Efficacy, Safety, and Confirmation of the Recommended Phase II Dose of Ruxolitinib Plus Panobinostat in Patients With Intermediate or High-Risk Myelofibrosis

Abstract #711

Kiladjian JJ, Heidel FH, Vannucchi AM, Ribrag V, Francesco P, Hayat A, Conneally E, Martino B, Kindler T, Lipka DB, Acharyya S, Gopalakrishna P, Ide S, Loechner S, Mu S, Harrison CN

Introduction

- **Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by bone marrow fibrosis, splenomegaly, and debilitating constitutional symptoms[1]**
- **Ruxolitinib, a potent JAK1/JAK2 inhibitor, demonstrated rapid and durable reductions in splenomegaly and MF-related symptoms, improved quality of life, and provided a survival advantage in the phase 3 COMFORT studies[2-5]**
- **Panobinostat, a potent oral pan-deacetylase inhibitor (pan-DACi),[6] reduced spleen size, symptoms, and *JAK2* V617F allele burden in patients with MF in phase 1/2 studies[7-9]**
- **Targeting multiple components of the JAK/STAT pathway, as well as parallel signaling pathways that may also be involved in the pathogenesis of MF, has the potential to have a synergistic therapeutic effect on the underlying disease**

1. Tefferi A, et al. *J Clin Oncol*. 2011;29:1356-1363.
2. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807.
3. Harrison C, et al. *N Engl J Med*. 2012;366:787-798.
4. Cervantes F, et al. *Blood*. 2013;122(25):4047-4053.
5. Verstovsek S, et al. *Haematologica*. 2013;98(12):1865-1871.
6. Wang Y, et al. *Blood*. 2009;114:5024-5033.
7. DeAngelo DJ. *Leukemia.* 2013;27:1628-1636.
8. DeAngelo DJ. *Br J Haematol*. 2013;162:326-335.
9. Mascarenhas J. *Br J Haematol*. 2013;161:68-75.

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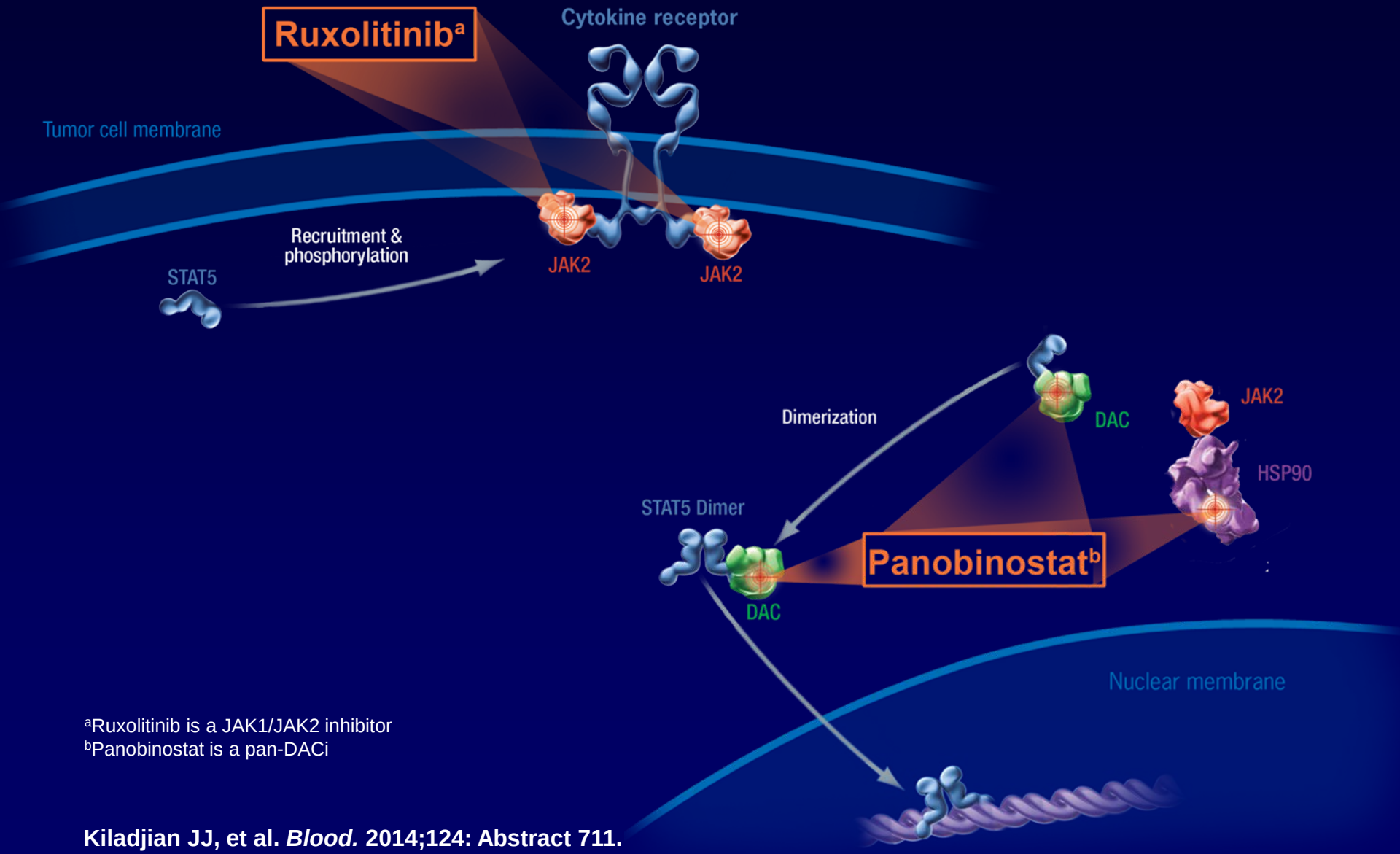
Rationale for Combination Therapy



[a]Ruxolitinib is a JAK1/JAK2 inhibitor
[b]Panobinostat is a pan-DACi

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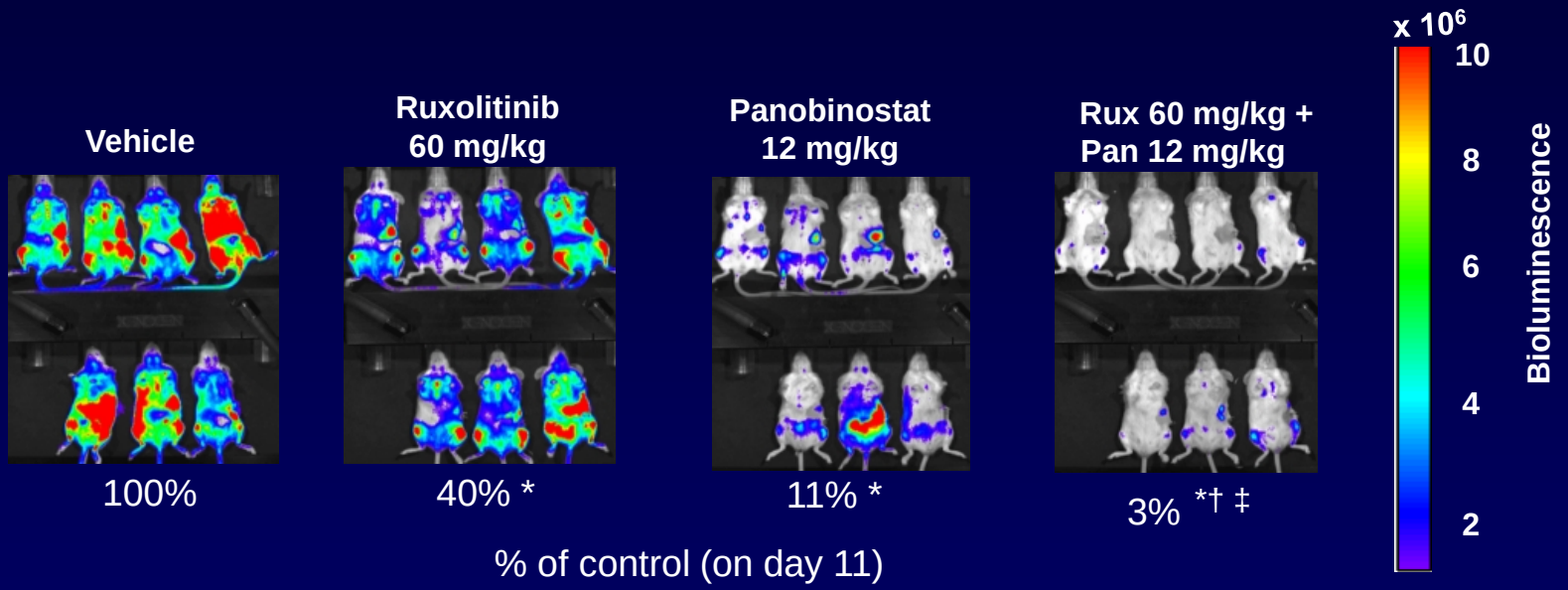
Combination Therapy *in a JAK2* Mutation-Driven Ba/F3 Murine Model



