Sierra Oncology

Developing Transformative Therapies for Rare Cancers

November 2021

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Sierra Oncology Overview

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- Profile has demonstrated anemia improvement, symptom and spleen control, without platelet decreases

~3 months from pivotal Phase 3 MOMENTUM data

- High probability of success trial; FDA approval and launch expected <18 months

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

- ~15K prevalent patients with anemia in the US

Could become the cornerstone of future combinations in myelofibrosis

- Momelotinib + SRA515 combination will provide proof-of-concept
- Targeting patient subsets where the unmet medical need remains

Current market cap of ~$506M

- ~22M FD shares outstanding(1)
- ~$97.1M cash as of 9/30/21(2)

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

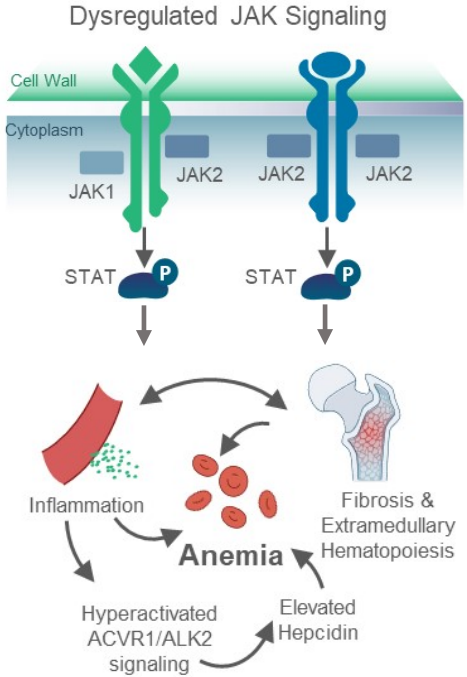
(1) Assuming treasury stock method to account for outstanding options and Series A warrants and $23 stock price See slide 23 for details.
(2) Additional $12.6M raised off ATM subsequent to the close of the third quarter.

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



Importance of Treating Anemia in Myelofibrosis

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Anemia and Hepcidin Predict Poor Survival in Myelofibrosis

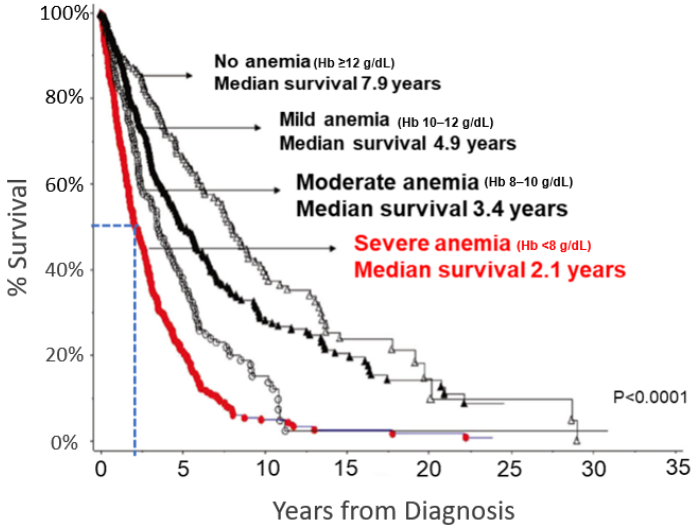
Anemia of inflammation driven by elevated hepcidin

Elevated hepcidin inhibits iron transport and iron homeostasis

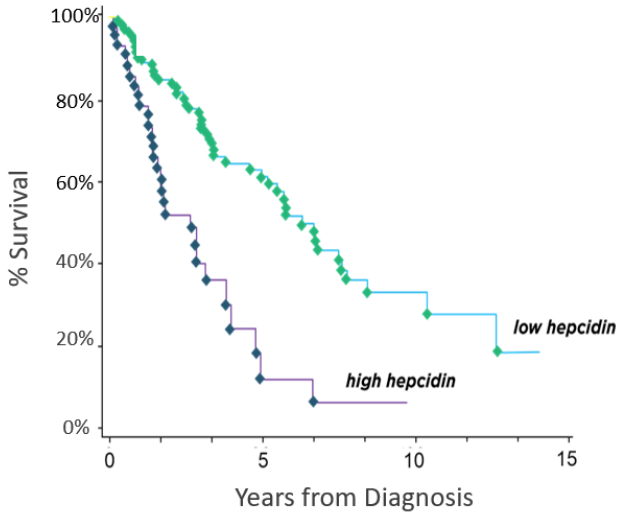
Anemia and elevated hepcidin are ***negative prognostic indicators***

