Myelodysplastic Syndromes
1. Alemtuzumab and Myelodysplasia– a story of love and hate

Sonkin V

Western Galilee Hospital, Nahariya, Israel

Background

Alemtuzumab (Campath-1H) (Cam) is a recombinant DNA-derived, humanized therapeutic monoclonal antibody (Mab) that recognizes CD52 antigen on chronic lymphocytic leukemia (CLL) cells. Monotherapy with Cam shows efficacy in relapsed and refractory CLL. Cam is also a safe and active therapeutic agent in intermediate-1 myelodysplastic syndrome (MDS) and may be an attractive alternative to antithymocyte globulin in selected patients likely to respond to immunosuppressive therapy. Adverse events related to Cam include hematologic toxicity. Cam causes transient cytopenia, which is usually resolved within 2 months of discontinuation of therapy.

MDS is a clonal abnormality of the hematopoietic stem cell presenting with peripheral cytopenias, usually in combination with a hyperplastic bone marrow. Most cases of MDS are idiopathic, but several factors (antineoplastic alkylating agent, purine analog, ionizing radiation or benzene) have been shown to have a clear association with MDS etiology. Usually, therapy-related MDS (t-MDS) develops at least 4 years after radiation/chemotherapy (after alkylating agents treatment, like melphalan, cyclophosphamide or fludarabine). MDS post CLL treatment is not the rule, especially post Mab therapy (like Cam).

Case reports: Three CLL patients, heavily pretreated in the past (included Fludarabine and Cyclophosphamide), were in hematological remission for months after the last treatment with Fludarabine-Cyclophosphamide-Rituximab. At time of relapse a bone marrow biopsy (BMB) was done, showing in all the cases a massive and diffuse infiltration of small lymphocytes. Cam therapy was started. A BMB repeated a short time after end of treatment found no CLL in all cases (as no monoclonal B population was found in peripheral blood and in bone marrow aspirate at immunophenotyping analysis). But surprisingly, a myelodysplastic picture in the bone marrow was found.

Discussion: Myelodysplastic features following Cam treatment are a very rare event. Only three cases have been described in the literature, but not in CLL patients (in T-cell lymphoma).

Another 13 cases were reported to FDA. The time a MDS was diagnosed was less than 6 months after Cam therapy. The M:F ratio was in these 13 cases 3:1 and the age was below 60 years in 85% of cases. The implication of Cam in MDS as an etiologic factor is supported by the evidence that the bone marrow biopsy was without signs of myeloid toxicities just prior to Cam therapy. Refuting this theory: the quick development of MDS after immunotherapy, in contrast with the well known t-MDS which develops slowly during years, in heavily pretreated patients with inducing MDS chemotherapy. Second possibility: the MDS clone exists when CLL relapses, but the CLL-relapsed clone inhibits it; this can be the reason that we did not see any sign of MDS in the bone marrow before the Cam therapy. Only after the eradication of CLL clone by Cam, the MDS clone reappears. Third possibility: The MDS changes were present before Cam treatment but intensive infiltration by CLL B-cells made it impossible to distinguish these dysplastic changes. In one patient in the pre-Cam treatment a myeloperoxidase stain of the bone marrow was strongly positive, demonstrating the presence of the myeloid cells, hidden by CLL infiltrates. Though we cannot conclude the presence of myelodysplastic changes in these cells, it is a possibility. Cytogenetic studies, unfortunately undone, would have helped our supposition.

Perhaps this is the time to recognize a new form of t-MDS – the ti-MDS (immunotherapy induced MDS)
2. High prevalence of SF3B1 mutations in RARS and RARS-T

Coucelo M¹, Caetano G¹, Horta M¹, Domingues S¹, Bento C¹, Ribeiro M.L¹

¹Serviço de Hematologia do Centro Hospitalar de Coimbra-CHUC, Portugal

Introduction: Dysfunction in mitochondrial metabolism has been implicated in the pathogenesis of ring sideroblasts (RS), a characteristic feature of some myelodysplastic syndromes (MDS). Recent studies in MDS and myelodysplastic/myeloproliferative neoplasms (MDS/MPN) report recurrent heterozygous missense mutations in the splicing factor 3B subunit 1 (SF3B1) gene, particularly when more than 15% of ring sideroblasts are present: refractory anemia with RS (RARS), refractory cytopenia with multilineage dysplasia-RS (RARS-RS), RARS with thrombocytosis (RARS-T). Gene expression studies revealed that SF3B1 mutations are associated with down regulation of core mitochondrial pathways.

