Sierra Oncology

Delivering Transformative Therapies for Rare Cancers

January 2022

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SIERRA ONCOLOGY

Sierra Oncology Overview

Momelotinib (MMB) met all pre-specified primary and key secondary endpoints with statistical significance in the Phase 3 pivotal MOMENTUM study

- Symptomatic, anemic, myelofibrosis (MF) patients previously treated with a JAK inhibitor

MOMENTUM data confirm momelotinib as a potential treatment option for certain myelofibrosis patients with anemia

- Topline data have demonstrated clinically significant benefit in anemia improvement, symptom and spleen control, with stable platelet counts

~$3B potential addressable market* in anemic MF patients in the US

- ~15K prevalent MF patients with anemia in the US

Planned clinical trials to evaluate MMB as a potential cornerstone in future combination therapies in MF

- Momelotinib + SRA515 combination clinical trial designed to provide proof-of-concept
- Targeting patient subsets where the unmet medical need remains
- Combination trial expected to begin in 2022

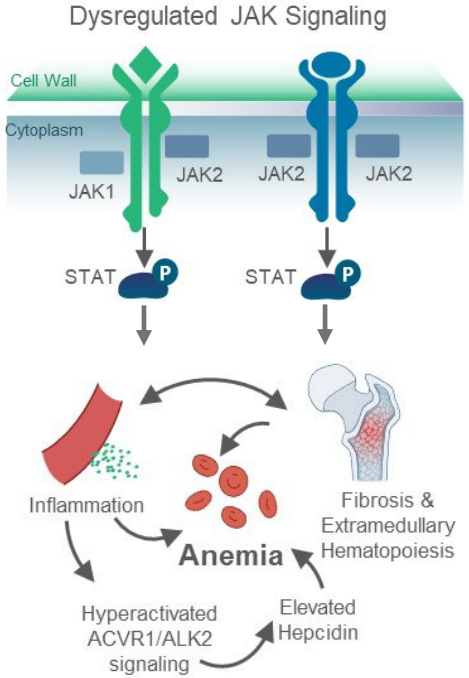
Source: Sierra Market Research
*Sierra estimates ~15k U.S. prevalent patients at $200k/patient/year

Myelofibrosis: Disease Overview

Myelofibrosis (MF): a bone marrow cancer
- Caused by constitutive activation of JAK-STAT signaling
- Inflammation and fibrosis impair red blood cell production

Common manifestations of disease include constitutional symptoms, enlarged spleen and progressive anemia

Current treatments: JAK inhibitors are the mainstay option for intermediate and high-risk patients



Anemia and Hepcidin Predict Poor Survival in Myelofibrosis

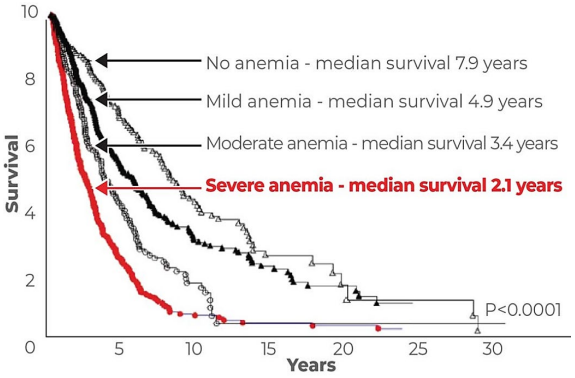
Anemia of inflammation driven by elevated hepcidin

Elevated hepcidin inhibits iron transport and iron homeostasis

Anemia and elevated hepcidin are ***negative prognostic indicators***

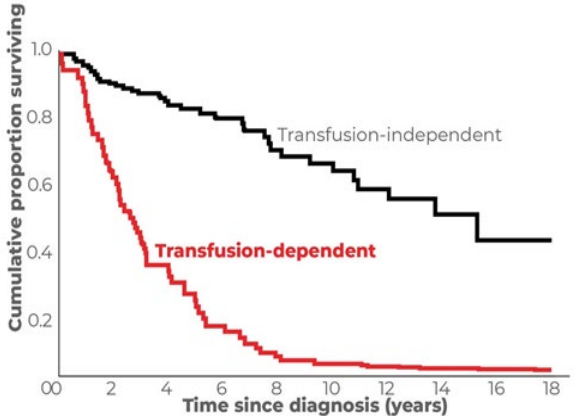
New therapies should aim to provide anemia benefits in addition to symptom, spleen benefits