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

Anemia Predicts Poor Survival in Myelofibrosis*



Hepcidin Predicts Poor Survival in Myelofibrosis**



*Nicolosi, M. *et al.* Sex and degree of severity influence the prognostic impact of anemia in primary myelofibrosis: analysis based on 1109 consecutive patients. *Leukemia* 1254–1258 (2018).

Pardanani, A., Finke, C., Abdelrahman, R. A., Lasho, T. L. & Tefferi, A. Associations and prognostic interactions between circulating levels of hepcidin, ferritin and inflammatory cytokines in primary myelofibrosis. *Am. J. Hematol.* **88, 312–316 (2013).

Momelotinib

A JAK1, JAK2 and ACVR1 (ALK2) Inhibitor

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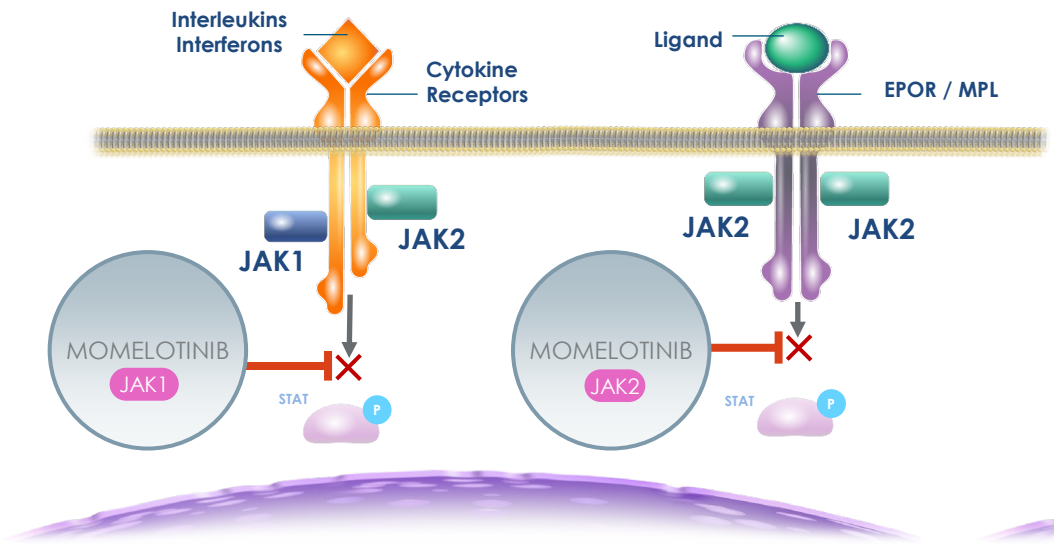
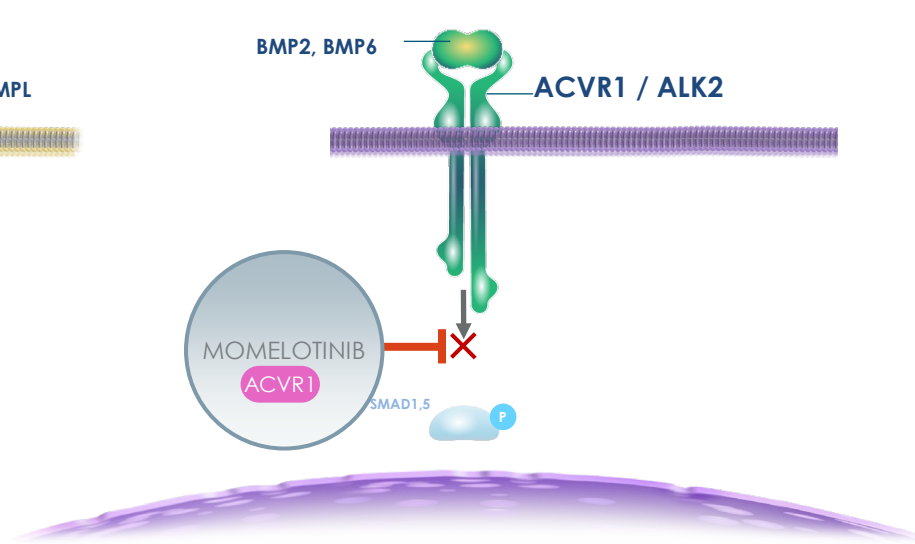
Momelotinib Inhibits JAK1, JAK2 *and* ACVR1/ALK2



