What's New in MPNs?

11th Annual Controversies in Hematologic Malignancies Symposium

May 7, 2022

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knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

Disclosures

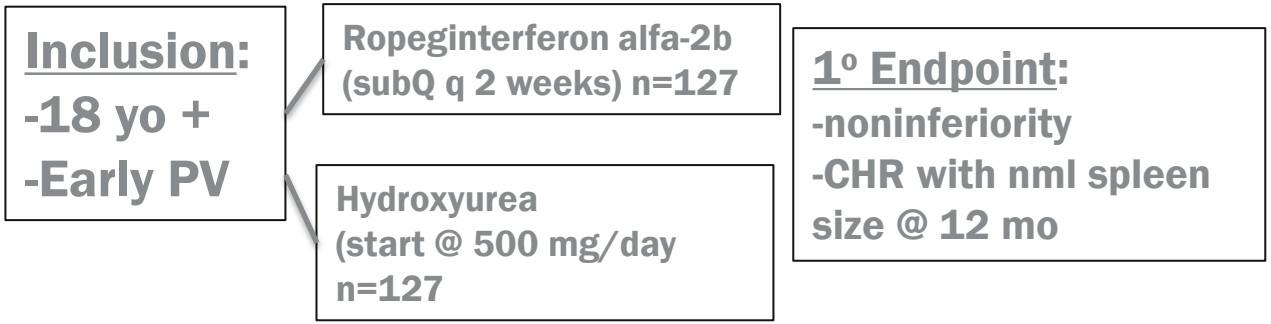
- None

Outline

- PV:
  - Ropeginterferon alfa-2b-njft (Besremi)
- MF:
  - Pacritinib
- SM:
  - Diagnosis
  - Avapritinib
- CNL
  - Diagnosis
  - Treatments?
- Clinical Trials

Polycythemia vera

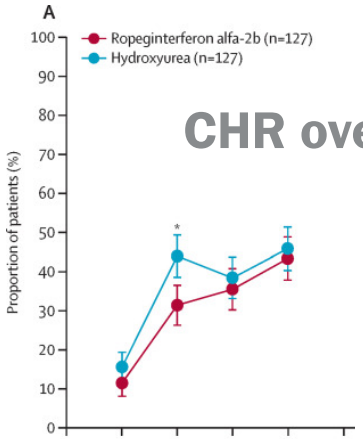
- Ropeginterferon alfa-2b – novel monopegylated interferon
- Extended ½ life, less frequent dosing, improved tolerability
  - PROUD-PV – phase 3, RCT, open label, 48 clinics in Europe



