplasia.

[a]Major and minor transfusion and Hb responses combined

[b]As determined by BM Prussian Blue Stain.

frequently mutated gene was *SF3B1* [mutated in 17/28 samples (61%); Supplementary Fig. S5]. HI-E was observed in six of 17 patients with a SF3B1 mutation and in three of 11 patients with no SF3B1 mutation. Eleven patients with a SF3B1 mutation [11/17 (65%)] did not experience HI-E. Interestingly, all four of the patients with an isolated mutation in SF3B1 without any other comutations responded to galunisertib and achieved a HI-E response. Given the small number of patients evaluated, other gene mutations (i.e., TET2 and ASXL1) could not be evaluated for correlation with response.

The median PFS in patients with an IPSS-R very low- or low-risk ($N = 33$) was not reached (95% confidence interval, 97 weeks–not reached; Supplementary Fig. S6). PFS was better among the patients who achieved HI-E compared with those who did not achieve HI-E; however, the difference in PFS was not statistically significant.

Bone marrow fibrosis was reported in 11 of the 31 patients (35%) who had both baseline and postbaseline assessments. Three patients had bone marrow fibrosis improvements (two from moderate to negative, one from mild to negative), although none of these patients had HI-E. Of the 10 patients who achieved HI-E, four had no change in bone marrow fibrosis grading, four could not be assessed (i.e., did not have a baseline and postbaseline assessment), and two had transient increases that subsequently decreased.

Because natural killer (NK) and T-cell subsets can produce TGF-β1, T-cell subsets were measured before and during treatment. While there was no clear evidence of a change in any of the subsets, it appeared that NK cells increased in numbers during treatment with galunisertib (Supplementary Fig. S7). Eight patients showed progressive increases of NK cell counts over time not associated with erythroid response to galunisertib

Pharmacokinetic profile

The pharmacokinetic profile was the same as in previous studies (22), with no unexpected variations. Dose-normalized steady-state observations for cycle 1 (Supplementary Fig. S8) showed that galunisertib was rapidly absorbed and had

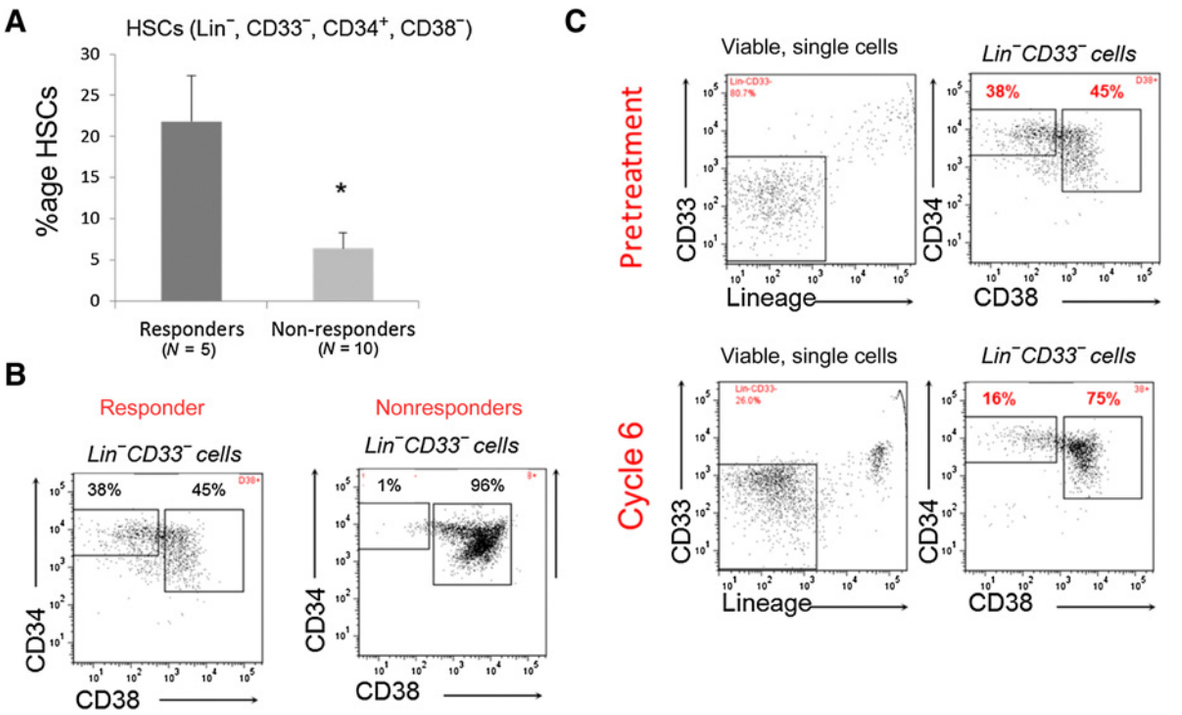

Figure 2.

