Review of Momelotinib for the Potential Treatment of Myelofibrosis

December 16, 2021

SIERRA ONCOLOGY

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Today's Agenda

Welcome & Introduction	**Stephen Dilly, MBBS, PhD** President & Chief Executive Officer
Anemia in Myelofibrosis & Prior Momelotinib Data in Anemic MF Patients	**Prithviraj Bose, MD** MD Anderson Cancer Center
Momelotinib: Phase 3 Clinical Trial Designs and Conclusions	**Barb Klencke, MD** Chief Medical Officer
Tracking For NDA Submission in Q2 2022	**William Turner** Chief Regulatory & Technical Operations Officer
Commercial Preparation	**Kevin Norrett, MBA** Chief Business Officer
Open Q&A	

Welcome and Introduction

Stephen Dilly, MBBS, PhD

President and Chief Executive Officer

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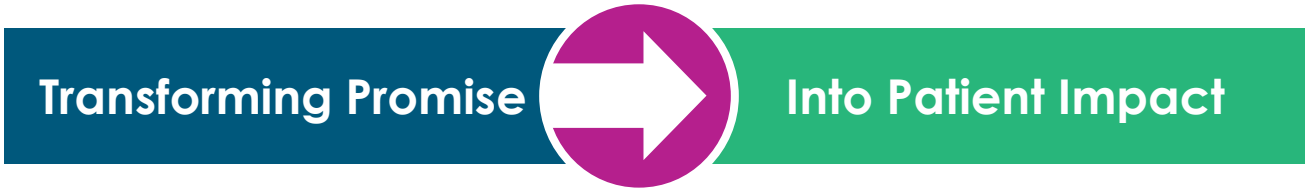
Sierra's Mission

*The Team at Sierra Oncology is on a mission to **deliver transformative therapies** that treat rare forms of cancer.*

*We take an **evidence-based approach** to understand the limitations of current treatments and **investigate new ways** to change the cancer treatment paradigm. We **explore options often ignored by others** so that even small and complex patient populations can live longer and healthier lives.*

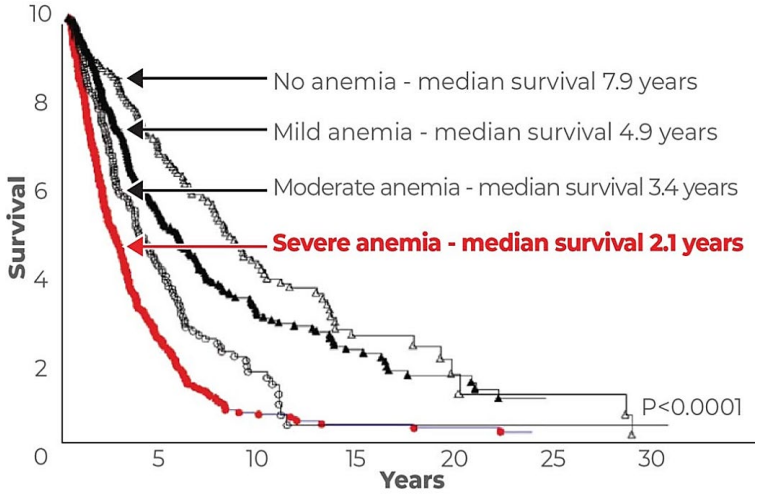
Together, we are:



We Are Developing Momelotinib to Meet an Unmet Need

- Anemia is a negative prognostic indicator in myelofibrosis patients
- Currently approved therapies do not address anemia in myelofibrosis patients
- Our data suggests momelotinib may improve anemia in these patients

