Ruben A. Mesa, MD, FACP
President, Enterprise Cancer Service Line Atrium Health
Executive Director Atrium Health Wake Forest Baptist Comprehensive Cancer Center
Enterprise Senior Vice President Atrium Health
Vice Dean for Cancer Programs – Wake Forest School of Medicine
Professor of Medicine
Ruben.Mesa@Atriumhealth.org

Guidelines and Gaps
2023 Joyce Niblack MPN Conference
Disclosures – Ruben Mesa, MD

• Consultant (Honoraria) over past 3 years
  • Novartis
  • Sierra Oncology
  • Genentech
  • Sierra
  • Blueprint
  • Geron
  • Telios
  • CTI
  • Incyte
  • BMS
  • Abbvie
  • GSK

• Research Support
  • Incyte
  • Sierra
  • CTI
  • BMS
  • Abbvie
  • Genentech
  • Blueprint
  • Morphosys
Gaps and Guidelines – MPNs 2023

• Goals and Targets
• ET and PV
• JAK Inhibitors as Foundation
• Non JAKi MOA
• Other Gaps
• Putting it all Together
Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story

**Vascular Events**
- PV/ET > MF
- Counts matter
- Can be unrecognized

**MPN Symptoms**
- MF > PV > ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive Rx frequently not effective

**Baseline Health**
Age/Medicines
Comorbidities

**Progression**
- PV/ET to MF
- PV/ET to AML
- MF to AML
- ? 2nd MDS

**Cytopenias**
- MF > ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
- TPN 30%

**Splenomegaly**
- MF > ET/PV
- Pain not always a function of size
What do symptoms tell us about MPN Biology?

MPN Symptoms

- Mood Disorders
- Anxiety over Uncertainty

Cytokine Driven Symptoms
- Spleen/Inflammation
Fatigue

Symptom

Pathways

Cytokines

Fatigue

Hypocortisolism

IL4, IL6, IL8, IL10, TNFa

HPA Axis Dysregulation

IL1, IL6

Cytopenias

IL1, IL6, TNFa

Depressed Mood

IL6

Abdominal Symptoms

Symptom Category

Abdominal Symptoms

Symptom

Abdominal Pain
Abdominal Discomfort
Early Satiety

Pathways

Splenomegaly, (Hematopoietic Expansion)
Abdominal Thrombosis
Portal HTN
Cytokine-Induced Nerve Hyperstimulation

Cytokines

TNF-α
MIG, HGF, IL-1RA
IL1b, IL6, IL8, hsCRP, IL-12, TNFα
hs-CRP and PTX3
TNF-α, IL-1, and IL-6
IL-2 mRNA and TNF-α mRNA
Constitutional Symptoms

Overview

Symptom
- Fevers
- Chills
- Night Sweats
- Weight Loss

Pathways
- Direct Activation
- Portal HTN/Thrombosis
- Cancer Cachexia
- Microbiome
- Splenomegaly/ Early Satiety
- Appetite Loss

Cytokines
- IL-1, IL-2, IL-6, TNF-α, and IFN
- Leptin, CD40L
- TNFa
- Other pathways as mentioned
Microvascular Symptoms

Symptom Category

- Microvascular Symptoms
- Sexual Dysfunction
- Cognitive Symptoms (Headaches, Dizziness, memory changes, N/T, Vertigo)

Symptom

- Itching
- Iron Deficiency
- Blood Brain Barrier Permeability
- Depression
- Thrombosis

Pathways

- Basophil and Mast Cell Activation, prostaglandin
- Altered Neurotransmitter Function
- IL-1β, TNF-α, IL-6, and CRP
- CRP

Cytokines

- Leukotriene, Histamine, Tryptase
- Low Ferritin
- RANTES and Pal1
- As detailed prior
What is Precise and Personalized Cancer Care?

Molecular Features of Disease

Individualized Supportive Care Needs?

Communication
Social DOH
Health Literacy

Individual Health Factors In Treatment Planning?

Geography
Employment
Financial Pressures

Disease impact Symptoms QoL?

Individual Cultural Value Factors In Treatment Planning?

Individualized Survivorship?
Weaving Molecular Data into Cancer Care

Screening
Diagnosis
Prognosis
Treatment Planning
Genetic Counseling
CHIP
Drug Toxicity
MRD
Trial Eligibility
Decision Support
Prevention

Image: Nature 2020
Therapy of MPNs 2023

- Goals and Targets
- ET and PV
- JAK Inhibitors as Foundation
- Non JAKi MOA
- Other Gaps
- Putting it all Together
What is a treatment guideline?