Anemia Predicts Poor Survival in MF



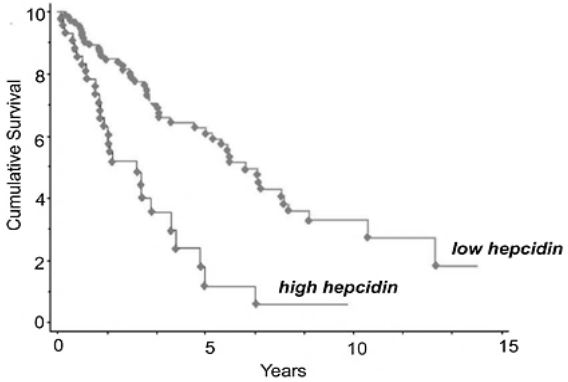
Nicolosi et al. *Leukemia*. 2018

Transfusion Dependency Predicts Poor Survival in MF



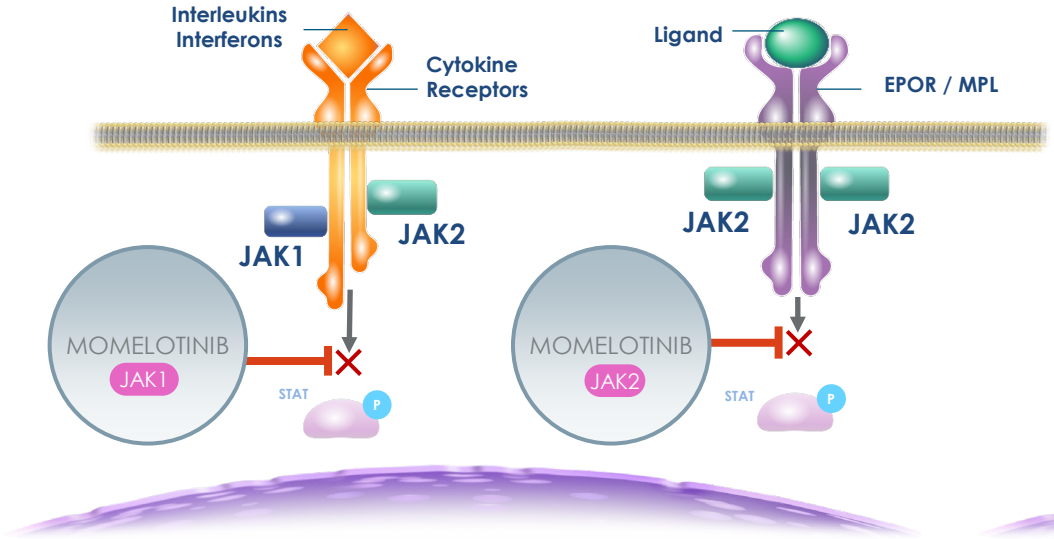
Elena et al. *Haematologica*. 2011

Elevated Hepcidin Predicts Poor Survival in MF

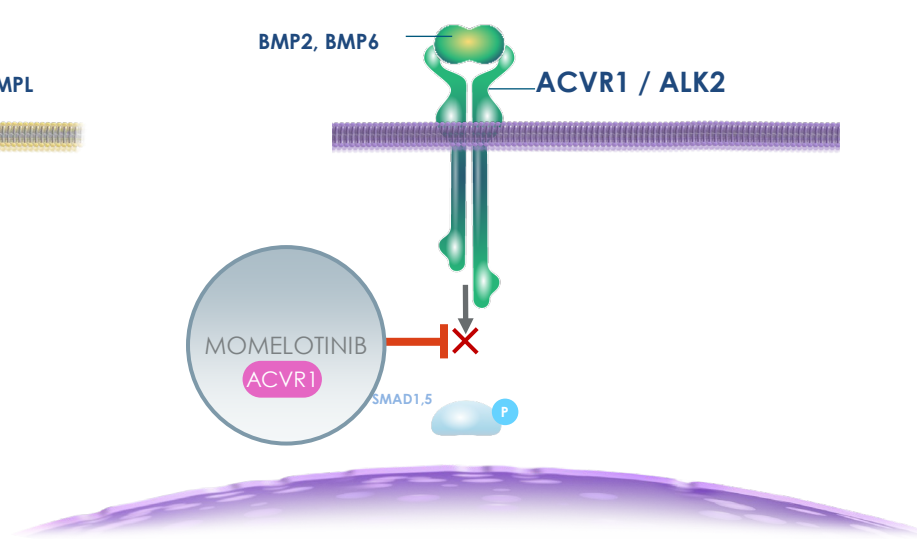


Pardanani et al. *Am. J. Hematol*. 2013

Momelotinib Inhibits JAK1, JAK2 *and* ACVR1/ALK2



Hyperactive JAK-STAT signaling is driving the disease in myelofibrosis



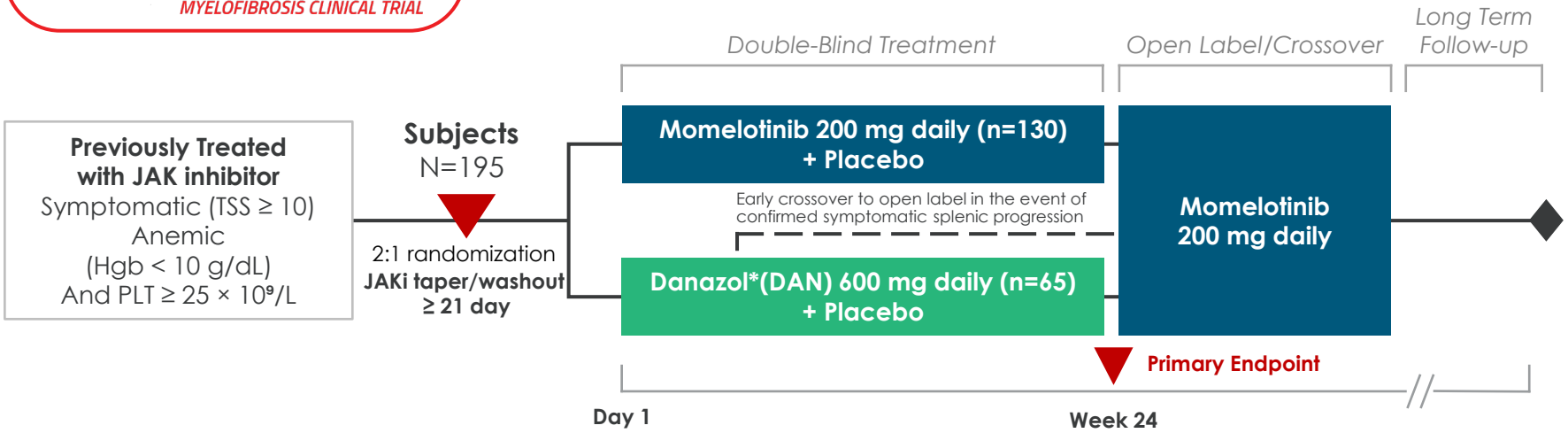
Preclinical studies and clinical trials suggest that the clinical anemia benefits of momelotinib result from suppression of ACVR1/ALK2-mediated hepcidin production

Momelotinib Inhibits all Three Disease Drivers, Potentially Improving Splenomegaly and Symptoms of Myelofibrosis While Maintaining or Improving Hemoglobin

Asshoff, M. et. al. *Blood*. 2017;129(13):1823-1830. Oh, S. et al. *Blood Advances*. 2020;4(18):4282-4291.

