MASTOCYTOSIS AND EOSINOPHILIC DISORDERS

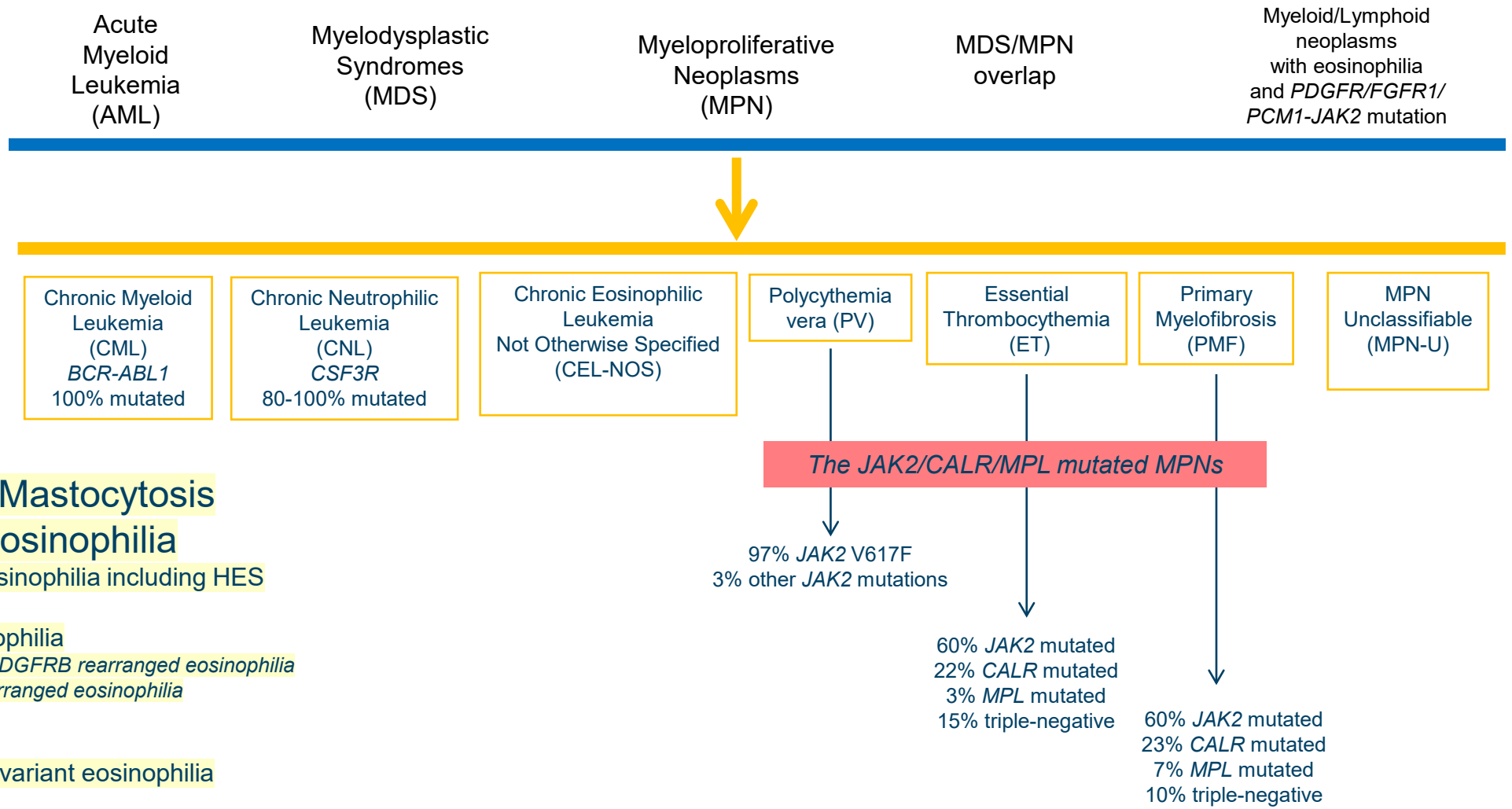
Ayalew Tefferi, MD
Barbara Woodward Lips Professor of Medicine
Mayo Clinic
Rochester, MN

I have nothing to declare

Disclosures for Ayalew Tefferi

Investigator role	Janssen, Geron, Celgene, Sanofi-Aventis, Gilead Sciences, Incyte
Employee	None
Consultant	None
Major Stockholder	None
Speakers' Bureau	None
Scientific Advisory Board	None

2016 WHO Classification of Myeloid Malignancies



Systemic Mastocytosis

Primary Eosinophilia

- Idiopathic eosinophilia including HES
- Clonal eosinophilia
  - *PDGFRA/PDGFRB rearranged eosinophilia*
  - *FGFR1 rearranged eosinophilia*
  - *CEL-NOS*
- Lymphocytic variant eosinophilia