Guideline – Guardrails

*The science of medicine*

How applied to an individual

*The art of medicine*
NCCN Guidelines Version 3.2022
Polycythemia Vera

Gap 1
Who needs treatment vs Risk?


Gap 2
Do we manage CV risk well?

Gap 3
We need more and better treatments for ET?

Gap 4
Predicting Progression and what is adequate response?

TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA

- Manage cardiovascular risk factors (see MPN-H)
- Aspirin (81–100 mg/day)
- Phlebotomy (to maintain hematocrit <45%)

Regimens for cytoreductive therapy:
- Preferred regimen: Hydroxyurea or Peginterferon alfa-2a or Other recommended regimen: Ropogeninterferon alfa-2b-njft for high-risk PV

- Monitor for new thrombosis or bleeding
- Monitor response and signs/symptoms of disease progression (MPN-10; MPN-E 2 of 2) every 3–6 months or more frequently as clinically indicated

Adequate response
- Potential indications for change of cytoreductive therapy:
  - Intolerance or resistance to hydroxyurea, or peginterferon alfa-2a
  - New thrombosis or disease-related major bleeding
  - Frequent phlebotomy or intolerant of phlebotomy
  - Splenomegaly
  - Progressive thrombocytosis and/or leukocytosis
  - Disease-related symptoms (eg, pruritus, night sweats, fatigue)

Inadequate response or Loss of response
- Ropogeninterferon alfa-2b-njft if not previously used or Hydroxyurea if not previously used or Peginterferon alfa-2a if not previously used

Disease progression to MF/AML

Preferred regimens:
- Clinical trial or Ruxolitinib (category 1 for high-risk PV)
- Other recommended regimens:

Continue treatment

Go to page 52
Therapy of MPNs 2023

- Goals and Targets
- ET and PV
- JAK Inhibitors as Foundation
- Non JAKi MOA
- Other Gaps
- Putting it all Together
JAK Inhibitor Landscape 2023

Approved
- Ruxolitinib
  1L - MF, 2L PV
- Fedratinib
  MF-1L
- Pacritinib
  MF (Low PLT)

NOW Approved

Seeking Approval
- Momelotinib
  MF
- Ruxolitinib Combinations
- NS - 018
  MF

Sierra Oncology
NCT04173494

Inactive
- XL-019
- BMS-911543
- AZD-1480
- LY-2784544
Gap 1: Who needs treatment vs Risk?

JAKi are helpful but how do we optimize and which agent when?

Gap 2: We still likely do transplant too late in too many

Gap 4: Predicting Progression and what is adequate response?

NCCN Guidelines Version 3.2022
Myelofibrosis

Gap 3: JAKi are helpful but how do we optimize and which agent when?

Not a transplant candidate and symptomatic \(^b\) anemia only

See MF-3

Gap 5: How do we get to deeper and broader impact?

Disease progression \(^g\)

Advanced-stage MF/AML (See MF-4)

Therapy of MPNs 2023

- Goals and Targets
- ET and PV
- JAK Inhibitors as Foundation
- Non JAKi MOA
- Other Gaps
- Putting it all Together
Current Phase III trials in MF

**Ruxolitinib**
- Pacritinib (JAKi) NCT03165734 (PACIFICA)

**Combination RX**
- Pelabresib (BETi) NCT04603495 (MANIFEST II)
- Navitoclax (Bcl-XL) NCT04472598 (TRANSFORM I)
- Parscilisib (PI3K Inhib) NCT04551053 (LIMBER 313)

**SubOpt JAKI ADD-ON**
- Luspatercept (Activin) NCT04717414 (INDEPENDENCE)
- Navitoclax (BCL-Xli) NCT04468984 (TRANSFORM II)
- Parscilisib (PI3Ki) NCT04551053 (LIMBER304)
- KRT-232 (HDM2) NCT03662126 (BOREAS)

**JAKI Fail**
- Imetelstat (Telomerase) NCT04576156
- Momelotinib (JAKI) NCT04173494 (MOMENTUM)
Immune Therapies

- **anti-CTLA-4**
  - ipilimumab 2011
  - melanoma

- **anti-PD-1**
  - pembrolizumab 2014
  - nivolumab 2014
  - melanoma, renal, lung
  - Hodgkin’s disease, head and neck, MSI+, DDR+
  - bladder, Merkel cell, ped’s colorectal, hepatocellular

- **anti-PD-L1**
  - atezolizumab 2017
  - avelumab 2017
  - durvalumab 2017
  - Merkel cell, bladder, lung
Target MF Stem Cell: NCI Funded MPN RC

