MYELOPROLIFERATIVE NEOPLASMS (MPNS) ROUNDS
NEW YORK CITY

Wednesday, February 5, 2025
6:30pm – 9:00pm

3 West Club
New York, NY

This activity is provided by The Leukemia & Lymphoma Society and Medical Learning Institute Inc, in collaboration with the Association of Cancer Care Centers™ (ACCC).

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WELCOMING REMARKS

John Mascarenhas, MD (Chair)
Director, Center of Excellence
Blood Cancers and Myeloid Disorders
Director, Adult Leukemia Program
Leader, Myeloproliferative Disorders Clinical Research Program
Tisch Cancer Institute
Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, NY

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TARGET AUDIENCE

This activity is intended for hematologists-oncologists, medical oncologists, physician associates, advanced practice providers, nurses and pharmacists involved in the care of patients with Myeloproliferative Neoplasms (MPNs).

EDUCATIONAL OBJECTIVES

At the conclusion of this activity, participants will be better able to:

- Apply diagnostic criteria for a correct diagnosis and grade
- Explain the latest treatment options for myeloproliferative neoplasms (MPNs), including updates on clinical trials
- Identify disparities and challenges in diagnosis and treatment of MPNs
- Describe side effects of treatment and management strategies
- Identify resources for patient education and support

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AGENDA

6:30 pm	Dinner and Networking
7:00 pm	Welcome and Overview of Program *John Mascarenhas, MD*
7:05 pm	Overview of LLS Resources *Lauren Berger, MPH*
7:10 pm	Case Presentation and Discussion on Management of "Lower-risk" Essential Thrombocythemia (ET) and Polycythemia Vera (PV) *Ghaith Abu-Zeinah, MD and Franco Castillo Tokumori, MD*
7:35 pm	Case Presentation and Discussion on Optimizing Jak Inhibitor Therapy in Myelofibrosis *Noa Rippel, MD and Megan Metzger, MD*
8:00 pm	Case Presentation and Discussion on Targeting Mastocytosis: Current and Emerging Strategies in Diagnosis, Risk Stratification and Treatment *Katherine Linder, MD and Sarvarinder Gill, MD*
8:25 pm	Case Presentation and Discussion on Newly Diagnosed Chronic Myeloid Leukemia (CML): Pros and Cons of the Approved Drugs *Karen Seiter, MD and Snigdha Ghanta, MBBS*
8:50 pm	Q&A, Discussion and Wrap-up *All Faculty*
9:00 pm	Conclusion *John Mascarenhas, MD*

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CE DESIGNATION

Accreditation, Support and Credit

In support of improving patient care, this activity has been planned and implemented by Medical Learning Institute Inc and The Leukemia & Lymphoma Society. Medical Learning Institute Inc is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Continuing Medical Education

Medical Learning Institute Inc (MLI) designates this live activity for a maximum of 2.0 *AMA PRA Category 1 Credits™*.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Statement

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Participation information will be shared through the ACCME's Program and Activity Reporting System (PARS).

For Physicians requesting MOC credit, the post-test and evaluation are required in their entirety as well as your ABIM ID number, DOB (MM/DD), and a score of 70% or higher is needed to obtain MOC credit.

Physician Associate

Medical Learning Institute Inc has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 2.0 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation.

Nursing Continuing Professional Development

Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under Provider Number CEP 5832 to award 2.0 continuing education contact hours through the California Board of Registered Nursing.

Pharmacy

Medical Learning Institute Inc designates this application-based continuing education activity for 2.0 contact hours (0.2 CEUs) of the Accreditation Council for Pharmacy Education.
Universal Activity Number: JA0007322-9999-25-006-L01-P

Providers

This activity is provided by The Leukemia & Lymphoma Society and Medical Learning Institute Inc in collaboration with the Association of Cancer Care Centers™ (ACCC).

Support Statement

There is no commercial support associated with this activity.

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ADVISORY GROUP/FACULTY

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Hackensack, NJ

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Director, Center for Hematologic Malignancies
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Karen Seiter, MD*
Professor of Medicine
New York Medical College
Valhalla, NY

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** Advisory Group and Faculty*

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DISCLOSURE

Disclosure & Conflict of Interest Policy
Medical Learning Institute Inc and The Leukemia & Lymphoma Society are committed to providing high quality continuing education to healthcare professionals, as individuals and teams, with a protected space to learn, teach, and engage in scientific discourse free from influence from ineligible companies that may have an incentive to insert commercial bias into education.

To that end, MLI & LLS require faculty, presenters, planners, staff, and other individuals who are in a position to control the content of this CE activity to disclose all financial relationships they have had in the past 24 months with ineligible companies as defined by the ACCME, as related to the content of this CE activity, regardless of the amount or their view of the relevance to the education. All identified COI will be thoroughly vetted and mitigated according to MLI & LLS policy. These disclosures will be provided to learners prior to the start of the CE activity.

Planning Committee and Content/Peer Reviewers
The planners and content/peer reviewers from Medical Learning Institute Inc and The Leukemia & Lymphoma Society do not have any relevant financial relationships to disclose with ineligible companies unless listed below.

Lauren Berger, MPH, has a financial interest/relationship or affiliation in the form of:
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All of the relevant financial relationships of individuals for this activity have been mitigated.

Disclosure of Unlabeled Use
This educational activity may contain discussions of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this CE activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the accredited CE activity are those of the presenters and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer
Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this CE activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this CE activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

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ADVISORY GROUP & FACULTY DISCLOSURES

Advisory Group

John Mascarenhas, MD (Chair)*, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Blueprint Medicines, Bristol Myers Squibb, Disc, Geron, GlaxoSmithKline, Incyte, Kartos, Karyopharm, Keros, Merck, MorphoSys, Novartis, PharmaEssentia, Pfizer, Roche, Sobi, Sumitomo
Research Funding: AbbVie, Ajax, Bristol Myers Squibb, Geron, Incyte, Kartos, Karyopharm, Novartis, Sobi
Contracted Researcher: AbbVie, Ajax, Bristol Myers Squibb, Geron, Incyte, Kartos, Karyopharm, Novartis, Sobi

Ghaith Abu-Zeinah, MD*, has a financial interest/relationship or affiliation in the form of:
Research Funding: AbbVie, Incyte, MorphoSys, Novartis, PharmaEssentia, SDP Oncology

Swati Goel, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Marina Kremyanskaya, MD, PhD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Agios, Constellation Pharmaceuticals/MorphoSys, Disc, Incyte, Protagonist, Silence Therapeutics
Speakers Bureau: Novartis
Research Funding: Dompé

James McCloskey, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity

Raajit K. Rampal, MD, PhD, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: AbbVie, Blueprint, Bristol Myers Squibb, Cogent, Constellation Pharmaceuticals/MorphoSys, CTI BioPharma/Sobi, Disc, Galecto, Incyte, Jazz Pharmaceuticals, Novartis, PharmaEssentia, Promedior, Sierra Oncology/GlaxoSmithKline, Kartos, Karyopharm, Stemline, Sumitomo Dainippon, Zentalis
Research Funding: Biomed Valley Discoveries, Constellation Pharmaceuticals/MorphoSys, Incyte, Ryvu, Stemline, Zentalis

Karen Seiter, MD*, has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Novartis, Takeda
Speakers Bureau: Alexion, Incyte, Novartis, Servier
Research Funding: Delta Fly, Rigel

Faculty

Lauren Berger, MPH, has a financial interest/relationship or affiliation in the form of:
Stock Ownership with Bristol Myers Squibb, Gilead Sciences, Inc., Merck & Co., Inc., Organon & Co., Pfizer Inc., and Viatris Inc.

Franco Castillo Tokumori, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Snigdha Ghanta, MBBS, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Sarvarinder Gill, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Katherine Linder, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity

Megan Metzger, MD, has a financial interest/relationship or affiliation in the form of:
Advisory Board: Sobi (one-time event, ended 10/23/2024)

Noa Rippel, MD, has no relevant financial relationships with ineligible companies to disclose for this educational activity.

**** Part of the faculty and advisory board***

All of the relevant financial relationships of individuals for this activity have been mitigated.

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INSTRUCTIONS FOR CREDIT

There are no fees for participating in or receiving credit for this CE activity. In order to receive credit, learners must participate in the entire CE activity, complete the evaluation form. A certificate of completion will be emailed within 30 days of receipt. If you have questions regarding the receipt of your certificate, please contact us via email at ndane@mlieducation.org.

For information on applicability and acceptance of continuing education credit for this activity, please consult your professional licensing board.

For Physicians requesting MOC credit, the post-test and evaluation are required in their entirety as well as your ABIM ID number, DOB (MM/DD), and a score of 70% or higher is needed to obtain MOC credit.

For Pharmacists, Medical Learning Institute will accept your completed evaluation form for up to 30 days post-activity and will report your participation to the NABP only if you provide your NABP e-Profile number and DOB (MM/DD). Within 6 weeks, you can view your participation record at the NABP website: https://nabp.pharmacy/

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Our Mission:
Cure blood cancer and improve the quality of life of all patients and their families.

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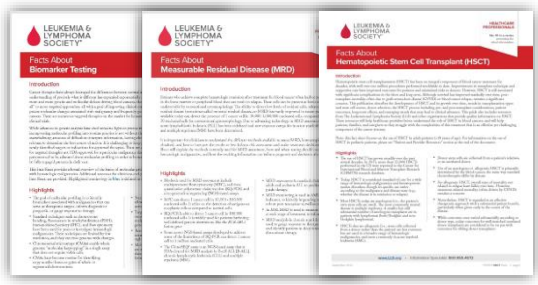
FREE LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

- ❑ CME & CE courses: www.LLS.org/CE
  - ➢ *New CME/CE Webinar on MPNs Coming Soon!*

- ❑ Fact Sheets for HCPs: www.LLS.org/HCPbooklets
- ❑ Videos for HCPs: www.LLS.org/HCPvideos
- ❑ Podcast series for HCPs: www.LLS.org/HCPpodcast



Coming soon!
MPN Fact Sheet for HCPs

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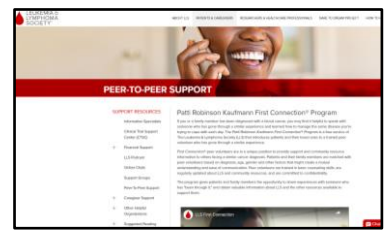
FREE LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- ❑ www.LLS.org/MPN
- ❑ **Webcasts, Videos, Podcasts, Booklets**:
  - ➢ www.LLS.org/Webcasts
  - ➢ www.LLS.org/EducationVideos
  - ➢ www.LLS.org/Podcast
  - ➢ www.LLS.org/Booklets
- ❑ **Support Resources**
  - ❑ Financial Assistance: www.LLS.org/Finances
    - Patient Aid
    - Travel Assistance
    - Urgent Need
  - ❑ Other Support: www.LLS.org/Support
    - LLS Regions
    - Online Weekly Chats Facilitated by Oncology SW
    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program



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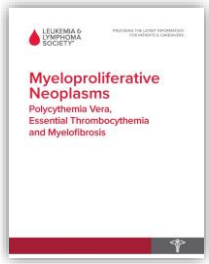
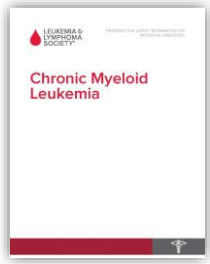
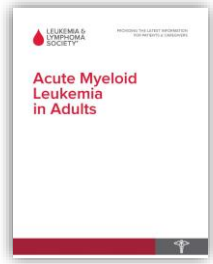
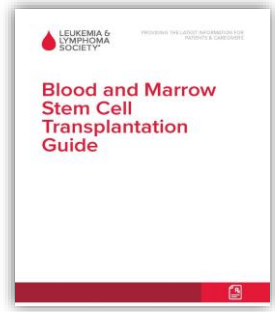
FREE LLS RESOURCES FOR YOUR PATIENTS









BOOKLETS AND FACT SHEETS

English – www.LLS.org/Booklets
Spanish – www.LLS.org/Materiales

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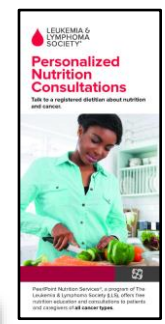
FREE LLS RESOURCES FOR PATIENTS

- **Information Specialists** – Personalized assistance for managing treatment decisions, side effects, and dealing with financial and psychosocial challenges (IRC).
  - www.LLS.org/IRC
- **Nutrition Education Services Center**–Free one-on-one consultations with registered dieticians for patients/caregivers of all cancer types by phone or email.
  - www.LLSnutrition.org
- **Clinical Trial Nurse Navigators** – RNs and NPs provide personalized service for patients seeking treatment in a clinical trial, sift through information and provide information to bring back to their HC team (CTSC).
  - www.LLS.org/CTSC
- **Reach out** **Monday – Friday, 9 am to 9 pm ET**
  - Phone: (800) 955-4572
  - Live chat and Email: www.LLS.org/IRC
  - HCP Patient Referral Form: www.LLS.org/HCPreferral



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HERE TO HELP: LLS COMMITMENT

LLS is committed to providing education and resources to help patients access clinical trials.

CLINICAL TRIAL SUPPORT CENTER

- A team of **highly trained** nurses and nurse practitioners experienced with hematological malignancies and clinical research.
- Provide **education** to patients about clinical trials, treatment options, and other disease specific information.
- Provide patients, families, and their caregivers with a professional, detailed, **individualized** search to discuss with their HCP.
- Provide **guidance** and serve as **advocates** throughout the clinical trial process. Help make connections between the patient and the trial site to facilitate enrollment as appropriate.
- Provide a **personal connection** and develop long term relationships to help better serve our patients.
- We serve as a **bridge** between technology and patients to make accessing clinical trial information easier.

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THE CLINICAL TRIAL SUPPORT CENTER TEAM

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Manager, CTSC

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Clinical Trial Nurse Navigator

Michelle Bibo
CTSC Operations Specialist

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HOW TO ACCESS THE CLINICAL TRIAL SUPPORT CENTER

Call the Information Resource Center (IRC) 1-800-955-4572

Patient or caregivers can complete an online referral form at:
https://www.LLS.org/navigation

Healthcare Providers can complete a referral form at:
https://www.LLS.org/article/clinical-trial-support-center-ctsc-portal-for-healthcare-providers

Email the CTSC directly with questions at: CTSC@LLS.org

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EQUITY IN ACCESS RESEARCH PROGRAM

The Leukemia & Lymphoma Society's (LLS) Equity in Access Research Program was created in 2021 to generate **actionable solutions** to the barriers that prevent all patients from accessing the care they need and deserve. www.LLS.org/EquityinAccess

Program Goals

1) Advance understanding of modifiable, underlying causes of inequitable access to care for blood cancer patients and survivors within the current healthcare system.
2) Generate actionable evidence to assist LLS in advocating for policies and developing programs that tangibly improve the lives of blood cancer patients and survivors.
3) Identify healthcare policies and practices that have the potential to increase equitable access to cancer care and improve the quality of life and outcomes for blood cancer patients and survivors.
4) Cultivate health services researchers in the blood cancer space and contribute to LLS being recognized as a funding and thought leader in this area.

Program Activities

- The program has awarded over $12 million in funding for seminal health services research addressing critical issues such as the cost of oral anticancer medications, the role of health insurance in financial toxicity, and access to clinical trials.
- In 2024 alone, the program awarded $4.8 million to studies testing multi-level interventions to improve clinical trial access and enrollment, with the aim of disseminating those that are effective.

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Application cycle for 2026-2027 academic year will open **June 1, 2025**

- Students must identify as Black/African American, Hispanic/Latino(a), American Indian/Alaska Native, Native Hawaiian/other Pacific Islander
- Applicants must be 2nd – 4th year medical students in good standing at an LCME-accredited medical school.
- Open to U.S. citizens or permanent residents of the U.S. or a U.S. territory
- Award includes
  - $75K for student living expenses
  - $10K for host lab
  - $5K for student relocation costs
  - $6K for student ASH attendance ($3K per year)

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THANK YOU

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MANAGEMENT OF "LOWER-RISK" ESSENTIAL THROMBOCYTHEMIA (ET) AND POLYCYTHEMIA VERA (PV)

Franco Castillo Tokumori, MD
Ghaith Abu-Zeinah, MD

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Agenda

- Case: “Low-risk” ET -> PV
- Diagnosis of ET vs PV
- Management of ET

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CASE: “LOW-RISK” ET -> PV

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35 YO Female Patient with Chronic Thrombocytosis

2008:

WBC 7.8, **Hgb 15.2, Hct 44,** MCV 86, **Plt 734**

RBC 5.07, EPO 5

PB JAK2 PCR: **positive for *JAK2V617F***

PMHx:

Spontaneous abortions, successful pregnancy with IUGR

BMBx

Normocellular. Megakaryocytes are increased in numbers, are atypical in appearance and exhibit some clustering

A reticulin stain shows very minimal fibrosis

Started ASA 81 mg

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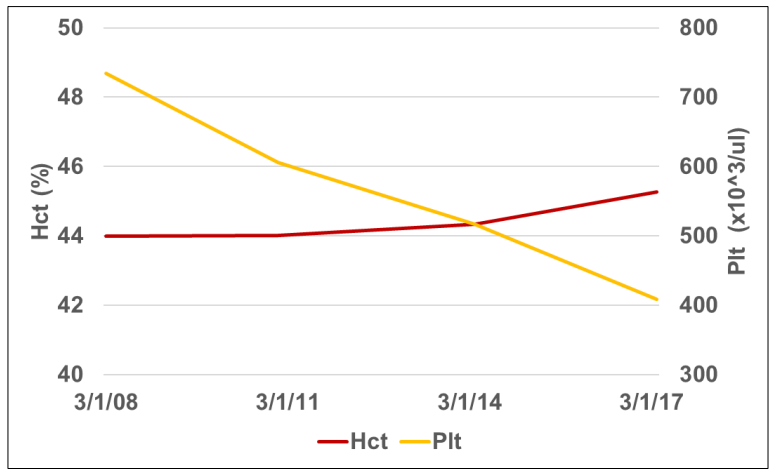
44 YO Female Patient with JAK2V617F ET



2016 PB NGS: *JAK2V617F* VAF 20%, co-occurring *ASXL1* p.K538Lfs*3 40%

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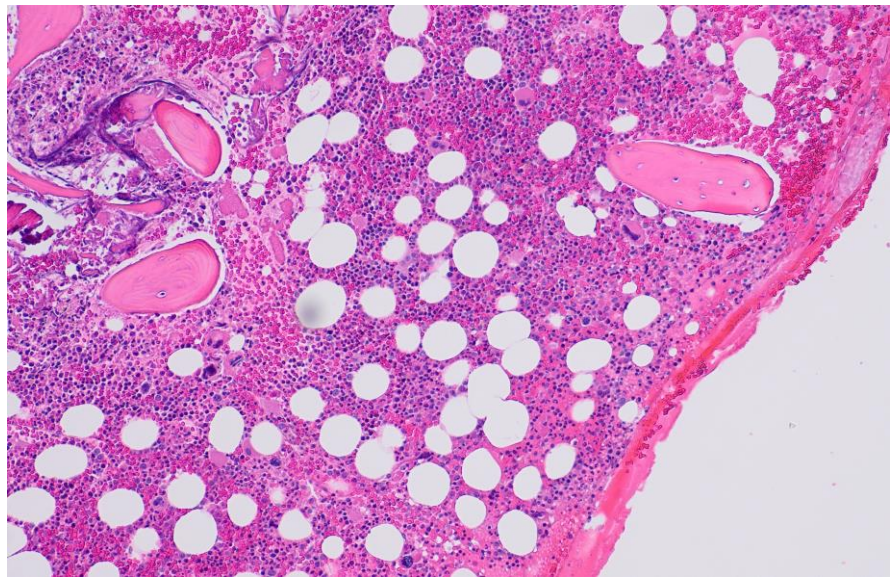
BMBX 2017



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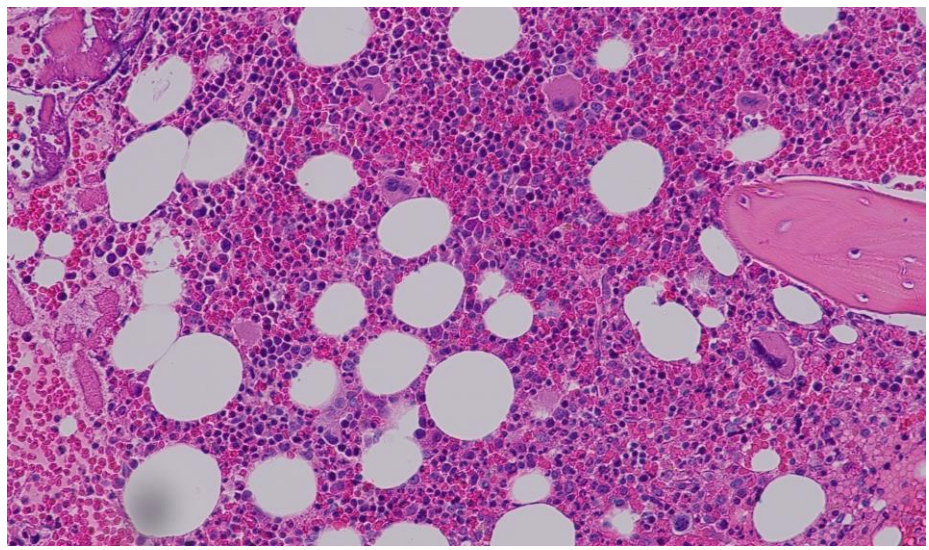
BMBX 2017



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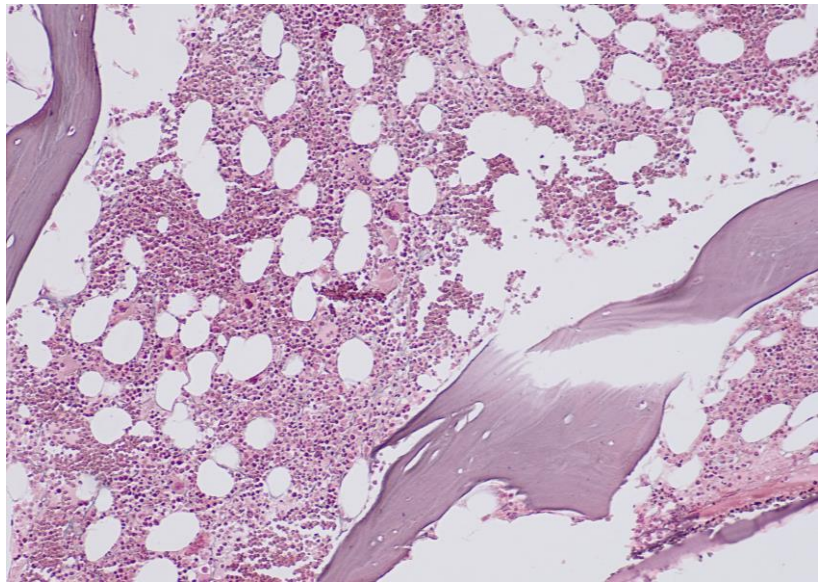
BMBX 2017



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47 YO Female Patient with JAK2V617F ET -> PV

2019:

WBC 7.8, **Hgb 16.5, Hct 48,** MCV 81, **Plt 431**

RBC 5.89, EPO 2

Complaining of facial numbness, lower leg pain

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TREATMENT?