Objective: Define the prevalence of SF3B1 mutations in a group of patients with RARS and RARS-T.

Material and Methods: We studied 5 RARS (2M/3F) and 6 RARS-T (6M) patients, with a mean follow up of 5.6 years and 2.3 years and mean age at diagnose 74 years and 80 years, respectively. All RARS-T patients were JAK2V617F positive. Genomic DNA was obtained from whole blood and direct sequencing of SF3B1 gene (exons 14-15) was performed in an ABI 3130 Genetic Analyzer.

Results: We found a mutated SF3B1 allele in all RARS and in 5/6 RARS-T patients. Four out of five RARS patients present the K700E (exon 15) mutation and 1 carries the H672D (exon 14) mutation. In the RARS-T group we found 3 different mutations: 3 patients have the K700E, 1 has the K666N (exon 14) and 1 present the K666E (exon 14). In 1 RARS-T patient we found no SF3B1 exons 14-15 mutations; this patient died at the age of 84 with a follow up of 1 year. All the other patients are alive.

Discussion: The current study confirms the high prevalence of SF3B1 mutations in RARS (100%) and RARS-T (83.3%), suggesting that these mutations are highly associated with the presence of ring sideroblasts, in line with recent literature. Some authors reported a relatively benign clinical outcome in patients with SF3B1 mutations. Further studies are necessary to elucidate the role of SF3B1 mutations in the pathophysiology of MDS/MPD with ring sideroblasts.
Myeloproliferative Neoplasms
3. Ruxolitinib Provides Reductions in Splenomegaly Across Subgroups: An Analysis of Spleen Response in the COMFORT-II Study

Harrison C1, Kiladjian J-J2, Gisslinger H3, Niederwieser D4, Passamonti F5, Sirulnik A6, Hollaender N7, Levy R8, Knoops L9, Cervantes F10, Vannucchi A11, Barbui T12, Barosi G13

1Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom, 2Hôpital Saint-Louis et Université Paris Diderot, Paris, France, 3Medical University of Vienna, Vienna, Austria, 4University of Leipzig, Leipzig, Germany, 5Ospedale di Circolo e Fondazione Macchi, Varese, Italy, 6Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States of America, 7Novartis Pharma AG, Basel, Switzerland, 8Incyte Corporation, Wilmington, Delaware, United States of America, 9Cliniques Universitaires Saint-Luc and de Duve Institute Université Catholique de Louvain, Brussels, Belgium, 10Hospital Clinic, IDIBAPS, Barcelona, Spain, 11University of Florence, Florence, Italy, 12A.O Ospedali Riuniti di Bergamo, Bergamo, Italy, 13IRCCS Policlinico San Matteo Foundation, Pavia, Italy

BACKGROUND: Ruxolitinib is a potent and selective oral JAK1/2 inhibitor that has been approved in the US and has demonstrated rapid and durable reductions in splenomegaly and improved disease-related symptoms and quality of life (QoL) in 2 phase 3 studies (COMFORT-I and –II) in patients with primary MF (PMF), post-polycythemia vera-MF (PPV-MF), or post-essential thrombocytemia-MF (PET-MF). The primary and key secondary endpoints of the study were both met: the proportion of patients achieving ≥35% reduction in spleen volume at week 48 (28.5%, ruxolitinib; 0%, BAT; P < .0001) and week 24 (31.9%; 0%, P < .0001), respectively. Subgroup analysis of data from COMFORT-II was performed on both the 48 and 24 week endpoints.

METHODS: 219 patients were randomized (2:1) to receive ruxolitinib (15 or 20 mg twice daily [bid] based on baseline platelet count [100 x 10^9/L – 200 x 10^9/L or > 200 x 10^9/L, respectively]) or BAT. The proportion of ruxolitinib-treated patients achieving the primary and key secondary endpoints were analyzed by subgroup for gender (male or female), age (≤65 years or >65 years), starting dose (15 or 20 mg bid), baseline MF type (PMF, PPV-MF, or PET-MF), previous hydroxyurea (hydroxycarbamide) use (yes or no), baseline palpable spleen length (≤10 cm or >10 cm), baseline spleen volume (>median or ≤median), JAK2V617F mutation (presence or absence), and International Prognostic Scoring System (IPSS) risk category (intermediate-2 or high) (Cervantes et al, Blood, 2009). In addition, the relationships between these factors and spleen volume reduction were investigated by multivariate logistic regression.