**Figure 1. Bench to bed strategy to deplete MF stem cells.**

**Table 1. Members of the MPN-RC**

<table>
<thead>
<tr>
<th>Institutions</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icahn School of Medicine at Mount Sinai, NY, NY*</td>
<td>Ronald Hoffman, MD (PI)</td>
</tr>
<tr>
<td>Cedars-Sinai Medical Center, Los Angeles, CA*</td>
<td>Ronald L. Paquette, MD*</td>
</tr>
<tr>
<td>Cleveland Clinic Lerner College of Medicine of CWRU, Cleveland, OH*</td>
<td>Aaron Gerds, MD*</td>
</tr>
<tr>
<td>Mayo Clinic Arizona, Scottsdale, AZ*</td>
<td>Amylou Dueck, PhD</td>
</tr>
<tr>
<td>Mays Cancer Center; University of Texas Health Science Center, San Antonio, TX*</td>
<td>Ruben Mesa, MD*</td>
</tr>
<tr>
<td>Moffitt Cancer Center, Tampa FL*</td>
<td>Andrew Kuykendall, MD*</td>
</tr>
<tr>
<td>St. Jude Children’s Research Hospital, Inc.</td>
<td>John Crispino, PhD</td>
</tr>
<tr>
<td>Sloan Kettering Institute for Cancer Research, NY, NY*</td>
<td>Ross Levine, MD</td>
</tr>
<tr>
<td>University of Kansas Medical Center Research Institute, Westwood, KS*</td>
<td>Abdulraheem Yacoub, MD*</td>
</tr>
<tr>
<td>Wake Forest University Health Sciences, Winston-Salem, NC*</td>
<td>Rupali Bhave*</td>
</tr>
<tr>
<td>Roswell Park Comprehensive Cancer Center, Buffalo, NY*</td>
<td>Eunice Wang, MD*</td>
</tr>
</tbody>
</table>

*Denotes PI of Clinical Sites

---

**Projects 1-3: Laboratory investigations**

- Characterizing MF Stem Cells and Microenvironment
- Depletion of MF Stem Cells and Dampening of Tumor Microenvironment

**Project 4: Translation to the clinic**

- Novel MPN Therapeutic Approaches/Combination Therapies
Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms

Edimara Reis¹, Rebecca Buonpane¹, Hamza Celik¹, Caroline Marty², Angela Lei¹, Fatoumata Jobe¹, Mark Rupar¹, Yue Zhang¹, Darlise DiMatteo¹, Rahel Awdew¹, William Vainchenker², Jing Zhou¹, Ian Hitchcock³, Isabelle Plo², Horacio Nasti¹, Patrick Mayes¹

¹Incyte Corporation, Wilmington, DE, USA; ²INSERM UMR 1287, Université Paris-Saclay, Gustave Roussy, Villejuif, France; ³York Biomedical Research Institute, Department of Biology, University of York, York, UK
Anti-mutCALR antibody selectivity inhibits oncogenic cell proliferation
INCA033989 selectively inhibits cell proliferation and induces death of mutCALR⁺ cells
Cellular Therapies

Tisagenlecleucel (Kymriah™) – ALL, DLBCL
Axicabtagene ciloleucel (Yescarta™) - Lymphoma
Consumer-based meditation app, calm, for treatment of sleep disturbance in hematological cancer patients

- NIH NCI-Funded (1R01CA262041-01A1)
- 5-year project period (2022-2027)
- Target enrollment = 276 heme cancer patients actively undergoing treatment
- 20-wk RCT comparing Calm meditation app to health education podcast app (8-wk intervention + 12-wk follow-up)
- Primary outcomes: Oura Ring sleep; PROMIS sleep, sleep diary
- Secondary outcomes: fatigue, anxiety, depression, and QoL (PROMIS); inflammatory biomarkers (TNF-a; IL-6; IL-8; CRP)

**R01 project kicked off in April 2022**

**Study preparation and planning**
- First ~6-9 months of project
- Prepare study documents and materials
- Receive regulatory approvals
- Establish partnerships and contracts
- Develop recruitment materials
- Setup and finalize meditation and podcast apps for study implementation

**Recruitment and enrollment**
- Begins at ~9 months into project
- Kickoff recruitment with project partners
- Primary recruitment methods include sharing of study on social media sites, partner websites and email listservs
- Targeted enrollment of 276 heme cancer patients over ~3.5 years