- Aspirin + phlebotomy only
- Hydroxyurea
- Interferon
- Ruxolitinib
- Clinical trial

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47 YO Female Patient with JAK2V617F ET

- May 2019:
- **Phlebotomy (Hct 48%)**
- Started **peginterferon alfa-2a 45 mcg weekly**
- **- Phlebotomy as needed, 3 in 2019**

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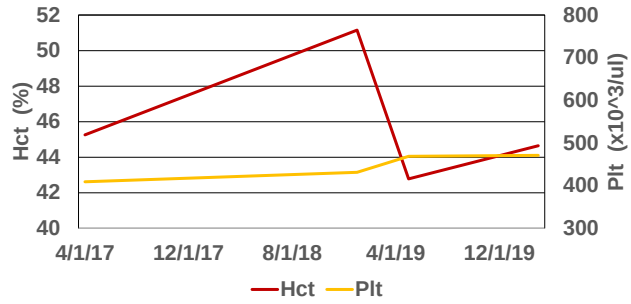
47 YO Female Patient with JAK2V617F PV



2020:

WBC 7.1, **Hgb 14.4, Hct 41.3,** MCV 69, **Plt 471**

RBC 6.34

peginterferon alfa-2a increased to 90 mcg weekly

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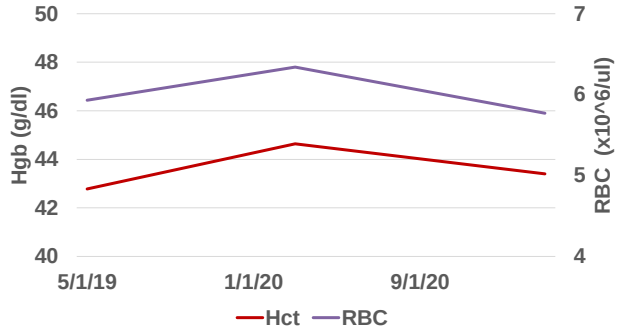
47 YO Female Patient with JAK2V617F PV



2021:

WBC 6.0, **Hgb 14.0, Hct 43,** MCV 73, **Plt 393**

RBC 5.77

peginterferon alfa-2a 90 mcg weekly

PB NGS: *JAK2V617F* VAF 34%, co-occurring *ASXL1* p.K538Lfs*3 44%

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DIAGNOSIS OF ET AND PV

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ET Presentation: Typically, Asymptomatic but 20-30% Present with Thrombosis or Symptoms

- Typically, a referral from PCP for asymptomatic thrombocytosis.
- ~30% present with microvascular symptoms (headaches, paresthesia, erythromelalgia).
- ~20% present with thrombosis (~13% arterial)
- Splenomegaly uncommon (~10-15%)…. ?PV vs prefibrotic PMF.
- Labs: isolated thrombocytosis, normal LDH

Gangat N. et al. Blood Cancer Jnl. 2024
Loscocco G. et al. Blood Cancer Jnl. 2024

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Diagnosis Criteria (WHO, ICC)

ET	PV
Major criteria 1. Platelet count ≥ 450 × 10^9/L 2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters*; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis† 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, PMF, or other myeloid neoplasms are not met 4. *JAK2*, *CALR*, or *MPL* mutation‡ Minor criteria • Presence of a clonal marker§ or absence of evidence of reactive thrombocytosis‖	Major criteria 1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass* 2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation† 3. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia Minor criterion • Subnormal serum erythropoietin level
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criteria	The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion‡

Bone marrow biopsy is required for diagnosis.
If JAK2, red cell parameters must be scrutinized.

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Arber D, et al. Blood. 2022, Khoury J, et al. Leukemia. 2022

37

Scenarios of Diagnostic Ambiguity (ET vs other MPNs)

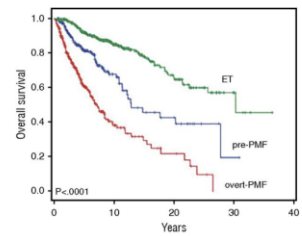
ET (JAK2) vs PV
- ET with secondary erythrocytosis (sleep apnea, smoking, lung disease, high altitude, testosterone use)

- PV with red cell parameters below WHO/ICC diagnosis cutoff (~2.6% at WCM)

ET vs CHIP

- CHIP is having a mutation without blood abnormalities or MPN. CHIP can be detected during ”reactive thrombocytosis”

ET vs prefibrotic MF



- Symptoms, Spleen size, CBC, LDH, and most importantly Marrow biopsy help.

Guglielmelli et al. Blood 2017.

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MANAGEMENT OF ET

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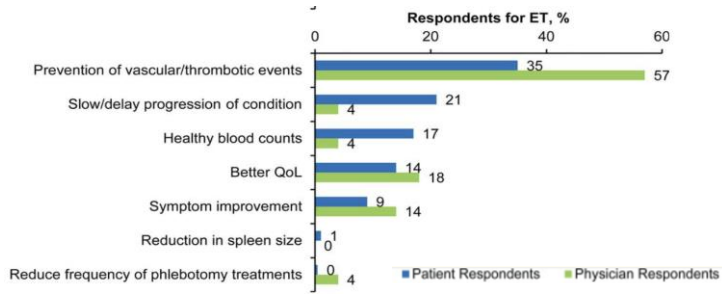
ET Goals of Treatment

- Improve symptoms/ QoL (~40% of patients report moderate to severe ET symptoms)
- Reduce thrombosis and bleeding risks
- ? Reduce risk of progression
- ? Improve OS



Mesa R, et al. Cancer 2016

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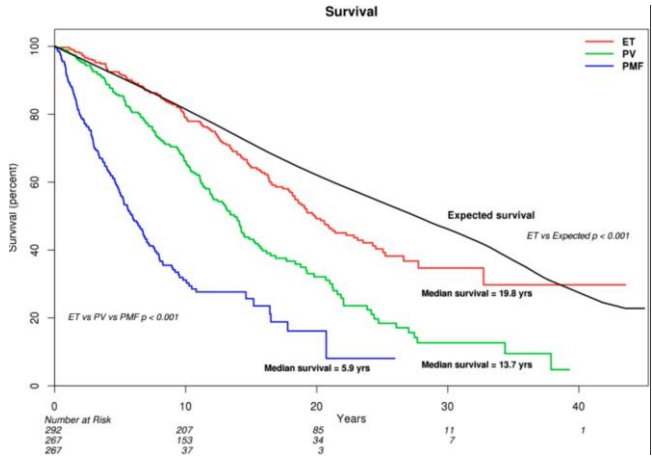
ET Prognosis – Overall Survival (OS) Shortened Compared to Control Population



Leading causes of death:
- Thrombosis/ cardiovascular
- Progression to MF/MDS/AML
- Second cancers

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Tefferi A, et al. Blood 2014

41

ET Prognosis: ET Molecular Subtypes Have Different Outcomes

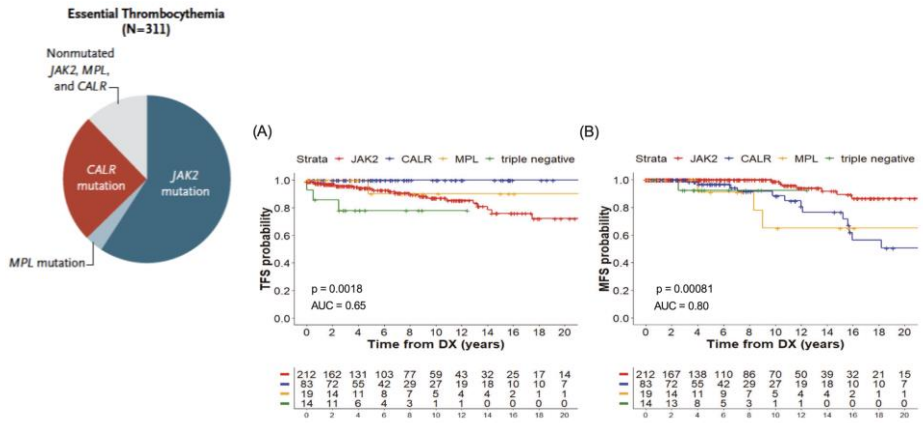

Fig. 1 Thrombosis-free (TFS) and myelofibrosis-free survival (MFS) by driver mutation. A TFS of ET patients stratified by driver n
B MFS of ET patients stratified by driver mutation.

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Klampfl T. et al. NEJM 2013
Abu-Zeinah G, et al. Blood Cancer Jnl. 2024

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ET Management: Thrombosis Prevention is Risk-Adapted (but low risk ≠ no risk)

- **Revised IPSET-Thrombosis risk factors:**
- **Age (1 point)**
- **Thrombosis history (2 points)**
- ***JAK2V617F* (2 points)**
- **CV comorbidities (1 point)**

Risk Group	>60 yrs	Clots	JAK2.V617F	Clot Risk/yr
Very Low Risk	N	N	N	0.44-1.1%
Low Risk	N	N	Y	1.4-1.6%
Intermediate Risk	Y	N	N	1.6-2.6%
High Risk	Y+JAK2	or Y	Y/N	2.4-4.2%

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Barbui T. et al. Blood Cancer Jnl 2015.

43

ET Management (Thrombosis Prevention): Very Low, Low, Intermediate Risk

- **Manage CV risk factors for all**
- **Aspirin for all except asymptomatic very-low-risk/ non-JAK2 or if contraindicated**
- **Cytoreductive therapy for some (eg symptomatic patients)**

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ET Management (Focus on Thrombosis): High-Risk

- **Manage CV risk factors for all**
- **Anticoagulation long-term versus aspirin must be discussed for all patients.**
- **Cytoreductive therapy for most (1st line HU versus IFN, 2nd line ANA, ?RUX)**

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ET Cytoreductive Treatment

- Limited RCT evidence in ET
- MPD-RC 112 (HU versus IFN 1st line): included high-risk ET and PV (heterogenous population), short study duration 1-2 years. Similar short-term hematologic response.
- Ongoing trials for IFN (ropeginterferon alfa-2b) in ET (SURPASS-ET (IFN v ANA 2nd line), EXCEED ET (single-arm 1st line))
- MAJIC-ET (RUX versus BAT 2nd line). Rux was not superior, except for management of pruritic symptoms.
- Investigational agents: BETi (eg pelabrisib), LSD1 inhibitor (bomedemstat)

Mascarenhas J et al. Blood 2022
Harrison C, et al. Blood 2017.

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Conclusions

- **Diagnostic rigor** is important to distinguish ET from masked PV
- In ET and PV **Low risk ≠ No risk.** Some patients require treatment.
- Not all ET is created equal. **Treatment goals may differ between JAK2, CALR, MPL.**
- **Indications for treatment of "low-risk" ET/PV** goes beyond primary prevention of thrombosis: improving symptoms, reducing/ eliminating phlebotomy (PV), preventing progression.

Mascarenhas J et al. Blood 2022
Harrison C, et al. Blood 2017.

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THANK YOU

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MPN Rounds:
Optimizing JAK Inhibitor Therapy in Myelofibrosis

Noa Rippel, MD and Megan Metzger, MD
Hematology/Oncology Clinical Fellows, ISMMS
February 5, 2025

Icahn School of Medicine at Mount Sinai

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Outline

- **Currently-Approved JAKi in MF**
- **Management of Anemia in MF**
- **JAKi Combination Strategies**
- **Summary**

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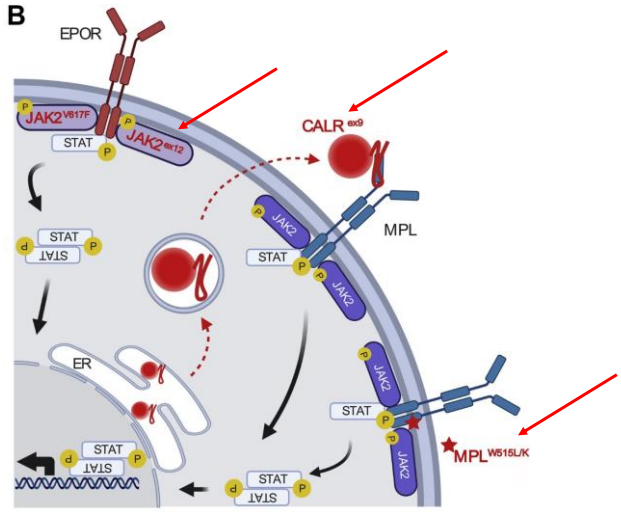
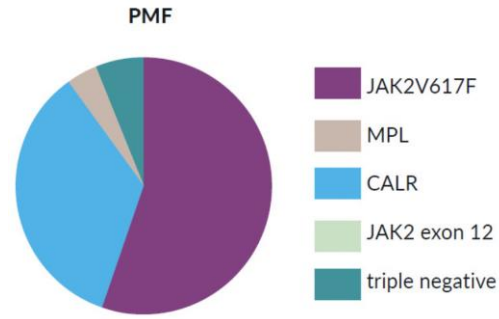
Constitutive JAK-STAT Signaling in MF

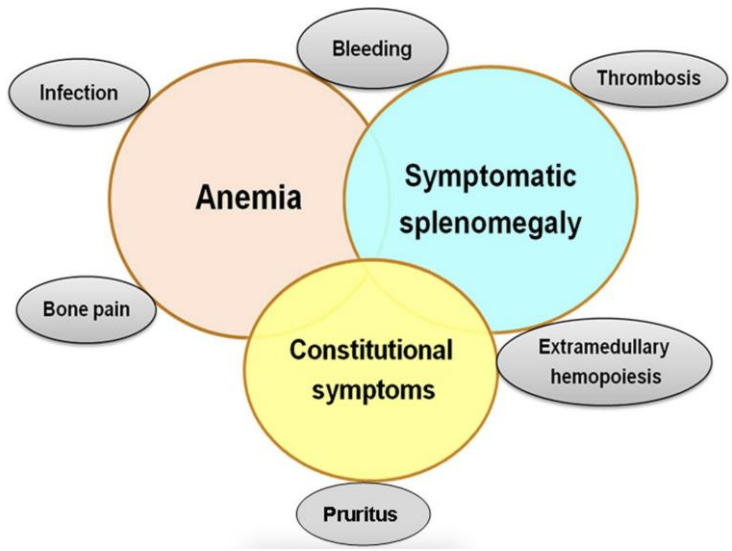




Hematol Oncol Clin North Am. 2021 Apr;35(2):217-236.

51

Clinical Presentation in MF



Blood (2014) 124 (17): 2635–2642.

52

Case #1

Mr. T is a 67 yo male who presents to your office with a year of early satiety and intermittent drenching night sweats, with a newly abnormal CBC+diff from a PCP office visit.

Studies demonstrate:

CBC+diff: WBC 13.2 x10^9/L (neutrophilic predominance, 2 immature granulocytes, 2 NRBCs, no blasts), Hgb 10.1 g/dL, plt 90K/µL

LDH: 312

Bone marrow aspiration and biopsy: megakaryocyte proliferation and atypia, reticulin fibrosis grade MF2, 1% myeloblasts, consistent with MF.

NGS: mutated CALR, SRSF2 **Karyotype**: 46, XY[20]

US abdomen: splenomegaly to 20 cm

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Primary Myelofibrosis ICC Diagnostic Criteria

Primary myelofibrosis (Overtly fibrotic stage) (*Diagnosis requires meeting all 3 major criteria and one minor criterion*)

***Major criteria*:**

1. Megakaryocyte proliferation and atypia,[a] accompanied by ≥grade 2 reticulin/collagen fibrosis[b]
2. Presence of *JAK2*, *CALR* or *MPL* mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis
3. Not meeting ICC criteria for other myeloid neoplasms

***Minor criteria*:**

Anemia not otherwise explained
Leukocytosis $\geq 11 \times 10^9/L$
Palpable splenomegaly
Increased serum lactate dehydrogenase
A leukoerythroblastic blood smear

Am J Hematol. 2023 May;98(5):801-821.

54

Molecularly Enhanced MF Risk Stratification Tools

Models	Variables	Risk categories: Very low	Low	Intermediate-1	Intermediate-2	High	Very high
MIPSS70 + v2[e]	Very high-risk karyotype[f] (4 points) Unfavorable karyotype[g] (3 points) ≥2 HMR mutations[c] (3 points) One HMR mutation[c] (2 points) Type 1/like *CALR* absent (2 points) Constitutional symptoms[a] (2 points) Severe anemia[i] (2 points) Moderate anemia[j] (1 point) Circulating blasts ≥2% (1 point)	(0 points) Not reached	(1–2 points) 16.4 years	(3–4 points) 7.7 years		(5–8 points) 4.1 years	(≥9 points) 1.8 years
DIPSS-plus[e]	Age > 65 years (1 point) Constitutional symptoms[a] (1 point) Hemoglobin <10 g/dl (1 point) Leukocytes >25 × 10(9)/L (1 point) Circulating blasts ≥1% (1 point) Unfavorable karyotype[h] (1 point) Platelet count <100 × 10(9)/L (1 point) Transfusion needs (1 point)	**NA**	(0 points) 15.4 years	(1 point) 6.5 years	(2–3 points) 2.9 years	(≥4 points) 1.3 years	**NA**

DIPSS+: Intermediate-2 risk

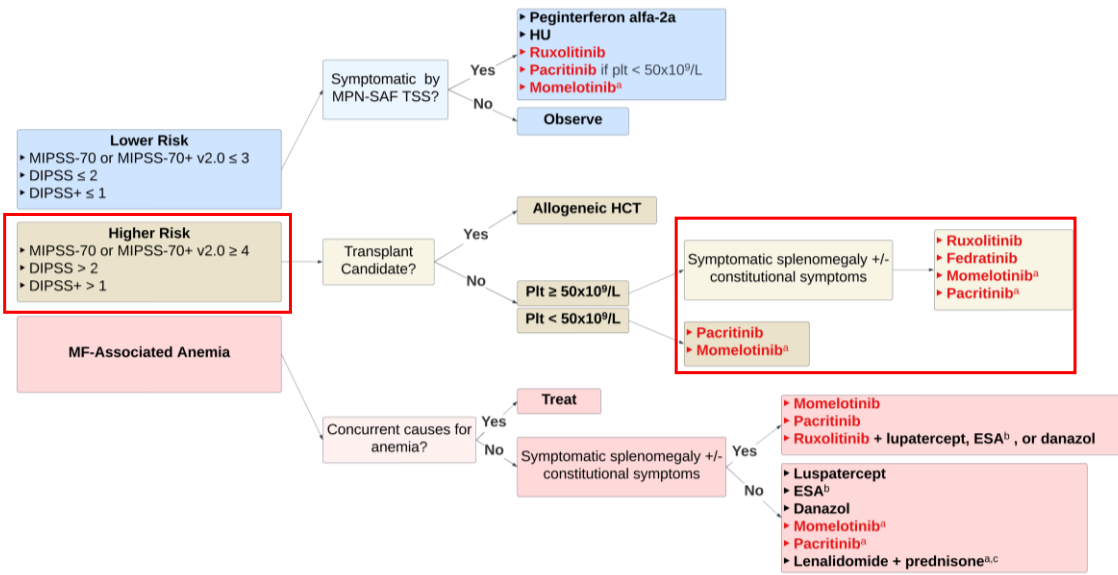
MIPSS70+ v2.0: Intermediate risk

[e] Parameters used at any time in the clinical course
[c] HMR for MIPSSv2 and GIPSS include *ASXL1*. *SRSF2* and *U2AF1*Q157

Am J Hematol. 2023 May;98(5):801-821.