*P < .05 vs. vehicle control; † P < .05 vs. ruxolitinib; ‡ P < .05 vs panobinostat at same dose

Evrot E, et al. *Clin Cancer Res*. 2013;19(22):6230-6241.

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Study Design

- Phase Ib, open-label, multicenter, dose-finding study (NCT01433445)

- **PMF or PPV/PET-MF**
- **≥1 IPSS risk factor[1]**
- **Palpable spleen ≥ 5 cm**

Dose-escalation phase

- **Determine MTD/RP2D (n = 9, minimum)**
- **Enroll cohorts until MTD and/or RP2D reached**

Safety-expansion phase

- **23 additional patients at RP2D**
- **2 x 28-day cycles**
- **Confirm RP2D**

Dose Level	Combination treatment dose	
	Ruxolitinib	Panobinostat
1	5 mg BID	10 mg TIW/QOW
2	10 mg BID	10 mg TIW/QOW
3	15 mg BID	10 mg TIW/QOW
4	15 mg BID	15 mg TIW/QOW
5	15 mg BID	20 mg TIW/QOW
6 (RP2D)	15 mg BID	25 mg TIW/QOW

- 10 sites across 5 countries (France, Germany, Ireland, Italy, and UK)
- Data cutoff, 29 Aug 2014 (Start date, Nov 2011; projected completion date, Jan 2016)

1. Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.

BID, twice daily; TIW, three times a week; QOW, every other week.

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Assessments

- The primary outcome measure was the rate of dose-limiting toxicities at the different dose levels
- Efficacy was assessed on the basis of:
  - ≥50% reduction in spleen length by palpation compared with baseline
  - ≥35% reduction in spleen volume as assessed by magnetic resonance imaging/computed tomography compared with baseline (expansion phase only)
  - Changes in bone marrow (BM) fibrosis grade, as assessed by BM biopsies
- Changes in *JAK2* V617F allele burden, BM fibrosis, and cytokines were measured in the expansion phase

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Baseline Patient Characteristics

n, (%)	Escalation phase (n = 38)	Expansion phase (n = 23)	Patients treated at RP2D (n = 34)
Age, median (range), years	63 (47-79)	67 (54-77)	65 (53-77)
Male	19 (50)	16 (69.6)	20 (58.8)
Female	19 (50)	7 (30.4)	14 (41.2)
MF classification			
PMF	17 (44.7)	10 (43.5)	14 (41.2)
PPV-MF	10 (26.3)	6 (26.1)	11 (32.4)
PET-MF	11 (28.9)	7 (30.4)	9 (26.5)
Time since initial MF diagnosis, median (range), months	19.8 (1.8-189.2)	23.7 (0.6-245.0)	22.4 (0.6-245.0)
Presence of constitutional symptoms[a]	30 (78.9)	19 (82.6)	28 (82.4)
Age > 65 years[a]	14 (36.8)	13 (56.5)	15 (44.1)
Hemoglobin < 10 g/dL[a]	13 (34.2)	7 (30.4)	9 (26.5)
WBC > 25 × 10^9/L[a]	8 (21.1)	7 (30.4)	9 (26.5)
Circulating blasts ≥ 1%[a]	17 (44.7)	9 (39.1)	19 (55.9)
Prior PRBC transfusion	17 (44.7)	3 (13.0)	7 (20.6)
Median (range) baseline spleen length, cm	13 (5-35)	12 (5-24)	12 (5-24)

[a] At study entry

- One patient in cohort 2 of the escalation phase received prior splenic irradiation

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Patient Disposition

n (%)	Escalation phase (n = 38)	Expansion phase (n = 23)	Patients treated at RP2D (n = 34)
Patient treated			
Ongoing	18 (47.4)	18 (78.3)	26 (76.5)
Discontinued	20 (52.6)	5 (21.7)	8 (23.5)
Primary reason discontinuation			
Adverse event	9 (23.7)	3 (13.0)	5 (14.7)
Withdrawal of consent	1 (2.6)	1 (4.3)	1 (2.9)
Death	2 (5.3)	0	0
Disease progression	7 (18.4)	1 (4.3)	1 (2.9)
Protocol deviation[a]	1 (2.6)	0	1 (2.9)

[a] Treatment interruption >4 weeks due to grade 3/4 thrombocytopenia

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Exposure to Study Medication

Duration of exposure

Median (range)	Escalation Phase (n = 38)	Expansion Phase (n = 23)	Patients Treated at RP2D (n = 34)
Panobinostat	82.6 weeks (2.6-144.6)	42.4 weeks (2.6-72.3)	51.1 weeks (2.6-97.6)
Ruxolitinib	83.7 weeks (3.4-144.9)	43.7 weeks (3.1-75.7)	52.9 weeks (3.1-101.0)

Patients with ≥1 dose interruption/change

n (%)	Escalation Phase (n = 38)	Expansion Phase (n = 23)	Patients Treated at RP2D (n = 34)
Panobinostat	24 (63.2)	12 (52.2)	22 (64.7)
Ruxolitinib	29 (76.3)	11 (47.8)	20 (58.8)

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Summary of Safety in the Escalation Phase

- The most common adverse events (> 30%) of any grade in the escalation phase were diarrhea (65.8%), anemia (63.2%), thrombocytopenia (52.6%), muscle spasms (36.8%), asthenia (36.8%), headache (34.2%), and nausea (31.6%)
- Anemia (42.1%) and thrombocytopenia (21.1%) were the most common grade 3/4 adverse events; 2 patients discontinued due to each AE
- There were 2 deaths within 30 days of last treatment:
  - 1 due to myocardial infarction (ruxolitinib 15 mg BID, panobinostat 15 mg TIW, QOW)
  - 1 due to progression of MF (ruxolitinib 15 mg BID, panobinostat 20 mg TIW, QOW)
  - Both were assessed by the treating investigator as not suspected to be treatment related
- No MTD was reached
- DLTs included:
  - Thrombocytopenia, grade 4, in cohort 2 (n =1) and cohort 5 (n =1)
  - Nausea, grade 3, in cohort 6 (n = 1)
- RP2D: Panobinostat, 25 mg TIW, QOW + ruxolitinib 15 mg BID

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Hematologic Adverse Events

- The most common hematologic AEs were anemia and thrombocytopenia

n (%)[a]	Expansion Phase n = 23		Patients Treated at the RP2D n = 34	
	All grade	Grade 3/4	All grade	Grade 3/4
Anemia	18 (78.3)	8 (34.8)	26 (76.5)	11 (32.4)
Thrombocytopenia	11 (47.8)	7 (30.4)	16 (47.1)	9 (26.5)
Neutropenia	1 (4.3)	1 (4.3)	3 (8.8)	2 (5.9)
Platelet count decreased	1 (4.3)	0	2 (5.9)	0
Leukopenia	1 (4.3)	1 (4.3)	2 (5.9)	1 (2.9)

[a]In ≥ 5% of patients treated at the RP2D; regardless of relationship to study treatment at any time during or up to 30 days after last dose.