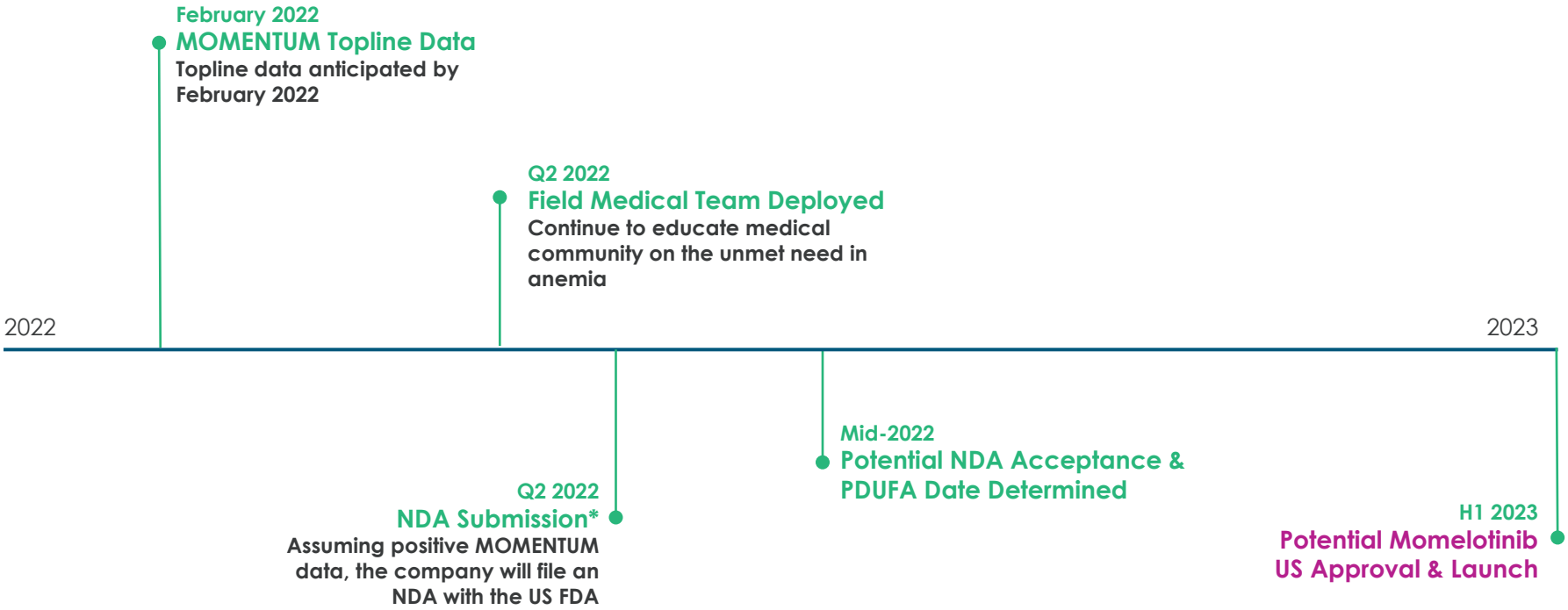
Anemia Predicts Poor Survival in MF



Nicolosi et al. *Leukemia*. 2018

New Therapies Should Provide Anemia Benefits in Addition to Symptom and Spleen Benefits

Two Months to Topline MOMENTUM Data



** Expected additional regulatory filings for EMA, MHRA and other jurisdictions approximately 6 months after NDA*

Highly Experienced Team Preparing for Topline Data & Rapid NDA Submission

Stephen G. Dilly, MBBS, PhD
President & Chief Executive Officer

Barbara Klencke, MD
Chief Medical Officer

Kevin Norrett, MBA
Chief Business Officer

William Turner
Chief Regulatory &
Technical Operations Officer

Anemia in Myelofibrosis & Prior Momelotinib Data in Anemic MF Patients

Prithviraj Bose, MD
Department of Leukemia, MD Anderson Cancer Center

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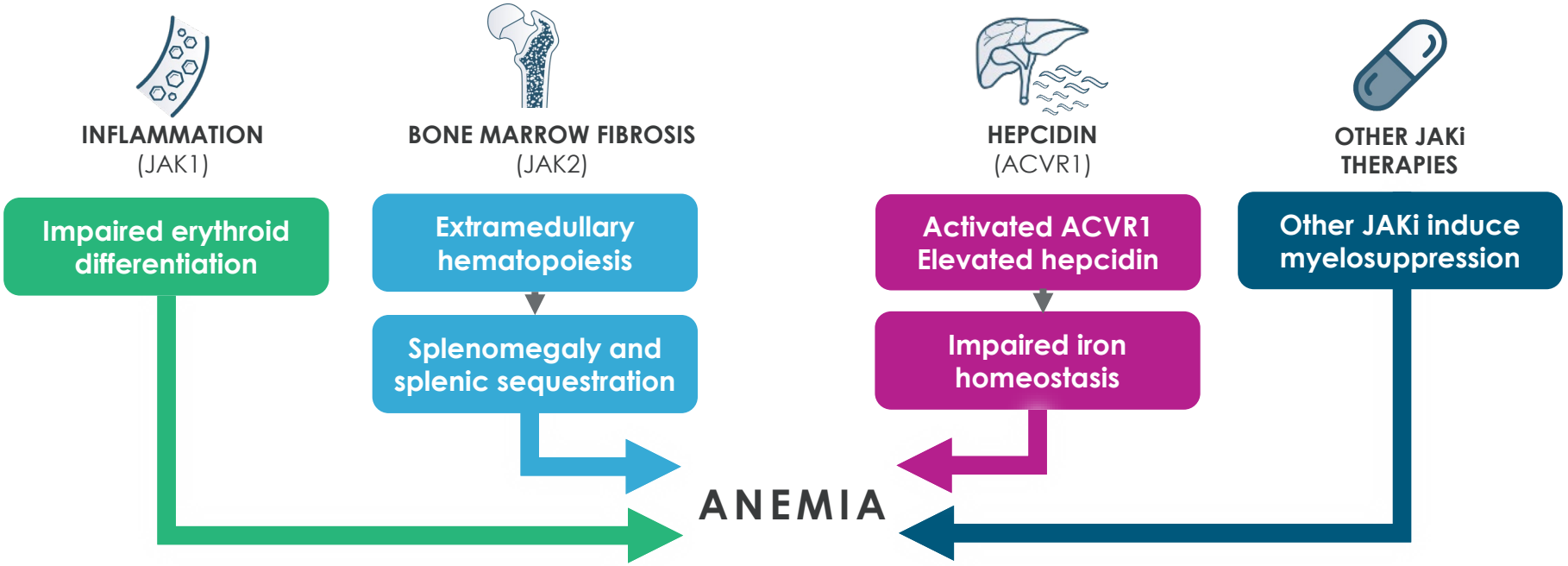
Anemia of Myelofibrosis: Multiple Complementary Pathways to Anemia



Myelofibrosis: The Unmet Medical Need

CURRENT TREATMENT OPTIONS (2-Dimensional Approach):

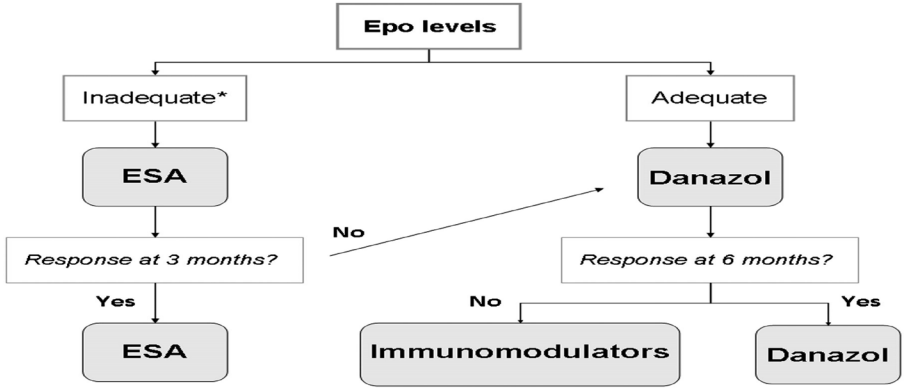
- Two approved agents: ruxolitinib (Jakafi®) and fedratinib (Inrebic®):
  - **Both treat only splenomegaly and symptoms while exacerbating anemia and thrombocytopenia**
  - **Dose reductions common** due to myelosuppression
  - Many patients **ineligible** due to cytopenias