55

Myelofibrosis – SOC Therapies



Expert Opin Pharmacother . 2024 Jun;25(9):1175-1186.

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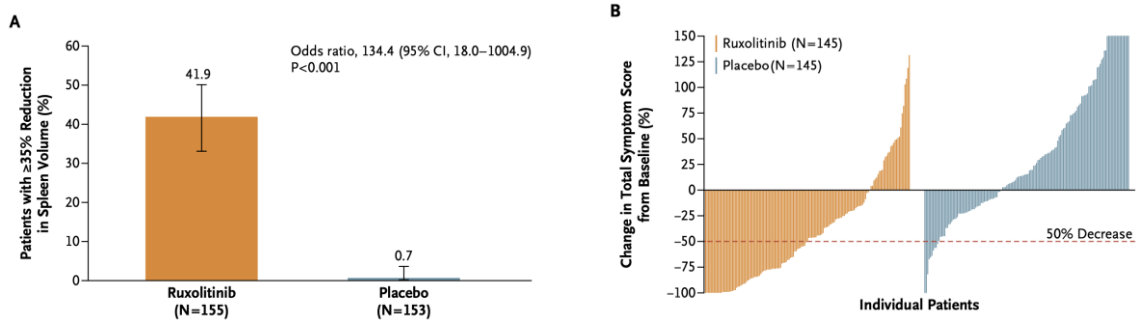
COMFORT-I:
Phase III Trial of RUX vs. Placebo in Int-2/HR MF

- Primary endpoint: Spleen volume reduction ≥ 35% (SVR35) at 24 weeks

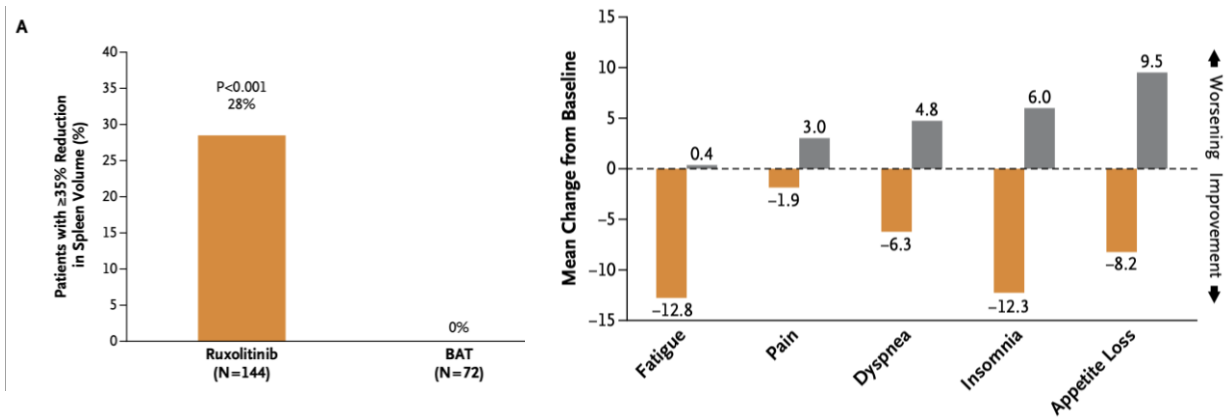


- RUX-induced reduction in spleen size (SVR35) and symptom burden (TSS50)

N Engl J Med. 2012 Mar 1;366(9):799-807.

57

COMFORT-II:
Phase III Trial of RUX vs. BAT in Int-2/HR MF



- RUX superior to BAT in spleen and symptom responses

N Engl J Med . 2012 Mar 1;366(9):787-98.

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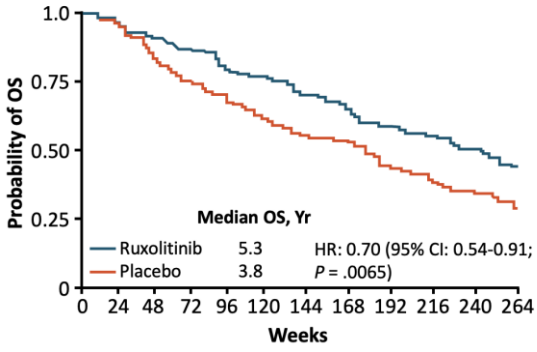
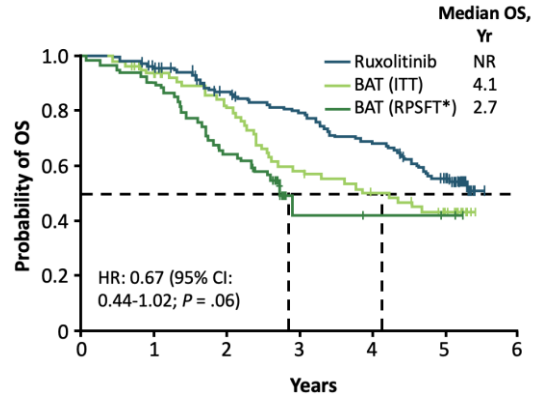
5-Year OS in COMFORT Trials

COMFORT-I:



- Significantly prolonged OS with RUX, despite crossover

COMFORT-II:

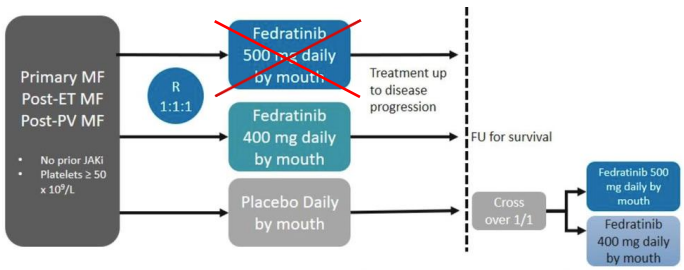


- Nonsignificantly prolonged OS with RUX compared to BAT

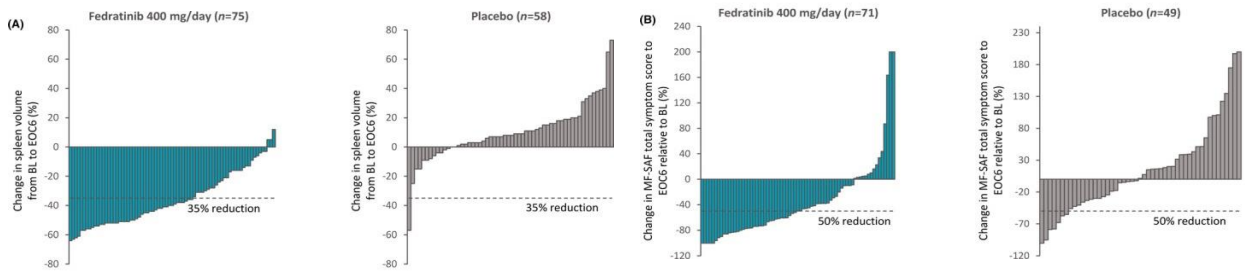
1) *J Hematol Oncol*. 2017 Feb 22;10:55. 2) *Leukemia*. 2016 Aug;30(8):1701-7.

59

JAKARTA: Phase III Study of Upfront FED in Int-2/HR MF



- Selective JAK2i
- Superior SVR35 and TSS50 vs. placebo
- Safety signal: Wernicke encephalopathy



SVR35 at W24: 36% vs. 1%, p<0.001

TSS50 at W24: 36% vs. 7%, p<0.001

1) *JAMA Oncol*. 2015 Aug;1(5):643-51. 2) *Br J Haematol* . 2021 Oct;195(2):244-248.

60

JAKARTA-2: Phase II Study of FED in RUX Intolerant/Resistant Int-2/HR MF

- Age ≥ 18 years
- Intermediate-2 or high-risk status[b,c]:
  - Primary MF
  - Post-PV MF
  - Post-ET MF
- Platelet count ≥ 50 × 10^9/L
- Received RUX for ≥ 14 days
- Discontinued RUX ≥ 14 days prior to starting fedratinib

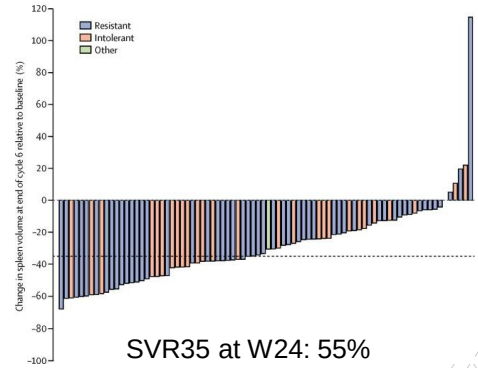
→ **Fedratinib once daily**
Starting dose 400 mg
Consecutive 4-week cycles

Investigator assessment

RUX resistant | **RUX intolerant**

Classification made by treating physician

- Effective in reducing splenomegaly and symptom burden



SVR35 at W24: 55%

Am J Hematol . 2020 Jun;95(6):594-603.

61

PERSIST-1: Phase III Study of PAC vs. BAT (excluding JAK2i) in Int-/HR MF with ANY Platelet Count

Key Eligibility Criteria
- Primary/ secondary MF
- No exclusion for baseline PLT
- No prior JAK2 inhibitors allowed

R 2:1

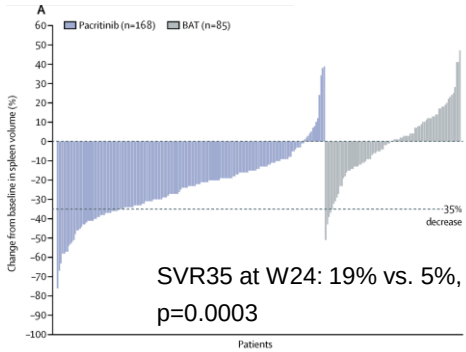
- PAC 400 mg daily
- BAT (excluding RUX)

N = 327

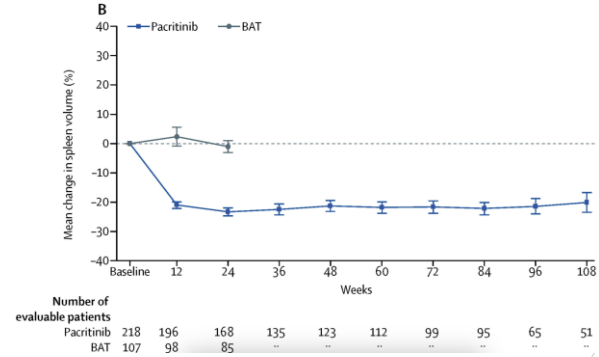
Primary Endpoint (week 24)
- % of patients achieving ≥ 35% SVR

Secondary Endpoint
- % of patients achieving ≥ 50% reduction in TSS

- JAK2/IRAK1/ACVR1/FLT3 inhibitor
- Superior SVR35 vs. BAT (exc. JAK2i)



SVR35 at W24: 19% vs. 5%, p=0.0003



Lancet Haematol. 2017 May;4(5):e225-e236.

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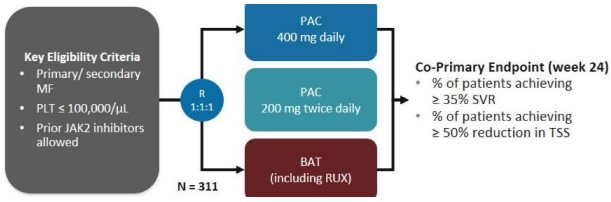
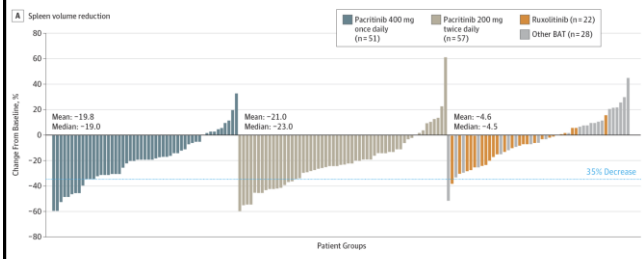
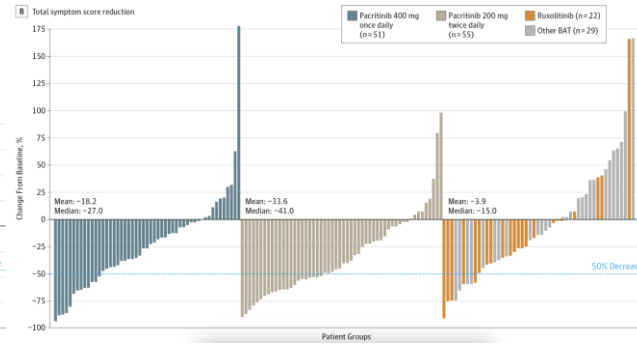
PERSIST-2: Phase III Study of PAC vs BAT in Thrombocytopenic Int-/HR MF



- Superior SVR35 and TSS50 of PAC 200 mg BID vs. BAT





SVR35 at W24:

22% (PAC 200 BID) vs 3% (BAT), p=0.001

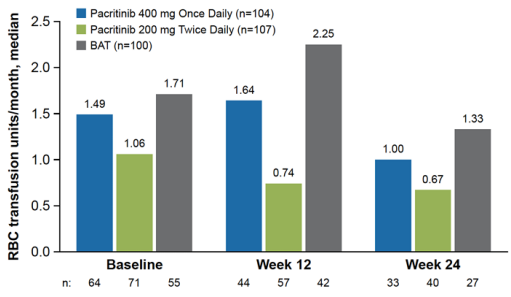
TSS50 at W24:

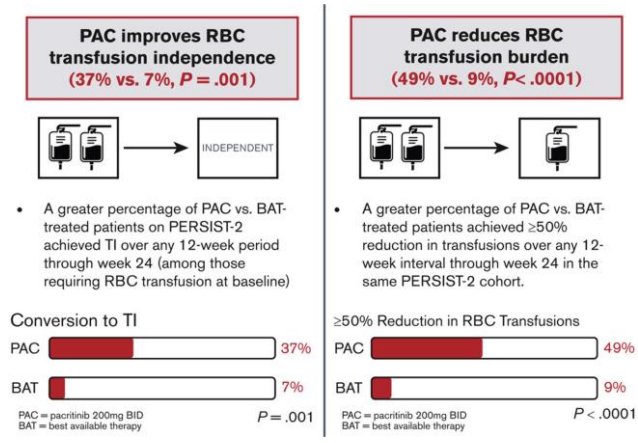
32% (PAC 200 BID) vs 14% (BAT), p=0.001

JAMA Oncol . 2018 May 1;4(5):652-659.

63

PERSIST-2 Anemia Response and Follow-Up ACVR1 Assessment





- PAC potently inhibits ACVR1
- Lower transfusion requirements in both PAC groups compared to BAT
- Clinical improvement in Hgb (≥ 2g/dL or TI ≥ 8 weeks): 25% (PAC 200 BID) vs 13% (PAC 400 daily) vs 12% (BAT)

1) *JAMA Oncol* . 2018 May 1;4(5):652-659. 2) *Blood Adv*. 2023 Oct 10;7(19):5835-5842.

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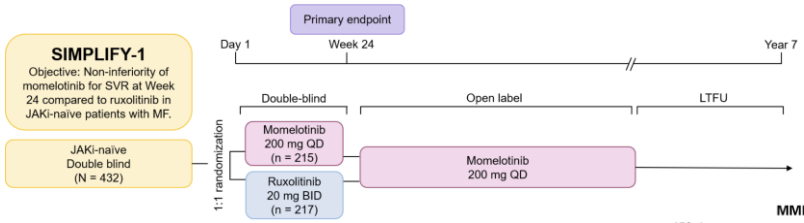
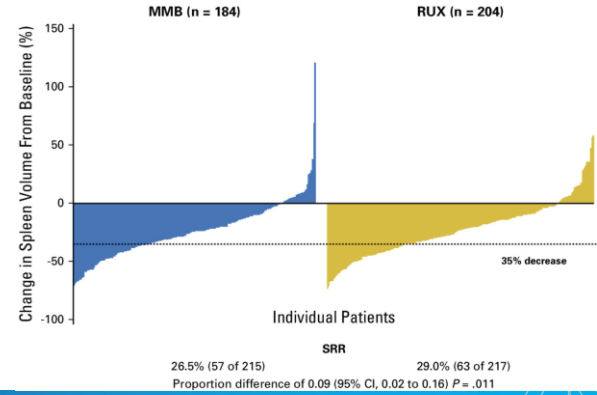
SIMPLIFY-1: Phase III Study of MMB vs RUX in Int/HR MF



- JAK1/2/3, TYK2, ACVR1 inhibitor

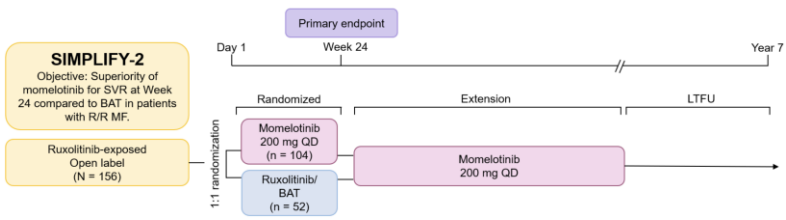
- Noninferior SVR35 at W24: 26.5% (MMB) vs 29.0% (RUX), p=0.011
- Did not demonstrate TSS50 noninferiority at W24
- TI correlated with superior 3-year OS



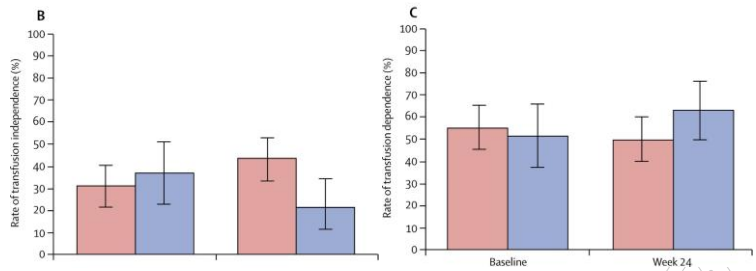
J Clin Oncol . 2017 Dec 1;35(34):3844-3850.

65

SIMPLIFY-2: Phase III Study of MMB vs. BAT in Int/HR MF



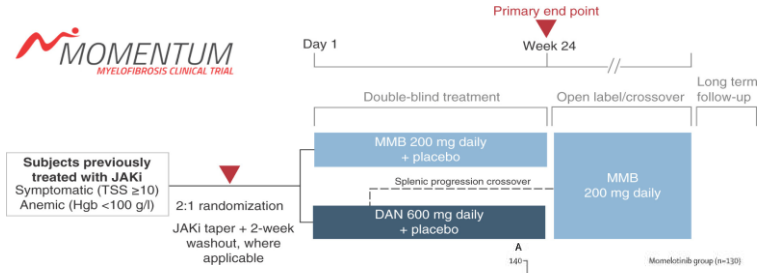
- Did not meet primary endpoint (SVR35 at W24)
- RBC transfusions until W24: 0.5 (MMB) vs 1.2 (BAT) U/month (median), p=0.39
- TI at W24: 43% vs 21%, p=0.012



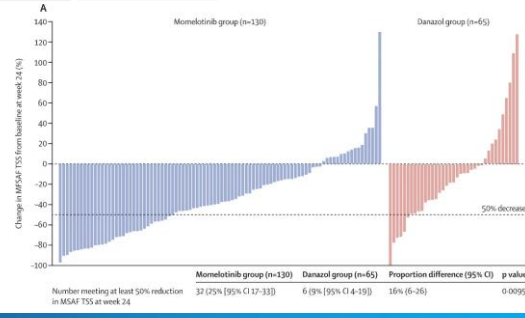
Lancet Haematol . 2018 Feb;5(2):e73-e81.

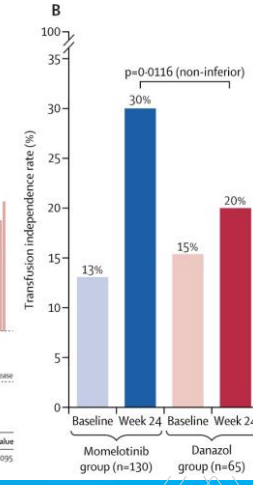
66

MOMENTUM: Phase III Study of MMB vs Danazol in Symptomatic, Anemic MF After Prior JAKi Exposure



- Superior TSS50 at W24: 25% vs 9%, p=0·0095
- Superior SVR35 at W24: 22% vs 3%, p=0·0011
- Non-inferior to danazol in achieving TI at W24





1) *Future Oncol.* 2021 Apr;17(12):1449-1458. 2) *Lancet*, 2023 Jan 28;401(10373):269-280.

67

Back to Mr. T

- Mr. T was started on ruxolitinib 10 mg PO bid. Over the subsequent year, his early satiety and night sweats resolve, and his spleen is no longer palpable.
- However, he develops a progressive decrease in energy levels and lightheadedness on rising from a seated position.
- His laboratory studies have been notable for progressive Hgb downtrend from 10s to 7s-8s, and he has required 2 pRBC transfusions over the past several months.
- An extensive anemia workup is nonrevealing, leading to your concern that his anemia may be MF-related.