- Among patients treated at the RP2D, 1 patient (expansion phase) discontinued due to anemia and 1 (escalation phase) due to thrombocytopenia[b]

[b]Patient had an interruption in study treatment for >4 weeks due to grade 3/4 thrombocytopenia and therefore was discontinued.

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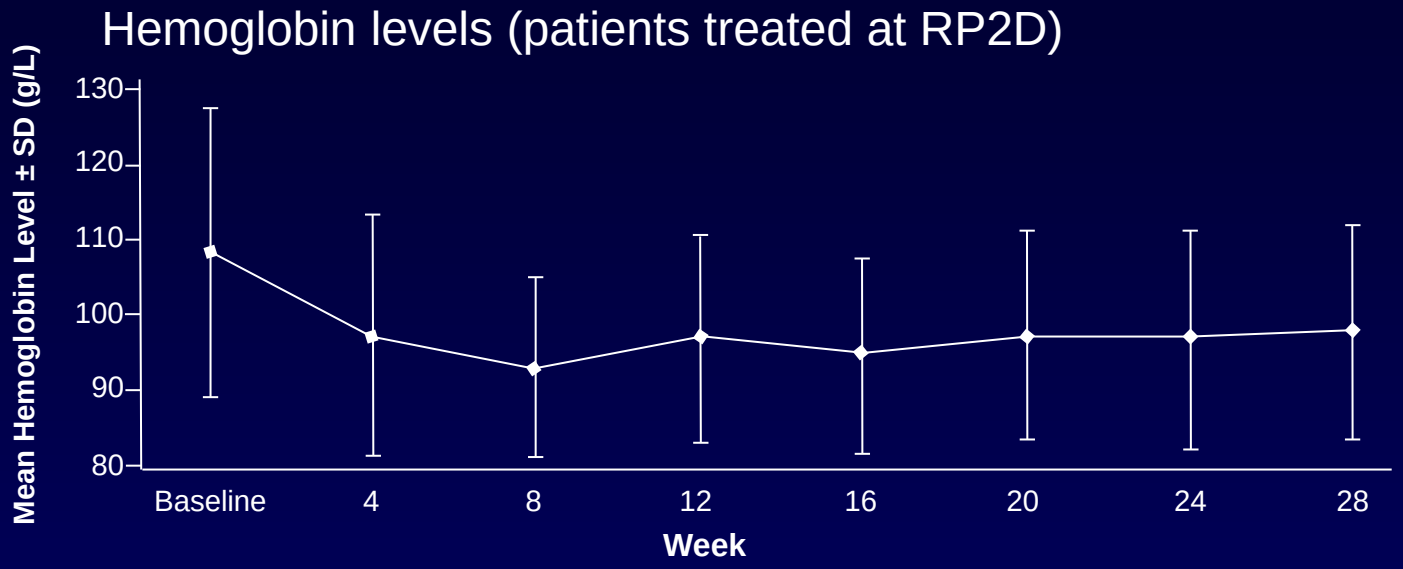
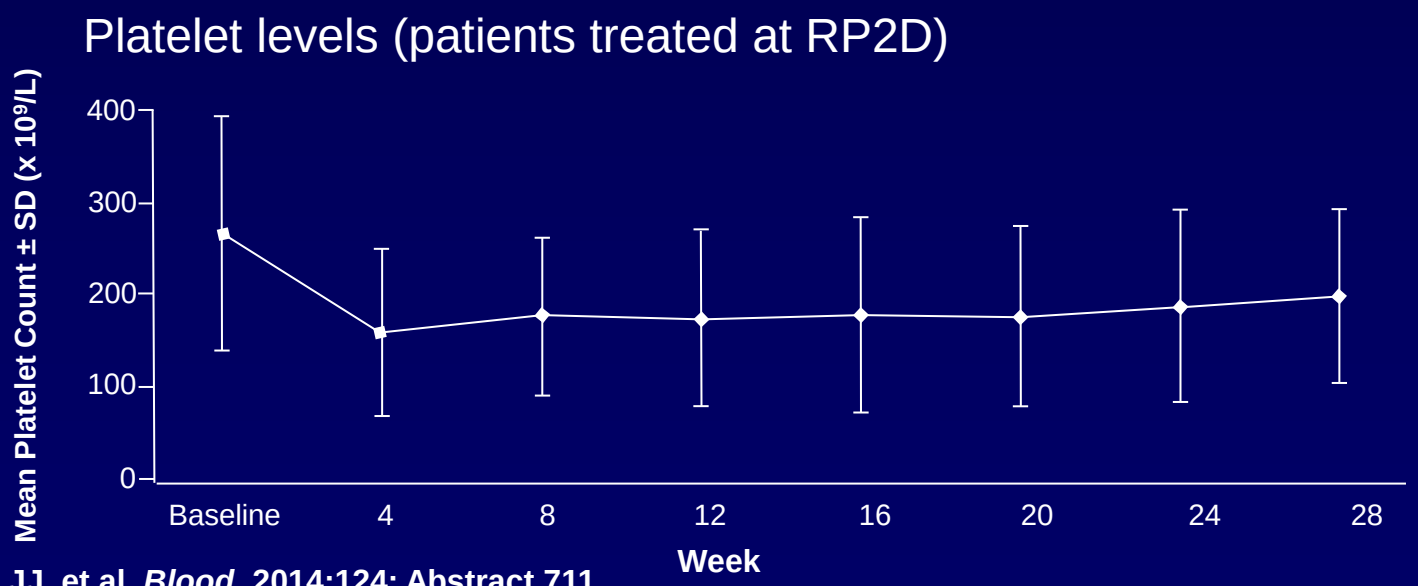
Hemoglobin and Platelet Levels Over Time





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Nonhematologic Adverse Events (>20%)

	Expansion Phase n = 23		Patients Treated at the RP2D n = 34	
n (%)[a]	All grade	Grade 3/4	All grade	Grade 3/4
Any AE	23 (100)	15 (65)	34 (100)	22 (65)
Diarrhea	14 (61)	3 (13)	23 (68)	5 (15)
Asthenia	10 (44)	1 (4)	15 (44)	3 (9)
Muscle spasms	7 (30)	0	12 (35)	0
Vomiting	6 (26)	0	12 (35)	1 (3)
Nausea	7 (30)	0	11 (32)	2 (6)
Fatigue	6 (26)	0	10 (29)	3 (9)
Headache	5 (22)	0	10 (29)	0
Dyspnea	5 (22)	0	10 (29)	2 (6)
Abdominal pain	5 (22)	0	8 (24)	1 (3)
Peripheral edema	4 (17)	0	7 (21)	0
Constipation	4 (17)	0	7 (21)	0
Dizziness	3 (13)	0	7 (21)	0