Hyperactive JAK-STAT signaling is driving the disease in myelofibrosis



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

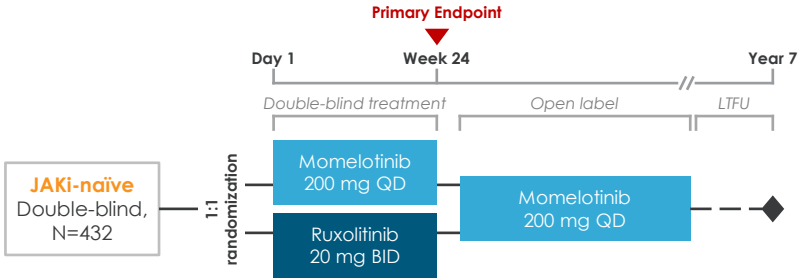
Momelotinib Inhibits all Three Disease Drivers, Potentially Improving Splenomegaly and Symptoms of Myelofibrosis While Maintaining or Improving Hemoglobin

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

Completed Phase 3 Studies SIMPLIFY-1 and -2

SIMPLIFY-1

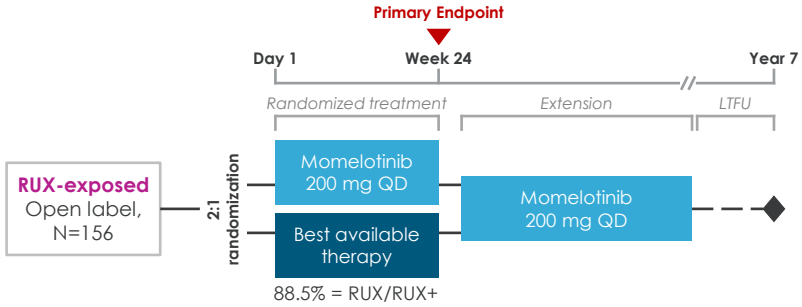
1st-Line Population
JAK inhibitor naïve



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

SIMPLIFY-2

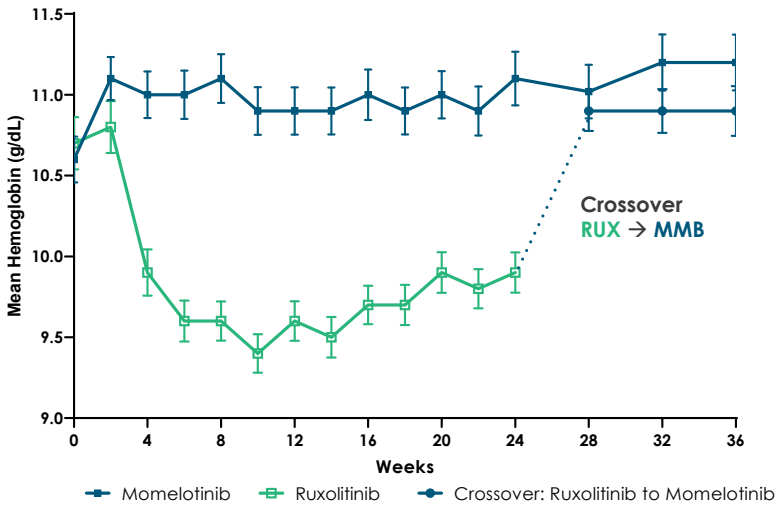
2nd-Line Population
Prior ruxolitinib complicated by hematologic toxicity