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Anemia in Myelofibrosis

- Assess and treat alternate etiologies (nutritional deficiencies, bleed, hemolysis, iatrogenic)
- MF-related anemia
  - Erythropoiesis
  - Splenomegaly
  - Inflammatory cytokines

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Anemia in Myelofibrosis

Anemia + Constitutional Symptoms and/or Symptomatic Splenomegaly...	
Well-controlled on current JAKi	**Uncontrolled** on current JAKi
Clinical trial (preferred)	
JAKi combination: -add luspatercept -add ESAs if EPO < 500 mU/mL -add danazol (category 2B)	**Change to momelotinib** (preferred)
Change to momelotinib	Change to pacritinib
Change to pacritinib	JAKi combination

Am J Hematol. 2023 May;98(5):801-821.

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Case #2

Mr. S is a 59 yo male who you have been following for 10+ years for a diagnosis of JAK2^{V617F}+ polycythemia vera. He has been managed with ropegIFN alfa-2b (besremi) for several years with occasional therapeutic phlebotomies (~4 per year).

For the past several months, he has complained of debilitating fatigue, early satiety, and abdominal bloating. He has not required TP in >8 months

CBC+diff: WBC 17.9 x10^{9}/L (neutrophilic predominance, 2 immature granulocytes, 2 NRBCs, no blasts), Hgb 13.5 g/dL, Hct 41.5%, plt 140K/µL (labs 6 months ago: WBC ~12, Hct ~45%, plts ~450)

LDH: 450

Bone marrow aspiration and biopsy: progression to myelofibrosis with reticulin fibrosis grade MF2, 1% myeloblasts

NGS: JAK2^{V617F} **Karyotype**: 46, XY[20]

Physical exam: palpable splenomegaly to 6cm below the left costal margin

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Limitations of Current MF Therapeutic Landscape

- JAKi provide marked symptomatic benefit, but lack significant disease-modifying potential
- Most patients ultimately experience RUX failure → limited alternate options and poor subsequent outcomes

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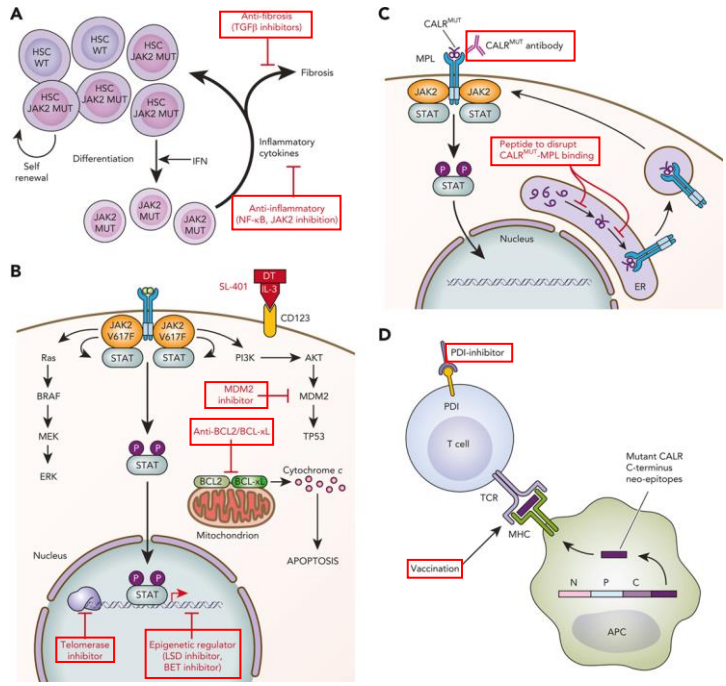
Novel MF Therapeutic Targets & Combination Therapy



Blood. 2023; 141 (16): 1922–1933.

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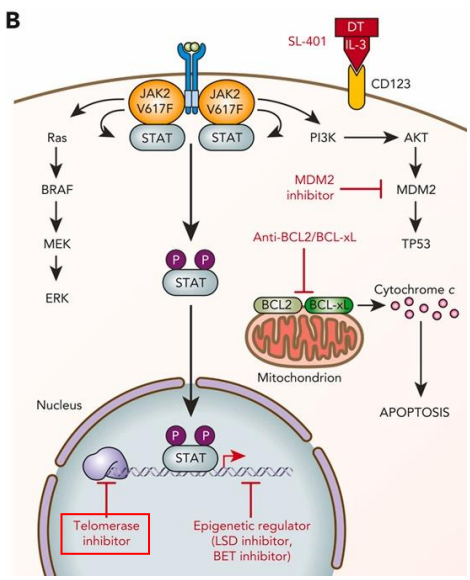
Imetelstat



- Telomerase inhibitor
- Induces apoptosis of MF malignant stem cells, but not normal stem/progenitor cells
- Suggestion of disease-modifying activity
  - Reversal of bone marrow fibrosis
  - Induction of morphologic and molecular remissions

1) Mol Cell. 2006 Feb 3;21(3):307-15. 2) *Blood Adv.* 2018 Sep 21;2(18):2378–2388.

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Clinical Studies of Imetelstat

- **IMbark**—phase II, imetelstat in MF R/R to JAKi
  - W24 SVR35 10.2%, TSS50 32.3%
  - Driver mutation VAF reduction ≥ 25% in 42.1% (imetelstat 9.4 mg/kg)
  - Spleen, symptom, and BMF responses greater in those who achieved ≥ 20% VAF reduction
  - Grade ≥ 3 TEAEs: thrombocytopenia (41%), anemia (39%), neutropenia (32%)

- **IMpactMF**—phase III, imetelstat vs. BAT in int-2/high-risk MF R/R to JAKi
  - First to evaluate **OS as primary endpoint** in R/R MF

- **IMproveMF**—phase I/Ib, imetelstat + RUX in int-1 to high-risk MF

1) *Blood* (2021) 138 (Supplement 1): 3581. 2) *Hemasphere*. 2023 Aug 8;7(Suppl):e72578ff. 3) *Blood*. 2021;138 (Supplement 1): 3581. 4) *Hemasphere*. 2023 Aug 8;7(Suppl):e72578ff.

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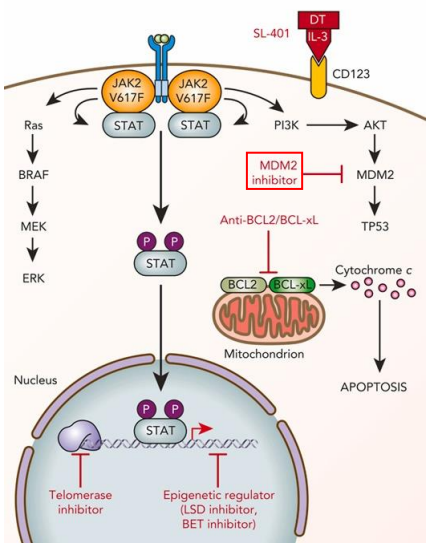
Navtemadlin



- First-in-class oral MDM2 inhibitor
- MDM2, a negative regulator of TP53, is overexpressed in MPN CD34+ HSCs
- MDM2 inhibition → restores TP53 function, targets MPN HSCs for apoptosis

Mol Cell. 2006 Feb 3;21(3):307-15.

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Clinical Studies of Navtemadlin

KRT-232-101—phase II, nvtm in MF R/R to JAKi

- W24 SVR35 16%, TSS50 30%
- ≥ 20% VAF reduction in 34%, complete VAF reduction in 29%
- TNFa reduction (median best decrease 41%), improved BMF ≥ 1 grade in 27%

KRT-232-109—phase Ib/II, nvtm + RUX in TP53^{wt} MF with suboptimal RUX response

- W24 SVR35 in 42%, TSS50 in 32%, VAF reduction ≥ 20% in 71%
- Grade 3/4 TEAEs: thrombocytopenia (29%), anemia (18%), nausea (7%), diarrhea (4%)

•**BOREAS**—phase II/III, nvtm vs. BAT in R/R MF

•**POEISIS**—phase III, RUX + nvtm vs. placebo in MF with suboptimal response to RUX

1) Al-Ali et al., EHA Annual Cong. Oral Abstract #S215; 2020 Jun 13. 2) *Hemasphere*. 2023 Aug 8;7(Suppl):e72578ff. 3) *Blood*. 2021;138 (Supplement 1): 3581. 4) *Hemasphere*. 2023 Aug 8;7(Suppl):e72578ff.

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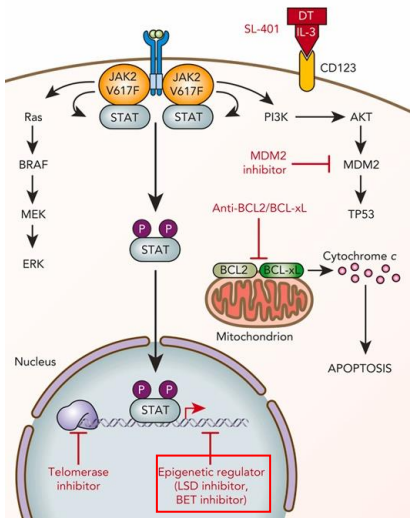
Pelabresib



- Oral BET inhibitor
- BET proteins augment expression of genes that contribute to MF pathophysiology via:
  - Cytokine upregulation → pro-inflammatory state
  - Megakaryocyte dysregulation
  - BM fibrosis

Mol Cell. 2014 Jun 5; 54(5): 728–736.

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Clinical Studies of Pelabresib

MANIFEST — phase II, pela +/- RUX in both JAKi-naïve and JAKi-exposed MF

- SVR35 at W24 68% in JAKi-naïve cohort treated with pela + RUX

MANIFEST-2 — phase III, RUX + pela vs RUX + placebo in ≥ Int-1 JAKi-naïve MF

- SVR35 at W24 (primary endpoint): 65.9% vs. 35.2%, p<0.001
- TSS50 at W24 (secondary endpoint): 52.3% vs. 46.3%, p=0.22
- Rapid **reduction in proinflammatory cytokines** and **reduction in BM fibrosis** at W24 – both greater with pela + RUX
- Notable TEAEs:
  - Anemia (43.9% vs. 54.7%)
  - Thrombocytopenia (52.8% vs. 37.4%)
  - Diarrhea (23.1% vs. 18.7%)

Future Oncol. 2022 Sep;18(27):2987-2997.

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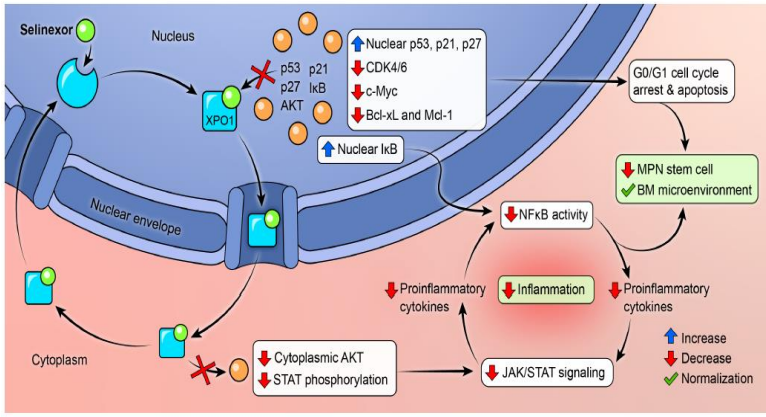
Selinexor



- Oral inhibitor of XPO1
- Broad range of XPO1 cargo proteins affects many pro-apoptotic and anti-inflammatory pathways:
  - Decreased JAK/STAT signaling
  - Nuclear localization of p53 and cell cycle arrest
  - Decreased NFkB and reduced inflammation

Blood Neoplasia. 2024 May 18 1 (2): 100010.

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Clinical Studies of Selinexor

Approved indications in MM and DLBCL

SENTRY Phase I — phase I, dose escalation of selinexor 40mg QW to 60mg QW in combination with ruxolitinib, followed by dose expansion, in JAKi-naïve MF

- Grade 3/4 TEAEs with Selinexor 60mg QW: anemia (43%), thrombocytopenia (29%), back pain (14%), neutropenia (7%)
- SVR35 at week 24: 91.7%
- SVR35 at any time: 100%

SENTRY Phase III — global, phase III, randomized, double blind trial of RUX + selinexor 60mg QW vs RUX + placebo in JAKi-naïve MF

Ali H et al, *Cancer Res*, 2023

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Back to Mr. S

- Mr. S was referred to a tertiary myeloproliferative neoplasm center.
- He has been evaluated by the bone marrow transplant team at this tertiary center and was identified as a transplant candidate. Typing of family members was initiated, however risks of transplant currently outweigh the benefits.
- He is currently being screened by the clinical trials team for JAKi-naïve trials including navtemadlin+rux and selinexor+rux.
- Plan will be to comanage this patient with his local hematologist.

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Take-Home Points

- For patients with higher risk MF:
  - If potentially transplant-eligible, refer to transplant center for preliminary evaluation
  - Utilize approved JAK inhibitors to control constitutional symptoms and/or symptomatic splenomegaly
  - Employ pacritinib and momelotinib as needed for cytopenic higher risk MF
- Refer to tertiary myeloproliferative disease center for co-management and potential clinical trial enrollment for newly diagnosed JAKi-naïve, refractory, and/or progressive disease

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Special thank you to:
Marina Kremyanskaya, MD, PhD
John Mascarenhas, MD
And the entire Myeloproliferative Disorders Program at ISMMS

Thank you!

Icahn School of Medicine at Mount Sinai

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Targeting Systemic Mastocytosis: Current and Emerging Strategies in Diagnosis Risk Stratification and Treatment.

James McCloskey, MD
Katherine Linder, MD
Sarvarinder Gill, MD

Hackensack Meridian *Health*
John Theurer Cancer Center

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Program Agenda

- Systemic Mastocytosis (SM) Overview
- Clinical Presentation and Diagnosis of SM
- Risk Stratification
- ISM and ASM Treatment Approaches
- Summary and Questions

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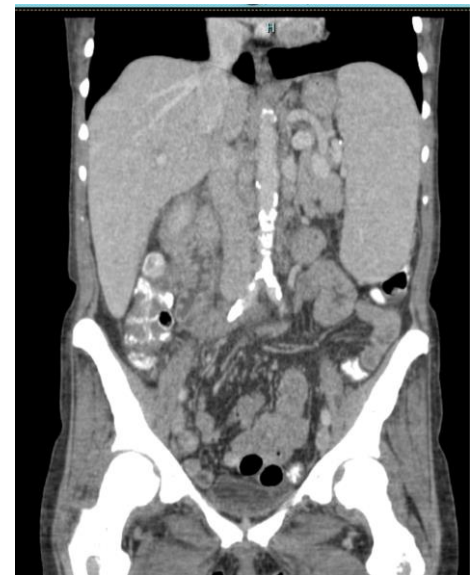
LD

- 66-year-old woman Presented to primary care with fatigue, watery diarrhea and 15 lb weight loss. PCP noted mild leukopenia (WBC 3.3). Alk Phos elevated at 300. Tumor markers negative. Referred her to GI.
- History of Tobacco use and little routine follow up
- Abd CT scan 3/5/22: Malignant disease with extensive sclerotic metastatic disease, trace ascites. Mild retroperitoneal and mesenteric adenopathy and splenic enlargement 15.5cm.
- CT chest 3/21/22: Extensive metastatic disease with a small right middle lobe lung nodule.
- PET 3/22/22: Extensive osteosclerosis with mild FDG uptake. Nonspecific uptake in a 1.3 cm caval node (1.3mm)
- Meets with local oncologist and informed she has lung cancer.



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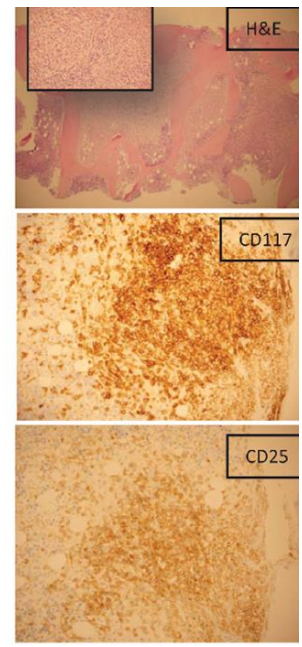
Workup Confirms SM, NOT Lung Cancer

- Bone Biopsy 3/24/22: Core containing bland spindle cell proliferation involving the marrow Cells positive for CD117, CD25,and tryptase negative for cytokeratin, AE1, E3, C2, CD20, TTF1, CDx2, PAX 9. Ki 67 low. Consistent with Systemic Mastocytosis.
- No evidence of dysplasia

- ROS: Episodic Diarrhea, weight loss, fatigue, nausea, GERD.

- Tryptase: 204
- KitD816V positive 3% by ddPCR
- NGS: KitD816V VAF: 34
  - Additional mutations in Notch (VAF:18) and TET 2 (VAF: 28)
- B findings - increased MC burden (tryptase, >30% MC and splenomegaly)
- C findings- impaired organ function due to MC infiltration-> GI symptoms (diarrhea/weight loss)



Path Courtesy of S. Veitch Ash 2023

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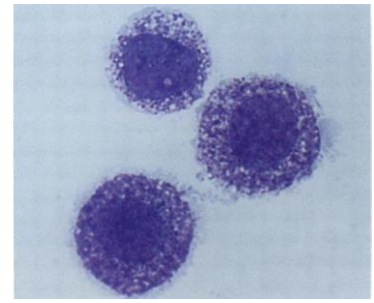
KIT Plays a Critical Role in Mast Cell Development and Activation

- Mast cells are hematopoietic cells of myeloid origin[1]
- Mast cells express KIT, a tyrosine kinase receptor[1,2]
- Normal KIT signaling drives mast cell proliferation, survival, and activation as a functioning part of our immune response
- Systemic Mastocytosis is a rare, clonal, neoplastic proliferation of mast cells[1]

- >90% of adult SM cases are driven by gain-of-function somatic mutations in the *KIT* tyrosine kinase domain[2]
- ~95% of *KIT* mutations are D816V[1]
- Additional somatic mutations are often present[2,3]
  - Most frequent: *TET2*, *SRSF2*, *ASXL1*, *RUNX1*, *JAK2*, *N/KRAS*, *CBL*, *EZH2*[3]

Activated mast cells release granules containing proinflammatory mediators[2]

Mast Cells[3]



Mast cells developed in a long-term (80-day) coculture of cord blood nucleated cells. (May-Grunwald/Giemsa staining, x3750.)

KIT, KIT proto-oncogene, receptor tyrosine kinase.
1. Metcalfe DD et al. Overview of mast cells in human biology. In: Akin C, ed. *Mastocytosis*. Cham, Switzerland: Springer Nature Switzerland AG; 2020:23-24. 2. Theoharides TC et al. *N Engl J Med*. 2015;373(2):163-172. 3. Furitsu T et al. *Proc Natl Acad Sci*. 1989;86(24):10039-10043.

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Systemic Mastocytosis is Classified as a Myeloid Neoplasm by WHO

Myeloid Neoplasms					
Mastocytosis	Myeloproliferative neoplasms (MPN)	Myeloid/lymphoid neoplasms with eosinophilia	Myelodysplastic syndromes/ myeloproliferative neoplasms (MDS/MPN)	Myelodysplastic syndrome	Myeloid neoplasms with germline predisposition

Cutaneous Mastocytosis (CM)[1]

Systemic Mastocytosis[1]

Mast Cell Sarcoma[1]

~95% of SM cases[1]

Non-Advanced SM[2]
- Indolent SM
- Smoldering SM

Advanced SM[2]
- Aggressive SM
- Mast Cell Leukemia (MCL)
- Associated Hematologic Neoplasm (AHN)

~5% of SM cases[1]

- Prevalence of systemic mastocytosis is estimated at ~1 in 10,000 adults[3]
- ISM represents the vast majority of systemic mastocytosis[3]
- Up to ~70% of patients with advanced systemic mastocytosis have an associated neoplasm[4]

ISM, indolent systemic mastocytosis; SM, systemic mastocytosis; WHO, World Health Organization.
1. Horny HP et al. Mastocytosis. In: Swerdlow SH et al, eds. *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues*. Lyon, France: International Agency for Research and Cancer (IARC);2017:62-69. 2. Sperr WR et al. *Lancet Haematol*. 2019;6(12):e638-e649. 3. Cohen SS et al. *Br J Haematol*. 2014;166(4):521-528. 4. Reiter A, et al. *Blood*. 2020;135(16):1365-1376.

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Systemic Mastocytosis is a Rare, Clonal Mast Cell Neoplasm

Patients with ISM and advanced SM may experience severe symptoms

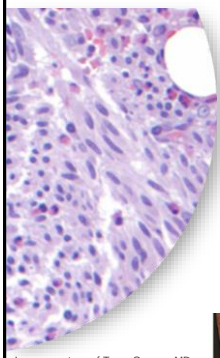
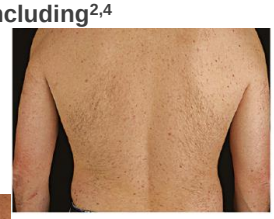
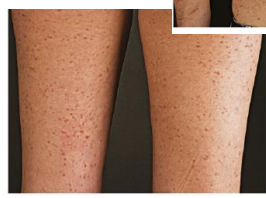


Image courtesy of Tracy George, MD, University of Utah.