[a]In ≥ 20% of patients treated at the RP2D; regardless of relationship to study treatment at any time during or up to 30 days after last dose

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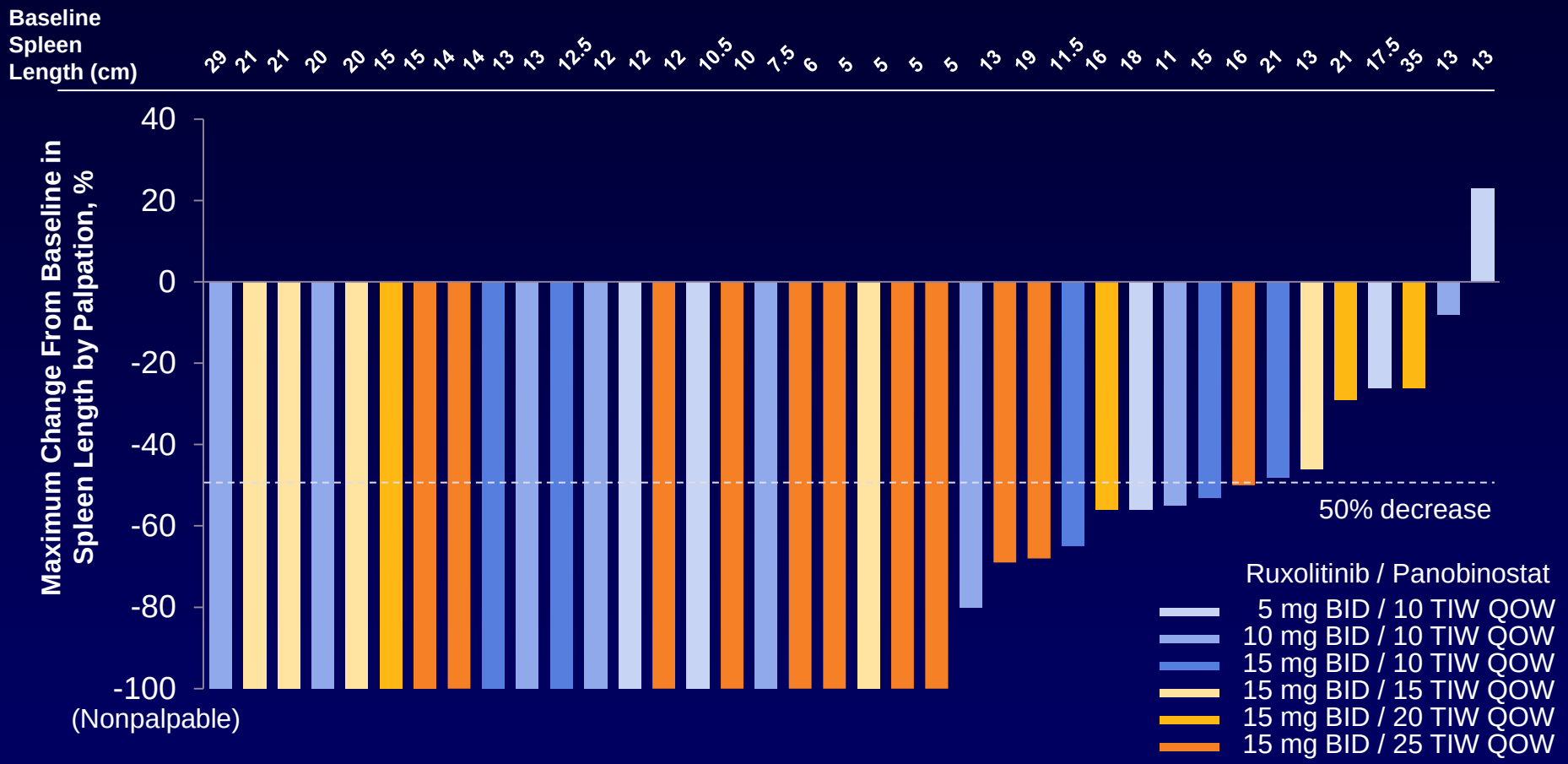
Change in Spleen Length: Escalation Phase



- **81.6% (31/38) of patients in the escalation phase achieved a ≥ 50% reduction in palpable spleen length at any time during the study**
  - **22 patients (57.9%) achieved a 100% reduction in spleen length (nonpalpable spleen)**

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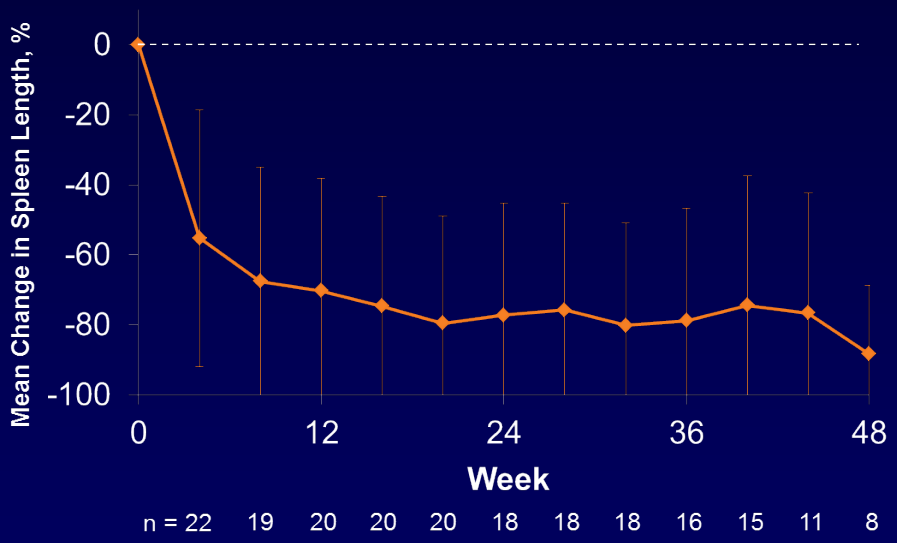
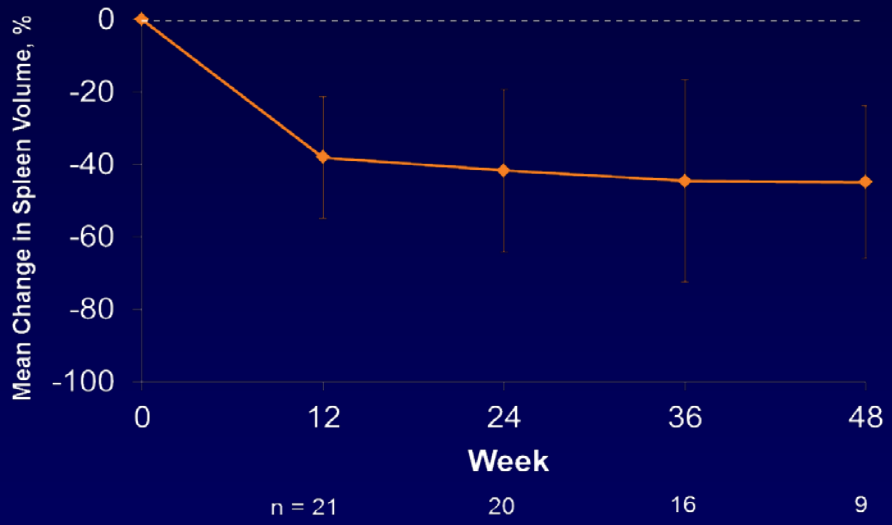
Change in Spleen Size Over Time: Expansion Phase