UNADDRESSED CLINICAL OPPORTUNITY (3-Dimensional Focused Therapy):

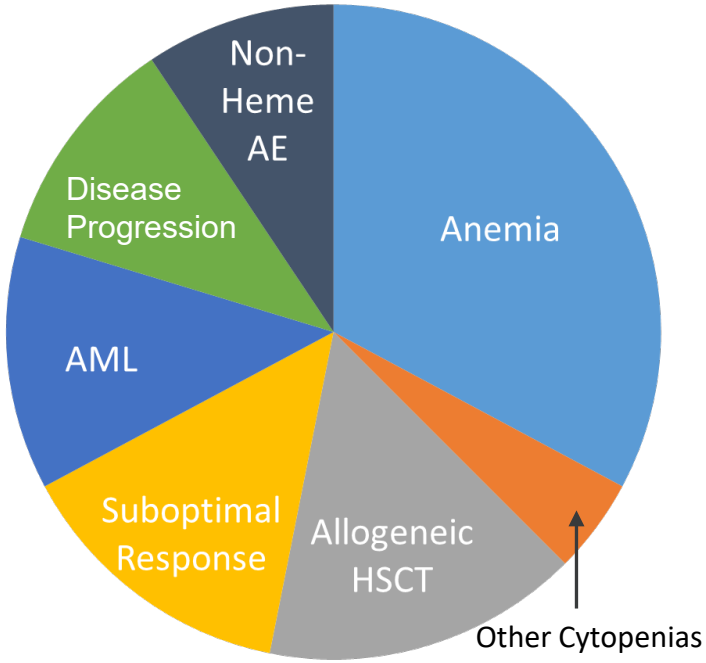
- Single-agent therapy **addressing symptoms, spleen and anemia** needed
- New options for **patients with cytopenia and anemia** are needed
  - Unmet needs exist in treatment naïve patients and in patients on therapy

- **Anemia is Not Addressed by Ruxolitinib or Fedratinib**
- **Physicians Need More Treatment Options**

Anemia of Myelofibrosis and from Ruxolitinib



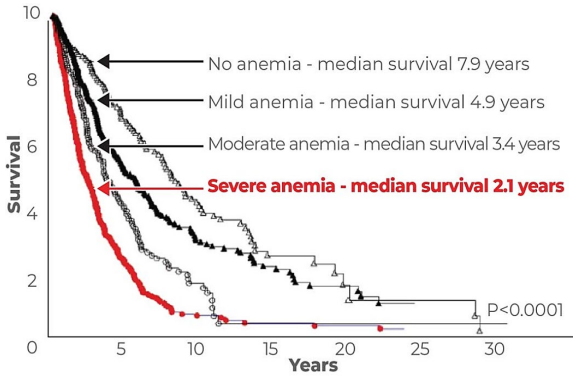
Reasons for Stopping Ruxolitinib



Cervantes F. Blood 2014. Verstovsek S *et al.* N Engl J Med 2012. Kuykendall AT *et al.* Ann Hematol 2018.

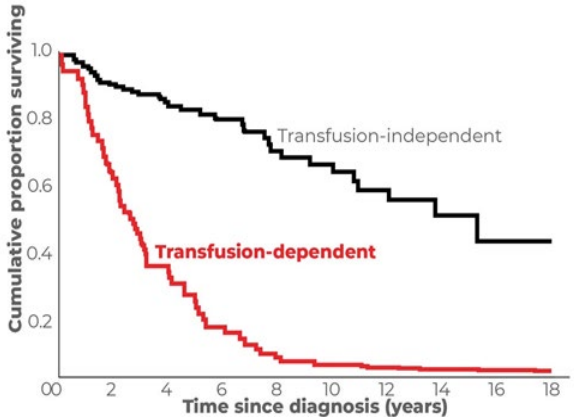
Anemia and Related Factors Predict Overall Survival (OS) in Myelofibrosis