RESULTS: The proportion of patients in each subgroup with ≥35% reduction in spleen volume from baseline at week 48 is shown below (Figure).
The response rate was higher among patients receiving ruxolitinib than in patients receiving BAT in all subgroups; no patients in the BAT group reached a ≥35% reduction in spleen volume at week 48. All subgroups receiving ruxolitinib responded and all subgroup comparisons had overlapping 95% confidence intervals. At week 24, a trend for a higher response rate was observed among patients who received a starting dose of 20 mg bid compared with those who received a starting dose of 15 mg bid; however, the response rates among these patients at week 48 were not different. There was no significant difference in response rates for patients with the JAK2V617F mutation compared with those without the mutation and at week 48, the vast majority of patients receiving ruxolitinib experienced spleen volume reductions, including JAK2V617F-positive (88% [66/75]) and JAK2V617F-negative (91% [20/22]) patients. Results of the subgroup analysis were confirmed by the multivariate models. A significant effect of ruxolitinib starting dose was seen when modeling response rates at week 24, but not at week 48.

**CONCLUSIONS:** Patients who received ruxolitinib had significantly greater reductions in splenomegaly than patients who received BAT. In this analysis, ruxolitinib was shown to be more effective than BAT at reducing spleen volume for all subgroups regardless of gender, age, mutation status, IPSS risk category, baseline spleen size, MF subtype, or ruxolitinib starting dose.
4. **Health-Related Quality of Life and Symptoms in Myelofibrosis Patients Treated with Ruxolitinib versus Best Available Therapy**

Harrison C\(^1\), Kiladjian J-J\(^2\), Al-Ali H-K\(^3\), Gisslinger H\(^4\), Knoops L\(^5\), Sirulnik A\(^6\), Zhou X\(^7\), Copley-Merriman C\(^5\), Levy R\(^9\), Cervantes F\(^10\), Passamonti F\(^11\), Vannucchi A\(^12\), Barbui T\(^13\), Barosi G\(^14\)

\(^1\)Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom, \(^2\)Hôpital Saint-Louis et Université Paris Diderot, Paris, France, \(^3\)University of Leipzig, Leipzig, Germany, \(^4\)Medical University of Vienna, Vienna, Austria, \(^5\)Cliniques Universitaires Saint-Luc and de Duve Institute Université Catholique de Louvain, Brussels, Belgium, \(^6\)Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States of America, \(^7\)RTI Health Solutions, Research Triangle Park, North Carolina, United States of America, \(^8\)RTI Health Solutions, Ann Arbor, Michigan, United States of America, \(^9\)Incyte Corporation, Wilmington, Delaware, United States of America, \(^10\)Hospital Clinic, IDIBAPS, Barcelona, Spain, \(^11\)Ospedale di Circolo e Fondazione Macchi, Varese, Italy, \(^12\)University of Florence, Florence, Italy, \(^13\)A. O. Ospedali Riuniti di Bergamo, Bergamo, Italy, \(^14\)IRCCS Policlinico San Matteo Foundation, Pavia, Italy

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**Methods:** The COMFORT-II study includes 219 patients (ruxolitinib, n = 146; best available therapy [BAT], n = 73). The European Organisation for the Research and Treatment of Cancer (EORTC) QoL Questionnaire—Core 30 (QLQ-C30) and Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym) questionnaires were assessed at baseline and weeks 8, 16, 24, and 48.

This analysis includes evaluable patients in the randomized treatment phase and assesses changes from baseline in HRQoL and MF symptom scores including the EORTC subscales, LymS, and FACT-Lym summary scores, which incorporate well-being and/or symptom subscales. Mixed model analyses, adjusted for age, sex, baseline score, and prognostic risk category, are used to evaluate treatment differences at each time point and overall across time.