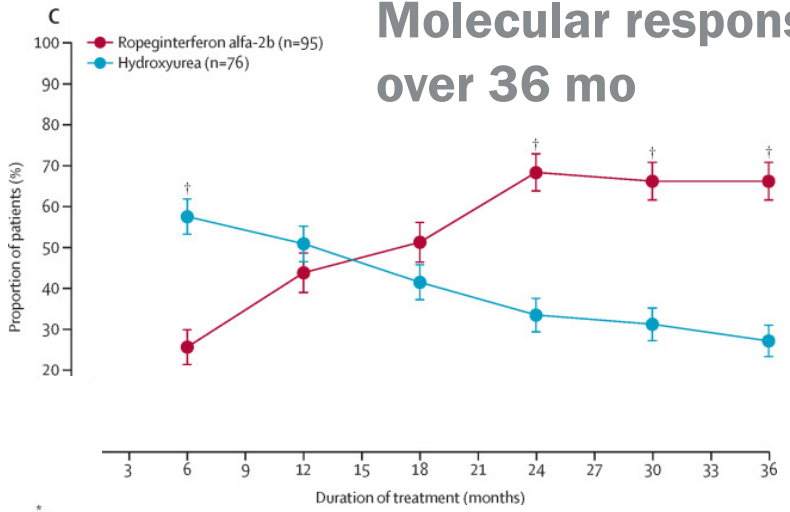
Ropeginterferon alfa-2b

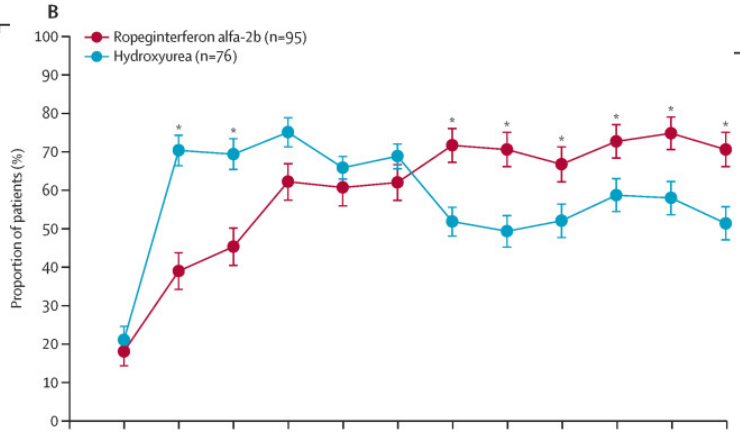
PROUD-PV (n=254)	Ropeginterferon alfa-2b	Control	Difference in responses (95% CI)	P value
CHR + nml spleen size at month 12	26/122 (21%)	34/123 (28%)	-6.57 (-17.23-4.09)	0.23

CHR over 12 mo



Molecular response over 36 mo





CHR over 36 mo

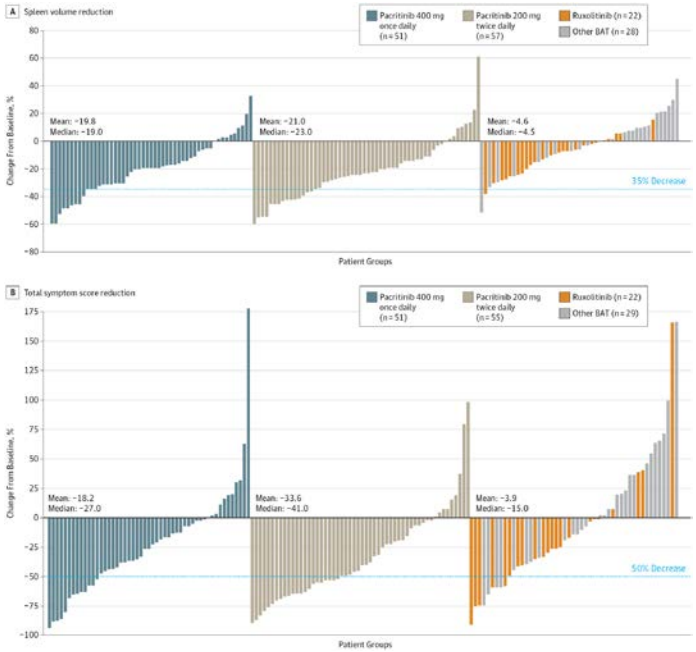
Adverse Events

- AEs led to dose reduction 40% vs 58% standard therapy + dose interruption of 23% vs 18%
- 8% of patients in IFN group discontinued due to drug related toxicity vs 4% discontinued in standard therapy
- Most common Aes (>10% patients)
  - TCP (22%)
  - Leukopenia (20%)
  - Increased LFTs (10-19%)
  - Fatigue (13%)
  - HA (12%)
  - Arthralgia (12%)
  - Dizziness (11%)

Myelofibrosis

- Pacritinib – oral JAK inhibitor
  - Approved 2/2022 for patients with MF and severe TCP (plt <50)
  - PAC203: phase 2, dose finding
  - PERSIST-1: phase 3
    - 327 patients with MF –pacritinib vs BAT
    - Wk 24: 19% pactritinib patients had spleen reduction of 35% or more; 5% in control; 90 patients in control crossed over
  - PERSIST-2: phase 3 randomized international multicenter study
    - 311 patients with MF who also had TCP; primary endpoint of efficacy; BID pacritinib had 18% with spleen reduction versus 3% on BAT
      - Cross-over allowed after week 24 or for progression of splenomegaly

Pacritinib



Waterfall plots for spleen volume reduction (A) and total symptom score reduction (B) from baseline for evaluable patients are shown.