The disease results in heterogenous symptoms due to infiltration of clonal mast cells in different organ systems, including[2,4]

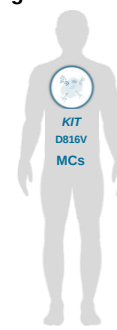




- Symptoms of SM manifest in numerous organ systems and most commonly include cutaneous, gastrointestinal, and neurocognitive symptoms, which may be **debilitating**[1–4]

SKIN
Darier's sign, **urticaria pigmentosa**, extreme flushing, pruritus

CARDIOVASCULAR
Syncope, dizziness, palpitations, hypotensive anaphylaxis



SYSTEMIC
Fatigue, malaise, weight loss

NEUROPSYCHIATRIC
Brain fog, depression, migraines, anxiety

MUSCULOSKELETAL
Bone/muscle pain, osteoporosis, osteopenia, bone fractures

GASTROINTESTINAL
Diarrhea, nausea/vomiting, abdominal pain

GI, gastrointestinal; KIT, KIT proto-oncogene, receptor tyrosine kinase; OS, overall survival; SM, systemic mastocytosis.

1. Vaes M et al. *Front Med.* 2017;4:110. 2. Jara-Acevedo M et al. *Mod Pathol.* 2015;28(8):1138-1149. 3. Garcia-Montero AC et al. Blood. 2006;108(7):2366-2372. 4. Rossignol J et al. *F1000Res*. 2019;8. 5. Hartmann K et al. *J Allergy Clin Immunol.* 2016;137(1):35-45. 6. Jennings SV et al. *Immunol Allergy Clin North Am.* 2018;38(3):505-525. 7. Lim KH et al. *Blood.* 2009;113(23):5727-5736. 8. Pardanani A. *Am J Hematol.* 2019;94(3):363-377.

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Prolonged Time to Diagnosis in Systemic Mastocytosis

Given that systemic mastocytosis is associated with nonspecific symptoms, patients may present to a diverse group of specialists leading to challenges in diagnosis[1,2]

Median time to diagnosis from symptom onset*[1]

- Before receiving diagnosis, patients with mastocytosis visited a median of 3 specialists*[1]
- ~50% consulted 3 to 6 physicians while seeking diagnosis*[1]

Patients with systemic mastocytosis face a diagnostic odyssey with a median time from symptom onset to diagnosis of ~7 years*[1]

GI, gastrointestinal; ISM, indolent systemic mastocytosis; SM, systemic mastocytosis.

Jennings SV et al. *Immunol Allergy Clin North Am.* 2018;38(3):505-525.

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Diagnostic Work-Up Includes Physical Exam and Imaging

Physical exam[1-3]

- Complete medical history
- Full-body skin exam (including Darier's sign)
- Palpation for hepatomegaly, splenomegaly, or lymphadenopathy

Imaging (when appropriate)[1,3]

- CT or ultrasound to look for enlarged liver, spleen, or lymph nodes
- Bone densitometry (DEXA scan)
- Skeletal x-ray or nuclear medicine bone scan
- Endoscopy/colonoscopy

CT, computed tomography; DEXA, dual-energy x-ray absorptiometry.
1. Arock M et al. *Leukemia.* 2015;29(6):1223-1232. 2. Theoharides TC et al. *N Engl J Med.* 2015;373(2):163-172. 3. The Mastocytosis Society. Tests. https://tmsforacure.org/tests/. Accessed July 6, 2021.

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Analysis of D816V Mutation in Peripheral Blood is Useful in Screening for SM

Peripheral blood can be used for initial screening, but thorough analysis of *KIT* mutational status should include bone marrow evaluation[1]

Test result in peripheral blood[1,2]

- *KIT* D816V detected*
- *KIT* D816V *not* detected in a patient with high suspicion of SM

→ **Perform detailed *KIT* mutational analysis on bone marrow**

High-sensitivity assays (<0.1%) are recommended for detection of *KIT* D816V in bone marrow[1,2,3]

*Following a positive test on peripheral blood, *KIT* mutational analysis may also be performed on the bone marrow aspirate.[3]
KIT, KIT proto-oncogene, receptor tyrosine kinase; SM, systemic mastocytosis.
1. Arock M et al. *Leukemia.* 2015;29(6):1223-1232. 2. Akin C et al. Anaphylaxis in mastocytosis. In: Akin C, ed. *Mastocytosis*. Cham, Switzerland: Springer Nature Switzerland AG; 2020:23-34. 3. Kristensen T et al. *Eur J Haematol.* 2016;96(4):381-388.

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WHO Criteria are Used to Diagnose Systemic Mastocytosis

Diagnosis of systemic mastocytosis per WHO criteria requires major and ≥1 minor criterion *OR* ≥3 minor criteria

Major criterion

Multifocal dense mast cells infiltrates (≥15 mast cells in aggregates) are detected in sections of bone marrow and/or sections of other extracutaneous organ(s)

Minor criteria

In bone marrow biopsy sections or biopsy sections from other extracutaneous organs, >25% of the mast cells in the infiltrate appear spindle-shaped or have atypical morphologic features; or >25% of all mast cells in bone marrow aspirate smears are immature or have atypical features

Presence of an activating point mutation in *KIT* at codon 816 in bone marrow, blood, or another extracutaneous organ

Mast cells in bone marrow, blood, or other extracutaneous organs express CD25 ± expression of CD2 in addition to normal mast cell markers*

Serum total tryptase persistently >20 ng/mL (if the patient has an associated myeloid neoplasm, this parameter is not valid)

*Normal median tryptase level in the healthy population is 5 ng/mL. †Elevated tryptase levels can also be observed in patients with hereditary alpha-tryptasemia without mastocytosis. ‡Unless there is an associated myeloid neoplasm, in which case this parameter is not valid.
KIT, KIT proto-oncogene, receptor tyrosine kinase; WHO, world health organization.
1. Theoharides TC et al. *N Engl J Med*. 2015;373(2):163-172. 2. Akin C, Valent P. *Immunol Allergy Clin North Am*. 2014;34(2):207-218. 3. Lyons JJ et al. *Nat Genet*. 2016;48(12):1564-1569. 4. Horny HP et al. Mastocytosis. In: Swerdlow SH et al, eds. *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues*. Lyon, France: International Agency for Research and Cancer (IARC);2017:62-69.

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Diagnostic Work-Up for a Suspected SM

KIT D816V Mutation testing

- If diagnosis of SM is suspected
- highly sensitive assay such as ASO-qPCR or ddPCR on the peripheral blood to detect *KIT* D816V
  - Full *KIT* sequencing recommended if D816V negative, other alterations in *KIT* are rare[1]

Pathology/biochemical testing[1]

- CBC and chemistry profile
- Serum tryptase, LDH, albumin, calcium, and ALP
- Tissue biopsy (eg. bone marrow) with phenotyping of mast cells by IHC and/or flow cytometry

*In combination with measurement of the serum tryptase level and evaluation of clinical signs and/or symptoms suggestive of SM-related organ involvement.
ALP, alkaline phosphatase; ASO-qPCR, allele-specific oligonucleotide-quantitative PCR; CBC, complete blood count; ddPCR, droplet digital PCR; IHC, immunohistochemistry; KIT, KIT proto-oncogene, receptor tyrosine kinase; LDH, lactic acid dehydrogenase;.
1.Arock M et al. *Leukemia*. 2015;29(6):1223-1232. 3. Lyons JJ et al. *Nat Genet*. 2016;48(12):1564-1569. 4. Akin C et al. Anaphylaxis in mastocytosis. In: Akin C, ed. *Mastocytosis*. Cham, Switzerland: Springer Nature Switzerland AG; 2020:23-34.

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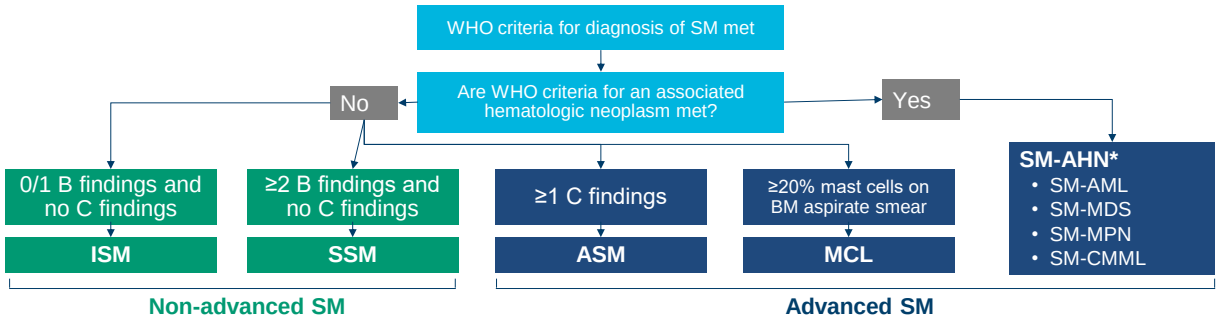
Overview of SM Subtyping



B findings[4]

- **>30% infiltration by mast cells** (focal, dense aggregates) in marrow and/or serum tryptase level >200 ng/mL
- Signs of **dysplasia or myeloproliferation** in non-mast cell lineage(s) with normal or slightly abnormal blood counts
- **Hepatomegaly** without impairment of liver function, and/or palpable **splenomegaly** without hypersplenism, and/or **lymphadenopathy** on palpitation or imaging

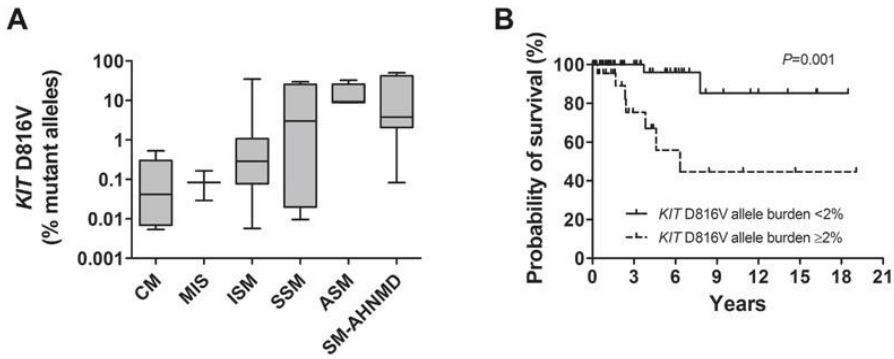
C findings[4]

- Bone marrow dysfunction manifested by **≥1 cytopenia(s)** (ANC <1.0 × 10^9/L, Hgb <10 g/dL, or platelets <100 × 10^9/L)
- Palpable **hepatomegaly with impairment** of liver function, ascites, and/or portal hypertension
- Palpable **splenomegaly with hypersplenism**
- Malabsorption with **weight loss due to gastrointestinal mast cell infiltrates**
- Skeletal involvement with **large osteolytic lesions and/or pathologic fractures**

*Not an exhaustive list.
AML, acute myeloid leukemia; ANC, absolute neutrophil count; ASM, aggressive SM; BM, bone marrow; CMML, chronic myelomonocytic leukemia; Hgb, hemoglobin; ISM, indolent SM; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; SM, systemic mastocytosis; SSM, smoldering SM; WHO, World Health Organization.
1. Mannelli F. *Ann Hematol.* 2021;100(2):337-344. 2. Nicolisi M, et al. *Medicina (Kaunas).* 2021;57(11):1135. 3. Sperr WR, et al. *Lancet Haematol.* 2019;6(12):e638-e649. 4. Vaes M, et al. *Front Med (Lausanne).* 2017;4:110.

97

Attempts at Risk Stratification: KIT VAF Predicts WHO Subtype and Survival



***KIT* D816V allele burden in different WHO-subtype of mastocytosis and its impact on survival.**(A) Highly significant differences in the *KIT* D816V allele burden were found between patients with cutaneous mastocytosis (CM), mastocytosis in the skin (MIS), indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), aggressive systemic mastocytosis (ASM), mast cell leukemia (MCL), and systemic mastocytosis with an associated hematologic non-mast cell lineage disease (SM-AHNMD) (P<0.001, Kruskal Wallis test). (B) Kaplan-Meier plot for overall survival of mastocytosis patients with a *KIT* D816V mutation burden <2% and patients with a *KIT* D816V burden of ≥ 2% at diagnosis. The difference in the probability of survival was significant (P=0.001).

Hoerman et al. Allergy. 2016

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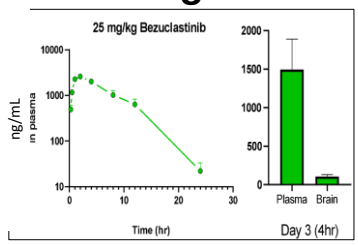
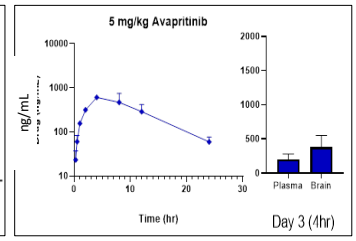
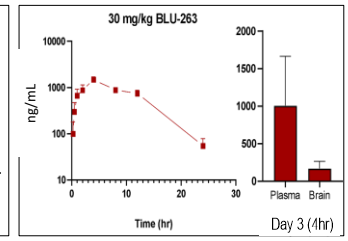
Three New Targeted TKI





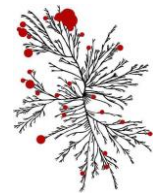
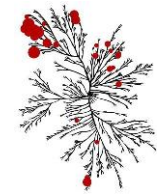


$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
7	2592 ± 364	21509 ± 2558	**0.07**

$t_{1/2}$ (h)	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
13	672 ± 102	6980 ± 1156	**2.0**

$t_{1/2}$ (h) s	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	Brain:Plasma ratio
4	1470 ± 222	16200 ± 414	**0.18**

Selectivity profiles of KIT D816V inhibitors in clinical development or approved for systemic mastocytosis

Drug:	Elenestinib	Avapritinib	Bezuclastinib
Kinome tree[a]:			
Selectivity S-score: (fraction of kinome bound by drug, more selective = lower s-score)	0.035	0.035	0.057
	First in human 2020, investigational	First in human Oct 2015, approved	First in human Mar 2015, investigational

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.
IC_{50}, half-maximal inhibitory concentration; QD, once daily; WT, wild-type. 1. Dave N et al. Presented at AACR 2021. Poster #CT122; 2. Castells M et al. Presented at EHA 2022. Poster #1017

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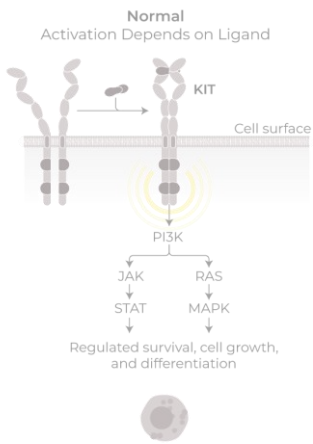
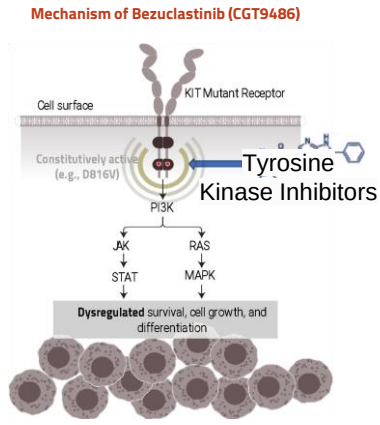
Systemic Mastocytosis (SM): Primarily Driven by KIT Exon 17 D816V Mutations





KIT exon 17 D816V mutation is detected in >95% of SM patients[1]

- Occurs within the activation loop domain and causes a conformational change in the enzymatic pocket of the receptor
- This conformational change results in ligand independent constitutive activation of KIT and leads to increased proliferation

Inhibition of KIT exon 17 mutations has shown clinical activity in both AdvSM and NonAdvSM

[1] Garcia-Montero et al. 2006; Jara-Acevedo et al. 2015; Vaes et al. 2017

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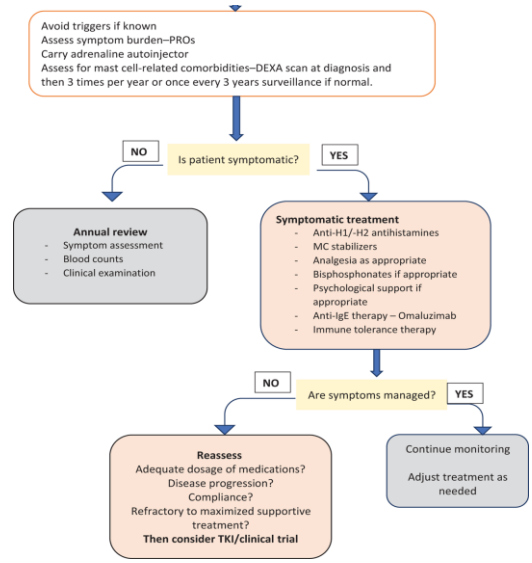
Management: Non-Advanced SM

ISM and SM



Scott Veitch,Deepti H. Radia, Mastocytosis demystified, Hematology Am Soc Hematol Educ Program, 2023, Figure 3.

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1248

Results from PIONEER: a randomized, double-blind, placebo-controlled, phase 2 study of avapritinib in patients with indolent systemic mastocytosis

Cem Akin[1], Hanneke Oude Elberink[2], Jason Gotlib[3], Vito Sabato[4], Karin Hartmann[5], Sigurd Broesby-Olsen[6], Mariana Castells[7], Tsewang Tashi[8], Mark L. Heaney[9], Tracy I. George[10], Frank Siebenhaar[11], Deepti H. Radia[12], Massimo Triggiani[13], Paul van Daele[14], Daniel J. DeAngelo[15], Oleg Schmidt-Kittler[16], Hui-Min Lin[16], Andrew Morrison[16], Brenton G. Mar[16], Marcus Maurer[11]

[1]University of Michigan, Ann Arbor, Michigan, USA; [2]University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [3]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, California, USA; [4]University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; [5]University of Basel, Basel, Switzerland; [6]Odense University Hospital, Odense, Denmark; [7]Brigham and Women's Hospital, Boston, Massachusetts, USA; [8]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA; [9]Columbia University Medical Center, New York, New York, USA; [10]ARUP Laboratories, University of Utah, Salt Lake City, Utah, USA; [11]Dermatological Allergology, Department of Dermatology and Allergy, Charité - Universitätsmedizin Berlin, Germany; [12]Guy's and St Thomas' NHS Foundation Trust, London, UK; [13]University of Salerno, Salerno, Italy; [14]Erasmus Medical Center, Rotterdam, Netherlands; [15]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [16]Blueprint Medicines Corporation, Cambridge, Massachusetts, USA

Corresponding author: cemakin@med.umich.edu

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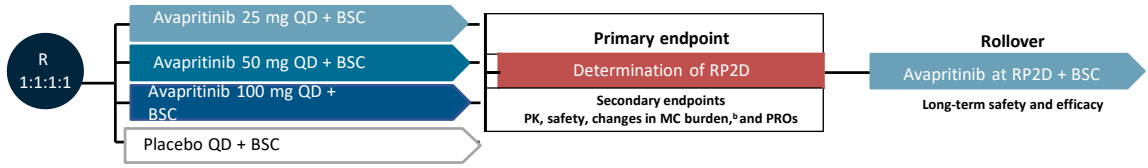
PIONEER Phase 2- avapritinib is Superior to Placebo for ISM with Uncontrolled Symptoms

Key eligibility criteria

- Indolent SM
- Moderate-to-severe symptoms[a] despite ≥2 BSC medications



- PIONEER part 2 assessed the safety and efficacy of avapritinib RP2D[1]
- ISM-SAF for indolent SM[2]

[a]Based on minimum mean TSS over the 14-day eligibility screening period. [b]Measured by reduction of serum tryptase, peripheral blood *KIT* D816V allele fraction and BM MCs.
BM, bone marrow; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PK, pharmacokinetics; PRO, patient reported outcome; QD, once daily; R, randomize; RP2D, recommended phase 2 dose; TSS, total symptom score; WHO, World Health Organization.
1. Akin C et al. Presented at the 62nd American Society of Hematology Annual Meeting. December 5–8, 2020. Abstract 1247; 2. Shields A et al. *Value Health.* 2019;22 (suppl 3):S867–868.

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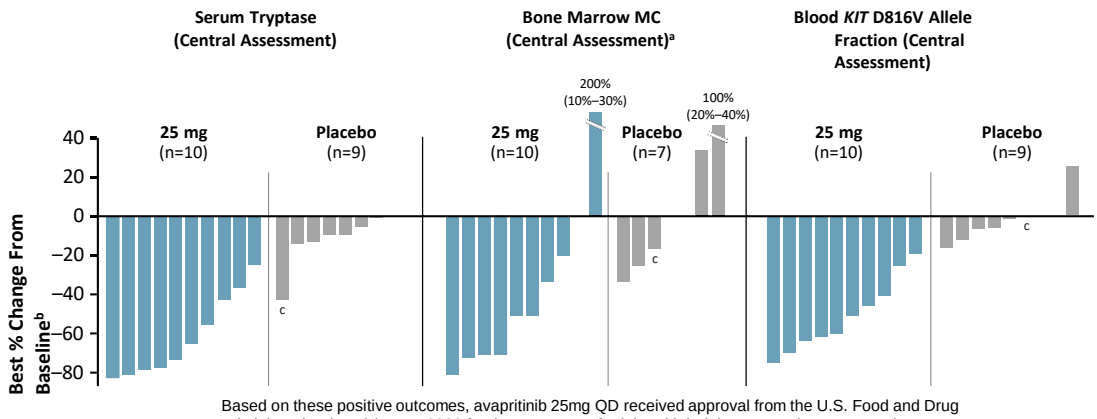
Avapritinib at 25 mg QD Improved Objective Measures of MC Burden, Tryptase and KIT D816V VAF



Based on these positive outcomes, avapritinib 25mg QD received approval from the U.S. Food and Drug Administration (FDA) in May 2023 for the treatment of adults with indolent systemic mastocytosis.