**Results:** HRQoL and MF symptoms, on average, improved compared with baseline for patients receiving ruxolitinib, but remained the same or worsened for patients receiving BAT.

Based on the EORTC QLQ-C30, the treatment differences in Physical Functioning, Role Functioning, Fatigue and Appetite loss were significantly in favor of ruxolitinib starting at week 8 (P < .05) and remained significant at week 48 (P < .05). The overall between-treatment differences (on average across time) in adjusted mean change from baseline for MF symptoms scores (95% confidence interval) were: Fatigue, −10.2 (−15.9, −4.5), P < .001; Dyspnea, −11.6 (−17.6, −5.6), P < .001; Appetite loss, −16.3 (−21.5, −11.1), P < .0001; Insomnia, −9.8 (−16.7, −3.0), P < .01; Pain, −9.0 (−14.9, −3.0), P < .01; and diarrhea, −8.4 (−13.9, −2.8), P < .01; negative values favor ruxolitinib. Compared with the BAT arm, Global Health Status/QoL (Figure) was significantly improved in the ruxolitinib arm at weeks 8, 16 and 48.

The LymS, including symptoms of pain, swelling, fever, night sweats, itching, trouble sleeping, fatigue, weight loss, loss of appetite, trouble concentrating, and other patient concerns, was also significantly improved during treatment (Figure). Additionally, the FACT–G, FACT–Lym TOI, and FACT–Lym total were all significantly (P < .05) improved for patients receiving ruxolitinib treatment compared with BAT.

Most EORTC QLQ-C30 and FACT-Lym scores significantly improved on ruxolitinib compared with BAT. The treatment effect between the high-risk and intermediate 2-risk prognostic groups was not significantly different based on an analysis of the risk group–by–treatment interaction.
**Conclusions:** These additional analyses from the COMFORT-II study further support that ruxolitinib significantly improves overall HRQoL and MF symptoms compared with BAT.

*Figure. Adjusted\(^a\) Mean Change from Baseline Scores by Treatment and Time*

\(^a\)Adjusted for age, sex, baseline score, and prognostic risk category.

Higher scores indicate better HRQoL.
5. Comparison of the Efficacy of Placebo and Best Available Therapy for the Treatment of Myelofibrosis in the COMFORT Studies

Mesa R1, Verstovsek S2, Cervantes F3, Sirulnik A4, Mendelson E5, Sun W5, Sandor V5, Levy R5, Harrison C6

1 Mayo Clinic, Scottsdale, Arizona, United States of America, 2 The University of Texas MD Anderson Cancer Center, Houston, Texas, United States of America, 3 Hospital Clinic, IDIBAPS, Barcelona, Spain, 4 Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States of America, 5 Incyte Corporation, Wilmington, Delaware, United States of America, 6 Guy’s and St Thomas’ NHS Foundation Trust, London, United Kingdom

BACKGROUND: Ruxolitinib is a potent and selective oral JAK1/2 inhibitor that has been approved in the US and has demonstrated rapid and durable reductions in splenomegaly and improved disease-related symptoms and quality of life (QoL) in 2 phase 3 studies (COMFORT-I and -II) in patients with primary MF, post-polycythemia vera-MF, or post-essential thrombocythemia-MF. Compared with the control group in each study (COMFORT-I, placebo; COMFORT-II, best available therapy [BAT]), a significantly higher proportion of patients receiving ruxolitinib achieved a ≥35% reduction in spleen volume at week 24 (COMFORT-I and -II; P<.0001) and week 48 (COMFORT-II; P<.0001). This analysis compares the efficacy outcomes between the placebo arm from COMFORT-I and the BAT arm from COMFORT-II.

METHODS: COMFORT-I is a randomized (1:1), double-blind, multicenter study comparing ruxolitinib 15 or 20mg twice daily (BID) with placebo, and COMFORT-II is a randomized (2:1), open-label, multicenter study comparing ruxolitinib 15 or 20mg BID with BAT (investigator-selected therapy, including no treatment). QoL was measured using patient responses with the EORTC QLQ-C30 as an exploratory endpoint in both studies.