**Study implementation and data collection**
- Months ~9-54 of the project
- Rolling enrollment of ~10 participants/month
- 20-wk study = 8-wk intervention + 12-wk follow-up
- Outcome measures at baseline, wk 8, and wk 20
- Remote blood draws for inflammatory biomarkers
- Oura ring to capture sleep
- Online surveys via Qualtrics to capture self-report outcomes

**Data analysis and manuscript development**
- Final ~6 months of project
- Complete data analysis
- Develop manuscripts for publication
Therapy of MPNs 2023

- Goals and Targets
- ET and PV
- JAK Inhibitors as Foundation
- Non JAKi MOA
- Other Gaps
- Putting it all Together
We lack effective early detection approaches to diagnose many types of cancer.

We have curative therapies that come at the cost of serious side effects.

We have too few methods to prevent cancer.

We have stark inequities in diagnosis, treatment and trial access, and patient outcomes, based on race, region and resources.

Cancer kills 600,000 people per year in the United States, including close to 1,800 aged 19 and under.

We have limited success in some of the toughest to treat and rare cancers.

Cancer as we know it today
What it will take to end cancer as we know it

<table>
<thead>
<tr>
<th>Build on 50 years of progress</th>
<th>Advance health equity</th>
<th>Personalize cancer care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embrace technology and innovation to learn from every patient</td>
<td>Inspire the next generation of diverse researchers</td>
<td>Prepare for the challenges of the future</td>
</tr>
</tbody>
</table>
Reignition of the Cancer Moonshot 2022

7 Pillars – Progress for
1. Cancer Early Detection
2. Prevention
3. Equity
4. Precision Medicine
5. Rare & Childhood Cancers
6. Supporting Patients & Caregivers
7. Learning From Patients

Priority Actions
• Close the Screening Gap
• Understand & Address Environmental/Toxic Exposures
• Decrease Preventable Cancers
• Bring Cutting Edge Research Through Pipeline to Patients & Communities
• Support Patients and Caregivers
A Team Based Approach for Care

Helping Cancer Patients RISE Beyond Their Cancer!

CANCER MEDICAL SPECIALTIES
- Cardio-Oncology
- Onco-Nephrology
- Ophtho-Oncology
- Palliative Medicine
- Survivorship Clinics
- Endocrine
- Medical Management Clinic

PATIENT & CAREGIVER SERVICES
- Nutrition
- Genetic Counseling
- Psycho-Social Support
- Social Work
- Transportation
- Holistic Support Programs
- Financial Counseling
Standardizing MPN Data Collection

<table>
<thead>
<tr>
<th>Pre MPN History</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Complete Demographics</td>
</tr>
<tr>
<td>• Co-morbidities</td>
</tr>
<tr>
<td>• Meds</td>
</tr>
<tr>
<td>• Fam Hx</td>
</tr>
<tr>
<td>• Prior Events/ Symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MPN Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Labs/ Exam</td>
</tr>
<tr>
<td>• MPN SAF</td>
</tr>
<tr>
<td>• Marrow and NGS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MPN Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Meds/ Toxicities (inc $)</td>
</tr>
<tr>
<td>• Events</td>
</tr>
<tr>
<td>• Serial Labs/ MPN SAF</td>
</tr>
<tr>
<td>• Repeat Marrow NGS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Events</td>
</tr>
<tr>
<td>• Progression</td>
</tr>
<tr>
<td>• Co-Morbidities</td>
</tr>
<tr>
<td>• Mortality</td>
</tr>
</tbody>
</table>
Advancing Inclusive Research®

Enterprise-wide initiative focused on tackling disparities in clinical research

**Situation**
There are well-characterized disparities in clinical research

**Belief**
Roche Genentech believes representation of real-world patient populations is required to improve clinical outcomes for patients

**Aspiration**
More representative patient populations in clinical research to realize the promise of personalized healthcare for all

Sources:
- https://www.census.gov/quickfacts/fact/table/US/PST045216
- https://i0.wp.com/www.brookings.edu/wp-content/uploads/2018/03/20180910_metro_Frey_census-datacharts-revised-Fig1.png?w=768&crop=0%2C0%2C100%2C9999px&ssl=1
- Nature 538, 161–164 (13 October 2016) doi:10.1038/538161a