Anemia Predicts Poor Survival in MF



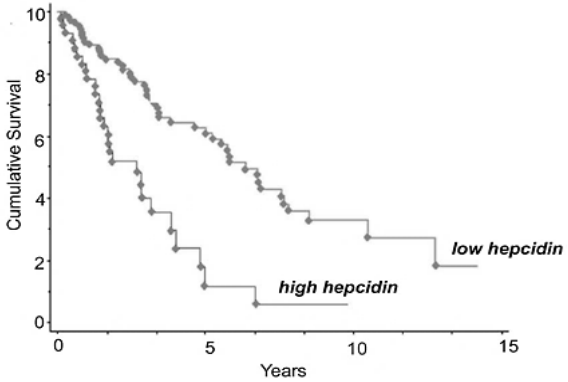
Nicolosi et al. *Leukemia*. 2018

Transfusion Dependency Predicts Poor Survival in MF



Elena et al. *Haematologica*. 2011

Elevated Hepcidin Predicts Poor Survival in MF

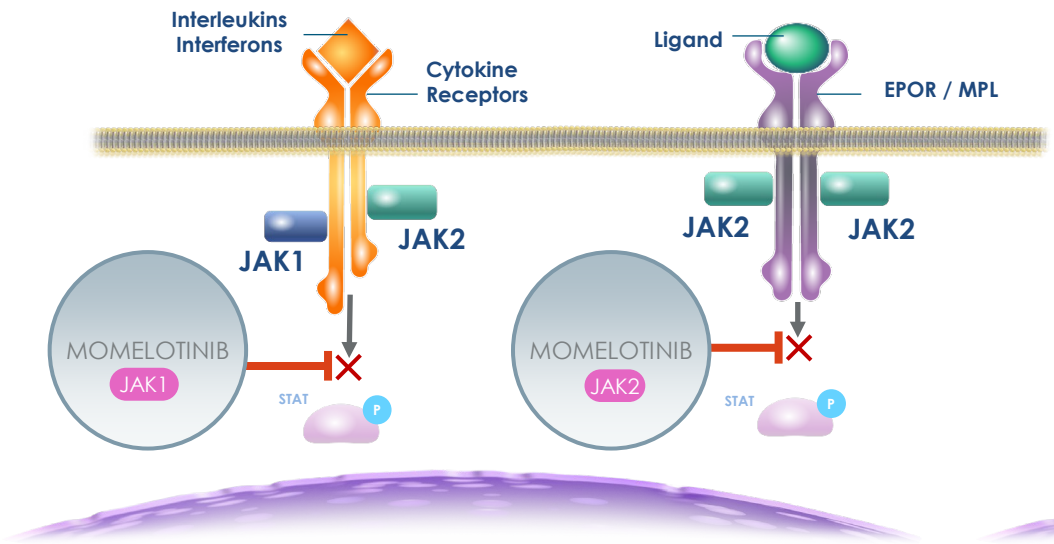


Pardanani et al. *Am. J. Hematol*. 2013

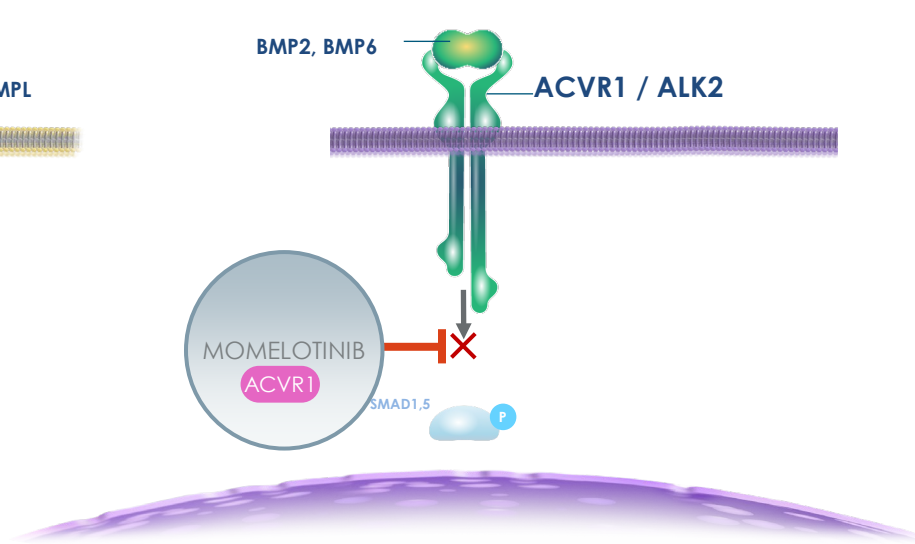
New therapies Should Provide Anemia Benefits in Addition to Symptom and Spleen Benefits

Elena, C. et al. *Haematologica*. 2011;96(1):167-170.
Nicolosi, M. et al. *Leukemia*. 2018;32:1254-8.
Pardanani, A. et al. *Am.J.Hematol*. 2013;88:312-6.

Momelotinib Inhibits JAK1, JAK2 *and* ACVR1/ALK2



Hyperactive JAK-STAT signaling is driving the disease in myelofibrosis



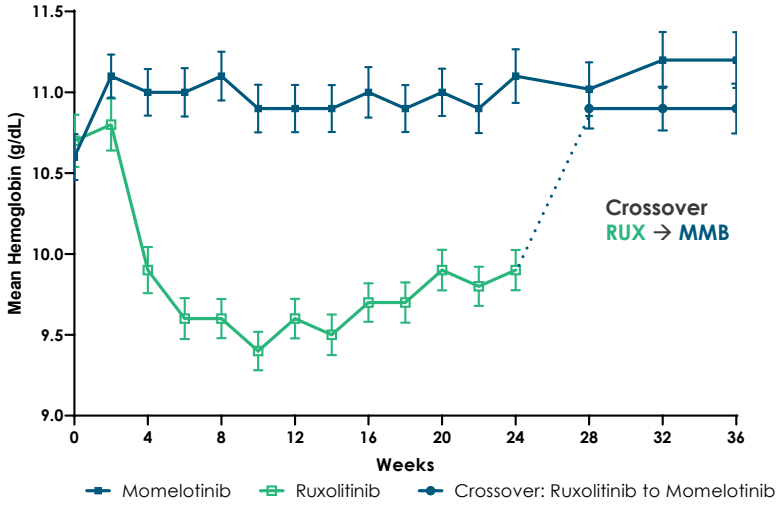
Preclinical and clinical studies suggest that the clinical anemia benefits of momelotinib result from suppression of ACVR1/ALK2-mediated hepcidin production