RESULTS: In the COMFORT-I and COMFORT-II studies, 154 patients received placebo (ruxolitinib, n=155), and 73 patients received BAT (ruxolitinib, n=146), respectively, and were included in the primary efficacy analyses. The demographic and baseline characteristics were similar between the control arms of the 2 studies including spleen size below the costal margin (mean [standard deviation], 16.4 [6.27] cm and 15.8 [6.71] cm in placebo and BAT, respectively). Only 1 patient (0.7%) who received placebo and no patients who received BAT had a ≥35% reduction in spleen volume from baseline to week 24 (Figure). The median percent increases in spleen volume from baseline to week 24 in both the placebo and BAT groups were numerically similar (placebo, 8.5% [range, 46.4% to 48.8%]; BAT, 5.1% [range, -33.3% to 29.7%]). In contrast, almost all patients who received ruxolitinib had a reduction in spleen volume from baseline at week 24 (COMFORT-I: median, -33.0%; COMFORT-II: median, -27.5%).

The QLQ-C30 provides a measurement of QoL and MF-related symptoms, including fatigue, pain, dyspnea, insomnia, and appetite loss. At 24 weeks, neither the placebo nor BAT arms had clinically meaningful changes from baseline (10 points [Osoba et al. J Clin Oncol. 1998]) in global QoL (decreases indicate worsening) or symptom scales (increases indicate worsening) (Table). Although differences exist between the placebo and BAT arms in the mean change from baseline, between-group comparison was not performed because of the large standard deviations that complicate any comparisons between the 2 groups.

CONCLUSIONS: This post hoc analysis shows that patients who received BAT in the COMFORT-II study fared no better in clinically meaningful QoL responses and had numerically similar increases in spleen size as those who received placebo in COMFORT-I. No clinically meaningful improvements in QoL or symptoms were seen on either the placebo or BAT arms. These new data strongly suggest that traditional therapies for MF provide little improvement in spleen size, symptoms, or QoL as compared with placebo.
Figure. Percent Change From Baseline in Spleen Volume at Week 24 for Individual Patients

Table. Mean EORTC QLQ-C30 Global Health Status and Subscale Results at Week 24 in the Placebo and BAT Arms (Observed Cases)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Mean change from baseline at week 24 (SD)</td>
</tr>
<tr>
<td>Global health status/QoL</td>
<td>104</td>
<td>-3.4 (21.53)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>107</td>
<td>1.8 (24.71)</td>
</tr>
<tr>
<td>Pain</td>
<td>104</td>
<td>8.3 (27.47)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>105</td>
<td>1 (27.53)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>105</td>
<td>-2.2 (32.12)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>107</td>
<td>0.6 (33.96)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}For patients with measurements at both baseline and week 24.

BAT, best available therapy; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire.
6. **Consistent benefit of ruxolitinib over placebo across myelofibrosis patient subgroups: results from COMFORT-I**


¹The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²Mayo Clinic, Scottsdale, AZ, USA; ³Stanford Cancer Institute, Stanford, CA, USA; ⁴Incyte Corporation, Wilmington, DE, USA; ⁵Princess Margaret Hospital, University of Toronto, Toronto, Canada; ⁶Washington University School of Medicine, St. Louis, MO, USA; ⁷Frankston Hospital, Frankston, Australia; ⁸Oregon Health and Science University, Portland, OR, USA and University of Utah Huntsman Cancer Institute, Salt Lake City, UT, USA; ⁹Saint Agnes Cancer Institute, Baltimore, MD, USA; ¹⁰Weill Cornell Medical College, New York, NY, USA; ¹¹University of Michigan, Ann Arbor, MI, USA; ¹²Emory University School of Medicine, Atlanta, GA, USA; ¹³Birmingham Hematology & Oncology, Birmingham, AL, USA; ¹⁴Duke University Health System, Durham, NC, USA; ¹⁵Abramson Cancer Center at The University of Pennsylvania, Philadelphia, PA, USA; ¹⁶Cancer Care Centers of South Texas/US Oncology, San Antonio, TX, USA; ¹⁷UCLA Medical Hematology & Oncology, Los Angeles, CA, USA; ¹⁸Columbia Presbyterian Medical Center, New York, NY, USA

*Currently at Division of Hematology and Hematologic Malignancies and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT.