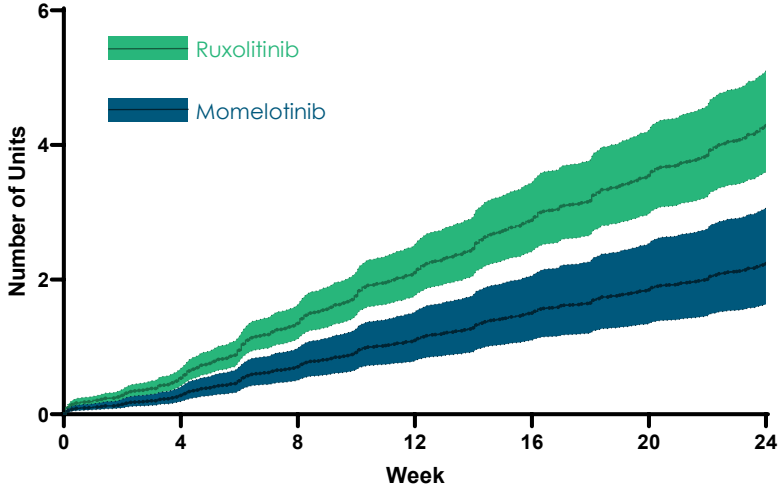
The Lancet Haematology, 2018 5(2): 7

S-1 Highlighted MMB's Unique Impact on Hemoglobin and Transfusions

Hemoglobin Level



Transfusion Requirement

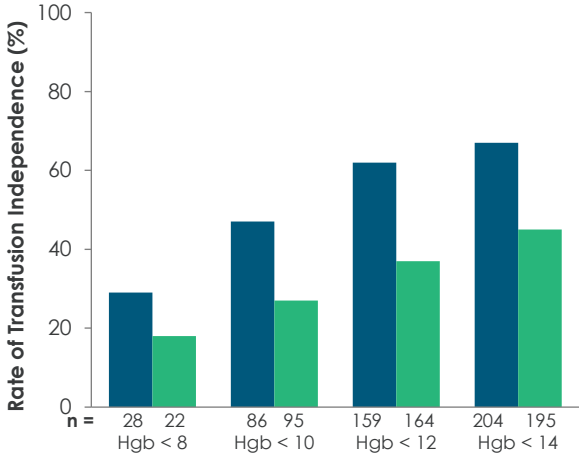


Transfusion requirement was ~half for MMB vs. RUX

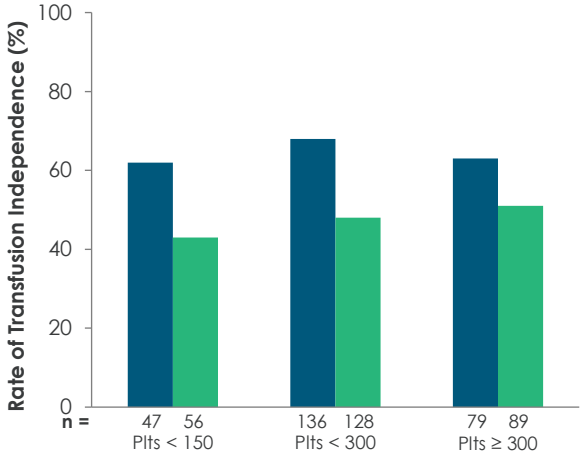
Momelotinib Demonstrated an Increase in Hemoglobin and a Decreased Transfusion Requirement vs. Ruxolitinib

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

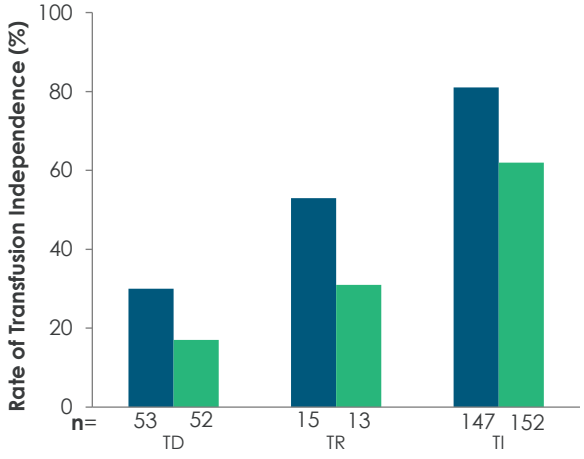
SIMPLIFY-1 Anemic Patients
W24 TI-Response by Baseline Hgb