Spleen Length



Spleen Volume



Best spleen size reduction at any time:

- Mean, -78.7% (SD, 29.36%)
- Median, -100% (range, 0% to -100%)

-100% = nonpalpable

- Mean, -48.3% (SD, 21.61%)
- Median, -46.7% (range, -8.7% to -84.4%)

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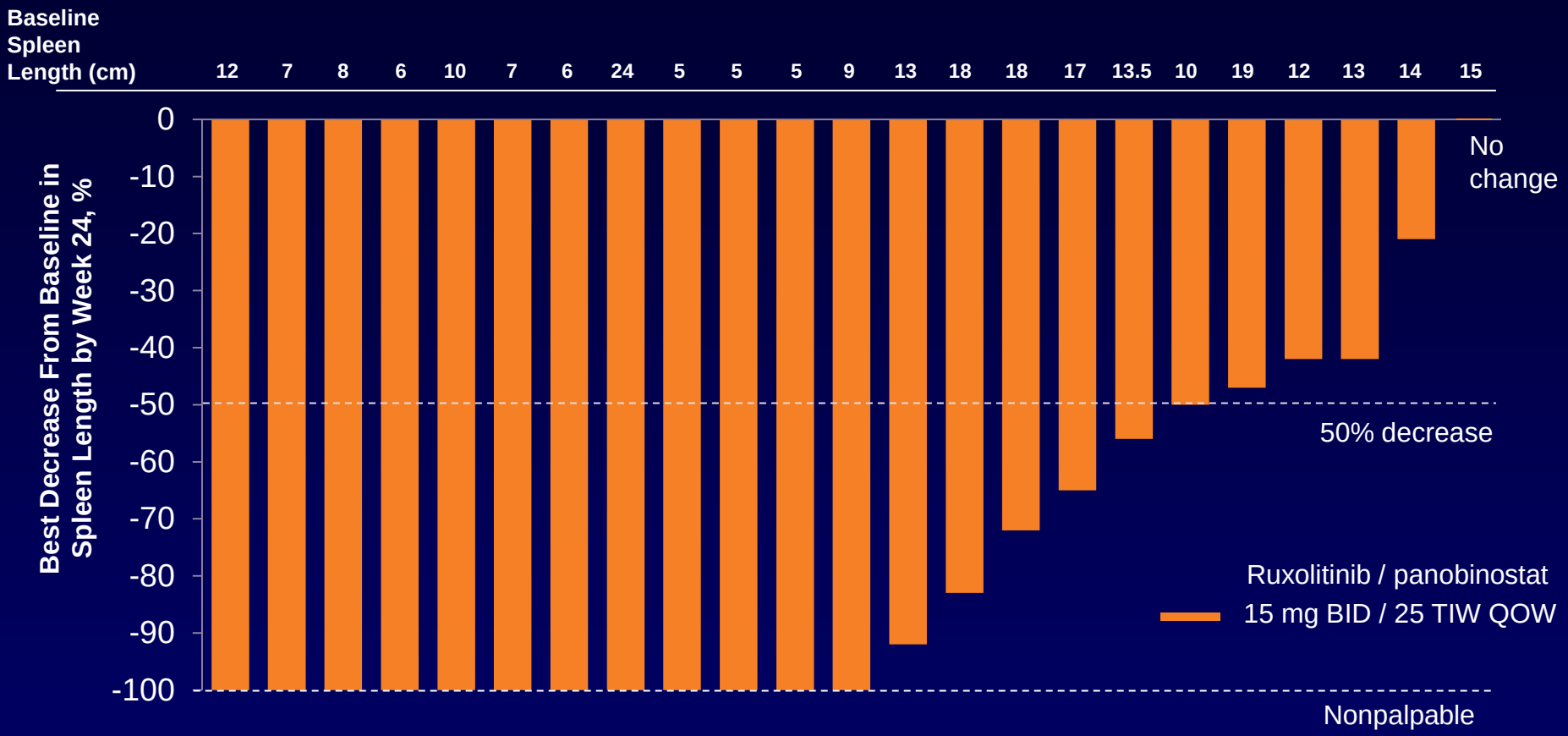
Change in Spleen Volume: Expansion Phase



- 78.3% (18/23) of patients achieved a ≥ 50% reduction in palpable spleen length on or before week 24 (C7D1)
  - 12 patients (52.2%) achieved a 100% reduction in spleen length (nonpalpable spleen)
  - In COMFORT-II, 62% (91/146) of patients achieved a ≥50% reduction in palpable spleen length by week 24

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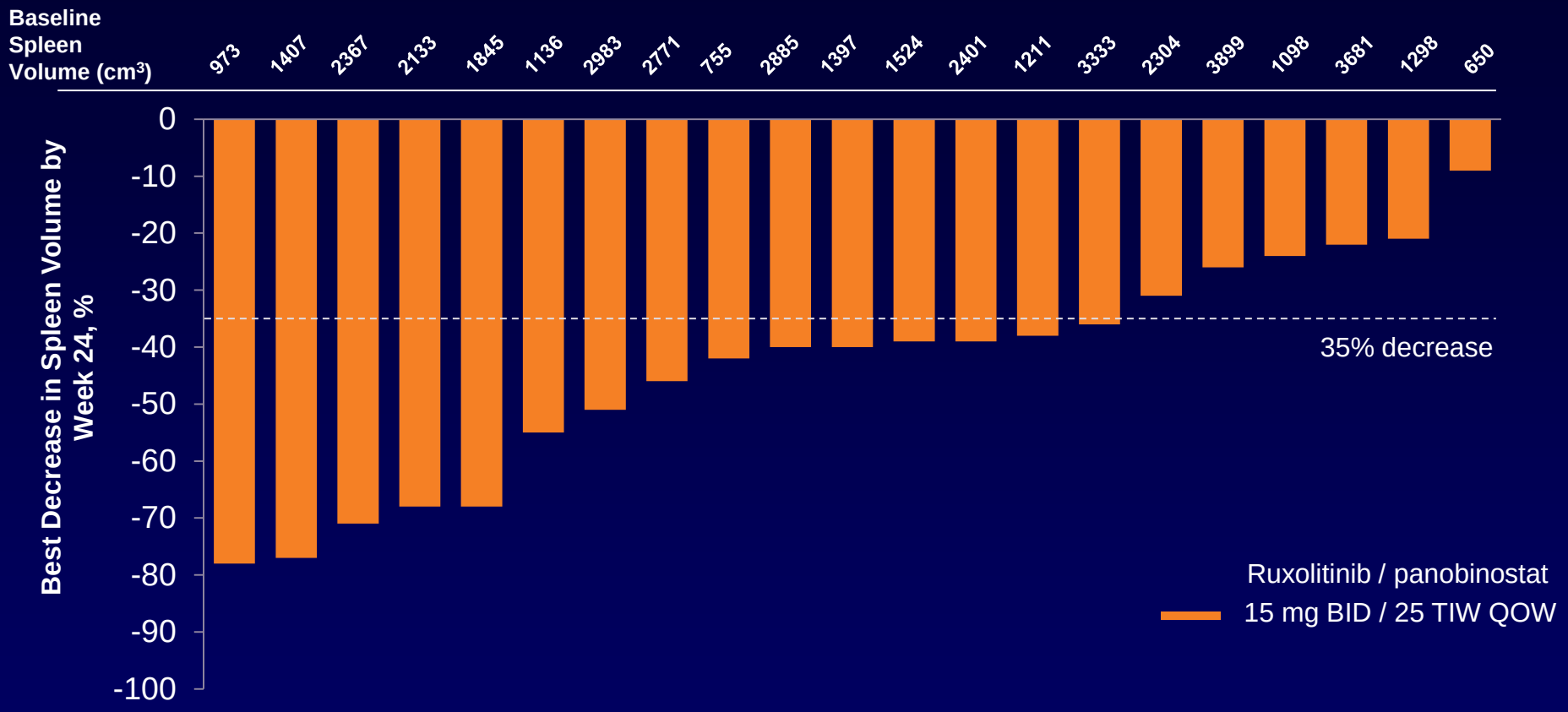
Change in Spleen Volume: Expansion Phase