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

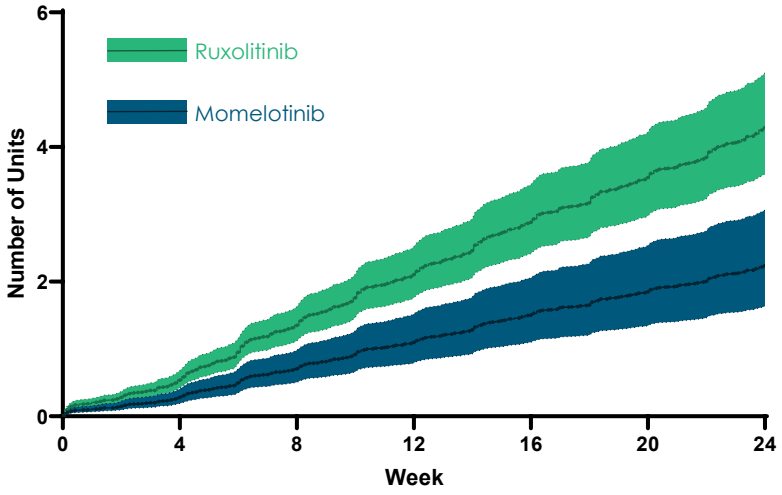
Asshoff, M. et. al. *Blood*. 2017;129(13):1823-1830. Oh, S. et al. *Blood Advances*. 2020;4(18):4282-4291.

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

Hemoglobin Level



Transfusion Requirement

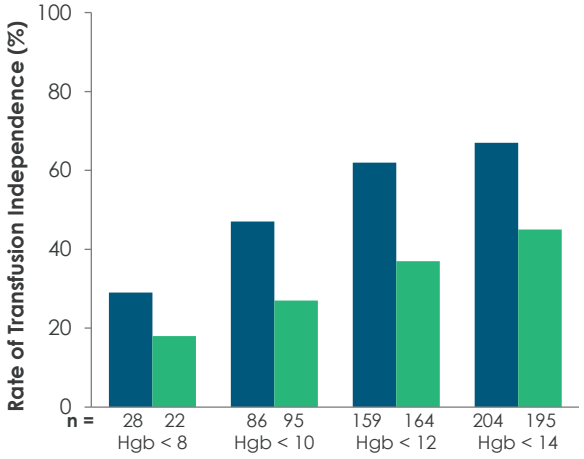


Momelotinib Demonstrated an Increase in Hemoglobin and a Decreased Transfusion Requirement vs. Ruxolitinib

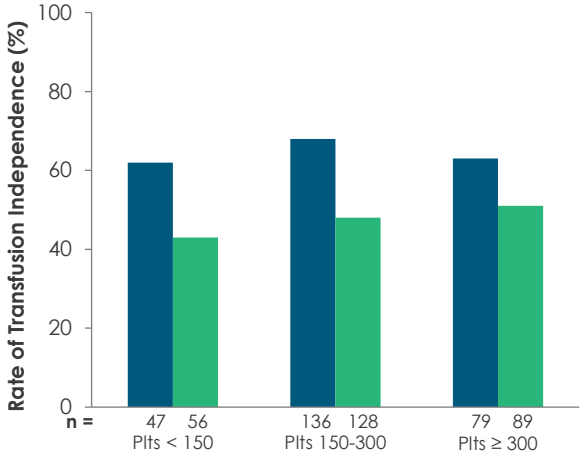
- Harrison C. et.al. European Hematology Association, June 2020, Poster #EP1113
- Mesa RA et.al. *American Society of Hematology*, Dec 2019, Abstract #1663

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

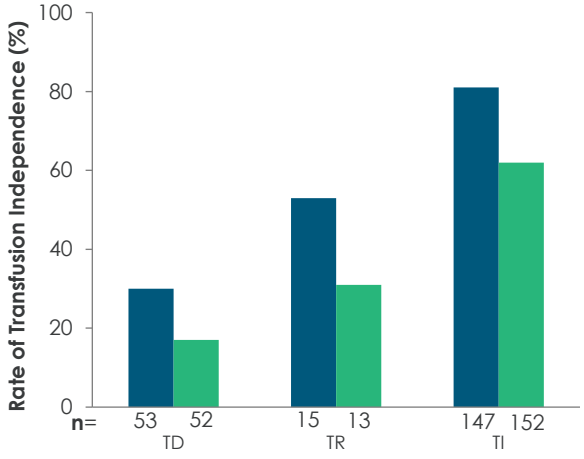
SIMPLIFY-1 Anemic Patients
W24 TI-Response by Baseline Hgb