SIMPLIFY-1
W24 TI-Response by Baseline PLT



SIMPLIFY-1
W24 TI-Response by Baseline Transfusion Status



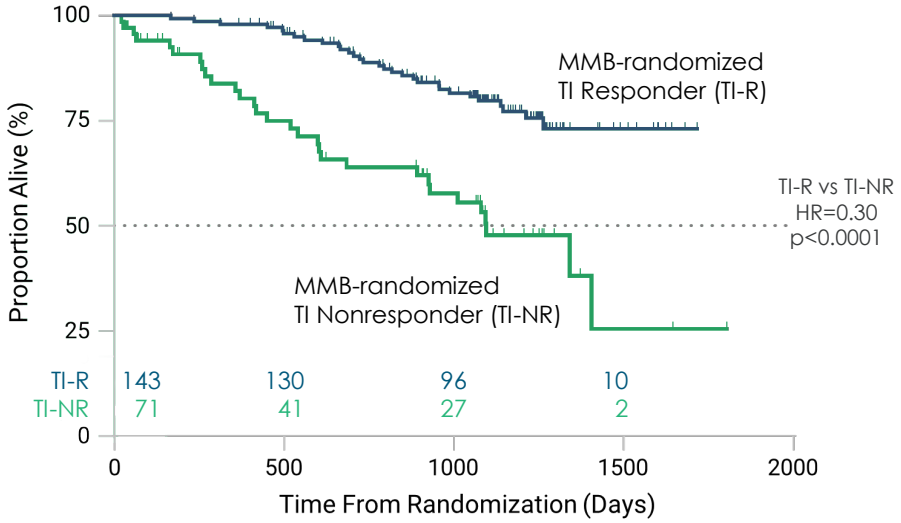
Momelotinib Ruxolitinib

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

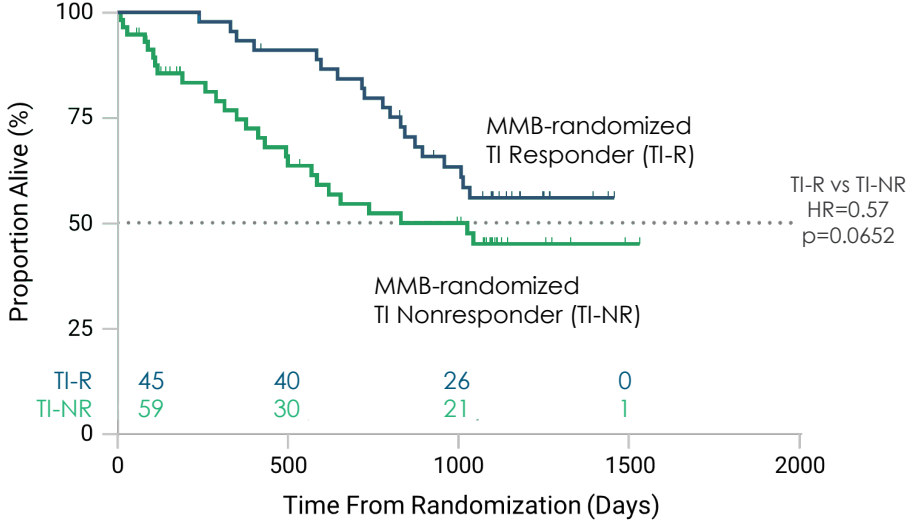
Week 24 Transfusion Independence Response (TI-R): no RBC transfusion within ≥ 12 weeks immediately prior to Week 24, with Hgb ≥ 8 g/dL
Transfusion Dependent (TD): ≥4 units of RBCs or Hgb level, ≤ 8 g/dL in the 8 weeks prior to randomization
Transfusion Independent (TI): absence of RBC transfusions and 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