Pivotal Phase 3 '*MOMENTUM*' Trial Overview

MOMENTUM
MYELOFIBROSIS CLINICAL TRIAL



Primary Endpoint

- Total symptom score (TSS) response rate at Week 24

Secondary Endpoints

- Transfusion independence (TI) rate at Week 24
- Splenic response rate (SRR) at Week 24

*Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by NCCN, ESMO guidelines.

MMB Showed Strong Activity Across Key Endpoints

Endpoint at Week 24	Test Order	Criterion for Significance	MMB (n=130)	DAN (n=65)	
MFSAF TSS 24 response (primary endpoint)[1]	1	Superiority (p≤0.05)	25%	9%	p=0.0095 (superior)
TI 24 Status [2]	2	Non-inferiority Boundary 0.8	31%	20%	p=0.0064 (non-inferior) [3]
SRR 24 (25% reduction)	3	Superiority (p≤0.05)	40%	6%	p<0.0001 (superior)
MFSAF TSS change from baseline	4	Superiority (p≤0.05)	-11.5[4]	-3.9[4]	p=0.0014 (superior) [4]
SRR 24 (35% reduction)	5	Superiority (p≤0.05)	23%	3%	p=0.0006 (superior)
Rate of no transfusion to week 24	6	Superiority (p≤0.05)	35%	17%	p=0.0012 (superior)

(1) TSS response is defined as a ≥ 50% reduction in mean TSS over the 28 days immediately prior to the end of Week 24 compared to baseline

(2) Proportion of subjects with TI status defined as not requiring RBC transfusion for ≥ 12 weeks, with all Hgb levels during the ≥ 12-week interval of ≥ 8 g/dL

(3) TI tested for superiority with a p-value (2-sided) of 0.0861

(4) Mean change from baseline for subjects with week 24 data available. P-value is from mixed model for repeated measures.

MFSAF* Total Symptom Score (TSS) Response Rate at Week 24

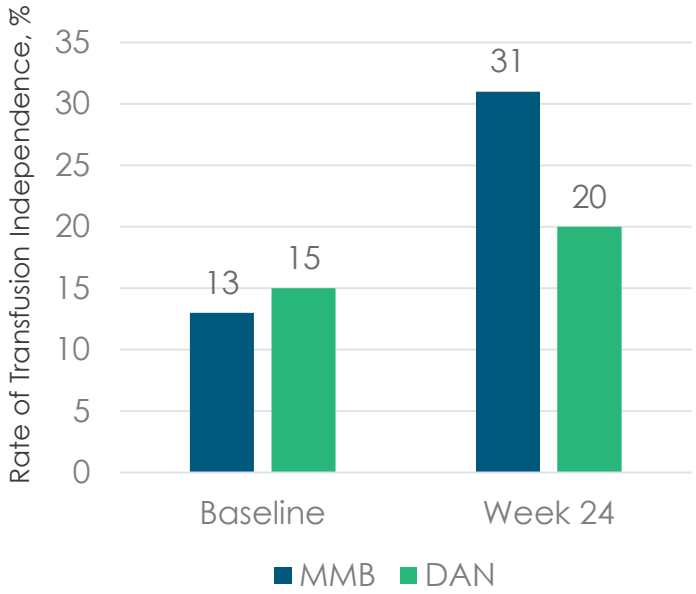
	MMB (N=130)	DAN (N=65)
TSS response rate of 50% at W24, n (%)	**32 (24.6%)**	**6 (9.2%)**
95% CI	(17.49, 32.94)	(3.46, 19.02)
p-value (superiority)	**0.0095**	
Mean TSS at Baseline (SD)	28.0 (13.8)	25.7 (12.8)
TSS Mean Change from baseline (SD)(1)	**-11.5 (12.9)**	**-3.9 (11.9)**
p-value (superiority)(1)	**0.0014**	

(1) Mean change from baseline for subjects with week 24 data available. P-value is from mixed model for repeated measures.

- **Total Symptom Score (TSS) Response Rate**
  - Proportion of subjects who achieve ≥ 50% reduction in TSS over the 28 days immediately prior to the end of Week 24 compared to baseline
- **Myelofibrosis Symptom Assessment Form (MFSAF) v4.0**
  - 7-item MFSAF v4.0 (scale 0-70) is a validated MF patient reported outcome (PRO) measure tool
  - 7 symptoms measured: Fatigue, Night Sweats, Itching, Abdominal discomfort, Rib pain, Fullness, Bone Pain
    - Each scored on a10-point scale from 0, Absent, to 10, Worst Imaginable
  - Daily assessment completed electronically by the patient on an ePRO device

*Myelofibrosis Symptom Assessment Form.

Transfusion Independence (TI) Rate at Week 24



	MMB (N=130)	DAN (N=65)
TI at Baseline, n (%)	17 (13.1%)	10 (15.4%)
TI Rate at W24, n (%)	**40 (30.8%)**	**13 (20.0%)**
95% CI	(22.98, 39.46)	(11.10, 31.77)
Non-inferiority difference (95% CI), One sided p-value	14.77 (3.13, 26.41), **p=0.0064**	
Superiority difference (95% CI), p-value	10.99 (-0.80, 22.77), **p=0.0861**	
Zero RBC Transfusions to W24, n (%)	**46 (35.4%)**	**11 (16.9%)**
p-value (superiority)	**0.0012**	

Safety Summary (through Week 24)