SVR: 18% vs 3% (p .001)

Symptom reduction: 25% vs 14% (p .08)

Mean and median percent decreases from baseline were greater with pacritinib vs BAT.

Of note, SVR≥10% was achieved in 72.5%, 78.9%, and 36.0% of evaluable patients with pacritinib once daily, pacritinib twice daily, and best available therapy, respectively.

Systemic Mastocytosis

At least 1 major + 1 minor or 3 minor

- Major:
  - Multifocal dense infiltrates of MC (≥ 15 MCs in aggregates) in BM or other tissues
- Minor:
  - >25% of all MCs are atypical on BM aspirate or spindle shaped on tissue sections
  - KIT mutation at codon 816
  - MCs express CD2 and/or CD25
  - Serum tryptase > 20 ng/mL (unless an AHN is present)

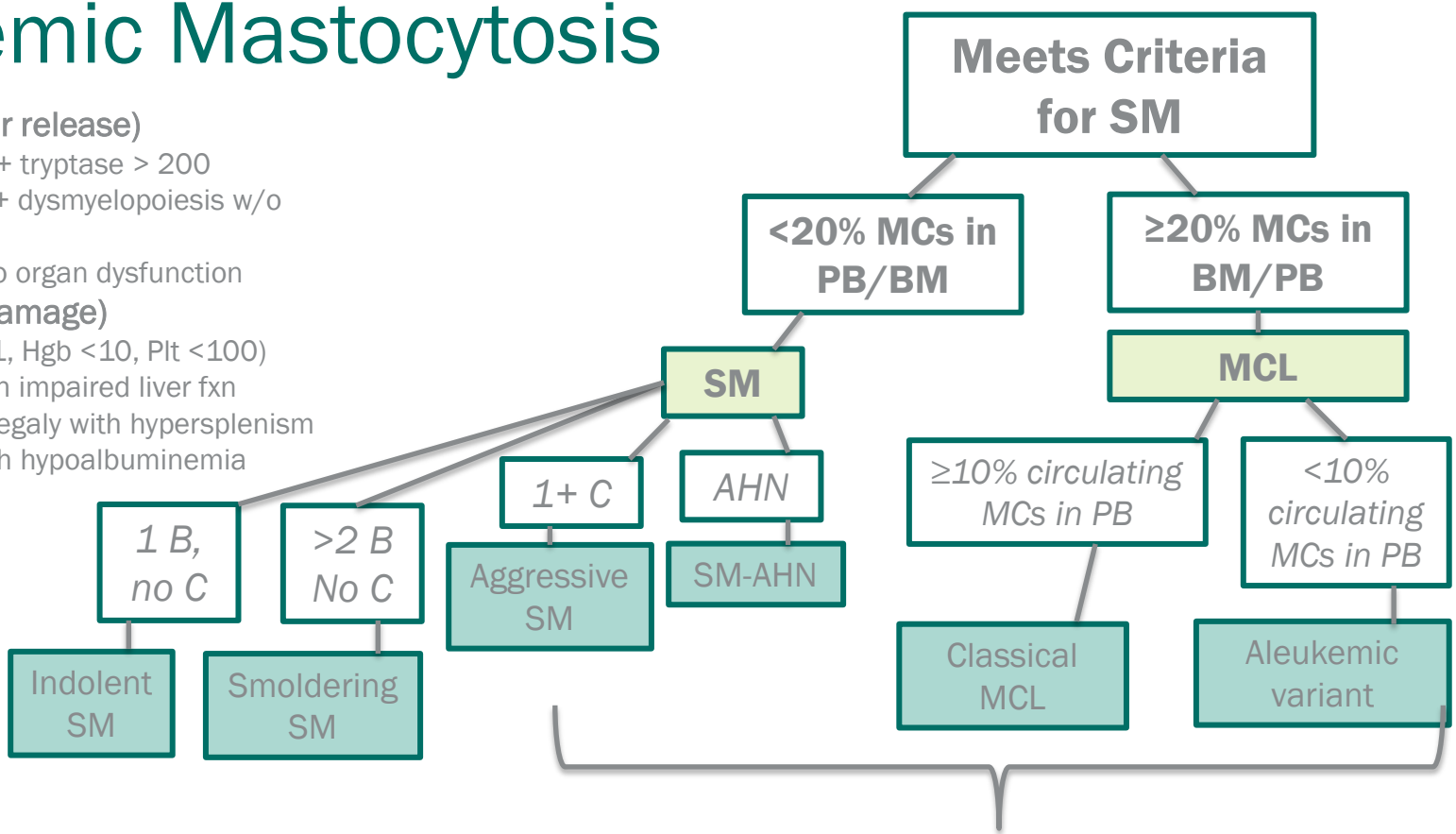
Systemic Mastocytosis

B findings (mediator release)

- MCs in BM >30% + tryptase > 200
- Hypercellular BM + dysmyelopoiesis w/o cytopenias
- Organomegaly w/o organ dysfunction

C findings (tissue damage)

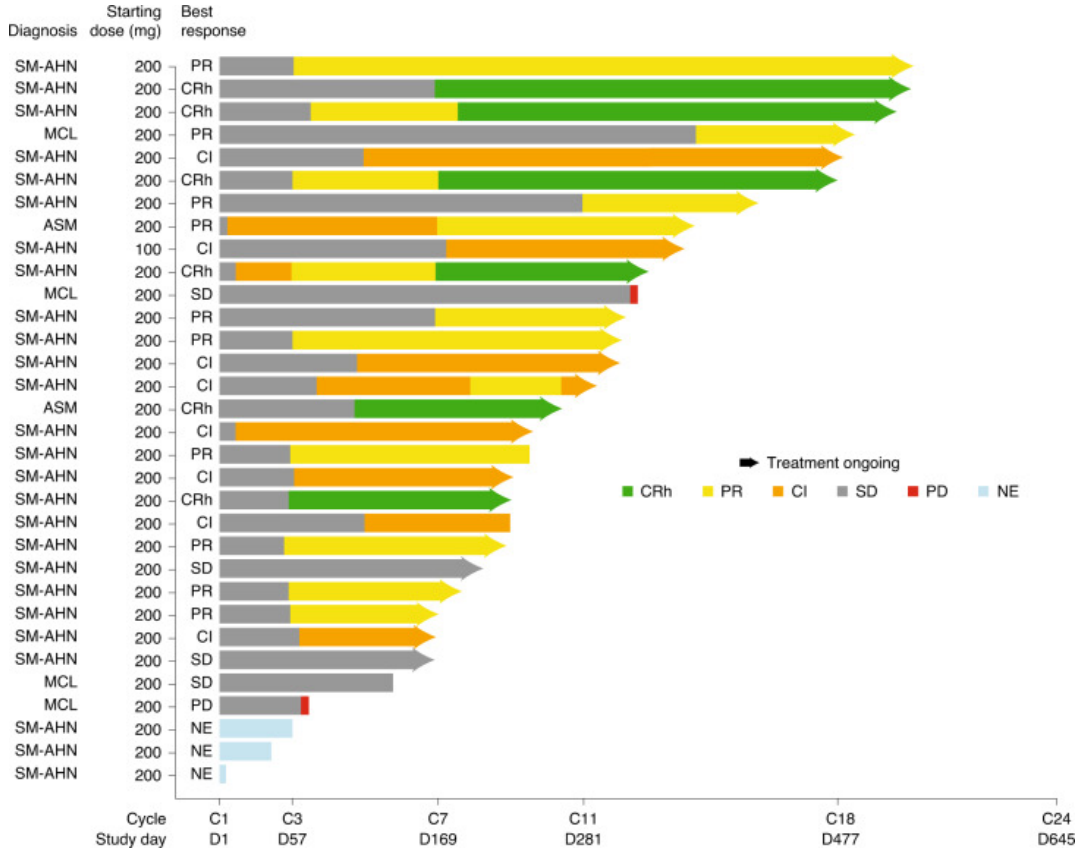
- Cytopenia (ANC <1, Hgb <10, Plt <100)
- Hepatomegaly with impaired liver fxn
- Palpable splenomegaly with hypersplenism
- Malabsorption with hypoalbuminemia
- Skeletal lesions