- 65% of patients (15/23) in the expansion phase achieved a ≥35% reduction from baseline in spleen volume on or before week 24 (C7D1)
  - 2 patients did not have postbaseline spleen volume assessments

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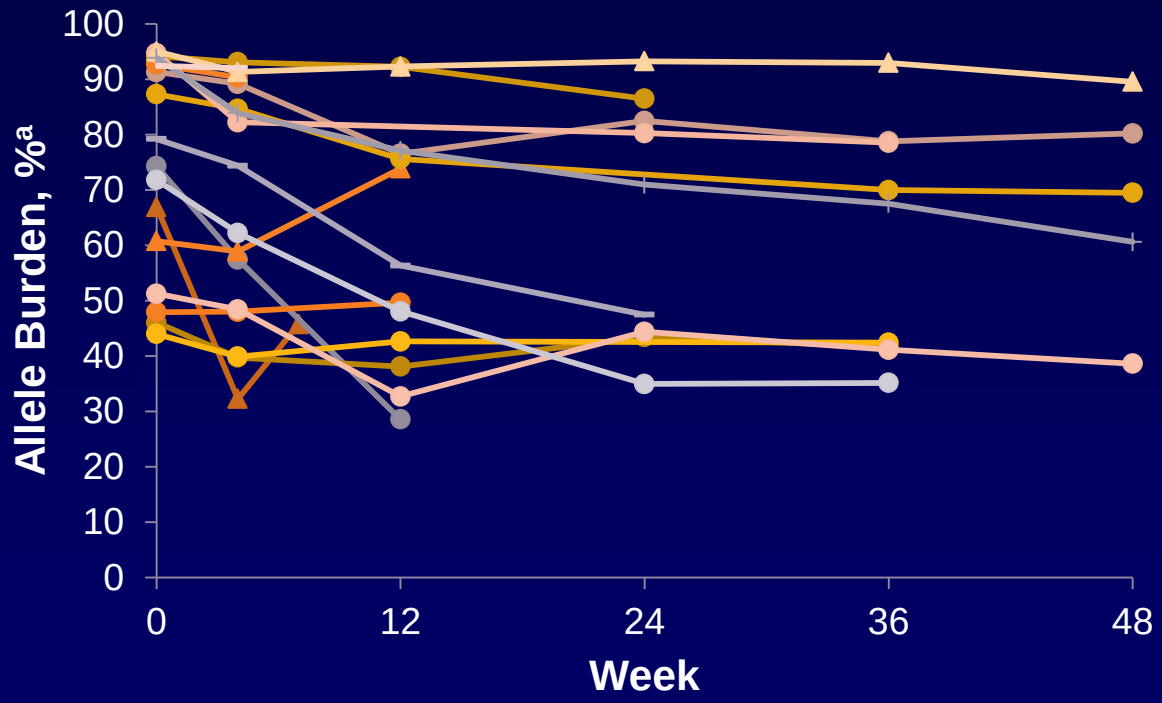
JAK2 V617F Allele Burden

- 17 of 22 patients were *JAK2* V617F-positive at baseline
  - 21 of 22 patients were ruxolitinib naive
- 5/17 patients (29%) had a ≥ 20% decrease from baseline in allele burden
  - This decrease tended to occur at the 12 week assessment
  - The prior ruxolitinib-treated patient had a 44% decrease from baseline



[a]Expansion phase; only patients with ≥2 on treatment assessments were included

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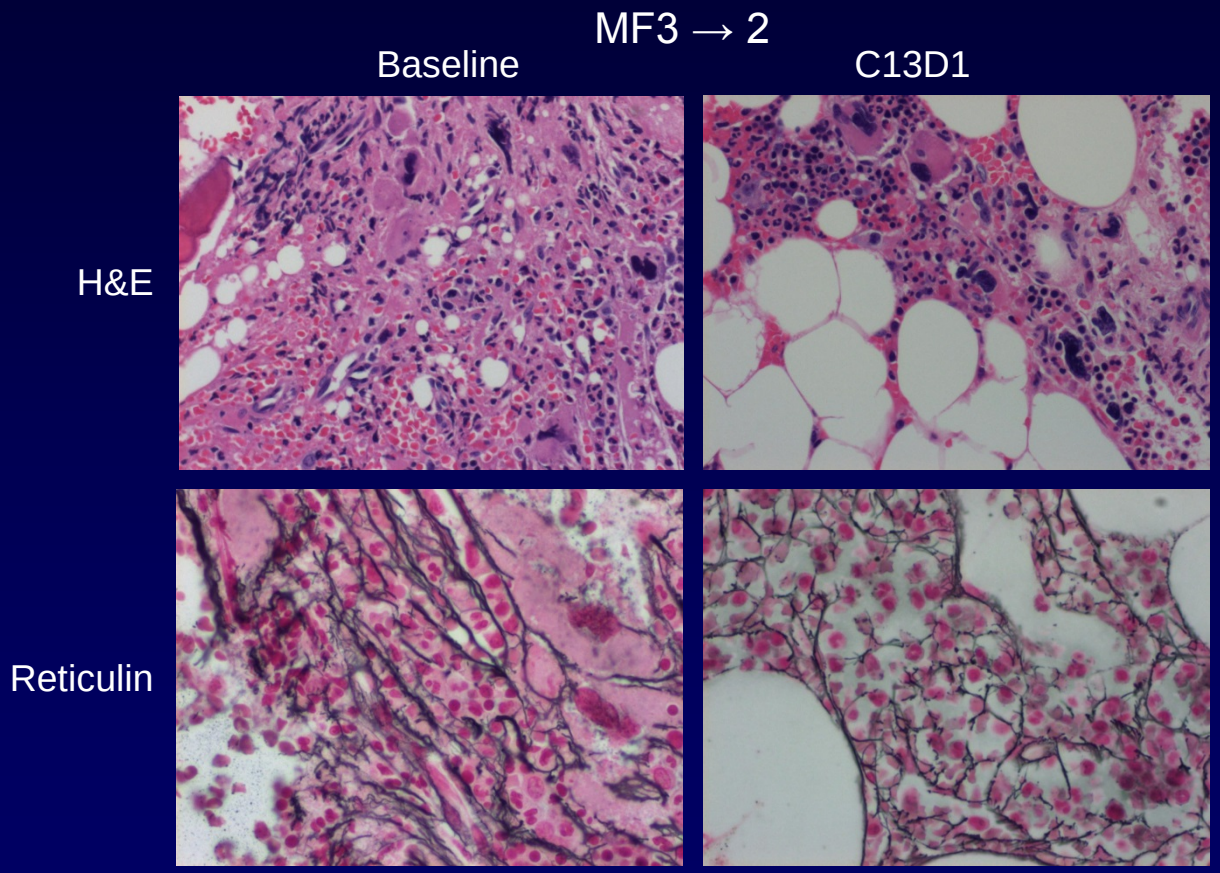
Bone Marrow Fibrosis (Central Review)