Stem cell differentiation block ($CD34^+$, $CD38^-$, Lin^-, and $CD33^-$) is associated with response to galunisertib. **A,** A total of 15 patients that included five responders and 10 nonresponders with evaluable samples were analyzed by multiparameter flow cytometry for stem and progenitor assessment. Patients who responded to galunisertib had an increased proportion of hematopoietic stem cells (HSCs) in their peripheral blood ($n = 5$) when compared with nonresponders ($n = 10$; means + SEM; *t* test; *, $P = 0.006$). **B,** Representative FACS plots from one responder and one nonresponder are shown. Lin^-, $CD33^-$, $CD34^+$, and $CD38^-$ HSCs and Lin^-, $CD33^-$, $CD34^+$, and $CD38^+$ progenitors are shown. **C,** Serial samples from one responder to galunisertib shows decreased HSC percentage and increased progenitor differentiation in posttreatment sample.

subsequent biphasic disposition. The observed plasma concentrations from this study were comparable with concentration observations in other solid tumor studies (23, 24). Galunisertib plasma concentrations in responders were similar to those observed in patients with no response.

Safety evaluation

Adverse events. Galunisertib 150 mg twice daily was well tolerated (Table 4; Supplementary Table S2). One patient had to interrupt treatment for a study treatment-related adverse event (retroperitoneal hemorrhage). The most common events in 41 patients were grade 1–3, particularly diarrhea ($n = 7$, 17%) and fatigue ($n = 8$, 20%). Grade 3 and 4 toxicity was observed in eight (20%) and four (10%) of 41 patients, respectively, most of which were nonhematologic. No apparent cardiac toxicity was observed during the comprehensive cardiac monitoring. There were three patients with grade 3 cardiac failure, all of whom had preexisting cardiac conditions, and two with an aortic dilatation by CT scan at baseline; none of the cardiac findings prevented the patients from maintaining therapy with galunisertib. Consistent with the clinical observations, BNP levels remained unchanged over the treatment time (Supplementary Fig. S9).

Discussion

Orally administered galunisertib is a first-in-class small-molecule inhibitor of the TGF-β kinase that has shown a manageable safety profile in solid tumor trials (12, 25, 26). On the basis of the previous clinical experiences, we investigated the role of galunisertib in patients with MDS (12, 25, 26). Recent studies with ACVR2B/ALK1/2 inhibitors (23, 24) suggest that targeting family members of the TGF-β signaling pathway may result in improvements in erythropoiesis in MDS. In contrast to the ALK1/2 inhibitors (27), galunisertib blocks the signaling mediated via ALK5, thus possibly inducing improvement of early bone marrow progenitor maturation as well as reducing inflammation (10).

In this study, galunisertib reduced transfusion requirements (Fig. 1A), including in patients with prior high transfusion requirements. We compared the erythroid response based on IWG 2006 [10/41 (24.4%) patients] with that according to IWG 2000 criteria [18/41 (43.9%) patients]. In the latter evaluation, minor and major erythroid improvements were considered. In our study, 28 of 41 patients (68.3%) treated with galunisertib 150 mg twice daily could be evaluated for erythroid response in terms of reduction in red blood cell transfusions (receiving ≥4 U/8 weeks), and their response rate was 32.1% (9/28 patients). Most patients remained on treatment for about 6 months, with stable HI-E in some cases and evident improvements in fatigue. Whether prolonged administration of galunisertib can achieve higher rates of HI-E has not been explored.

On the basis of the observed reduction in TGF-β1 levels during galunisertib treatment in patients with baseline levels >2,000 ng/L, and the known relevance of such elevated

Table 4. CTCAE safety: all treatment-emergent adverse events reported in ≥3 patients or with any grade ≥3 events, regardless of causality

	Galunisertib 150 mg twice daily ($N = 41$) Maximum grade				
TEAE	**Any grade**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Subjects with ≥ 1 TEAE	33 (80%)	20 (49%)	8 (20%)	4 (10%)	1 (2%)
Fatigue	8 (20%)	7 (17%)	1 (2%)	0 (0%)	0 (0%)
Diarrhea	7 (17%)	7 (17%)	0 (0%)	0 (0%)	0 (0%)
Pyrexia	5 (12%)	5 (12%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	5 (12%)	5 (12%)	0 (0%)	0 (0%)	0 (0%)
Anemia	4 (10%)	3 (7%)	0 (0%)	1 (2%)	0 (0%)
Cardiac failure	4 (10%)	1 (2%)	3 (7%)	0 (0%)	0 (0%)
Neutrophil count decreased	3 (7%)	0 (0%)	2 (5%)	1 (2%)	0 (0%)
Respiratory failure	2 (5%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Aortic injury[a]	2 (5%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)
Eczema	2 (5%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Peripheral edema	2 (5%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)
Pain	2 (5%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)
Platelet count decreased	2 (5%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)
Retroperitoneal hemorrhage	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Dyspnea	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Cataract	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Crohn disease	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Febrile neutropenia	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Pleural effusion	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Pulmonary edema	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Tongue abscess	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)
White blood cell count decreased	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)

NOTE: Data are *n* (%) except where indicated otherwise.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse events.