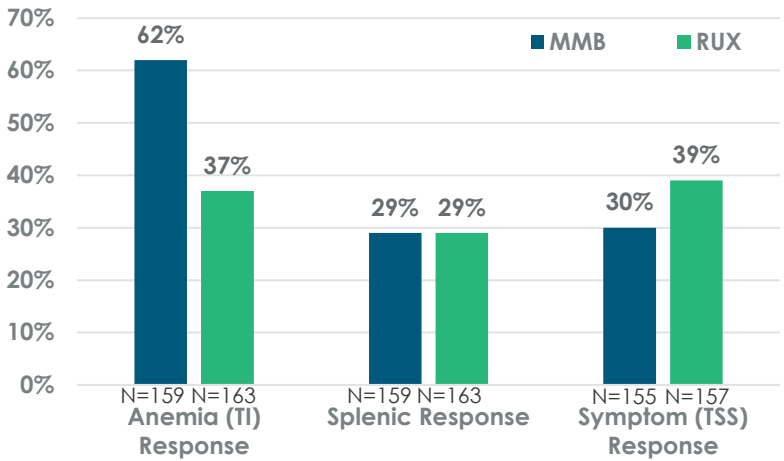
Week 24 TI response = no RBC transfusion for ≥ 12 weeks immediately prior to Week 24, Hgb level ≥ 8 g/dL.
Mesa, R. et.al. *European Hematology Association*, June 2021, oral presentation S202; Virtual.

Comparative Efficacy MMB vs RUX/BAT in Anemic Patients

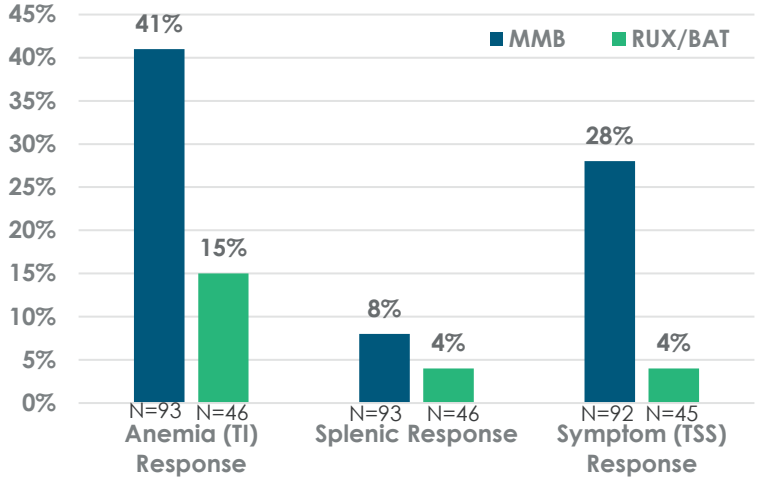
MMB's anemia benefits are accompanied by similar splenic and symptomatic response rates in SIMPLIFY-1 and significantly better symptom control relative to BAT in SIMPLIFY-2

Week 24 Response Rates

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



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

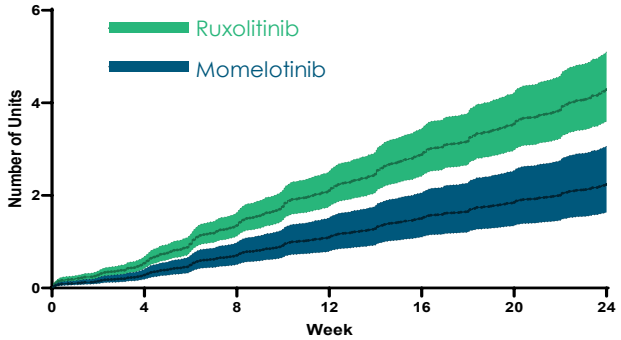


SIMPLIFY-1: *JAK Inhibitor-naïve Patients*

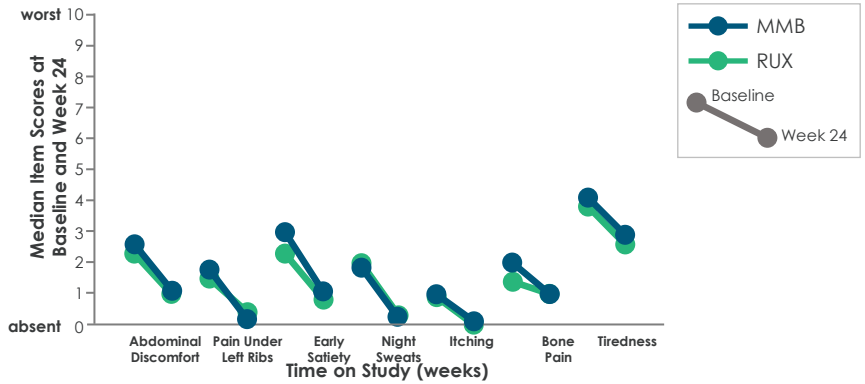
Potential for MMB to improve outcomes in JAK-naïve patients:

- **Splenic control with MMB equivalent** to that achieved with RUX (27% vs. 29%)
- **Symptom benefit clinically comparable** when measured longitudinally and as individual scores
- **Higher rates of transfusion independence** for MMB-treated patients
- **Long overall survival:** Medians of 53 months and not reached

Transfusion Requirement was ~half for MMB vs. RUX



Comparable Symptom Benefit for all 7 items within the TSS



Mixed-Effect Model Repeated Measure (MMRM) Based TSS Change from Baseline (70-point scale)

	ITT Population		Symptomatic Population	
	MMB	RUX	MMB	RUX
Baseline TSS, LS mean	19.0	17.5	25.1	23.1
Week 24 Change from Baseline, LS Mean	- 6.4	- 7.9	- 8.8	- 10.5
Difference from RUX in W24 Change from Baseline, LS Mean	1.5		1.7	

In patients previously treated with a JAK inhibitor:

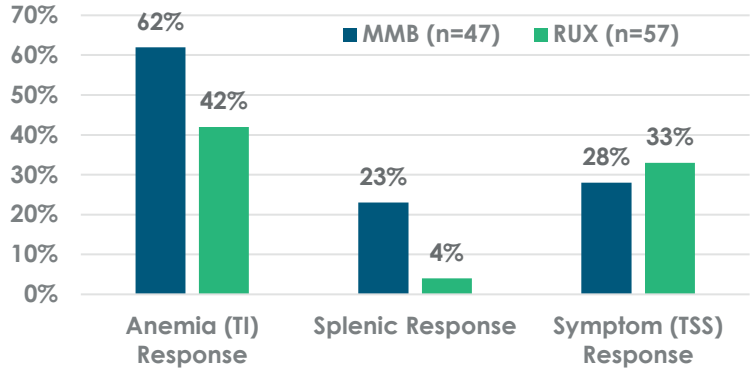
- MMB maintains **splenic control**
  - MMB provides some measure of **splenic shrinkage** in 35% of MMB treated patients at Week 24
  - The mean percent change in spleen volume at Week 24 was 0.2% in the MMB group
- **Higher rates of symptom response and transfusion independence** achieved for MMB-treated patients
- **Long overall survival observed** in this JAK inhibitor-exposed setting
  - Median of 37.5 and 34.3 months

Comparative Efficacy MMB vs RUX in Patients with Low Platelet Counts

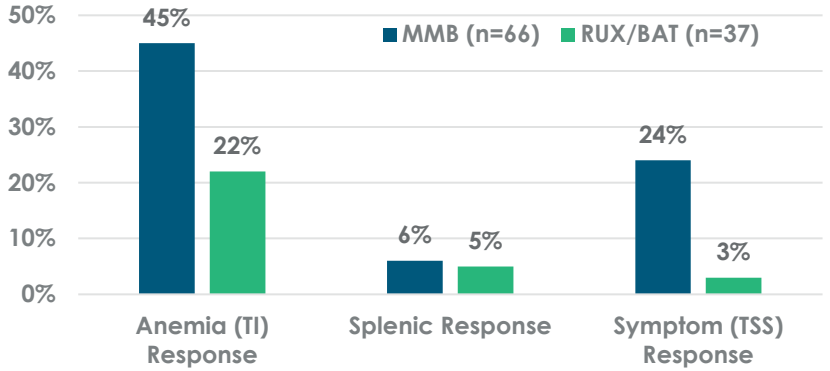
MMB does not require dose adjustment based on platelet count. By retaining full dose intensity, efficacy is maintained with MMB in contrast to RUX in patients with low platelet counts