Avapritinib

- FDA approved in 6/2021
  - EXPLORER
    - Ph1 trial in patients with ASM
      - Primary endpoint: MTD/RP2D
      - Secondary endpoints: ORR, change in measures of mast cell burden
        - » Noted a 75% ORR
  - PATHFINDER
    - International, multicenter, open label single arm phase 2 registrational trial
    - Avapritinib 200 mg daily in adult patients with AdvSM
      - Primary endpoint: ORR (CR/CRh, PR, CI)

	Safety Population (*n*=62)	Interim Analysis Efficacy Population (*n*=32)	Population not included in Interim Analysis (*n*=30)
Median age, years (range)	69 (31-88)	68 (37-85)	70 (31-88)
Male / female, *n* (%)	34 (55) / 28 (45)	18 (56) / 14 (44)	16 (53) / 14 (47)
ECOG performance status, *n* (%)			
0-1	43 (69)	21 (66)	22 (73)
2-3	19 (31)	11 (34)	8 (27)
AdvSM subtype per central assessment, *n* (%)			
ASM	9 (15)	2 (6)	7 (23)
SM-AHN	43 (69)	26 (81)	17 (57)
MCL	10 (16)	4 (13)	6 (20)
KIT D816V mutation status in peripheral blood by central ddPCR, *n* (%)			
Positive	59 (95)	30 (94)	29 (97)
Negative	3 (5)	2 (6)	1 (3)
KIT D816V variant allele fraction in blood, median percent (range)	18 (0-47)	15 (0-45)	19 (0-47)
SRSF2/ASXL1/RUNX1 mutation per central assay, *n* (%)			
Positive	26 (42)	17 (53)	9 (30)
Negative	36 (58)	15 (47)	21 (70)
Prior anti-neoplastic therapy, *n* (%)			
Any	42 (68)	23 (72)	19 (63)
Midostaurin	34 (55)	17 (53)	17 (57)
Cladribine	8 (13)	4 (13)	4 (13)
Imatinib	5 (8)	4 (13)	1 (3)
Interferon	6 (10)	2 (6)	4 (13)
Bone marrow biopsy mast cell burden, median percent (range)	45 (1-95)	50 (10-95)	35 (1-90)
Serum tryptase level, median ng/mL (range)	283 (24-1600)	293 (24-1600)	276 (31-1208)
Spleen volume, median mL (range)	748 (44-2601)	939 (150-2270)	671 (44-2601)


Diagnosis
Starting dose (mg)
Best response
SM-AHN 200 PR
SM-AHN 200 CRh
SM-AHN 200 CRh
MCL 200 PR
SM-AHN 200 CI
SM-AHN 200 CRh
SM-AHN 200 PR
ASM 200 PR
SM-AHN 100 CI
SM-AHN 200 CRh
MCL 200 SD
SM-AHN 200 PR
SM-AHN 200 PR
SM-AHN 200 CI
SM-AHN 200 CI
ASM 200 CRh
SM-AHN 200 CI
SM-AHN 200 PR
SM-AHN 200 CI
SM-AHN 200 CRh
SM-AHN 200 CI
SM-AHN 200 PR
SM-AHN 200 SD
SM-AHN 200 PR
SM-AHN 200 PR
SM-AHN 200 CI
SM-AHN 200 SD
MCL 200 SD
MCL 200 PD
SM-AHN 200 NE
SM-AHN 200 NE
SM-AHN 200 NE
Treatment ongoing
CRh PR CI SD PD NE
Cycle C1 C3 C7 C11 C18 C24
Study day D1 D57 D169 D281 D477 D645

