Placebo-Controlled, Randomized, Phase I/II Trial Of The Thrombopoietin Receptor Agonist Eltrombopag In Thrombocytopenic Patients With Advanced Myelodysplastic Syndromes Or Acute Myeloid Leukemia

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Background: Patients (pts) with advanced myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) often develop platelet (plt) transfusion-dependent thrombocytopenia. Eltrombopag (EPAG), an oral thrombopoietin receptor agonist, increases plts in chronic immune thrombocytopenia, hepatitis C virus-associated thrombocytopenia, and severe aplastic anemia.

Aims: To evaluate the safety and tolerability of EPAG in thrombocytopenic pts with advanced MDS and AML (primary end point). Secondary end points include plt transfusions, plt response, and overall survival (OS).

USEFUL LINKS

- All EHA 2013 MDS-related abstracts at The Beacon
- All MDS-related conference abstracts at The Beacon
- Discuss this abstract

Methods: Pts with relapsed/refractory MDS or AML ineligible for antileukemic therapies, with 10%>50% bone marrow (BM) blasts and plts <30 Gi/L were randomized 2:1 to EPAG 50 mg qd (increases q2 weeks in pts without a plt response, up to 300 mg [150 mg for Asian pts]) or placebo (PLB) for 6 months. Standard supportive care and disease-modifying treatments were permitted at the investigator's discretion.

Results: Overall, 98 pts were enrolled (EPAG: n=64; PLB: n=34). Most pts had AML (Table) and received ≥1 prior antileukemic treatments, including hypomethylating agents (EPAG: 24 [38%];

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PLB: 11 [32%]) and chemotherapy (EPAG: 10 [16%]; PLB: 3 [9%]). Most pts received the maximum dose (EPAG: 36 [56%]; PLB: 20 [59%]). Mean treatment duration was 102 days for EPAG and 78 days for PLB; 9 (14%) pts on EPAG continued treatment >6 mo versus 1 (3%) pt on PLB. Twenty-one (33%) EPAG and 17 (50%) PLB pts died on therapy or <30 days from the last dose; primary cause of death in both arms was underlying disease. The most common (≥20% in the EPAG arm) adverse events (AEs) on therapy +30 days were pyrexia, nausea, diarrhea, fatigue, decreased appetite, and pneumonia. Serious AEs in ≥5% of pts in either arm included sepsis, pyrexia, febrile neutropenia, and pneumonia. Hepatobiliary events were reported in 11 (17%) EPAG and 5 (15%) PLB pts; 3% (EPAG: 2; PLB: 1) reported thromboembolic events. Of 26 pts with MDS (WHO criteria) at baseline, 14 (EPAG: 9; PLB: 5) had postbaseline BM examination results available; 8 (EPAG: 5 [56%]; PLB: 3 [60%]) of 14 pts developed BM blasts ≥20% during treatment. Plt transfusion independence for ≥8 weeks was reported for 24 (38%) EPAG and 7 (21%) PLB pts (*P*=0.0979). Ten (16%) EPAG and 9 (26%) PLB pts had ≥Grade 3 hemorrhages (*P*=0.1472). More EPAG versus PLB pts started antileukemic/palliative treatment during the study (26 [41%] versus 11 [32%], respectively), including hypomethylating agents and salvage chemotherapy. Median OS was 27 weeks for EPAG versus 15.7 weeks for PLB (hazard ratio=0.71,*P*=0.1931). During treatment weeks 5-12, fewer pts receiving EPAG experienced clinically relevant thrombocytopenic events (plt counts <10 Gi/L, plt transfusions, or ≥Grade 3 hemorrhagic events) per week than PLB (weighted average [range]: EPAG: 38% [30%>48%]; PLB: 66% [56%>88%]).

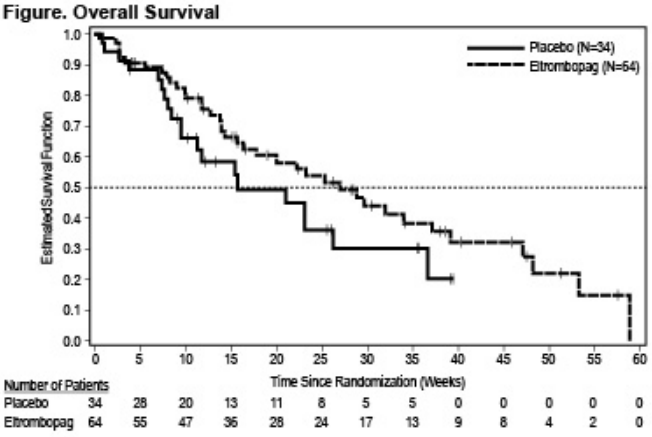
Images / Pictures:

Table. Baseline Disease Characteristics

	Placebo (N=34)	Eltrombopag (N=64)
WHO criteria, n (%)[a]		
MDS	11 (32)	15 (23)
AML	22 (65)	48 (75)
French-American-British criteria n, (%)[b]		
MDS	15 (44)	23 (36)
AML	19 (56)	41 (64)
Poor prognosis karyotype, n (%)	14 (41)	19 (30)
Received prior treatments, n (%)[c]	21 (62)	46 (72)
	Median (range)	
Absolute neutrophil count, Gi/L	0.55 (0-9.8)	0.85 (0-17.6)
Hemoglobin, g/dL	8.5 (6.0-11.2)	8.8 (4.3-13.2)
Platelets, Gi/L[d]	12 (2-38)	17 (2-71)
% BM blasts	20 (10-50)	26 (10-50)

[a]Two pts (1 PLB, 1 EPAG) had missing information. [b]FAB criteria assessed by local morphology review. [c]Excludes palliative treatments (eg, hydroxyurea). [d]Baseline platelet count was derived using an average of platelet counts during screening, excluding within 3 days of a transfusion.

Figure. Overall Survival



Summary / Conclusion: EPAG ≤300mg was well tolerated in pts with advanced MDS or AML. Pts treated with EPAG showed a trend toward fewer plt transfusions, fewer ≥Grade 3 hemorrhages, and improved OS compared with PLB. Additional studies with EPAG to evaluate potential antileukemic activity in advanced MDS or AML are warranted.

Tags: EHA 2013 Meeting Abstract, Myelodysplastic Syndromes

Related Articles:

- FDA Approves New Dacogen Dosing Schedule For Myelodysplastic Syndromes
- Beacon NewsFlashes – August 23, 2010

- Tipifarnib-Based Combination Therapy May Be Effective And Safe For MDS Patients
- Beacon NewsFlashes – October 4, 2010
- Personal Perspective: Symptoms Of Menopause Lead To MDS Diagnosis

Current Physician Forum Discussions

- Highlights of recent scientific meetings (2 posts)
- Landmark MDS article: seed-soil hypothesis for MDS (1 post)
- Relevance of lenalidomide+EPO trial results? (4 posts)
- Practical implications of molecular genetics research? (3 posts)

News

- Popular
- Recent
- Most Commented
    - Dacogen Is Safe And Effective In Older Myelodysplastic Syndromes Patients (ASH 2009)
    - Vitamin K2 And Vitamin D3 Combination Therapy May Increase Red Blood Cell and Platelet Counts In Low-Risk MDS Patients
    - Vidaza, Revlimid Spur Search for New Myelodysplastic Syndromes Drugs
    - Five-Day Intravenous Vidaza For MDS Shows Mixed Results Compared To Standard Dosing Regimen
    - Vidaza and Dacogen Improve Overall Survival Of MDS Patients (EHA 2009)
        - Acquired Chromosomal Abnormalities Affect Prognosis Of Lower-Risk MDS Patients
        - Blood Transfusions: Friend Or Foe?
        - Low-Dose, Subcutaneous Dacogen May Be Effective and Safe In Lower-Risk MDS Patients
        - Revlimid Trial In Leukemia Halted – No Immediate Impact On Drug's Approved Use In MDS Expected
        - Vatalanib Shows Limited Activity In Myelodysplastic Syndromes
    - Dacogen Is Safe And Effective In Older Myelodysplastic Syndromes Patients (ASH 2009)
    - "Myelodysplastic Syndromes" -- What's In The Name? Part 1: History
    - Higher-Risk MDS Patients May Achieve Similar Survival With Stem Cell Transplant Or Treatment With Vidaza Or Dacogen (ASH 2011)
    - I Have A Myelodysplastic Syndrome: Is My Family At Risk?
    - The Revised International Prognostic Scoring System Decoded

Resources

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    - Signs and Symptoms
    - Prognosis
    - The H1N1 Swine Flu Vaccine And Myelodysplastic Syndromes: A Comprehensive Review
    - Personal Perspective: "I Have MDS."
    - Caring For A Loved One With Myelodysplastic Syndromes – Part 2: Doctor Appointments
        - Low-Dose Chemotherapy And Differentiating Agents As Post-Remission Maintenance Prolonged Disease-Free And Overall Survival In A Case-Control Retrospective Study On Poor Prognosis AML/MDS Patients
        - Functional Analysis Of Cohesin Mutations In Myeloid Neoplasms
        - Midostaurin (Mido) Demonstrates A Favorable Safety Profile In Older Patients (Pts) With Acute Myeloid