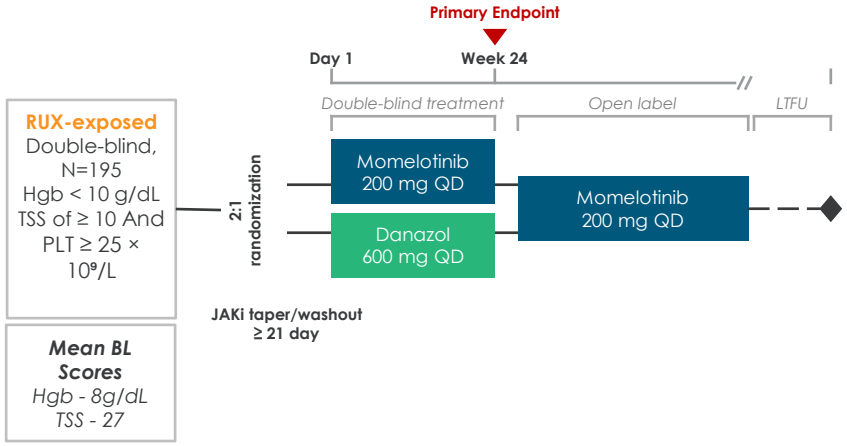
Subjects with at least one, n (%)	MMB (N=130)	DAN (N=65)	Total (N=195)
Treatment Emergent Adverse Events (TEAEs)	122 (93.8%)	62 (95.4%)	184 (94.4%)
Grade ≥3 TEAEs	70 (53.8%)	42 (64.6%)	112 (57.4%)
Serious TEAEs	45 (34.6%)	26 (40.0%)	71 (36.4%)

Favorable trend for overall survival observed at Week 24

- HR 0.506 and p value = 0.072, favoring MMB

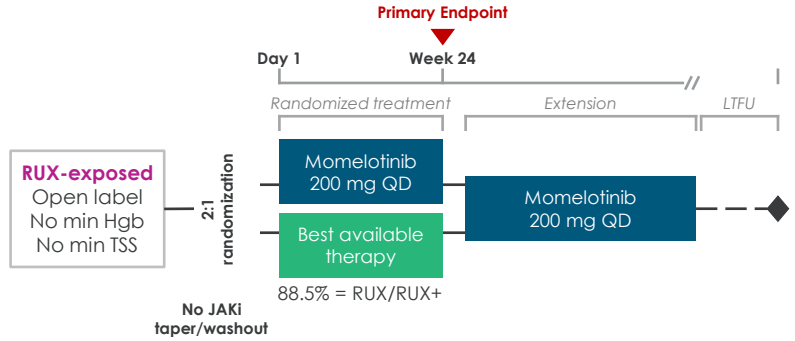
MOMENTUM Confirms and Reinforces the Potential Effect Observed in SIMPLIFY-2 in a More Symptomatic and Anemic Population

MOMENTUM



Endpoint	Week 24 Response Rate	
	MMB	DAN
N	130	65
SRR ≥35%	23%	3%
TSS ≥50%	25%	9%
TI for ≥ 12weeks at W24	31%	20%

SIMPLIFY-2



Endpoint	Week 24 Response Rate	
	MMB	RUX/BAT
N	104	52
SRR ≥35%	7%	6%
TSS ≥50%	26%	6%
TI for ≥ 12weeks at W24	43%	21%
TI for ≥ 12weeks at W24 in patients with baseline Hgb<10*	33%	13%

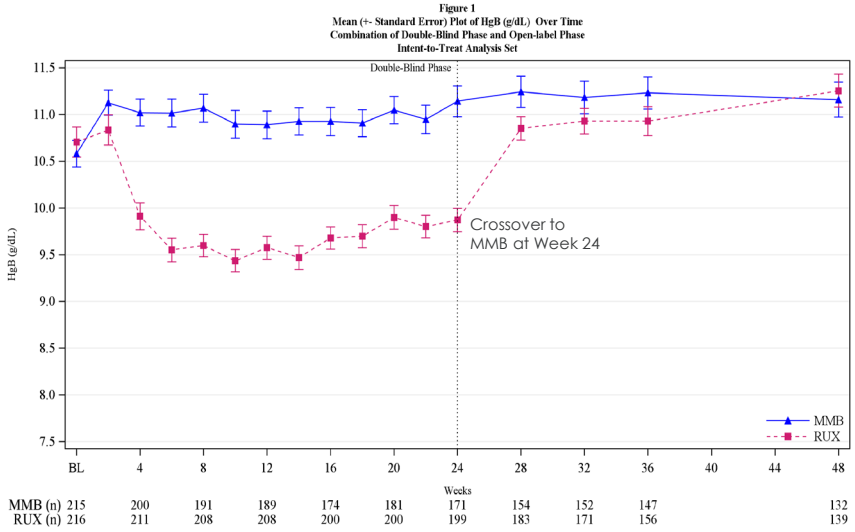
Harrison, et al, The Lancet Haematology, 2018

*** Retrospective analysis not pre-specified**

MMB Demonstrated Impact on Hemoglobin in SIMPLIFY-1 and MOMENTUM

SIMPLIFY-1

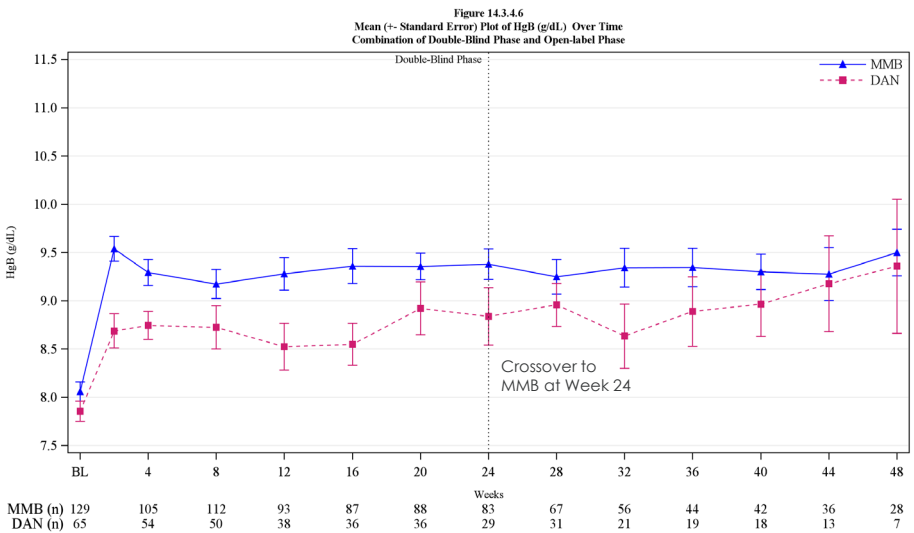
Hemoglobin Levels



Source: Harrison, C. et al. EHA 2020.