**Background:** Myelofibrosis is a rare and life-threatening myeloproliferative neoplasm characterized by debilitating symptoms, cytopenias, and splenomegaly. COMFORT-I is a phase III, double-blind, randomized, placebo-controlled study of ruxolitinib, a JAK1 and JAK2 inhibitor. In this study, ruxolitinib demonstrated a significant reduction in spleen volume and a significant improvement in myelofibrosis-related symptoms in patients with myelofibrosis. As clinical characteristics and disease course can vary greatly among individual patients with myelofibrosis, we evaluated the efficacy of ruxolitinib across patient subgroups in COMFORT-I.

**Methods:** Patients with myelofibrosis (N=309) received placebo or ruxolitinib starting at 15 or 20 mg BID for baseline platelet counts of ≥100–200 or >200 X 10⁹/L, respectively. Spleen volume was assessed by MRI (or CT in applicable patients) and myelofibrosis-related symptoms were assessed using the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 electronic diary. A Total Symptom Score (TSS) from the MFSAF was calculated based on the sum of individual symptom scores for abdominal discomfort, pain under left ribs, early satiety, night sweats, itching, and bone/muscle pain (maximum possible score of 60). Percent changes from baseline to week 24 in spleen volume and TSS were evaluated in patients receiving ruxolitinib and placebo across the following subgroups: myelofibrosis subtype (primary, post-polycythemia vera, or post-essential thrombocythemia), age (≤65 or >65 years), International Prognosis Scoring System (IPSS) risk category (intermediate-2 or high), JAK2V617F mutation (positive or negative), baseline hemoglobin level (≥10 or <10 g/dL), baseline palpable spleen length (≤10 or >10 cm), and baseline symptom severity (TSS quartile).

**Results:** Patients in the ruxolitinib group experienced spleen volume reduction and TSS improvement while patients on placebo experienced spleen volume increases and TSS worsening, regardless of myelofibrosis subtype, age, IPSS risk category, JAK2V617F mutation status, baseline hemoglobin level, or baseline palpable spleen length (Figure). Mean percent changes in spleen volume and TSS across subgroups were similar to those seen in the total study population (~31.6% vs +8.1% and +46.1% vs −41.8%, ruxolitinib vs placebo, respectively). Patients treated with ruxolitinib also experienced reductions in spleen volume and improvements in TSS regardless of their baseline symptom severity (measured by baseline TSS quartile). In ruxolitinib-treated patients, the mean percent change in spleen volume ranged from −28.0% in quartile 1 (lower TSS) to −34.8% in quartile 4 (higher TSS). In contrast, the change in all placebo patients was +8.1%. Similarly, mean percent change in TSS for ruxolitinib-treated patients ranged from −40.5% in quartile 1 to −48.2% in quartile 4; the change in all patients receiving placebo was +41.8%.

**Conclusion:** Within the patient population evaluated in COMFORT-I, patients with more and less severe myelofibrosis benefited from ruxolitinib treatment, and efficacy did not depend on myelofibrosis subtype or the presence of the JAK2V617F mutation.

Supported by Incyte Corporation.
**Figure:** Mean percent change from baseline to week 24 in spleen volume (A) and Total Symptom Score (B) in COMFORT-I patient subgroups

**A**

- **Type of MF**: PMF, PPV-MF, PET-MF
- **IPSS Risk**: High, Int-2
- **Age (y)**: ≤65, >65
- **V617F Mutation**: Positive, Negative
- **Baseline Spleen Length (cm)**: ≤10, >10, ≥10, <10
- **Baseline Hgb (g/dL)**: ≤70, >70, ≥70, <70

**B**

- **Type of MF**: PMF, PPV-MF, PET-MF
- **IPSS Risk**: High, Int-2
- **Age (y)**: ≤65, >65
- **V617F Mutation**: Positive, Negative
- **Baseline Spleen Length (cm)**: ≤10, >10, ≥10, <10
- **Baseline Hgb (g/dL)**: ≤70, >70, ≥70, <70

*Hgb, hemoglobin; IPSS, International Prognostic Scoring System; MF, myelofibrosis; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post-polycythemia vera; SEM, standard error of mean.*

*P*-value for interaction of MF subtype by treatment=0.52.

*P*-value for interaction of mutation status by treatment=0.07.

Dashed lines represent the mean percent change from baseline for overall treatment group.

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