Week 24 Response Rates

SIMPLIFY-1: Patients with 50 - 150 x10⁹ platelets/L at Baseline



SIMPLIFY-2: Patients with ≤150 x10⁹ platelets/L at Baseline*



*Including patients with <50 x 10⁹ platelets / L

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

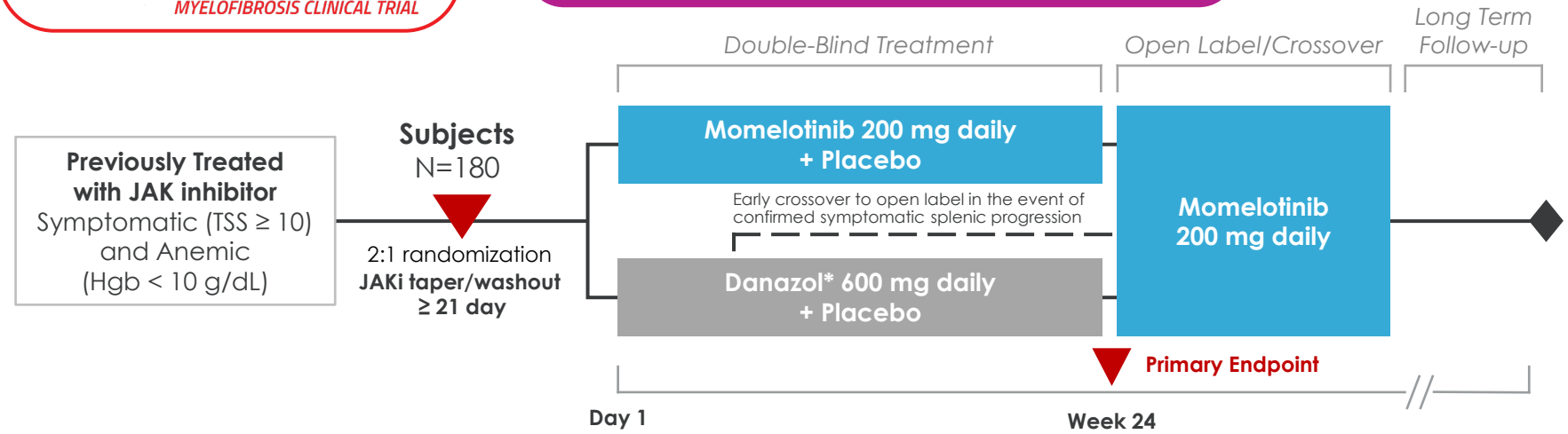
Most Frequent TEAEs[1] by PT	Extended duration MMB Final Safety Analysis (N=411)
Pts with any TEAE, n (%)	397 (96.6%)
Diarrhea	99 (24.1%)
Anemia	93 (22.6%)
Thrombocytopenia	94 (22.9%)
Nausea	85 (20.7%)
Fatigue	84 (20.4%)

[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

Pivotal Phase 3 '*MOMENTUM*' Study: Topline Results Expected February 2022

MOMENTUM
MYELOFIBROSIS CLINICAL TRIAL

Enrollment complete with 195 patients



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.

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 of MMB + BET combination

- SRA515 has synergistic preclinical efficacy 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 the most potent BETi with selective target inhibition**
  - Novel bivalent binding mode; Allows for maintained dosing durability
- ✓ **MMB may be the best combination agent as only JAKi with anemia benefit in MF**
  - Novel JAK1, JAK2 and ACVR1/ALK2 MOA does not add to myelosuppression of BETi
- ✓ **Sierra wholly owns 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 expected February 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

SRRA Ownership and Capitalization

SRRA ownership is highly concentrated with quality long-term shareholders – the top10 own ~80% of common shares outstanding [1]

- *Vivo Capital*
- *Longitude Capital*
- *Orbimed Advisors*
- *Rock Springs Capital*
- *Abingworth Management*
- *Adage Capital*
- *Frazier Healthcare Partners*
- *Gilead Sciences*
- *Ikarian Capital*
- *Caxton Associates*

With conversion of warrants and options, fully diluted shares outstanding are ~22M resulting in a market cap of ~ $506M at a $23 stock price

Common shares outstanding [2]	15,055,040
Series A warrants for common stock (treasury stock method)	3,319,592
Series B warrants for common stock	2,524,732
Gilead warrants for common stock (treasury stock method)	309,034
Employee stock options [3]	812,671
Total FD Shares Outstanding	22,021,068
Fully Diluted Market Cap	$ 506,484,566

(1) Source: public filings as of 11/5/21
(2) Source: public filings as of 11/5/21. Note that common shares outstanding will change as the ATM is used and this number should not be relied upon for investment decisions.
(3) Based on 4.8M options outstanding with a weighted average exercise price of $19.11per 10-Q for the period ending 9/30/21. Calculation uses treasury stock method.

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