MOMENTUM

Hemoglobin Levels



Source: Preliminary data from MOMENTUM.

Momelotinib Demonstrated an Increase in Hemoglobin in both JAKi Naïve and Previously JAKi-Treated Patients

MOMENTUM Data Confirm Momelotinib can be a Potential Option for Certain Myelofibrosis Patients with Anemia

Positive pivotal Phase 3 MOMENTUM topline results for momelotinib in symptomatic anemic MF patients previously treated with a JAK inhibitor

- Met all pre-specified primary and key secondary endpoints with statistical significance in a difficult to treat patient population
  - Symptomatic, anemic, MF patients previously treated with a JAK inhibitor
- Topline data have demonstrated clinically significant benefit in anemia improvement, symptom and spleen control, with stable platelet counts
- Replicated strong impact on anemia as observed in SIMPLIFY-2 in a more difficult to treat patient population

Data support planned clinical trials to evaluate MMB as a potential cornerstone in future combination therapies in MF

Momelotinib Phase 3 Topline findings

Momelotinib met all pre-specified primary and key secondary endpoints with statistical significance in the pivotal MOMENTUM Study

- Symptomatic, anemic, MF patients previously treated with a JAK inhibitor

SIMPLIFY-1 and SIMPLIFY-2 Phase 3 trial data expected to be included in NDA submission to FDA in Q2 2022

- SIMPLIFY-1 met primary endpoint in first-line setting in comparison to ruxolitinib*
- Post-hoc analyses from SIMPLIFY-1
  - Demonstrated improvement in Hgb and transfusion status over course of treatment
  - Transfusion independence (TI) was achieved for anemic patients and all patients, irrespective of baseline platelets or transfusion status
  - TI was associated with improved overall survival

Safety profile has enabled long duration of dosing

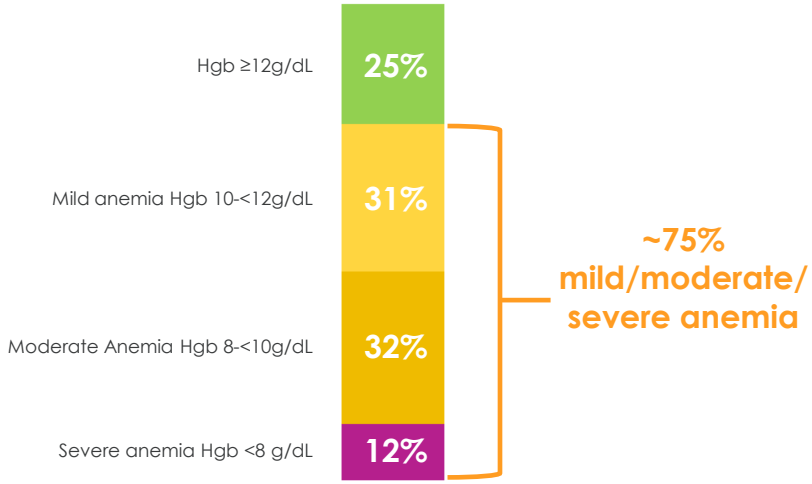
- Several patients from early trials have now received >10 years of continuous momelotinib therapy
- Many patients from SIMPLIFY-1 and -2 continue to receive momelotinib

* (215 patients in the MMB arm, 217 patients in the ruxolotinib arm)

Anemia Could Become the Primary Driver of JAKi Choice

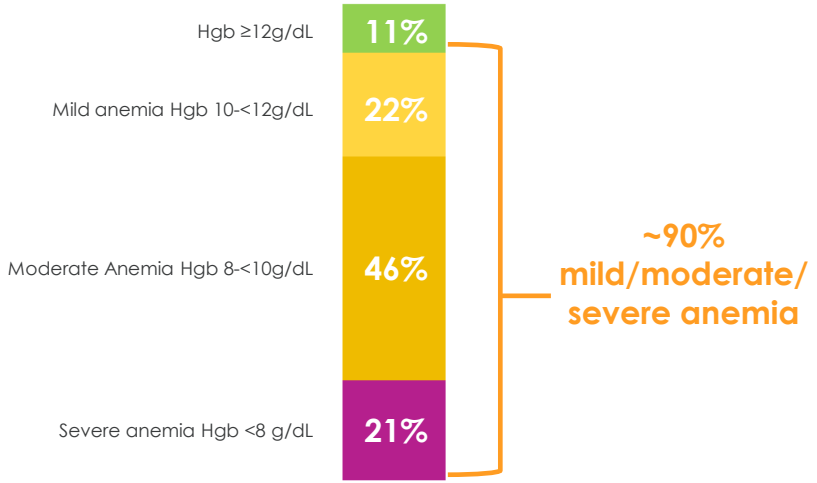
- Momelotinib, if approved, could offer unique benefits for anemic myelofibrosis patients
  - In S-1 at baseline, ~75% of anemic with 30% requiring transfusions
  - In Rux-experienced patients, 90% are anemic with more than two thirds require transfusions
- A differentiated JAKi could allow hem/oncs to transition patients early in their treatment journey
- Upside potential with a potential future indication that allows for use in JAKi-naïve patients