[a]Aneurysmic dilatation of the ascending aorta was identified just prior to cycle 2 with an angio CT. The angio CT was consistent with the baseline CT, which demonstrated similar enlargement of the aorta. Baseline and repeat echocardiograms demonstrated a tortuous aorta without aneurysm unchanged between the two echocardiograms. The investigator felt that the lesion was present at baseline and that there was no relationship between the aortic finding and galunisertib.

levels for cancer progression (28), we interpret the reduction in TGF-β1 levels as a signal of an effective drug treatment as previously reported in solid tumors (29).

Although the number of cases is limited, it appears that patients with normal cytogenetics and with a WHO diagnosis of RCMD were more likely to obtain erythroid improvement. In addition, we observed that patients with isolated mutations in SF3B1 without other comutations all responded to galunisertib. Of note, the WHO 2008 classification eliminated the subtype RCMD-RS present in WHO 2001, and may account for the responses with RCMD and SF3B1 mutations we saw in this study. These observations can be followed up in future larger studies (27) and suggest a distinct modulation of TGF-β signaling by galunisertib.

To further understand the characteristics of the patients with MDS in whom the ALK5 inhibition may have a pharmacologic effect, we determined the size of the stem cell population in some patients prior to treatment. We observed that patients with MDS with a pronounced stem cell differentiation block at baseline, characterized by a higher proportion of stem cells (Lin^-, $CD33^-$, $CD34^+$, and $CD38^-$) in peripheral blood, obtained HI-E. These findings suggest that early progenitor differentiation block could originate from increased TGF-β signaling and/or greater SMAD7 deficit, and therefore could be responsive to ALK5 inhibition. This is different from what was observed in clinical studies with luspatercept and sotatercept, in which apparently late stage hematopoiesis was selectively restored (23, 24). It is possible that TGF-β acts on early stages, while GDF11 and other ACVR2B ligands act as inhibitory ligands on late stages of erythropoiesis. These findings also show that with advances in purified FACS analytical capabilities, cellular biomarkers can be incorporated in future trials with agents that act at the level of MDS stem cells.

To our knowledge, this is the first phase II study of patients with IPSS-R lower-risk MDSs treated with the oral drug galunisertib. Galunisertib demonstrated clinical activity as determined by reduction in fatigue and in transfusion requirements for patients with very low-, low-, and intermediate-risk MDSs. The tolerability profile of galunisertib in this study was consistent with previous observations (25, 26), and was favorable compared with other agents evaluated in patients with lower-risk MDS, with minimal hematologic toxicity (7, 8, 30). Moreover, oral administration is relevant for quality of life issues in patients with long-surviving, transfusion-dependent MDS. Together, the improvement of fatigue, reduction in transfusion requirements, and oral administration points to potential efficacy of ALK5 inhibition for selected patients with MDS and symptomatic anemia resistant to ESAs.

Disclosure of Potential Conflicts of Interest

V. Santini reports receiving speakers bureau honoraria from Celgene, Novartis, and Janssen, and is an advisory board member/unpaid consultant for Acceleron, Menarini, Amgen, Celgene, and Novartis. D. Valcarcel reports receiving speakers bureau honoraria from Celgene, Novartis, and Amgen, and is an advisory board member/unpaid consultant for Celgene, Jazz, Novartis, and Amgen. U. Platzbecker reports receiving commercial research grants from and is an advisory board member/unpaid consultant for Celgene. R.S. Komrokji is an employee/paid consultant for Celgene, DSI, Pfizer, Jazz, Janssen, Incyte, and Agios, and reports receiving speakers bureau honoraria from Jazz, Novartis, and Aalexion. M.M. Lahn, A. Chiang, and A. Girvan are employees/paid consultants for Eli Lilly. U. Steidl reports being scientific co-founder of Stelexis, on the board of directors and having an equity position in the company, receiving commercial research grants from GlaxoSmithKline, Bayer Healthcare, and Aileron Therapeutics, holds ownership interest (including patents) in Stelexis Therapeutics, and is an advisory board member/unpaid consultant for Celgene, Aileron Therapeutics, Stelexis Therapeutics, and Pieris Pharmaceuticals. A. Verma reports receiving commercial research grants from Eli Lilly, Novartis,

and Bristol-Myers Squibb, holds ownership interest (including patents) in Stelexis, and is an advisory board member/unpaid consultant for Stelexis, Celgene, and Acceleron. No potential conflicts of interest were disclosed by the other authors.

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