Based on data cut-off date of December 27, 2019

[a]Bone marrow MC assessment in SM may have variability in sampling due to patchy nature of disease. No patient on study has progressed to advanced disease; [b]Serum tryptase assessments at Weeks 1, 2, 3, 4 and every 4 weeks thereafter; bone marrow assessment at Week 12; mutation burden assessments at Weeks 2 and 4 and every 4 weeks thereafter; [c]Patient received high dose intravenous steroids.
Shields A et al. Value Health. 2019;22 (suppl 3):S867–868.

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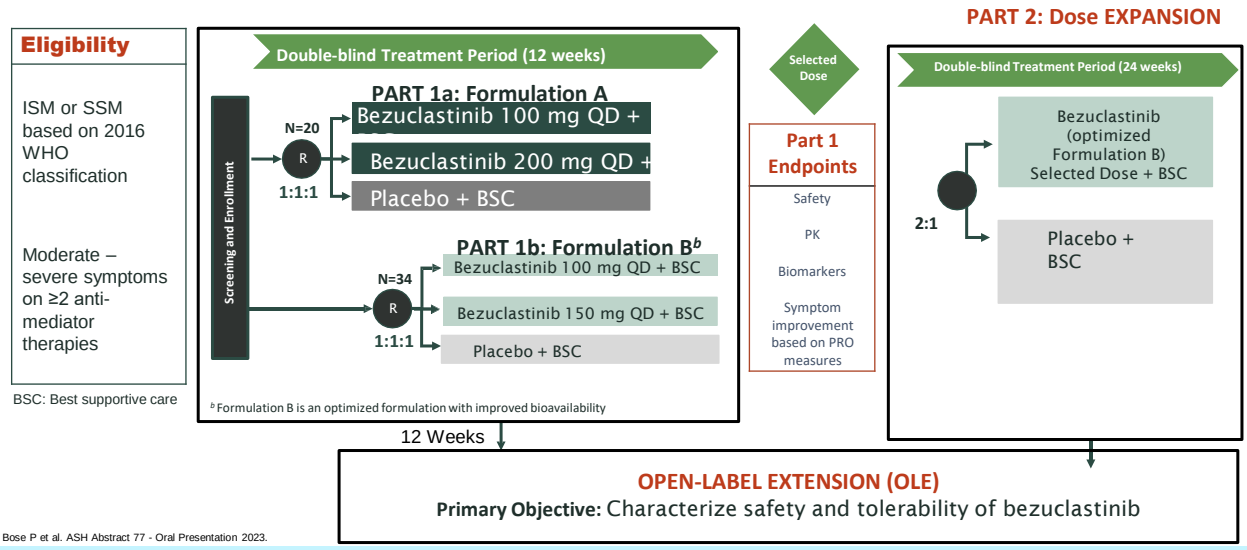
Summit: Phase 2 Clinical Study Evaluating Bezuclastinib in NonAdvSM

PART 1: DOSE OPTIMIZATION



Bose P et al. ASH Abstract 77 - Oral Presentation 2023.

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Summit Part 1a Enrolled Highly Symptomatic SM Patients with Moderate to Severe Disease

Patient Demographics	All patients (N=20)
Female, n (%)	15 (75)
Median Age in years, n (range)	50.5 (38 – 75)
ECOG PS, n (%)	
0	3 (15)
1	15 (75)
2	2 (10)
Clinical Characteristics	**All patients (N=20)**
NonAdv Subtype per PI, n (%)	
Indolent SM (ISM)	18 (90)
Smoldering SM (SSM)	2 (10)
Median (range) MAS Total Score at Eligibility	45.56 (26.3 – 71.6)
Mast Cell Burden	**All patients (N=20)**
KIT D816V in Whole Blood, Positive, n (%)	15 (75)
Median KIT D816V VAF, % (range)	0.49 (0 – 32.48)
Median Bone Marrow MC Burden, % (range)	22.5 (1 – 80)
Median Serum Tryptase, ng/mL (range)	74.35 (10.2- 592.0)
<20 ng/mL, n (%)	3 (15)
≥20 ng/mL, n (%)	17 (85)

SM Therapy	All patients (N=20)
Prior avapritinib, n (%)	1 (5.0)
Baseline Supportive Care Medications, Median (range)	3 (2-7)
H1 blockers, n (%)	19 (95)
H2 blockers, n (%)	18 (90)
Leukotriene receptor antagonists, n (%)	8 (40)
Proton pump inhibitors, n (%)	7 (35)
Cromolyn sodium, n (%)	4 (20)
Omalizumab, n (%)	3 (15)
Corticosteroids, n (%)	1 (5)
Patient Disposition	**All patients (N=20)**
Months on Study (Part 1a + OLE), median (range)	7.03 (2.8 – 16.0)
Completed Part 1a, n (%)	20 (100)
On Study as of Data Cut-off, n (%)	18 (90)
Discontinued study, n (%)	2 (10)
AE, n (%)	1 (5)
Patient Decision, n (%)	1 (5)

As of Data Cut-off of 25-Oct-2023

Bose P et al. ASH Abstract 77 - Oral Presentation 2023.

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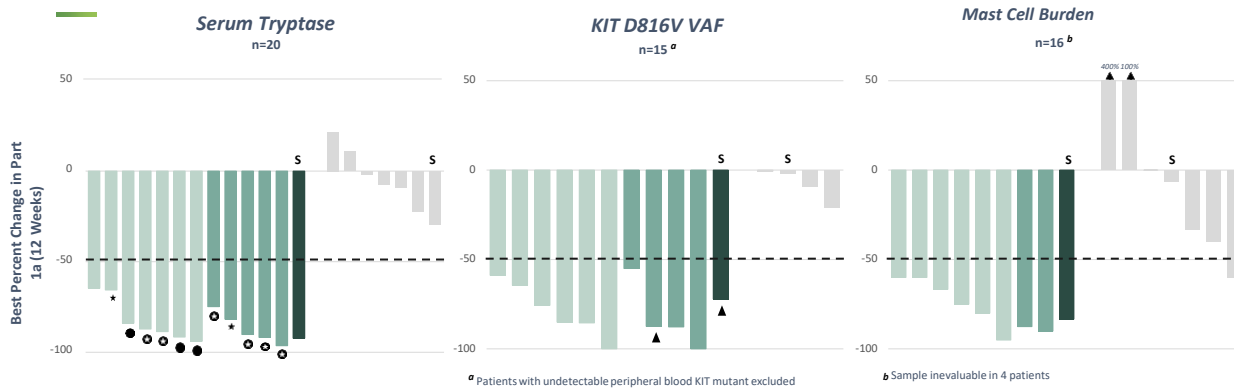
Within 12 Weeks, 100% of Bezuclastinib Treated Patients Achieved >50% Reduction in Markers of Mast Cell Burden



- 90% (9/10) of patients with baseline serum tryptase ≥20ng/mL achieved <20ng/mL after 12 weeks of bezuclastinib
- 67% (8/12) of patients with baseline serum tryptase ≥11.4ng/mL achieved <11.4ng/mL after 12 weeks of bezuclastinib

Dose
100 mg QD bezuclastinib
200 mg QD bezuclastinib
400 mg QD bezuclastinib
Placebo

Serum Tryptase Outcomes
Achieved <20ng/mL[a]
Achieved <11.4ng/mL[a]
Achieved both[a]

KIT D816V VAF Outcomes
Achieved <0.03% (LLD)
S SSM

[a]In order to achieve, serum tryptase must have been above the threshold at baseline LLD, lower limit of detection

As of Data Cut-off of 25-Oct-2023

Bose P et al. ASH Abstract 77 - Oral Presentation 2023.

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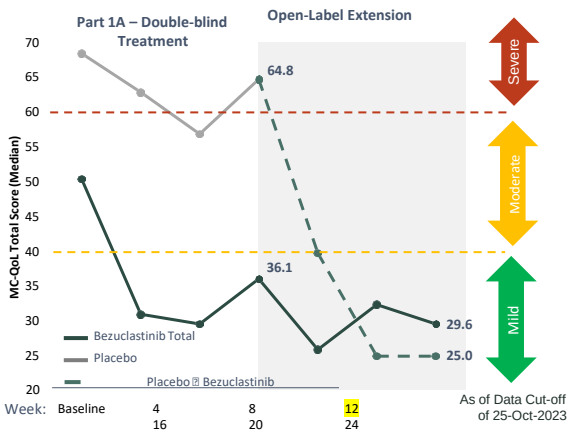
Encouraging Signs of Rapid Improvement in Symptom Severity and Quality of Life



- Median best percent improvement in patients treated with bezuclastinib (n=8) was 37% in Part 1a and 57% in OLE
- After placebo crossover to bezuclastinib in OLE, the median best percent improvement was 75%

Symptom Severity assessed by MAS

Mastocytosis Activity Score (MAS) % change from baseline at week 12[a]		
	Total Bezuclastinib (N=8)	Placebo (N=4)
Median	-35.53	-27.76
Min, Max	-60.1, -5.0	-73.1, 3.3

[a] Not collected in OLE

As of Data Cut-off of 25-Oct-2023

- 49% median decrease in MAS for patients treated with 100 mg QD dose level

Bose P et al. ASH Abstract 77 - Oral Presentation 2023.

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Updated Efficacy and Safety Results of Patients Receiving Selected 100mg Bezuclastinib Dose and Participating in the Open-Label Extension of Summit: A Randomized, Double-Blind, Placebo Controlled Phase 2 Clinical Trial of Bezuclastinib in Adult Patients with Nonadvanced Systemic Mastocytosis

Lindsay A.M. Rein, MD[1], *Daniel J. DeAngelo, MD, PhD*[2], *Brian Modena, MD*[3*], *Stephen Oh, MD, PhD*[4], *Bulai Livideanu Cridtina*[5*], *Celalettin Ustun, MD*[6], *Nathan Boggs*[7*], *Michael Manning, MD*[8*], *Anthony M. Hunter, MD*[9], *Cem Akin, MD, PhD*[10*], *Arnold Kirshenbaum, MD*[11*], *Ingunn Dybedal, MD, PhD*[12], *Cecilia Y. Arana Yi, MD*[13], *Richard Herrscher*[14*], *Mariana Castells, MD, PhD*[15*], *Frederick Lansigan, MD*[16*], *Tracy I. George, MD*[17], *Jay Patel, MD*[18], *Lei Sun*[19*], *Nisha Shah*[19*], *Jenna Zhang, PhD*[19*], *Amanda Pilla*[19*], *Priya Singh*[19*], *Marcus Carden, MD*[19*], *Frank Siebenhaar, MD*[20*] *and Prithviraj Bose, MD*[21]

[1]Division of Hematologic Malignancies and Cellular Therapy, Duke Cancer Institute, Durham, NC [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA [3]Modena Allergy & Asthma, San Diego, CA [4]Washington University School of Medicine, Saint Louis, MO [5]Department of Dermatology, CEREMAST Toulouse, CHU Toulouse, Toulouse, France [6]Rush University Medical Center, Chicago, IL [7]Walter Reed, Bethesda, MD [8]Allergy, Asthma, & Immunology Associates, Scottsdale [9]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA [10]University of Michigan, Ann Arbor, MI [11]Allervie Clinical Research, Glenn Dale, MD [12]Oslo University Hospital, Oslo, Norway [13]Division of Hematology/Oncology, Mayo Clinic, Scottsdale, AZ [14]AdCare, Plano, TX [15]Department of Medicine, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, MA [16]Dartmouth-Hitchcock Medical Center, Lebanon [17]University of Utah and ARUP Laboratories, Salt Lake City, UT [18]University of Utah, ARUP Laboratories, Salt Lake City, UT [19]Cogent Biosciences, Waltham, MA [20]Charité - UniversitätsmedizinBerlin, Berlin, DEU [21]The University of Texas MD Anderson Cancer Center, Houston, TX

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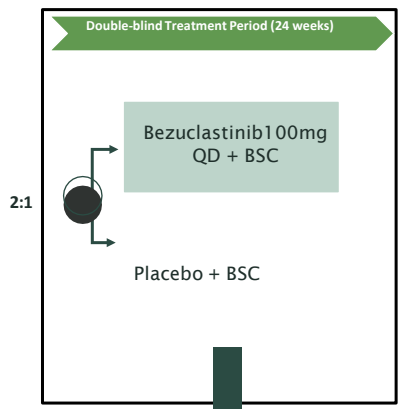
Summit: Phase 2 Clinical Study Evaluating Bezuclastinib in NonAdvSM

PART 2 (still enrolling)

Primary Objective: Determine the Efficacy and safety outcomes of pts treated with bezuclastinib at 100 mg at 24 weeks

Interim Report on the durability and safety/tolerability data beyond the 12 wks for those pts in part 1 randomized to 100 mg and pts who crossed over from placebo in Part 1 to bezuclastinib 100mg in Part 3 OLE



More than 90% of pts had at least a 50% reduction in basal serum tryptase, *KIT* p.D816V variant allele frequency, and bone marrow MCs

Pts treated with 100 mg bezu had reduction in MS2D2 TSS by 49.1% vs 21.1% with PBO.

OPEN-LABEL EXTENSION (OLE)
Primary Objective: Characterize safety and tolerability of bezuclastinib

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At the 12-wk assessment in Part 1 (datacut 18Dec2023), the safety and tolerability profile was encouraging, with the majority of TEAEs low grade and reversible without dose modification.

The most common TEAEs (>10% in 100 mg bezu) included hair color changes, nausea, diarrhea, peripheral edema, GERD, taste disorder, and neutropenia.

*There were no reported bleeding or cognitive impairment events.

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Advanced SM: Associated with Decreased Overall Survival[1]

Overall survival was examined in a retrospective study that included 342 consecutive adult patients with SM (includes 183 adults with advanced SM) seen at the Mayo Clinic between 1976 and 2007[1]

Median overall survival in advanced SM, by WHO subtype*[1]

In the overall SM cohort‡, 6% (21/342) of patients had leukemic transformation (18/21 to AML and 3/21 to MCL)[1]

*Median follow-up was 20.7 months. †A later study with 23 MCL patients demonstrated a median overall survival for patients with MCL of 1.9 years, with a 10-year survival of 29.9%.2 ‡The overall cohort included 159 patients with ISM, 138 patients with SM-AHN, 41 patients with ASM, and 4 patients with MCL.
AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; WHO, World Health Organization.
1. Lim KH et al. Blood. 2009;113(23):5727-5736. 2. Sperr WR et al. Lancet Haematol. 2019;6(12):e638-e649.

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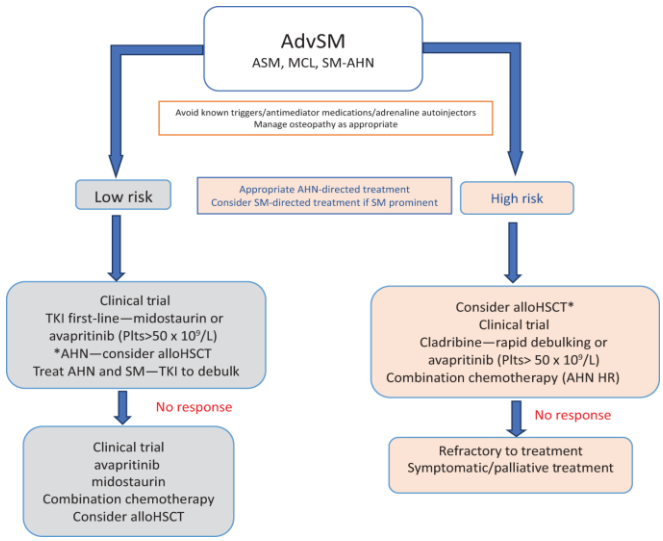
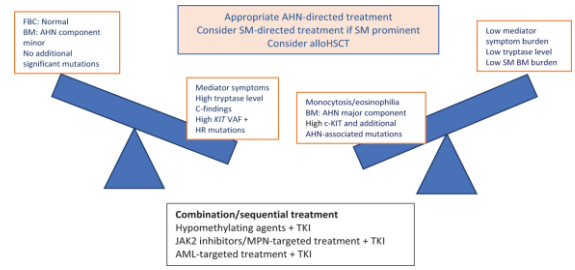
MANAGEMENT: Advanced SM





Scott Veitch,Deepti H. Radia, Mastocytosis demystified, Hematology Am Soc Hematol Educ Program, 2023, Figure 4.

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ALLERGY & CLINICAL IMMUNOLOGY
DEDICATED TO ALLERGY SCIENCE,
COMMITED TO YOUR HEALTH

Avapritinib improves overall symptoms, skin lesions and quality of life in patients with advanced systemic mastocytosis in the PATHFINDER study

Marcus Maurer[1], Frank Siebenhaar[1], Karin Hartmann[2],Andreas Reiter[3], Deepti Radia[4], Michael W. Deininger[5], Jayita Sen[6], Hui-Mun Lin[6], Brenton J. Mar[6], Jason Gotlib[7], Daniel J. DeAngelo[8], Sigurd Broesby-Olsen[9]

[1]Dermatological Allergology, Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany; [2]Division of Allergy, Department of Dermatology, University Hospital of Basel and University of Basel, Basel, Switzerland; [3]University Hospital Mannheim, Mannheim, Germany; [4]Guy's and St Thomas' NHS Foundation Trust, London, UK; [5]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, USA; [6]Blueprint Medicines Corporation, Cambridge, Massachusetts, USA; [7]Stanford University School of Medicine/Stanford Cancer Institute, Stanford, California, USA; [8]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [9]Odense University Hospital, Odense, Denmark

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PATHFINDER Phase 2 Pivotal Study in Advanced SM (AdvSM)

- Central diagnosis of AdvSM
- ≥18 years of age
- ECOG PS 0–3
- **Platelets <50×10⁹/L excluded**

Enrolled (N=62)

Avapritinib 200[a] mg QD starting dose

mIWG Evaluable, Cohort 1 (n=52)
AdvSM with ≥1 evaluable C-finding[b]

mIWG Non-Evaluable, Cohort 2 (n=10)
AdvSM without any evaluable C-findings[b]

Primary Endpoint (Cohort 1)

- Adjudicated ORR by mIWG-MRT-ECNM criteria

  Response primarily based on resolution of organ damage (C-findings)

Secondary Endpoints (both cohorts)

- Reduction in MC burden (including serum tryptase)
- Safety

Symptom-related Secondary Endpoints (both cohorts)

- **Total Symptom Score** of the AdvSM-Symptom Assessment Form (AdvSM-SAF), mean change from baseline
- **Global symptom severity** by Patient Global Impression of Symptom Severity (**PGIS**) Questionnaire
- **QoL** on the EORTC QLQ-C30 survey

Symptom-related Exploratory Endpoints

- **Cutaneous disease** in patients by photography

Based on data cut-off date of June 23, 2020
[a]60 patients received 200 mg and 2 patients received 100 mg. [b]Per mIWG-MRT-ECNM criteria, response assessment requires ≥1 evaluable C-finding at baseline. MCL without an evaluable C-finding may be assessed for response based on disease burden alone (Gotlib et al. *Blood*. 2013;21:2393–2401). ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire- core questionnaire 30; MCL, mast cell leukemia; QD, once-daily.
Maurer M et al. EAACI Hybrid Congress 2021. Oral Presentation.

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Baseline Characteristics of PATHFINDER Population

Patient demographics	All doses (n=62)
Age (years), median (range)	69 (31–88)
Sex, n (%), female	28 (45)
ECOG PS, n (%)	
0–1	43 (69)
2–3	19 (31)
AdvSM subtype per central assessment, n (%)	
ASM	9 (15)
SM-AHN	43 (69)
MCL	10 (16)
Bone marrow biopsy MC burden median percent (range)	45 (1–95)
Serum tryptase level, median ng/mL (range)	283 (24–1600)
KIT D816V positive in peripheral blood by central ddPCR, n (%)	59 (95)
Prior anti-neoplastic therapy, n (%)	42 (68)
Midostaurin	34 (55)
Cladribine	8 (13)
Baseline supportive medications, median (range)	3 (0–11)
H1 antihistamines	36 (58)
H2 antihistamines	24 (39)
Leukotriene receptor antagonists	12 (19)
Proton pump inhibitors Cromolyn	10 (16)
sodium Corticosteroids	6 (10)
(systemic)	20 (32)
Other	19 (31)

ASM, aggressive systemic mastocytosis; ddPCR, droplet digital polymerase chain reaction; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.
Maurer M et al. EAACI Hybrid Congress 2021. Oral Presentation.