JAKi Naïve Patients (S-1) – at Baseline



~30% Require Transfusions

RUX Experienced Patients (S-2) – at Baseline



~70% Require Transfusions

Source: SIMPLIFY-1, -2 analysis

Momelotinib + SRA515 Combinations Could Expand the Myelofibrosis Opportunity

Myelofibrosis landscape is evolving with multiple combination studies ongoing

- BET inhibition has shown initial proof-of-concept with disease-modifying potential
- Unlike other BET inhibitors, SRA515 has a novel bivalent binding bode
  - A stronger connection on the cellular level leads to improved potency
- SRA515 has favorable PK, PD and safety profile when dosed as monotherapy and in combination

Clinical validation plans for MMB + BET combination

- SRA515 has synergistic preclinical activity in combination with diverse agents
  - Best-in-class potential
- As a non-myelosuppressive inhibitor of JAK1, JAK2, and ACVR1, MMB is an ideal combination partner for novel agents
- SRA515+MMB has the potential to improve outcomes in patients with MF

Momelotinib + SRA515 may provide the opportunity for longer and more durable responses for myelofibrosis patients

MMB + SRA515 May be the "Winning" Combination

- ✓ **SRA515 potentially a highly potent BETi with selective target inhibition**
  - Novel bivalent binding mode; Allows for maintained dosing durability
- ✓ **MMB is a promising combination candidate as only JAKi with anemia benefit in MF**
  - Novel JAK1, JAK2 and ACVR1/ALK2 MOA does not add to myelosuppression of BETi
- ✓ **Sierra controls both compounds, allowing for data-driven development approach**
- ✓ **Distinct advantage of extensive MMB clinical experience with almost 1,000 MF patients dosed**
- ✓ **Can create intelligent development plan due to both internally- and externally-derived data sources**

Sierra Oncology Clinical Program

Sierra's pipeline affords numerous combination opportunities, with SOC and with other investigational agents

Program	Indication	Phase 1	Phase 2	Phase 3	Registration
Momelotinib monotherapy	Myelofibrosis	Topline results announced January 2022			
Momelotinib + **SRA515***	Myelofibrosis	Planned for H1 2022			
SRA515 monotherapy and/or **SRA515** + **SRA737**	Heme malignancies**	Finalizing Design			
SRA515 monotherapy and/or **SRA515** + **SRA737**	Solid tumor in combo with SOC**	Finalizing Design			
SRA737 + IO/gemcitabine	Solid tumors	Finalizing Design			

*Formerly AZD5153

**Opportunities currently under consideration include co-operative trials

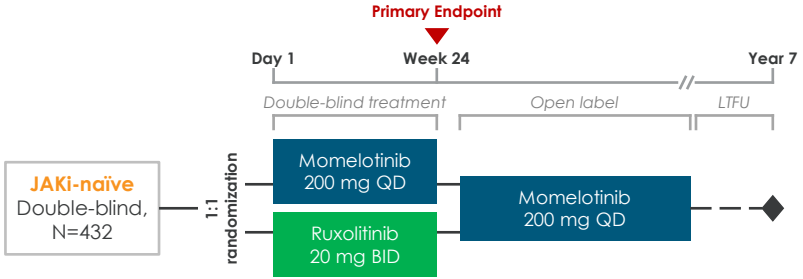
Appendix

SIERRA ONCOLOGY

Completed Phase 3 Studies SIMPLIFY-1 and 2

SIMPLIFY-1

1st-Line Population
JAK inhibitor naïve

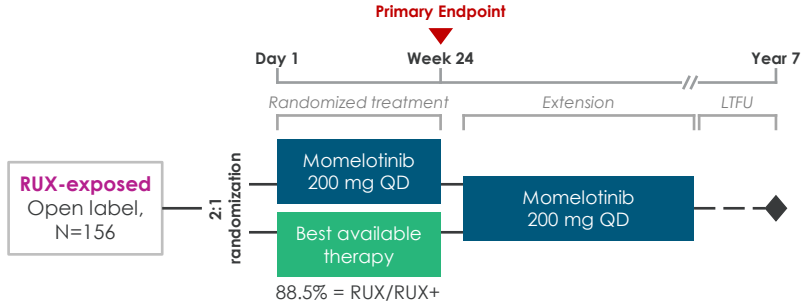


Goal:	Non-Inferiority	
Endpoints at Week 24:	**MMB (n=215)**	**RUX (n=217)**
SRR ≥35% (primary)*	27%	29%
Symptom score reduction ≥50%	28%	42%
TI for ≥ 12weeks	67%	49%

*Met endpoint
Journal of Clinical Oncology, 2017 35(34):3844

SIMPLIFY-2

2nd-Line Population
Prior ruxolitinib complicated by hematologic toxicity



Goal:	Superiority	
Endpoints at Week 24:	**MMB (n=104)**	**RUX/BAT (n=52)**
SRR ≥35% (primary)	7%	6%
Symptom score reduction ≥50%	26%	6%
TI for ≥ 12weeks	43%	21%

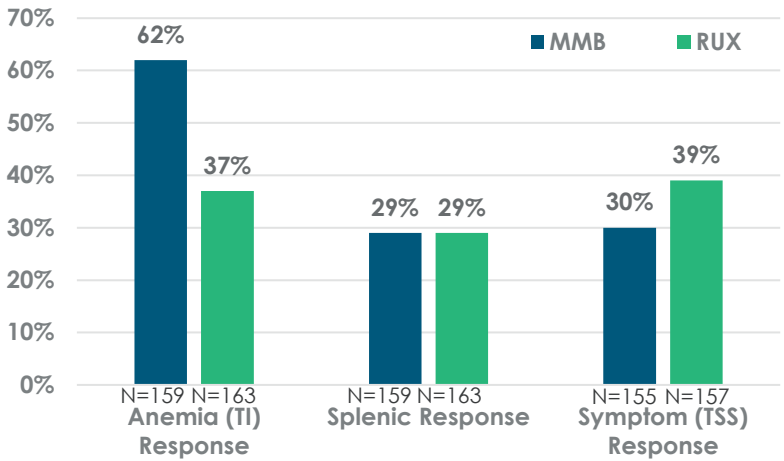
Harrison, et al, The Lancet Haematology, 2018