- 3 patients had improved fibrosis (MF3 → 2, 2 → 1, 1 → 0)



- 10 patients had stable fibrosis grading (no change)
- 2 patients worsened (MF1 → 2)

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Bone Marrow Fibrosis (Central Review)

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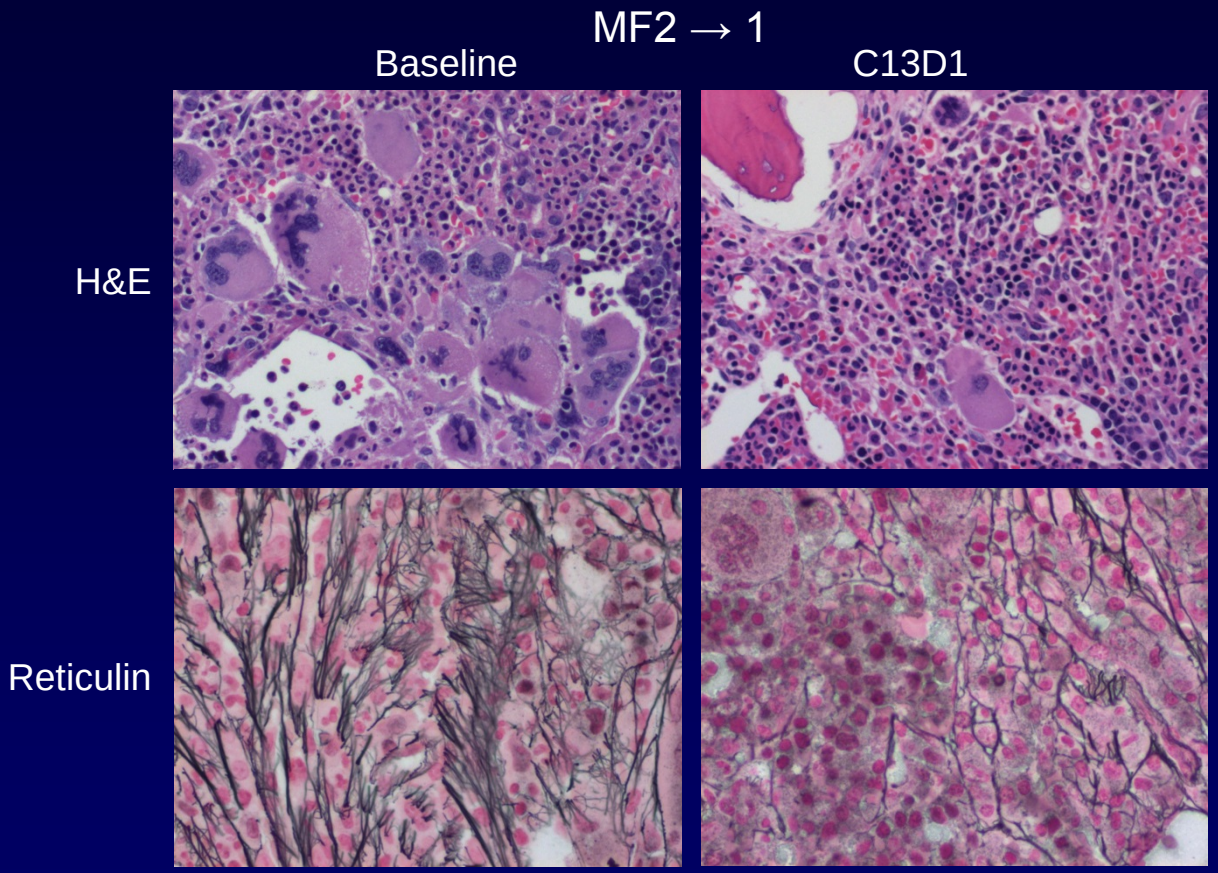

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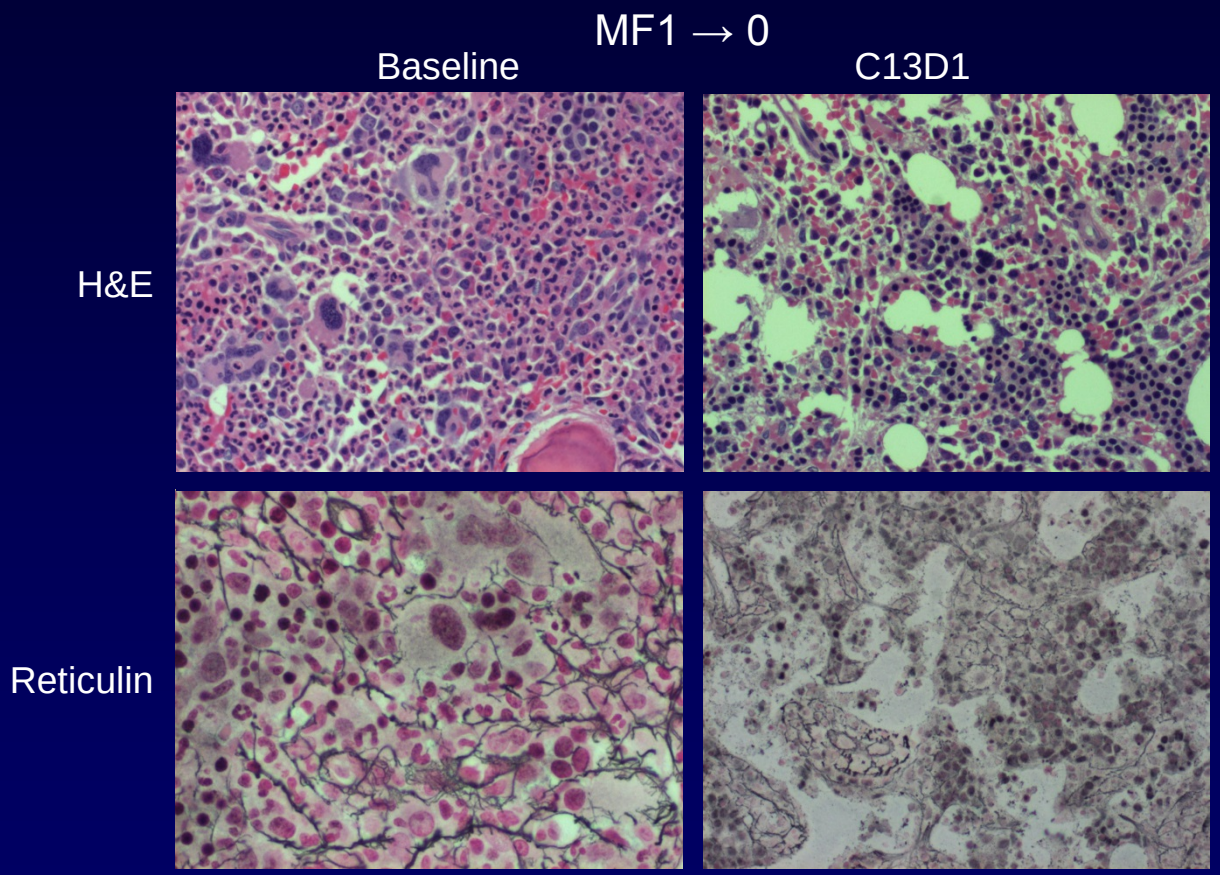

- 10 patients had stable fibrosis grading (no change)
- 2 patients worsened (MF1 → 2)