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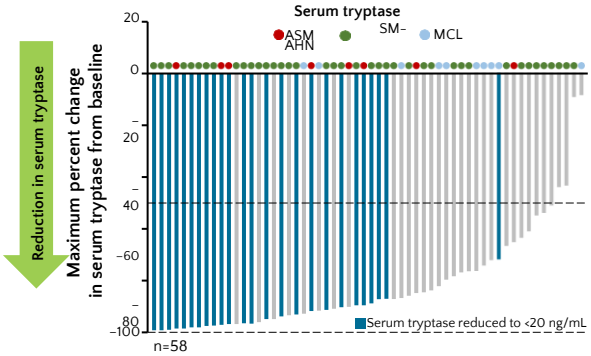
PATHFINDER High Confirmed Response Rate of Avapritinib in AdvSM

- 75% confirmed ORR per mIWG-MRT-ECNM criteria
- 52% CR rate
- 93% of patients achieved ≥50% reduction in serum tryptase



- Overall, 43% of patients achieved reduction to <20 ng/mL

- Avapritinib was generally well tolerated; only 3 (5%) patients discontinued due to treatment-related AEs
- Cytopenias are the most common Grade ≥3 AEs

Adverse Events (AEs) in ≥15%	Any-cause AEs	
Non-hematologic, n (%)	**Any Grade**	**Grade 3/4**
Peripheral edema	31 (50)	2 (3)
Periorbital edema	30 (48)	2 (3)
Diarrhea	14 (23)	1 (2)
Nausea	11 (18)	1 (2)
Vomiting	11 (18)	1 (2)
Fatigue	9 (15)	2 (3)
Hematologic, n (%)		
Thrombocytopenia	28 (45)	10 (16)
Anemia	20 (32)	10 (16)
Neutropenia	15 (24)	15 (24)[a]

AE table includes pooled similar AE terms for periorbital edema, thrombocytopenia, anemia, and neutropenia.

Neurocognitive events (125) and CNS hemorrhagic events (3.8%) were seen

[a]Five (8%) patients had Grade 4 neutropenia.
AEs, adverse events. DeAngelo et al. Presented at the American Association for Cancer Research Annual Meeting, virtual format, April 10–15, 2021.
Maurer M et al. EAACI Hybrid Congress 2021. Oral Presentation

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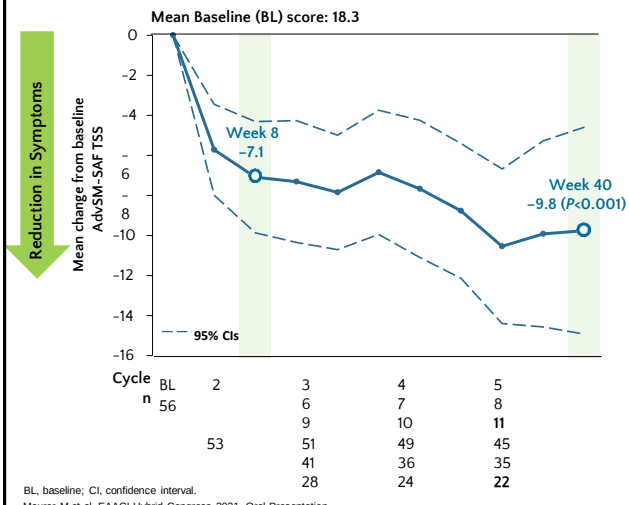
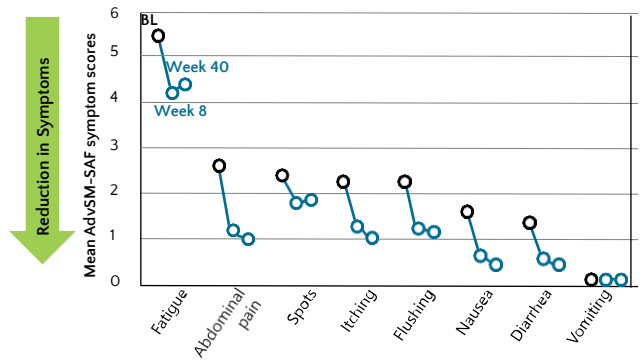
Avapritinib Led to Rapid and Durable Reduction in AdvSM Symptoms

Significant reduction in TSS



Individual Symptom Scores



BL, baseline; CI, confidence interval.
Maurer M et al. EAACI Hybrid Congress 2021. Oral Presentation

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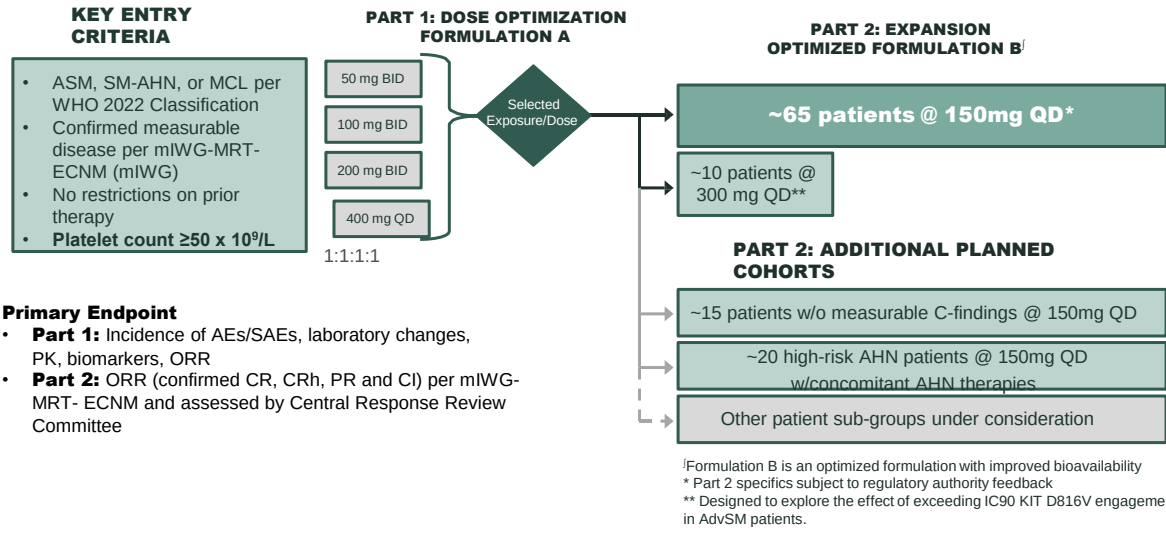
Apex (NCT04996875): A Phase 2 Open-Label, Multicenter Clinical Study of Bezuclastinib in Patients with Advanced Systemic Mastocytosis



Primary Endpoint

- **Part 1:** Incidence of AEs/SAEs, laboratory changes, PK, biomarkers, ORR
- **Part 2:** ORR (confirmed CR, CRh, PR and CI) per mIWG-MRT- ECNM and assessed by Central Response Review Committee

[j]Formulation B is an optimized formulation with improved bioavailability
* Part 2 specifics subject to regulatory authority feedback
** Designed to explore the effect of exceeding IC90 KIT D816V engagement in AdvSM patients.

Vachhani P, et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

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Patient Demographics and Characteristics

33 patients enrolled[§]; median age: 68 years; range: 33-87

	Total (N=32)	50mg BID (N=8)	100mg BID (N=7)	200mg BID (N=8)	400mg QD (N=9)
Male, n (%)	**21 (65.6)**	6 (75.0)	4 (57.1)	5 (62.5)	6 (66.7)
ECOG PS 0-1, n (%)	**27 (84.4)**	8 (100)	5 (71.4)	7 (87.5)	7 (77.8)
AdvSM Subtype per Central Eligibility Review, n (%)					
ASM	**7 (21.9)**	2 (25)	0	0	5 (55.6)
SM-AHN	**23 (71.9)**	5 (62.5)	6 (85.7)	8 (100)	4 (44.4)
MCL	**2 (6.3)**	1 (12.5)	1 (14.3)	0	0
Prior therapy for AdvSM, n (%)[j]					
TKI Naïve*	**22 (69)**	7 (88)	4 (57)	6 (75)	5 (56)
Avapritinib	**5 (16)**	0	2 (29)	2 (25)	1 (11)
Midostaurin	**10 (31)**	1 (13)	3 (43)	2 (25)	4 (44)
SRSF2/ASXL1/RUNX1 Mutation in Peripheral Blood	**19 (59.4)**	5 (62.5)	5 (71.4)	5 (62.5)	4 (44.4)
***KIT* D816V in Whole Blood, Positive, n (%)**	**29 (90.6)**	8 (100)	6 (85.7)	7 (87.5)	8 (88.9)
Median KIT D816V VAF, % (range)	**6.1 (0-47.2)**	3.4 (0-39.0)	29.2 (0-38.9)	2.9 (0-47.2)	1.9 (0-42.2)
Median Bone Marrow MC Burden, % (range)	**30 (5-90)**	50 (20-70)	70 (5-90)	10 (5-30)	40 (10-80)
Median Serum Tryptase, ng/mL (range)	**153.5 (35.0-1578.0)**	178.0 (130.0-605.0)	233.0 (53.6-1578.0)	97.1 (35.0-131.0)	182.0 (50.2-370.0)

[§]One patient never dosed was excluded
[j] Additional therapies included cytoreductives and biologics
*Patients who have received no prior SM-directed therapy with midostaurin and/or avapritinib

Data as of: 25Sep2023
Vachhani P,. et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

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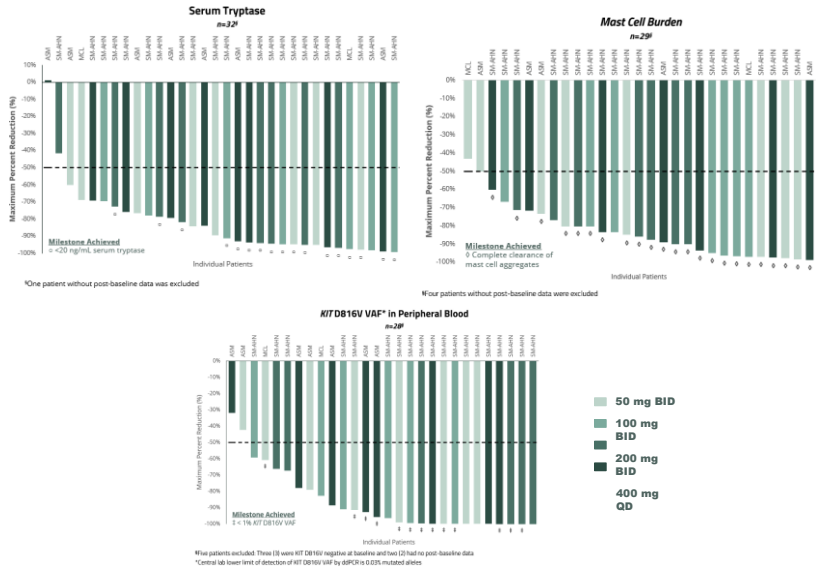
APEX Trial in Patients with AdvSM

Bezuclastinib Demonstrates Rapid and Deep Clinical Activity

- Serum Tryptase
  - 94% (30/32) of patients achieved a ≥ 50% Reduction
- Bone Marrow MC Burden
  - 97% (28/29) of patients with ≥ 50% reduction.
- KIT D816V VAF in Peripheral Blood
  - 93% (26/28) of patients achieved a ≥ 50% reduction



[a]One patient without post-baseline data was excluded

[b]Four patients without post-baseline data were excluded

[c]Five patients excluded. These (3) were KIT D816V negative at baseline and two (2) had no post-baseline data

*Central lab lower limit of detection of KIT D816V VAF by ddPCR is 0.035 mutated alleles

Data as of: 25Sep2023

Vachhani P, et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

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Apex Part 1: Responses Observed by mIWG-MRT-ECNM and PPR Criteria

[α]5 patients without measurable C-finding at baseline were not mIWG-MRT-ECNM evaluable (inevaluable, IE) and therefore are excluded; one additional patient was excluded due to discontinuation prior to first dose (not dosed [ND]).

*responses require **12-week** confirmation duration

‡ SM-directed therapy with midostaurin and/or avapritinib

† Primary endpoint of Apex study

Best Response, n (%) [α]	Total* Confirmed mIWG-MRT-ECNM Responses per CRRC Assessment (n=27)	mIWG-MRT-ECNM per CRRC Assessment* (TKI‡ Therapy Naïve) (n=18)	mIWG-MRT-ECNM per CRRC Assessment* (Prior TKI‡ Exposure) (n=9)
Overall response rate			
CR + CRh + PR + CI†	14 (52)	11 (61)	4 (44)
CR + CRh + PR	14 (52)	10 (56)	4 (44)
Complete Response (CR + CRh)	6 (22)	6 (33)	0 (0)
Partial Response (PR)	8 (30)	4 (22)	4 (44)
Clinical Improvement (CI)	1 (4)	1 (6)	0 (0)
Stable Disease (SD)	9 (33)	6 (33)	3 (33)
Not evaluable	3 (11)	1 (6)	2 (22)

[α]One patient was excluded due to discontinuation prior to first dose (Not Dosed [ND]).

‡ SM-directed therapy with midostaurin and/or avapritinib

Best Response, n (%) [α]	Total (n=32)
Best response rate (CR + CRh + PR) Pure pathological Response	28 (88)
Complete Response (CR)	14 (44)
Partial Response (PR)	10 (31)
Stable Disease (SD)	5 (16)
Not Evaluable	3 (9)

Median time to the start of confirmed response was 2.1 (range 1.9-4.8) months

Median duration of response was not yet reached in response-evaluable patients (range 2.8 to 19.4 months).

The rate of pure pathologic response (CR/CRh+PR) was 88% (28/32).

Data as of: December 2024

DeAngelo et al. American Society of Hematology (ASH) 2024; San Diego, CA, 8 Dec 2024; Publication Number 659

Vachhani P, et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

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Apex Part 1: Updated Assessment of Bezuclastinib (CGT9486), a Selective KIT D816V Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis (AdvSM)

IWG-MRT responses

Overall Response Rate (ORR): 52% per modified IWG criteria
83% ORR in patients receiving 100 mg twice daily (BID).

Pure Pathological Response (PPR):
88% ORR
achieving 100% in the 100 mg BID cohort.

Biomarker Improvements:

94% of patients experienced a ≥50% reduction in serum tryptase levels
93% had a ≥50% decrease in KIT D816V variant allele fraction;
100% of evaluable patients saw a ≥50% reduction in bone marrow mast cell burden

The trial is ongoing, with top-line data from Part 2 expected in mid-2025.

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Bezuclastinib Continues to Demonstrate a Differentiated Safety Profile

18Jun2024, median treatment duration was 60 (range, 0.3 – 124.1) weeks.

- Bezuclastinib demonstrated a favorable safety profile, with most adverse events being low-grade and reversible.
- The majority of hematological adverse events were of low grade, reversible and did not require dose reduction.
- Related SAEs reported including Gr4 Thrombocytopenia
- 11/32 (34%) patients required dose reduction due to adverse events, 6 of whom were at 400 mg
- 2 (6%) discontinued due to TRAEs [1 Gr3 drug induced liver injury (DILI); 1 Gr3 ALT/AST increased]. No treatment-related deaths occurred.

Treatment Related Adverse Events in > 10% Patients

	Total (n=32) n (%)		50 mg BID (n=8) n (%)	100 mg BID (n=7) n (%)	200 mg BID (n=8) n (%)	400 mg QD (n=9) n (%)
Preferred Term	All grade	Grade ≥3	All grade	All grade	All grade	All grade
Hair color changes	11 (34)	0	0	4 (57)	3 (38)	4 (44)
Thrombocytopenia*	8(25)	2 (6)	0	4 (57)	1 (13)	2 (22)
Transaminase increased AST ALT*	9 (28)	2 (6)	3 (38)	2 (29)	1 (13)	1 (11)
Neutropenia*	8(25)	3 (9)	1 (13)	2 (29)	1 (13)	2 (22)
Taste disorder*	6 (19)	0	1 (13)	1 (14)	1 (13)	3 (33)
Peripheral edema	4 (13)	0	0	1 (14)	1 (13)	2 (22)
Periorbital edema	4 (13)	1 (3)	0	0	3 (38)	1 (11)

*Includes pooled preferred terms

*No reports of treatment-related cognitive impairment or bleeding events.

Data as of: 25Sep2023
Vachhani P,. et al. American Society of Hematology (ASH) 2023; San Diego, CA, 11 Dec 2023: Publication Number: 4567

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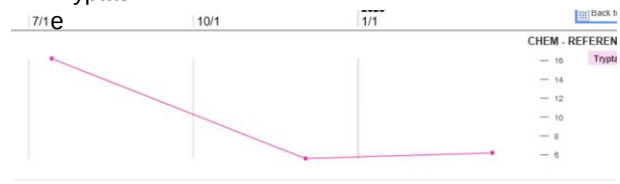
LD on TKI Treatment with Avapritinib

- Started on avapritnib 200mg daily.
- Tolerated treatment well with some dry skin and periorbital edema.
- Alk Phos and tryptase normalized: 16.2 -> 5.6
- Dexa Scan showed improved Bone marrow density
- Dose reduced to 100mg due to mild anemia.
- Restaging CT and Nuclear Bone scan showed resolving sclerotic lesions and decreased SM to 12cm.
- Restaging BM biopsy 10/2023 shows normocellular marrow without mast cell aggregates.
- ddPCR: KitD816V 1.2% -> negative
- NGS: VAF 15
  - Additional mutations in Notch (VAF: 17) and TET2 (VAF: 7)
- Seen by BMT but patient decided to not proceed with transplant
- Remains on Avapritib 100mg in CR

Alk Phos

Tryptase



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Summary and Future Questions

SM is a rare clonal mast cell neoplasm driven by the *KIT* D816V mutation in ~95% of patients. This molecular signature can be exploited as screening and as a therapeutic target. DD PCR should be used in screening.

Many patients experience a prolonged time from onset to diagnosis, with an average time from symptom onset to diagnosis of ~7 years, so improved screening approaches and increased clinical suspicion is critical for early diagnosis are crucial. Multidisciplinary approach is necessary.

There is continued need for risk stratification tools and disease modifying therapies. Can VAF be standardized as a measure of disease modification and does early intervention improve survival rates?

New TKIs are progressively more selective offering more potent KIT inhibition with fewer side effects. It is likely in the coming years that we will have multiple options. How do we dose them appropriately? How will we sequence them?

AlloHSCT improves outcomes when patients are appropriately selected, but more needs to be understood in regard to timing and preparatory approach.

Could TKI's have a role in other KIT mutated myeloid diseases?

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Thank you!

Hackensack Meridian *Health*

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Case Presentation

Snigdha Ghanta, MBBS

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Initial Presentation

- Patient presented in September 2024 with several weeks of easy fatigability and lethargy
- Associated with unintentional weight loss ~ 20 pounds
- Intermittent fever and chills, and left upper quadrant pain

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Pertinent History

PMH: H/O Pituitary adenoma s/p resection 30 years ago, now with iatrogenic pituitary deficiency

PSH: R shoulder lipoma s/p excision

SH: Drinks 2-3 drinks a week, non smoker, works as an auto-mechanic

FH: H/O CVA in father

Allergies: No known allergies

Medications: Levothyroxine 137 mcg Daily, Hydrocortisone 10 mg BID, Testosterone 200 mg IM q2 weeks

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Initial Results

Labs	Results
WBC	226.22 k/mm3
Hb	8.3 g/dL
PLT	74 k/mm3
MCV	99.2 fL
HCT`	26.3 %

The spleen was palpable 18 cm BLCM

Labs	Results
Neutrophils	33.0%
Lymphocytes	2.0%
Monocytes	6.0%
Eosinophils	2.0%
Basophils	7.0%
Blasts	11.0%
Myelocytes	22.0%
Metamyelocytes	7.0%
Promyelocytes	4.0%
Band Neutrophils	6.0%

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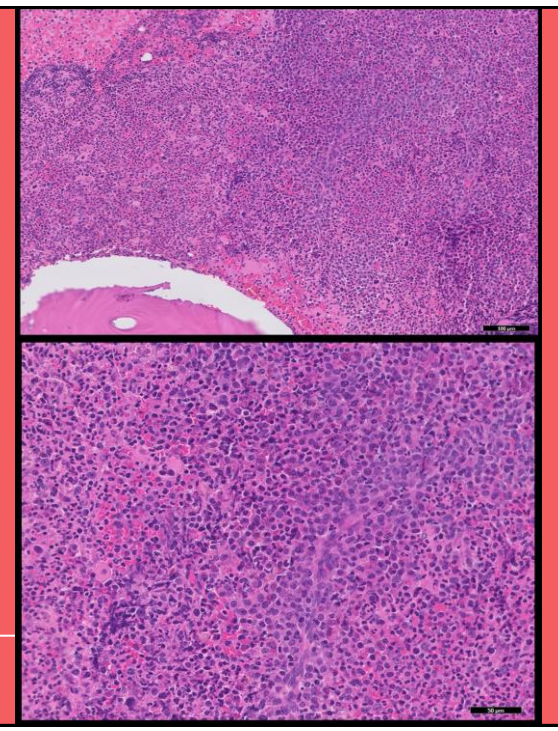
Bone Marrow Biopsy



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Bone Marrow Biopsy Results

Morphology: Markedly hypercellular bone marrow with myeloid hyperplasia, morphologically consistent with chronic myeloid leukemia, chronic phase. No morphologic evidence of accelerated or blast phase.