SIMPLIFY-1
W24 TI-Response by Baseline PLT



SIMPLIFY-1
W24 TI-Response by Baseline Transfusion Status



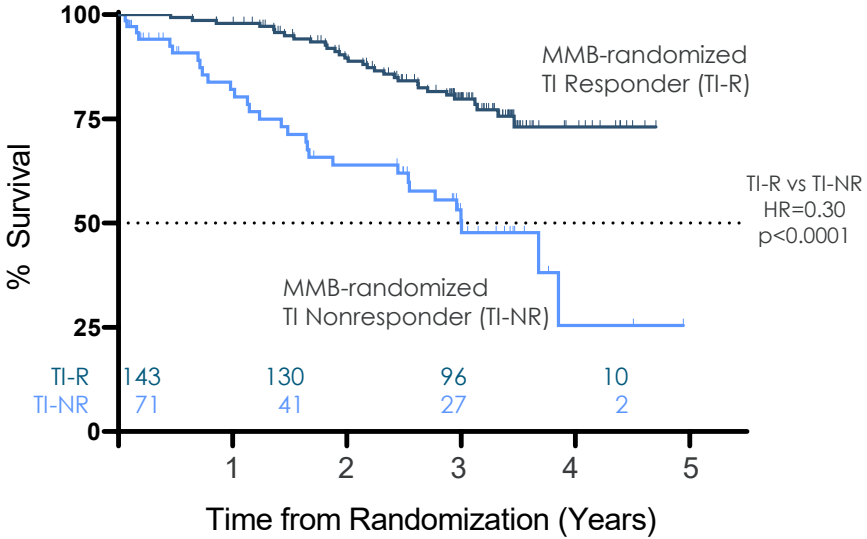
Momelotinib Ruxolitinib

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

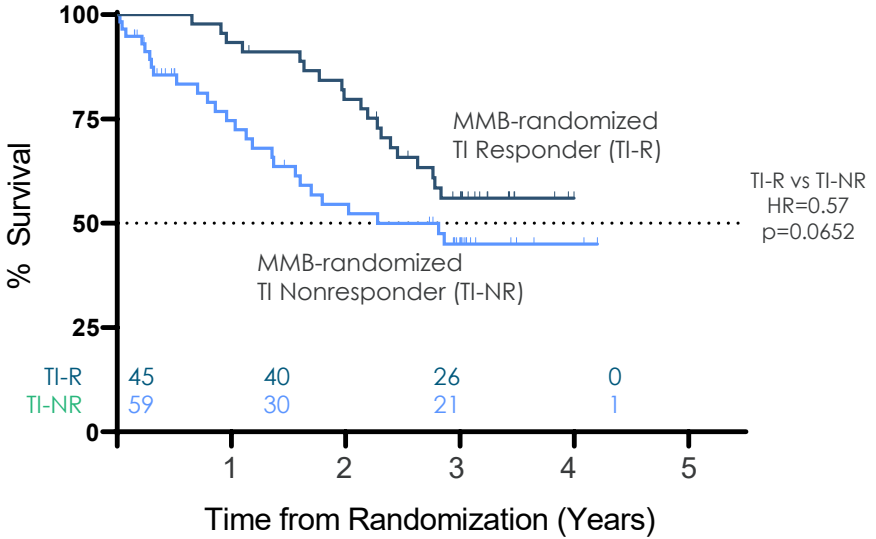
Week 24 Transfusion Independence Response (TI-R): no RBC transfusion within ≥ 12 weeks immediately prior to Week 24, with Hgb ≥ 8 g/dL
Transfusion Dependent (TD): ≥4 units of RBCs or Hgb level, ≤ 8 g/dL in the 8 weeks prior to randomization
Transfusion Independent (TI): absence of RBC transfusions and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

Achieving or Maintaining Transfusion Independence Predicted Improved Survival in MMB-Treated Patients Across Both Completed Phase 3 Trials

SIMPLIFY-1



SIMPLIFY-2



Achieving Transfusion Independence Could Become an Important Consideration when Selecting a Treatment in Myelofibrosis

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.

Conclusions

- Anemia is common in MF and current treatments are unsatisfactory
  - Currently approved JAKi's do not improve and actually worsen anemia, esp. early on in therapy
  - Dose reduction due to treatment-emergent anemia may compromise benefits of RUX/FEDR
- MMB potentially combines JAK1/2 inhibition with anemia improvement through ACVR1/ALK2 inhibition and suppression of hepcidin
- RBC-TI rates were significantly higher for MMB compared with RUX in head-to-head phase 3 trials
- RBC-TI on MMB was durable and associated with OS benefit
- Pending positive results in the phase 3 MOMENTUM trial, and if approved, MMB might be used for 1L and 2L settings, particularly in anemic patients, with or without thrombocytopenia

Momelotinib: Phase 3 Clinical Trial Designs and Conclusions

Barbara Klencke, MD
Chief Medical Officer

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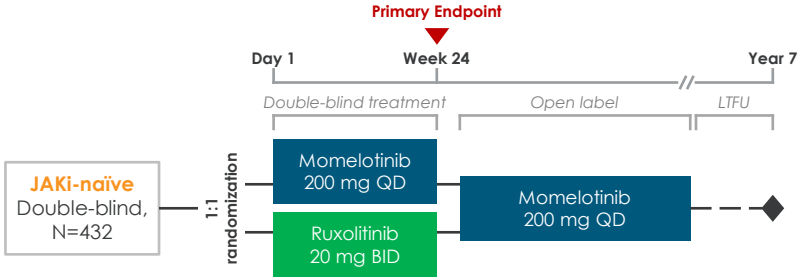
Completed Phase 3 Studies SIMPLIFY-1 and 2

SIMPLIFY-1

1st-Line Population
JAK inhibitor naïve

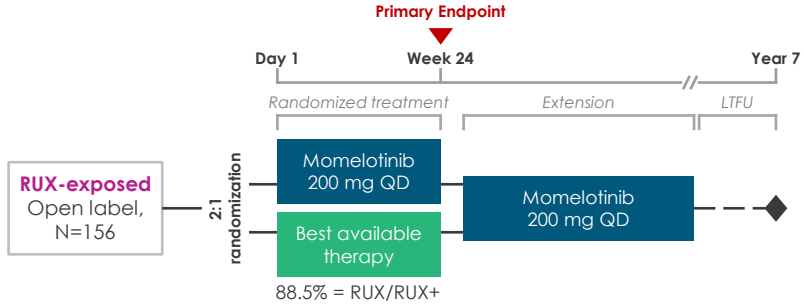


Goal:	Non-Inferiority	
Endpoints at Week 24:	**MMB**	**RUX**
SRR ≥35% (primary)*	27%	29%
Symptom score reduction ≥50%	28%	42%
TI for ≥ 12weeks	67%	49%

*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**	**RUX/BAT**
SRR ≥35% (primary)	7%	6%
Symptom score reduction ≥50%	26%	6%
TI for ≥ 12weeks	43%	21%