Comparative Response Rates MMB vs RUX/BAT in Anemic Patients

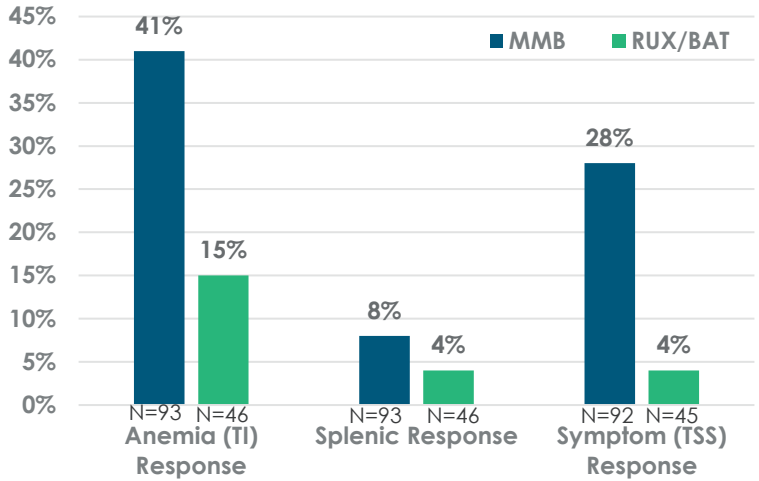
MMB's anemia benefits are accompanied by similar splenic and symptomatic response rates in SIMPLIFY-1 and significantly better symptom control relative to BAT in SIMPLIFY-2

Week 24 Response Rates

SIMPLIFY-1: Patients with Hgb ≤12 g/dL at Baseline

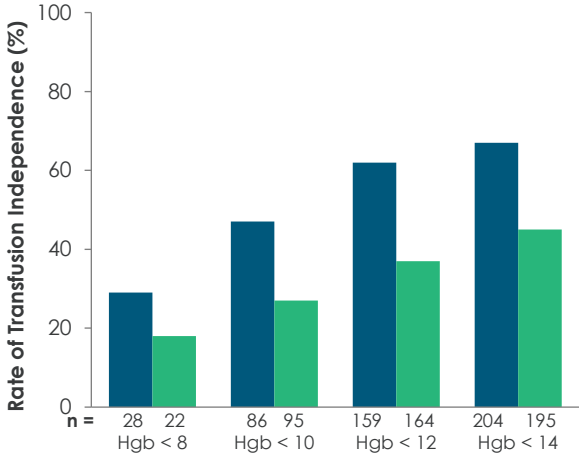


SIMPLIFY-2: Patients with Hgb ≤ 12 g/dL at Baseline

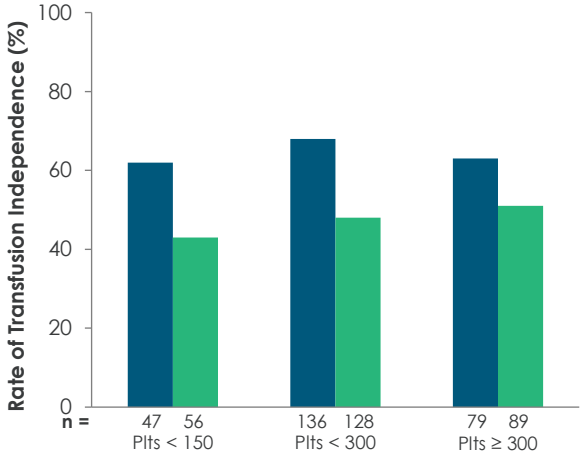


Transfusion Independence is Achieved for Anemic Patients and all Patients, Irrespective of Baseline Platelets or Transfusion Status

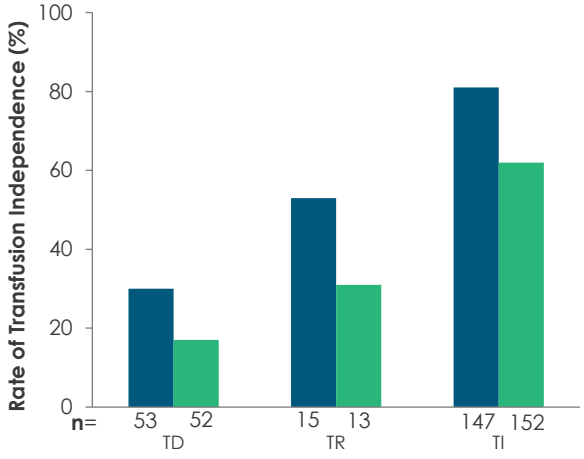
SIMPLIFY-1 Anemic Patients
W24 TI-Response by Baseline Hgb