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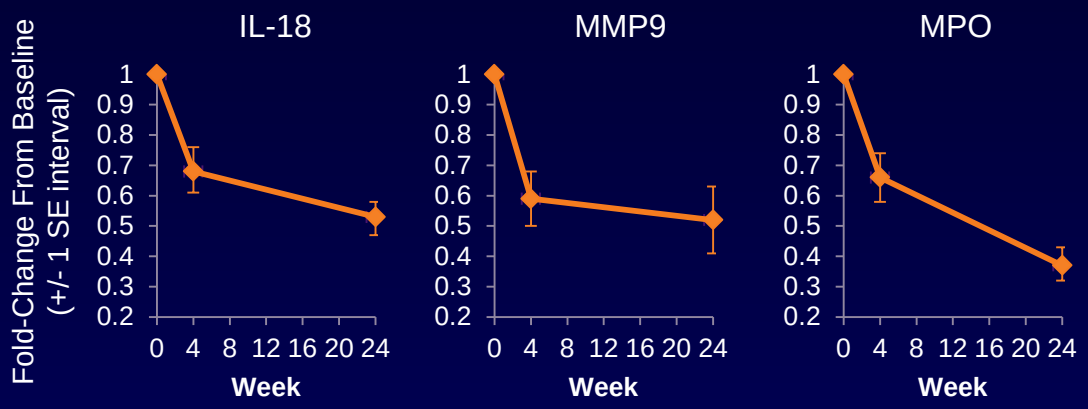
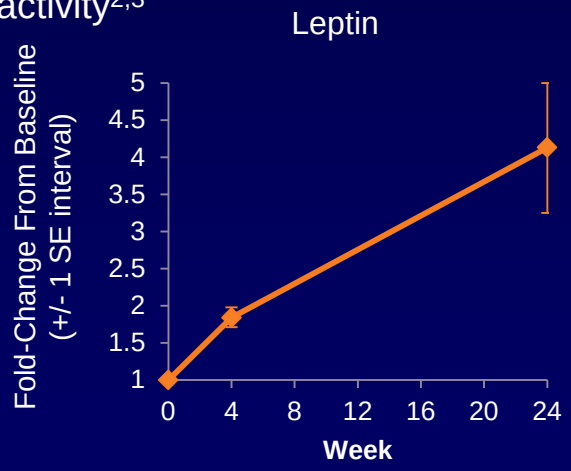
Change in Cytokine Levels



- Three different cytokines with median baseline levels in the abnormal range[a] normalized on treatment
  - IL-18 is a pro-inflammatory cytokine
  - IL-18 levels were also downregulated at 4 weeks in another JAK2i MF study[1]
- Myeloperoxidase (MPO) and matrix metalloproteinase 9 (MMP9) are both markers of inflammatory disease activity[2,3]



- Leptin levels increased on treatment; this effect was also seen in COMFORT-II, where increases were associated with improvement in weight loss[4]
  - Leptin was also up-regulated at 4 weeks in the SAR302503 study[1]

Method: MRBM HumanMAP® V2.0

[a]Reference ranges based on MRBM data of ~100 healthy individuals and are for research use only.

1. Talpaz M, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 7110.
2. Anatoliotakis N, et al. *Curr Top Med Chem*. 2013;13(2):115-138.
3. Biasi F, et al. *PLoS One*. 2012;7(7):e41839.
4. Squires M, et al. *Blood.* 2013;122(21): Abstract 2070.

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Conclusions

- **The combination of ruxolitinib 15 mg BID and panobinostat 25 mg TIW QOW was well tolerated and resulted in substantial reductions in splenomegaly**
  - **Most patients treated at the RP2D of combination therapy achieved a spleen response**
- **Combination treatment at the RP2D had an acceptable safety profile**
  - **The rates of AEs observed in this trial are in line with the expected and known AEs of these two agents when used as monotherapies[1-5]**
- **For some patients, the combination of ruxolitinib and panobinostat resulted in decreases in *JAK2* V617F allele burden and bone marrow fibrosis**
- **In summary, the combination of panobinostat and ruxolitinib in MF is associated with favorable treatment benefits and encourages further exploration**

1. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807.
2. Harrison C, et al. *N Engl J Med*. 2012;366:787-798.
3. DeAngelo DJ. *Leukemia*. 2013;27:1628-1636.
4. DeAngelo DJ. *Br J Haematol*. 2013;162: 326-335.
5. Mascarenhas J. *Br J Haematol*. 2013;161: 68-75.

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Hematologic Adverse Events

- The most common hematologic AEs were anemia and thrombocytopenia

n (%)[a]	Escalation phase n = 38		Expansion phase n = 23		Patients treated at the RP2D n = 34	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Anemia	24 (63.2)	16 (42.1)	18 (78.3)	8 (34.8)	26 (76.5)	11 (32.4)
Thrombocytopenia	20 (52.6)	8 (21.1)	11 (47.8)	7 (30.4)	16 (47.1)	9 (26.5)
Neutropenia	3 (7.9)	2 (5.3)	1 (4.3)	1 (4.3)	3 (8.8)	2 (5.9)

[a]Regardless of relationship to study treatment at any time during or up to 30 days after last dose.

- In the escalation phase, 2 patients discontinued due to anemia and 2 discontinued due to thrombocytopenia
- Among patients treated at the RP2D, 1 patient (expansion phase) discontinued due to anemia and 1 (escalation phase) due to thrombocytopenia[a]

[a]Patient had an interruption in study treatment for > 4 weeks due to grade 3/4 thrombocytopenia and therefore was discontinued.

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Nonhematologic Adverse Events (> 20%)

	Escalation phase n = 38		Expansion phase n = 23		Patients treated at the RP2D n = 34	
%[a]	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Any AE	100	71	100	65	100	65
Diarrhea	**66**	**8**	**61**	**13**	**68**	**15**
Asthenia	**37**	**5**	**44**	**4**	**44**	**9**
Muscle spasms	37	0	30	0	35	0
Headache	34	0	22	0	29	0
Nausea	32	8	30	0	32	6
Abdominal pain	29	8	22	0	24	3
Peripheral edema	29	0	17	0	21	0
Vomiting	26	3	26	0	35	3
Dyspnea	26	5	22	0	29	6
Creatinine increased	26	0	9	0	15	0
Dizziness	24	0	13	0	21	0
Fatigue	**21**	**8**	**26**	**0**	**29**	**9**
Pruritus	21	0	17	0	15	0
Pain in extremity	21	0	13	0	18	0
Pyrexia	21	0	13	4	15	3
Cough	16	0	22	0	18	0
Nasopharyngitis	11	0	22	0	15	0
Constipation	11	0	17	0	21	0

[a] Regardless of relationship to study treatment at any time during or up to 30 days after last dose.

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Nonhematologic Adverse Events (>20%)

	Expansion phase n = 23		Patients treated at the RP2D n = 34	
%[a]	All grade	Grade 3/4	All grade	Grade 3/4
Any AE	100	65	100	65
Diarrhea	61	13	68	15
Asthenia	44	4	44	9
Muscle spasms	30	0	35	0
Vomiting	26	0	35	3
Nausea	30	0	32	6
Fatigue	26	0	29	9
Headache	22	0	29	0
Dyspnea	22	0	29	6
Abdominal pain	22	0	24	3
Peripheral edema	17	0	21	0
Constipation	17	0	21	0
Dizziness	13	0	21	0

[a] In ≥ 20% of patients treated at the RP2D; regardless of relationship to study treatment at any time during or up to 30 days after last dose.

Kiladjian JJ, et al. *Blood.* 2014;124: Abstract 711.