The Lancet Haematology, 2018 5(2): 7

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

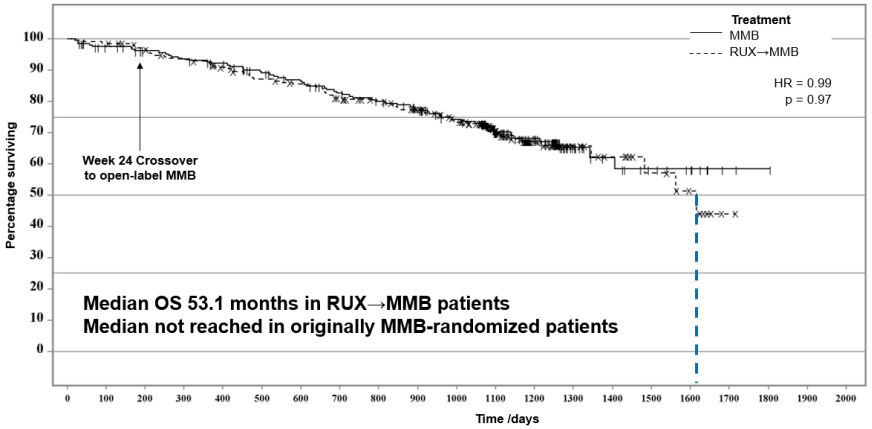
Most Frequent TEAEs[1] by PT	Extended duration MMB Final Safety Analysis (N=411)
Pts with any TEAE, n (%)	397 (96.6%)
Diarrhea	99 (24.1%)
Anemia	93 (22.6%)
Thrombocytopenia	94 (22.9%)
Nausea	85 (20.7%)
Fatigue	84 (20.4%)

[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

Intriguing OS Seen in Both JAKi-naïve and JAKi-exposed Patients

SIMPLIFY-1

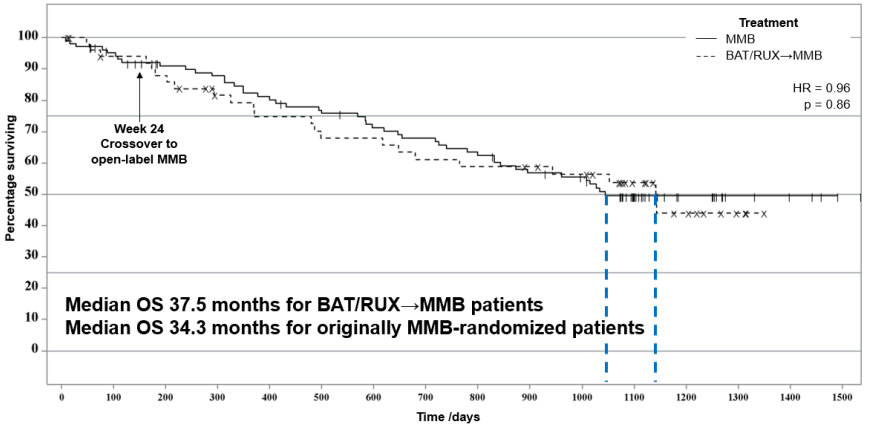
JAKi-naïve Patients



Durable survival potentially reflects momelotinib benefit on extended treatment or crossover to momelotinib, regardless of starting therapy

SIMPLIFY-2

JAKi-exposed Patients



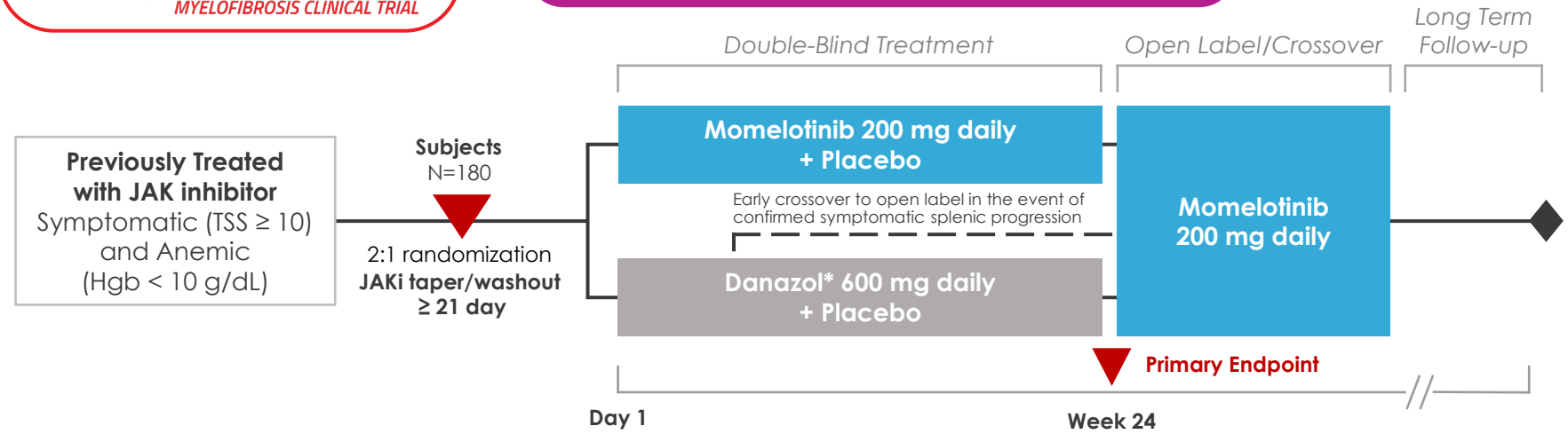
The OS results are amongst the best survival reported in patients who have been previously treated with ruxolitinib

Source: Verstovsek, S. et al. ASH 2020.