SIMPLIFY-1
W24 TI-Response by Baseline PLT



SIMPLIFY-1
W24 TI-Response by Baseline Transfusion Status



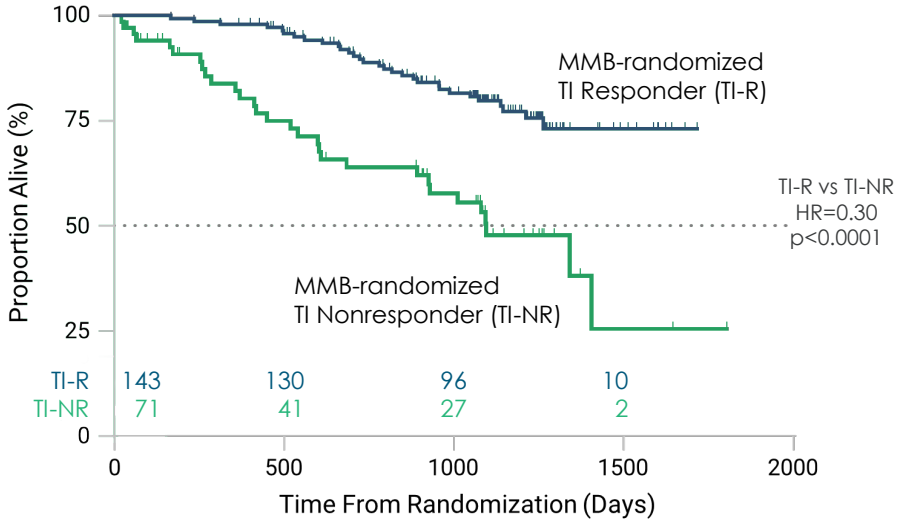
Momelotinib Ruxolitinib

The W24 TI-R Rate in S1 Was Higher in Patients Randomized to MMB vs RUX, Irrespective of the Degree of Baseline Anemia, or the Baseline PLT Count or Transfusion Status

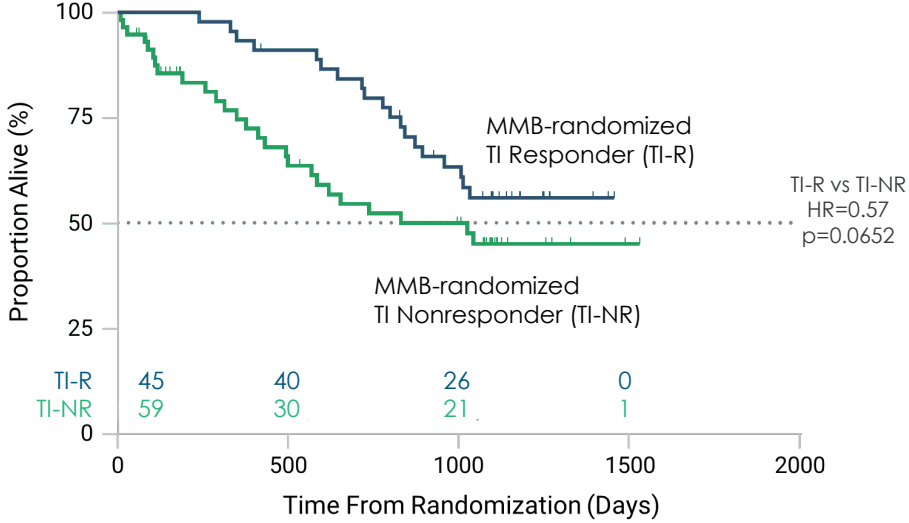
Week 24 Transfusion Independence Response (TI-R): no RBC transfusion within ≥ 12 weeks immediately prior to Week 24, with Hgb ≥ 8 g/dL
Transfusion Dependent (TD): ≥4 units of RBCs or Hgb level, ≤ 8 g/dL in the 8 weeks prior to randomization
Transfusion Independent (TI): absence of RBC transfusions and no Hgb < 8 g/dL in the 12 weeks prior to randomization
Transfusion Requiring (TR): neither TD nor TI
HgB = hemoglobin, MMB = momelotinib, Plts = platelets, RUX = ruxolitinib, TD = transfusion dependent, TI = transfusion independent, TR = transfusion requiring
Kiladjian JJ. et.al. *European Hematology Association*, June 2021, poster EP1081; Virtual.

Transfusion Independence (TI) with Momelotinib is Associated with Improved Overall Survival

SIMPLIFY-1



SIMPLIFY-2



Achieving or Maintaining TI Predicted Better Survival in Patients Treated with Momelotinib – The Goal of Achieving TI Should Become an Important Driver of Treatment Decisions

Week 24 TI response = no RBC transfusion for ≥ 12 weeks immediately prior to Week 24, Hgb level ≥ 8 g/dL.
Mesa, R. et.al. *European Hematology Association*, June 2021, oral presentation S202; Virtual.

Safety and Tolerability from the SIMPLIFY Phase 3 Trials

- Safety generally similar for momelotinib, ruxolitinib in the 24-week double-blind period
  - Anemia and thrombocytopenia were more common in the ruxolitinib arm
  - Nausea was more common with momelotinib, as was the early withdrawal rate in S-1
- Tolerability persists with extended treatment
  - No evidence of long-term cumulative toxicity observed
- Safety profile enables long duration of dosing
  - Several patients from early trials have now received >10 years of continuous momelotinib therapy
  - Many patients from SIMPLIFY-1 and -2 continue to receive momelotinib

SIMPLIFY-1

Frequent TEAEs[1] by PT	Randomized Treatment Period	
	MMB (N=214)	RUX (N=216)
Pts with any TEAE, n (%)	198 (92.5%)	206 (95.4%)
Diarrhea	39 (18.2%)	43 (19.9%)
Anemia	31 (14.5%)	81 (37.5%)
Thrombocytopenia	40 (18.7%)	63 (29.2%)
Nausea	34 (15.9%)	8 (3.7%)
Fatigue	31 (14.5%)	26 (12.0%)

S-1 Extended

Most Frequent TEAEs[1] by PT	Extended duration MMB Final Safety Analysis (N=411)
Pts with any TEAE, n (%)	397 (96.6%)
Diarrhea	99 (24.1%)
Anemia	93 (22.6%)
Thrombocytopenia	94 (22.9%)
Nausea	85 (20.7%)
Fatigue	84 (20.4%)

[1] TEAEs occurring in >20% pts in the "Overall exposed to MMB" population including the 214 subjects receiving blinded momelotinib and 197 additional subjects who received momelotinib after cross-over from ruxolitinib