Adverse Events

- Peripheral edema/periorbital edema (50%, 3%)
- Diarrhea (23%, 2%)
- Nausea (18%, 2%)
- Vomiting (18%, 2%)

- TCP (45%, 16%)
- Anemia (32%, 16%)
- Neutropenia (24%, 24%)*grade 4 rare at 8%

1 ICB (1.6%) in pt with severe TCP at baseline

safety analysis of these + other ph1 events identified patients with baseline severe TCP at substantially increased risk of ICB, therefore pt with plt <50 were subsequently excluded

3 deaths due to AEs: disease progression, nec fasc, hemorrhagic shock

Chronic Neutrophilic Leukemia (CNL)

- Rare, BCR-ABL negative MPN characterized by sustained predominantly mature neutrophil proliferation + HSM
- Constitutional symptoms – fatigue, bone pain, pruitus, easy bruising, gout
- Linked to bleeding diathesis
  - ?TCP, platelet dysfunction, vascular infiltration
- Mild anemia and/or TCP
- Elevated LDH, LAP score, B12, low G-CSF levels
- Disproportionately high # associated with plasma cell neoplasms

Chronic Neutrophilic Leukemia

- 2016 WHO criteria
  - PB WBC ≥ 25
    - Segmented neutrophils + bands ≥ 80% of WBCs
    - Neutrophil precursors <10% of WBCs
    - Myeloblasts rarely observed
    - Monocyte count <1 x 10^9
    - No dysgranulopoiesis
  - Hypercellular BM
    - Neutrophil granulocytes increased in percentage and number
    - Neutrophil maturation appears normal
    - Myeloblasts <5% of nucleated cells
  - Not meeting WHO criteria for BCR-ABL+ CML, PV, ET or PMF
  - No rearrangement of PDGFRA, PDGFRB, FGFR1 or PCM1-JAK2
  - Presence of **CSF3R** T618I or other activating CSF3R mutations

In ABSENCE of CSFR3 mutation, persistent neutrophilia (at least 3 mo), splenomegaly and no identifiable cause of reactive neutrophilia including absence of plasma cell neoplasm, or if present, demonstration of clonality of myeloid cells by CG or molecular studies

Chronic Neutrophilic Leukemia

- DDx:
  - Reactive/leukomoid reaction
  - CML; neutrophilic-CML (CML-N)
    - CML-N: prominent neutrophilia, an uncommon BCR-ABL translocation (p230)
  - MPN/MDS overlap – aCML, CMML
    - aCML: leukocytosis, prominent granulocytic dysplasia
  - Rare paraneoplastic leukocytosis from ectopic production of G-CSF from solid tumors (urological, lung, mesothelium, thyroid)

Chronic Neutrophilic Leukemia

- Treatment
  - Splenic irradiation/splenectomy (worsens neutrophilia post-op)
  - Hydroxyurea
  - IFN-alpha
  - HMAs
  - **Ruxolitinib**
  - Thalidomide
  - Cladribine
  - Imatinib
  - ~~3+7~~

  -HSCT

Clinical Trials

- Constellation
  - phase 2 study of CPI-0610 (BET i)+/- rux for **MF**
- Kartos
  - Phase 2 study of KRT-232 (MDM2 inhibitor) in **PMF, post PV MF or post ET MF** patients who have failed prior treatment with a JAK inhibitor
- Pharmaessentia
  - Phase 3 open label multicenter randomized active controlled study of P1101 (Ropeginterferon alfa-2b) vs anagrelide as second line for **ET**

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Questions?