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's Unique MOA Could Fill an Important Unmet Need in MF

MMB Has the Potential to Provide Significant and Durable Benefits for Patients with MF

- Potentially meaningful **anemia benefits**, **symptom and spleen control, without impacting platelets**
- **Low potential for myelosuppression** supports dosing intensity & durable activity
- **~90% of patients receiving momelotinib remained on full dose over time**
- **Some patients** have remained on therapy for **>11 years,** consistent with favorable safety profile
- **Meaningful survival duration** demonstrated in both JAKi-naïve and JAKi-exposed patients

MMB's Differentiation Enables Clear Patient Segmentation

- **Reduced transfusion burden** and **improved Hgb** for **anemic patients**
- **Robust activity irrespective of** baseline **platelet count or** anemic or **transfusion status**
- **Could become the optimal treatment for patients** who are, or are at risk of becoming, **anemic and/or thrombocytopenic**

Tracking for NDA Submission in Q2 2022

William Turner
Chief Regulatory & Technical Operations Officer

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NDA Preparation Remains on Track - Targeting Submission Q2 2022

Module 1 Administrative information, prescribing information
- Includes prescribing information and package labeling

Module 2 Summaries of non-clinical, clinical, and CMC information
- Summaries will be finalized at completion of relevant modules

Module 3 Manufacturing and quality information
- Contract commercial manufacturing and testing locations in place
- Methods transferred and validated
- Process validation underway

Module 4 Non-clinical studies (toxicology, animal studies)
- All tox and key animal studies complete

Module 5 Clinical study reports (SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM)
- SIMPLIFY-1 and SIMPLIFY-2 CSRs complete
- Momentum CSR will be finalized upon analysis of topline data

Significant Progress Made Across all Modules

Regulatory Process – Next Steps

- Pre-NDA meeting Q1 2022
  - Run through topline data and basis of our submission
- NDA submission Q2 2022
  - Priority review request at time of submission
- NDA PDUFA date determination within 60 days of submission
- Priority Review timeline if granted is approximately 8 months from submission
- Label negotiations will occur when FDA has evaluated all the data – late in review
- Potential approval early 2023
- Launch shortly after approval

Commercial Preparation

Kevin Norrett, MBA
Chief Business Officer

Momelotinib Provides an Attractive Commercial Opportunity

$3 Billion Addressable Market* for MMB in Anemic MF Patients in the US

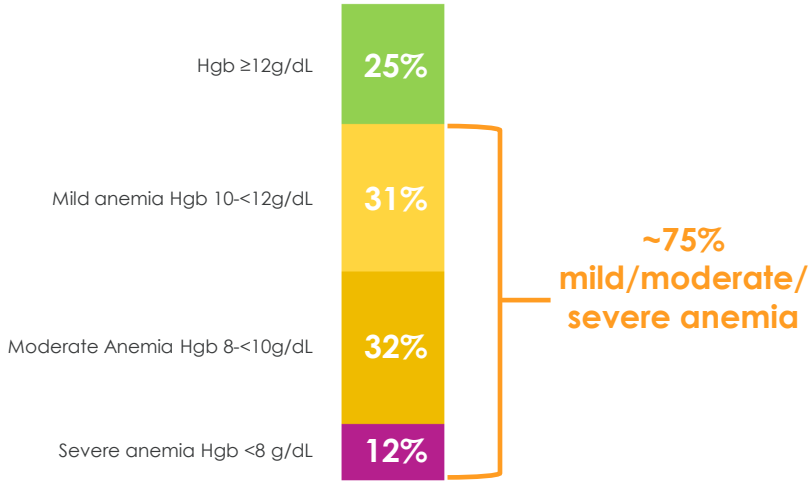
- **Differentiation in an established market is key to our success**
  - MMB could become the JAKi that has the potential to address anemia, maintain spleen and symptoms, without impacting platelets
  - MMB's hematologic safety and tolerability profile could support long-term dosing
  - MMB is conveniently dosed once a day and seldom requires dose reductions
- **Focused educational efforts and launch preparation, particularly with community prescribers**
  - Positive feedback from academic KOLs; many citing a need for options that address more than spleen
- **Modest investment required to access the majority of the opportunity**
  - Modest field force size of ~40-60 individuals targeting ~3,500 JAKi prescribing hem-oncs
- **Evaluating partnerships for ex-US commercialization**

Source: Sierra Market Research
*Sierra estimates ~15k US prevalent anemic MF patients and assumes a price of $200k/patient/year

Anemia Could Become the Primary Driver of JAKi Choice

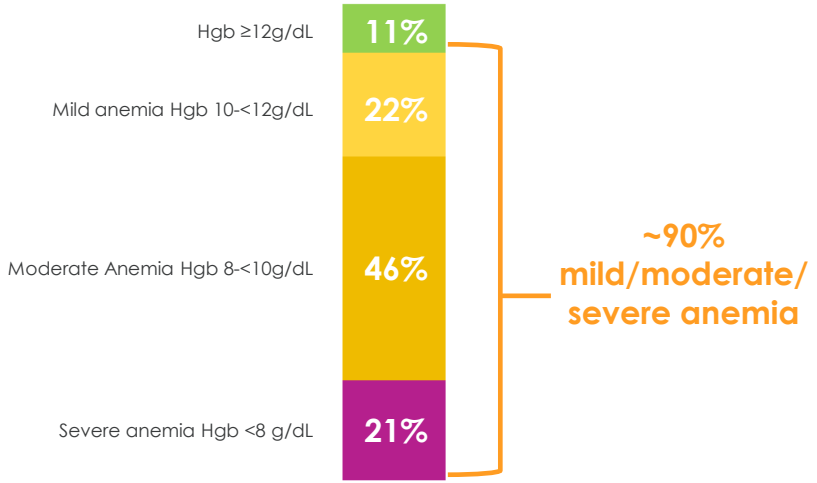
- Momelotinib could become the JAKi of choice for anemic myelofibrosis patients
  - In S-1 at baseline, ~75% of anemic with 30% requiring transfusions
  - In Rux-experienced patients, 90% are anemic with more than two thirds require transfusions
- A differentiated JAKi could allow hem/oncs to transition patients early in their treatment journey
- Upside potential if broad label obtained 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

Final Thoughts

Stephen Dilly, MBBS, PhD
President & Chief Executive Officer

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Q&A

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