---

62% CA RESIDENTS ARE NON-WHITE

6 STATES & D.C. HAVE MINORITY-MAJORITY POPULATIONS

2045 WHEN U.S. WILL BE A MINORITY-MAJORITY POPULATION

90% OF GENOMIC MATERIAL AVAILABLE TO SCIENTISTS IS OF EUROPEAN ANCESTRY

LATINOS COMPRIS 17% OF UNITED STATES POPULATION

YET REPRESENT 1-8% OF PATIENTS ON CLINICAL TRIALS

---

62% CA RESIDENTS ARE NON-WHITE

6 STATES & D.C. HAVE MINORITY-MAJORITY POPULATIONS

2045 WHEN U.S. WILL BE A MINORITY-MAJORITY POPULATION

90% OF GENOMIC MATERIAL AVAILABLE TO SCIENTISTS IS OF EUROPEAN ANCESTRY

LATINOS COMPRIS 17% OF UNITED STATES POPULATION

YET REPRESENT 1-8% OF PATIENTS ON CLINICAL TRIALS
What is inclusivity?

1) Race?
2) Ethnicity?
3) Gender?
4) Age span (across the lifespan)?
5) Sexual Orientation?
6) Basically a trial should reflect the population, not a subset
TOPIC: Diversity on Clinical Trials in setting of FDA User Fee Reauthorization Bills
Multiple Challenges to Address to Improve Representation

- Lack of awareness or invitation to participate
- Scientific legacy or bias
- Absence of trust and privacy issues
- Lack of health literacy
- Out of pocket costs for trial patients
- Lack of diversity in genomic research
- Complexity of race with ancestry, lifestyle, environment
- Only 20% global trial patients in US
- Lack of site resources

Advancing Inclusive Research
Why make a trial inclusive?

1) All patients should have a chance to benefit from the benefits of a trial (JUSTICE)

2) Inclusive trials help identify differences in efficacy between subgroups that might better lead to treatment planning (GOOD SCIENCE)

3) Inclusive trials might help to identify differences between subgroups in terms of toxicity that might lead to more precise dosing and use (GOOD PATIENT CARE)
Therapy of MPNs 2023

- Goals and Targets
- ET and PV
- JAK Inhibitors as Foundation
- Non JAKi MOA
- Other Gaps
- Putting it all Together
What is Precise and Personalized Cancer Care?

Molecular Features of Disease
- Multi-Omic
- Dx, treatment, survivorship

Communication
Social DOH
Health Literacy

Individual Health Factors
In Treatment Planning?

Individualized Survivorship?

Individualized Supportive Care Needs?

Disease impact
Symptoms QoL?

Geography
Employment
Financial Pressures

Individual Cultural Value Factors
In Treatment Planning?

Atrium Health

Wake Forest University
School of Medicine
## MPN Patient Community

<table>
<thead>
<tr>
<th>MPN Group</th>
<th>Focus</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPN Research Foundation</td>
<td>RES-ED-ADV</td>
<td><a href="http://www.Mpnresearchfoundation.org">www.Mpnresearchfoundation.org</a></td>
</tr>
<tr>
<td>Leukemia and Lymphoma Society*</td>
<td>RES-ED-ADV</td>
<td><a href="http://www.lls.org">www.lls.org</a></td>
</tr>
<tr>
<td>MPN Advocacy &amp; Education International*</td>
<td>ED-ADV</td>
<td><a href="http://www.mpnadvocacy.com">www.mpnadvocacy.com</a></td>
</tr>
<tr>
<td>MPN Education Foundation*</td>
<td>ED-COMM</td>
<td><a href="http://www.mpninfo.org">www.mpninfo.org</a></td>
</tr>
<tr>
<td>AAMDS Foundation</td>
<td>ED</td>
<td><a href="http://www.aamds.org">www.aamds.org</a></td>
</tr>
<tr>
<td>MPN Voice</td>
<td>ED</td>
<td><a href="http://www.mpnvoice.org.uk">www.mpnvoice.org.uk</a></td>
</tr>
<tr>
<td>MPN HUB*</td>
<td>ED</td>
<td><a href="http://www.mpn-hub.com">www.mpn-hub.com</a></td>
</tr>
<tr>
<td>MPN Advocates Network</td>
<td>ED-ADV</td>
<td><a href="http://www.mpn-advocates.net">www.mpn-advocates.net</a></td>
</tr>
<tr>
<td>Global MPN Scientific Foundation*</td>
<td>RES-ED-ADV</td>
<td><a href="http://www.gmpnsf.org">www.gmpnsf.org</a></td>
</tr>
<tr>
<td>MPN Forum Facebook Group</td>
<td>ED-COMM</td>
<td><a href="https://www.facebook.com/groups/ourmpnforum/">https://www.facebook.com/groups/ourmpnforum/</a></td>
</tr>
</tbody>
</table>