FISH: BCR-ABL/ASS1 detected

PCR: BCR-ABL1 Translocation t(9;22) Detected

% BCR-ABL1/ABL1 (IS) 71.8377

Cytogenetics: No metaphase cells were available for analysis

NGS:

EP300 p.G2037Sfs*96 NM_001429.4:c.6109_6112del Frameshift Pathogenic 5.4 1579

Variants of Unknown Clinical Significance Consequence Variant Allele Frequency (%)

KMT2C C960F NM_170606.3:c.2879G>T Missense 9.3

RB1 Q631R NM_000321.2:c.1892A>G Missense 52.0

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Assessment of Risk

Risk Calculator	Result
Sokal	1.37, High
EUTOS	121, High
ELTS	4.2, High

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Course

9/10/2024: Started on hydroxyurea 2000 mg BID after bone marrow biopsy
9/11/2024: Hydroxyurea dose reduced to 1000 mg Daily
9/12/2024: Started on dasatinib 100 mg daily
9/16/2024: Hydroxyurea discontinued
9/18/2024: Discharged home. Pt opted to be followed closer to home.

10/29/2024: Pt returned to WMC after his physician was concerned about his thrombocytopenia (platelet count nadir 20,000). His local oncologist had reduced the dasatinib dose to 50mg and then discontinued it altogether.

Labs at WMC showed PLT count of 89,000/mm3
Dasatinib 100 mg was resumed

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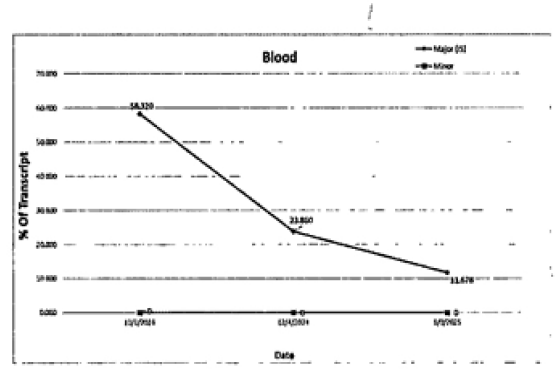
Course Contd.
BCR-ABL International Scale value

09/10/2024: 71.8377%

11/06/2024: 58.320%.
No ABL1 mutations

12/12/2024: 38.877%

1/14/2025: 11.678%



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Newly Diagnosed Chronic Myeloid Leukemia (CML): Pros and Cons of the Approved Drugs

Karen Seiter, MD
New York Medical College, Valhalla, New York
February 5, 2025

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Summary of Case

- Young patient
- Comorbidities
- Patient presented with high-risk disease
- High % blasts in the blood
- Thrombocytopenia

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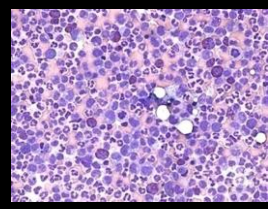
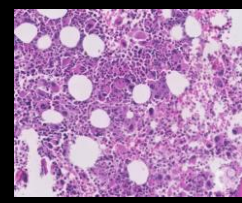
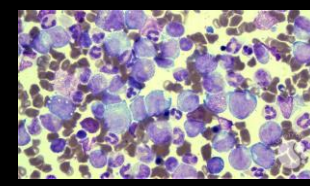
A Word About Staging







Chronic Phase
3-5 years prior to TKIs

Accelerated Phase
9-18 months prior to TKIs

Blast phase
3-6 months prior to TKIs

Images courtesy of ASH Image Bank

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The 2016 Revision to the World Health Organization Classification of Myeloid Neoplasms and Acute Leukemia

CML, accelerated phase criteria	
Any 1 or more of the following hematologic/cytogenetic criteria or response-to-TKI criteria:	
• Persistent or increasing WBC (>10 × 10^9/L), unresponsive to therapy	**"Provisional" response-to-TKI criteria**
• Persistent or increasing splenomegaly, unresponsive to therapy	• Hematologic resistance to the first TKI (or failure to achieve a complete hematologic response* to the first TKI) or
• Persistent thrombocytosis (>1000 × 10^9/L), unresponsive to therapy	• Any hematological, cytogenetic, or molecular indications of resistance to 2 sequential TKIs or
• Persistent thrombocytopenia (<100 × 10^9/L) unrelated to therapy	• Occurrence of 2 or more mutations in *BCR-ABL1* during TKI therapy
• 20% or more basophils in the PB	
• 10%-19% blasts† in the PB and/or BM	
• Additional clonal chromosomal abnormalities in Ph^+ cells at diagnosis that include "major route" abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2	
• Any new clonal chromosomal abnormality in Ph^+ cells that occurs during therapy	

Arber DA, et al Blood 2016 May 19; 127(20):2391-405

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The 5th Edition (2022) of the World Health Organization Classification of Haematolymphoid Tumors: Myeloid and Histiocytic/Dendritic Neoplasms

- "Chronic myeloid leukemia risk factors are refined, and accelerated phase is no longer required"
- With TKI therapy and careful disease monitoring, the incidence of progression to advanced phase disease has decreased, and the 10-year overall survival rate for CML is 80%–90%
- The designation of AP has thus become less relevant. Accordingly, AP is omitted in the current classification in favor of an emphasis on high-risk features associated with CP progression and resistance to TKI

Khoury JD et al. Leukemia 36, 1703-1719 (2022)

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Modern Assessment of Risk

- Sokal score
  - Age, spleen size, platelet count, % blasts in blood
- EUTOS score
  - Spleen size, % blood basophils
- ELTS score
  - Age, spleen size, % blasts in blood, platelet count
- Hasford score
  - Age, spleen size, % blasts in blood, % eosinophils in blood, % basophils in blood, platelet count

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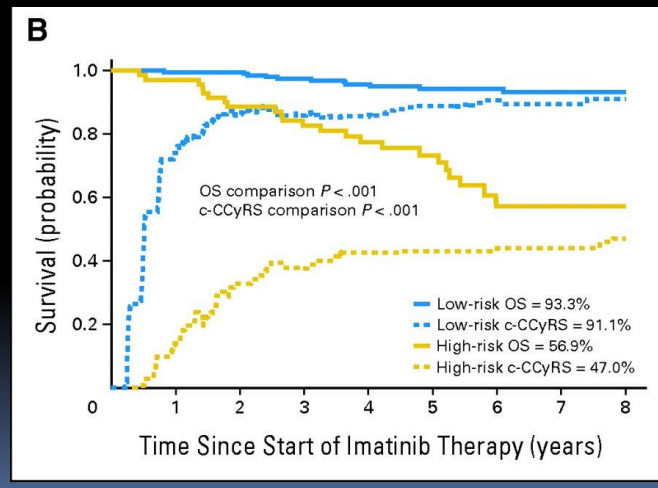
Assessment of *BCR-ABL1* Transcript Levels at 3 Months is the Only Requirement for Predicting Outcome for Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors



Marin D, et al. J Clin Oncol. 2012

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Removal of Accelerated Phase Why Does it Matter?

- FDA approved doses of most TKIs are higher for accelerated phase
  - Imatinib 600 mg daily (c/w 400 mg for CP)
  - Dasatinib 140 mg daily (c/w 100 mg for CP)
  - Nilotinib 400 mg BID (c/w 300 mg BID for CP)
  - Bosutinib 500 mg daily (c/w 400 mg for CP)
  - Asciminib: only approved for CP (80 mg daily)
- Early referral for transplant - now based on response to TKI therapy

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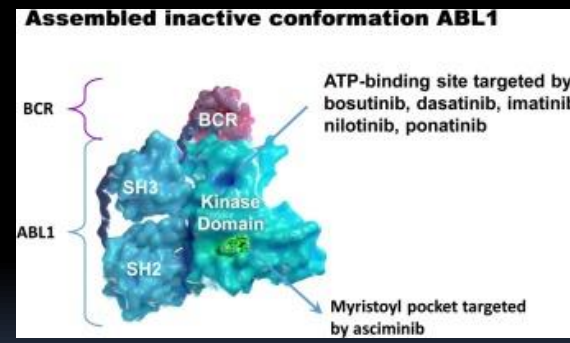
CML: Frontline Therapy
What Are the Options?

- Targeting ATP-binding site
  - Imatinib
  - Dasatinib
  - Nilotinib
  - Bosutinib
- Targeting myristoyl pocket
  - Asciminib



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Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia IRIS Trial 10-year Follow-Up

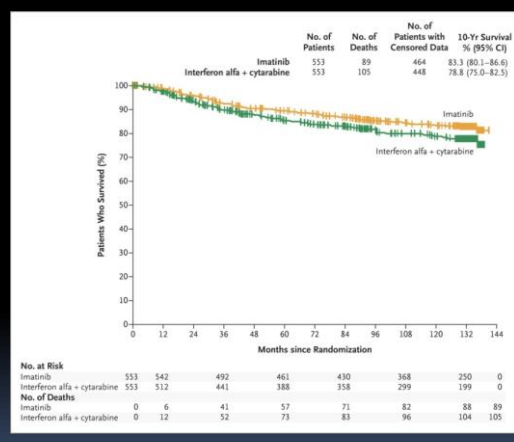

Table 2. Deaths during the Trial among Patients Randomly Assigned to Imatinib.

Variable	Patients (N=553)
	no. (%)
Total deaths	89 (16.1)
Cause of death	
Chronic myeloid leukemia	
Without hematopoietic stem-cell transplantation	37 (6.7)
After hematopoietic stem-cell transplantation	13 (2.4)
Secondary malignant condition*	11 (2.0)
Cardiac disorder or cardiovascular disease	7 (1.3)
Infectious disease	5 (0.9)
Other	16 (2.9)

* Reported causes of death due to secondary malignant condition were metastases to the liver (in two patients) and *BCR-ABL1*–negative acute myelogenous leukemia, bronchial carcinoma, esophageal carcinoma, lung cancer, prostate cancer, rectal cancer, renal-cell carcinoma, sarcoma, and transitional-cell carcinoma (in one patient each).

Hochhaus A, et al. N Engl J Med 2017;376:917-927.

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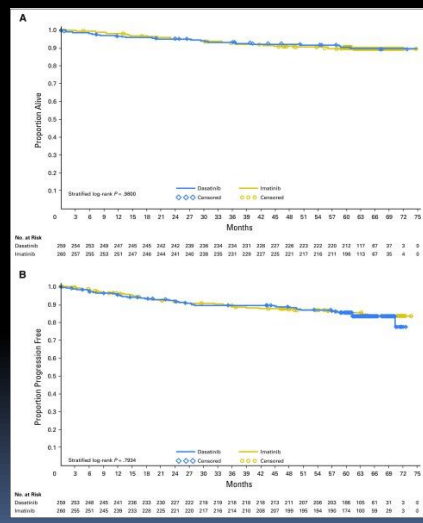
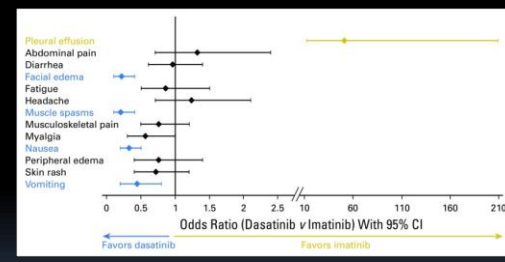
Final 5-year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial





Cortez J, et al. J Clin Oncol 2016 May 23;34(20):2333-2340

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Long-term Outcomes with Frontline Nilotinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase: ENESTnd 10-year Analysis

	Nilotinib 300 BID	Nilotinib 400 BID	Imatinib 400 daily
Freedom from progression to AP/BP %			
At 5 years	96.3 (94.1–98.6)	97.8 (96.0–99.5)	92.2 (89.1–95.4)
At 10 years	95.9 (93.5–98.3)	97.3 (95.3–99.3)	90.8 (87.3–94.3)
HR vs imatinib (95% CI)	0.45 (0.22–0.92)	0.28 (0.12–0.66)	NA
P vs imatinib	0.02	<0.005	NA
Overall Survival %			
At 5 years	93.7 (90.8–96.6)	96.3 (94.0–98.5)	91.8 (88.5–95.1)
At 10 years	87.6 (83.5–91.7)	90.3 (86.5–94.1)	88.3 (84.2–92.4)
HR vs imatinib (95% CI)	1.07 (0.64–1.76)	0.79 (0.46–1.36)	NA
P vs imatinib	0.80	0.40	NA

Kantarjian HM, et al. Leukemia 2021 Feb;35(2):440-453

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Long-term Outcomes with Frontline Nilotinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase: ENESTnd 10-year Analysis

	Nilotinib 300 BID	Nilotinib 400 BID	Imatinib 400 daily
CVEs, *n*[a]	279	277	280
All CVEs	46 (16.5)	65 (23.5)	10 (3.6)
Ischemic heart disease	22 (7.9)	36 (13.0)	8 (2.9)
Peripheral arterial occlusive disease	18 (6.5)	20 (7.2)	0
Ischemic cerebrovascular disease	13 (4.7)	21 (7.6)	1 (0.4)
Other CVEs	4 (1.4)	4 (1.4)	1 (0.4)

Kantarjian HM, et al. Leukemia 2021 Feb;35(2):440-453

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Bosutinib Versus Imatinib for Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia: Final Results from the BFORE Trial

- Original BELA trial did not meet primary endpoint (complete cytogenetic response)
- BFORE trial designed to have MMR as primary endpoint
- Overall survival not reported
- GI toxicity prominent

	Bosutinib	Imatinib	
Cumulative response rates, % (95% CI)	*n* = 268	*n* = 268	OR (95% CI)
MMR	73.9 (68.6–79.1)	64.6 (58.8–70.3)	1.57 (1.08–2.28)
MR^4	58.2 (52.3–64.1)	48.1 (42.2–54.1)	1.50 (1.07–2.12)
$MR^{4.5}$	47.4 (41.4–53.4)	36.6 (30.8–42.3)	1.57 (1.11–2.22)

Brummendorf TH, et al. Leukemia. 2022 Jul;36(7):1825-1833

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Asciminib

- Asciminib binds to the myristoyl pocket of the ABL1 portion of the BCR ABL fusion protein and locks it into an inactive conformation, preventing its oncogenic activity.
- Effective against most ABL1 kinase mutations that confer resistance to ATP-competitive TKIs, including the T315 mutation.
- Approved October 2021 for previously treated patients.
- Approved October 2024 for newly diagnosed patients in CP.

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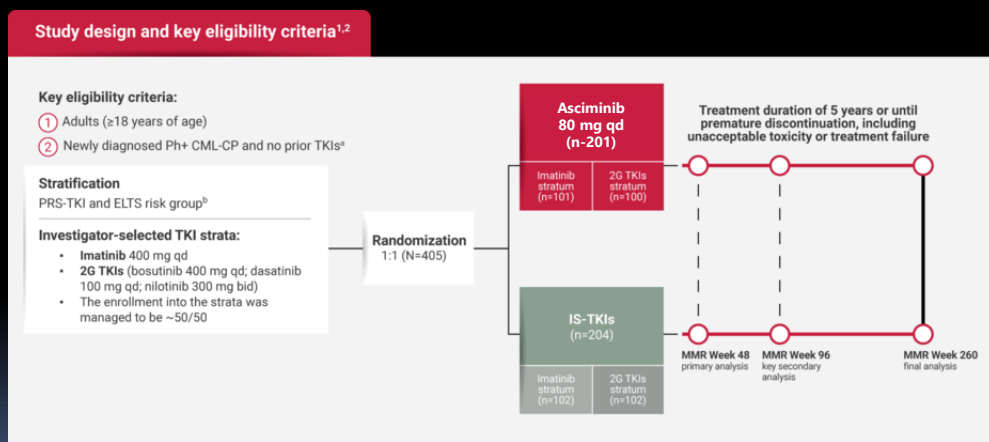
Asciminib in Newly Diagnosed Chronic Myeloid Leukemia



Hochhaus A. N Engl J Med 2024;391:885-898

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Asciminib in Newly Diagnosed Chronic Myeloid Leukemia

Pts with MR	All Asciminib	All Comp.	Imatinib Asciminib	Imatinib Imatinib	2G Asciminib	2G 2G
MMR at wk 48 no. (%)	136 (67.7)	100 (49.0)	70 (69.3)	41 (40.2)	66 (66.0)	59 (57.8)
p value	<0.001		<0.001			
MMR wk 12 no. (%)	180 (89.6)	143 (70.1)	89 (88.1)	61 (59.8)	91 (91.0)	82 (80.4)

Hochhaus A. N Engl J Med 2024;391:885-898

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Asciminib in Newly Diagnosed Chronic Myeloid Leukemia

	Asciminib Any Grade	Asciminib ≥ Grade 3	Imatinib Any Grade	Imatinib ≥ Grade 3	2G TKI Any Grade	2G TKI ≥ Grade 3
Any Event	93.5%	38%	93.9%	44.4%	100%	54.9%
Neutropenia	25.0%	10.0%	31.3%	17.2%	34.3%	13.7%
Diarrhea	15.5%	0%	26.3%	0%	25.5%	1.0%
Lipase	11.5%	3%	14.1%	10.0%	10.8%	3.9%
DC due to toxicity		4.5%		11.1%		9.8%

Hochhaus A. N Engl J Med 2024;391:885-898

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A Word About Dosing

- Many are encouraging use of lower doses of TKIs
  - Example: Dasatinib 70 mg or 50 mg
- However, most data is Phase 2 or retrospective
- Unclear if high-risk patients were included

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How to Decide

- 5 drugs approved for newly diagnosed patients
- Is treatment-free remission a goal?
  - All of the 2G TKIs and asciminib give faster, deeper molecular responses. Greater opportunity for treatment-free remission
- Are comorbidities a consideration?
  - Choose most tolerable drug

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Our Patient

- High-risk disease
  - Chose second generation TKI
  - Patient also eligible for asciminib now (was not approved for front line when he presented)
  - Did not meet 3-month molecular milestone. Consequence of missed/reduced doses?
  - Plan to monitor closely. Will consider change to another agent if he doesn't meet 6-month milestone molecular response

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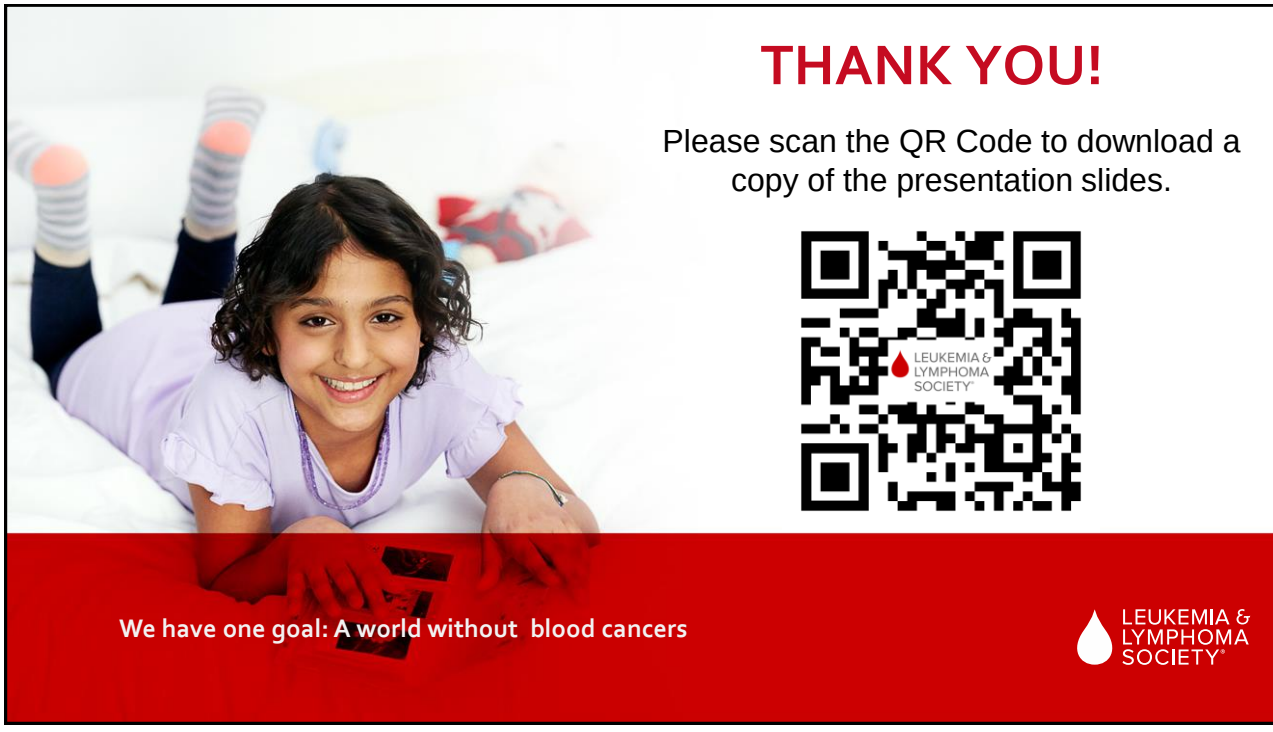
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