***Blood*. 2016 May 19;127(20):2391-405**

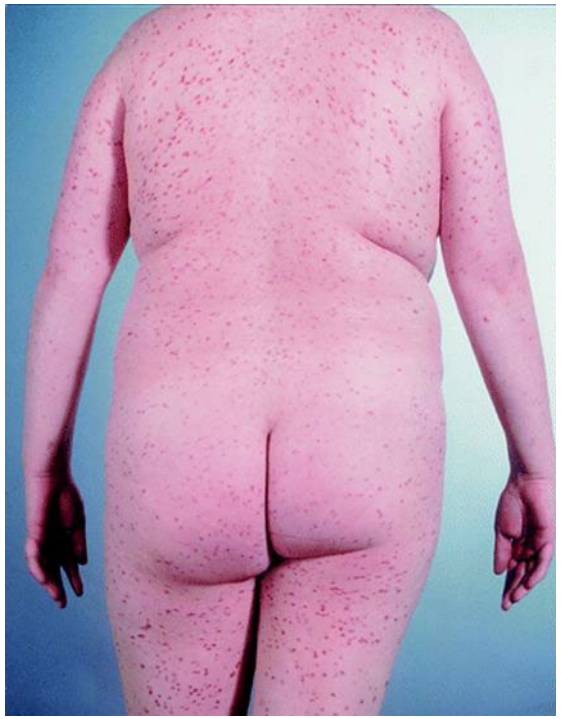
Learning objectives

- Discuss a practical approach to diagnosis and classification
- Describe a practical approach to prognostication
- Select a practical approach to treatment

Mastocytosis

When should you suspect it?

- Urticaria pigmentosa-like lesions
- Mast cell mediator symptoms
  - Anaphylactoid symptoms/dizziness
  - Diarrhea
  - Flushing/urticaria
- Osteopenia/unexplained fractures



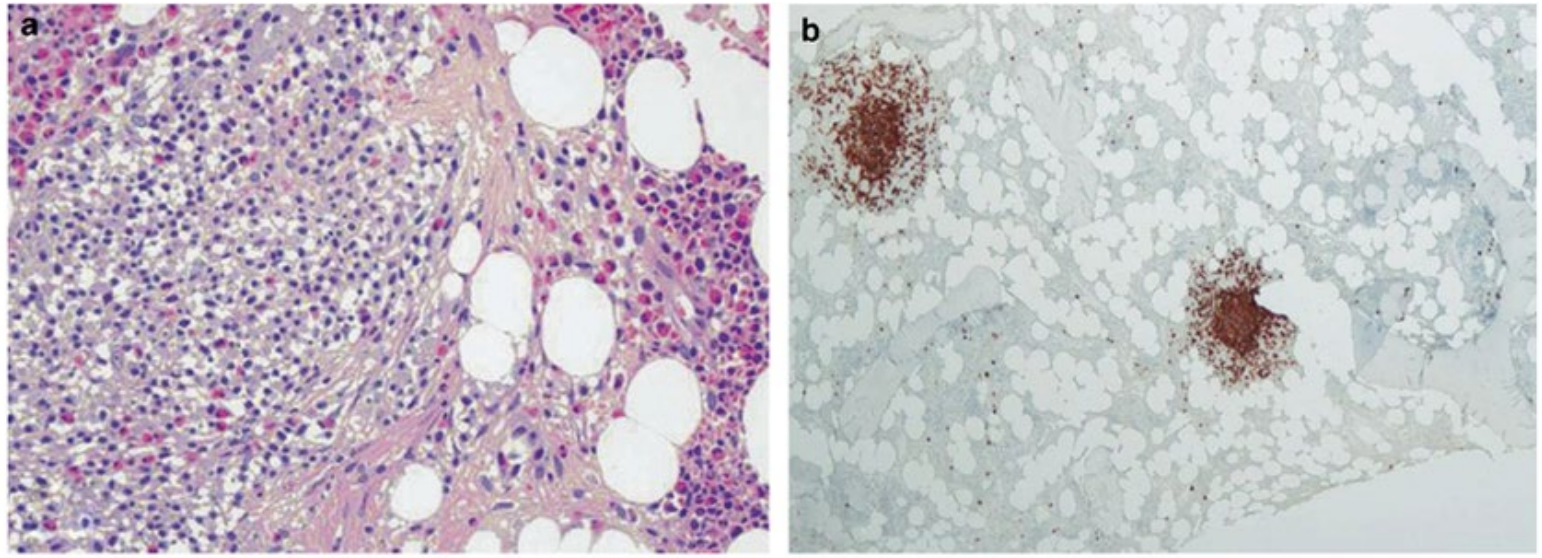
Deb A, Tefferi A.N Engl J Med. 2003;349

Diagnosis requires one major criterion + 1 minor criterion or ≥3 minor criteria

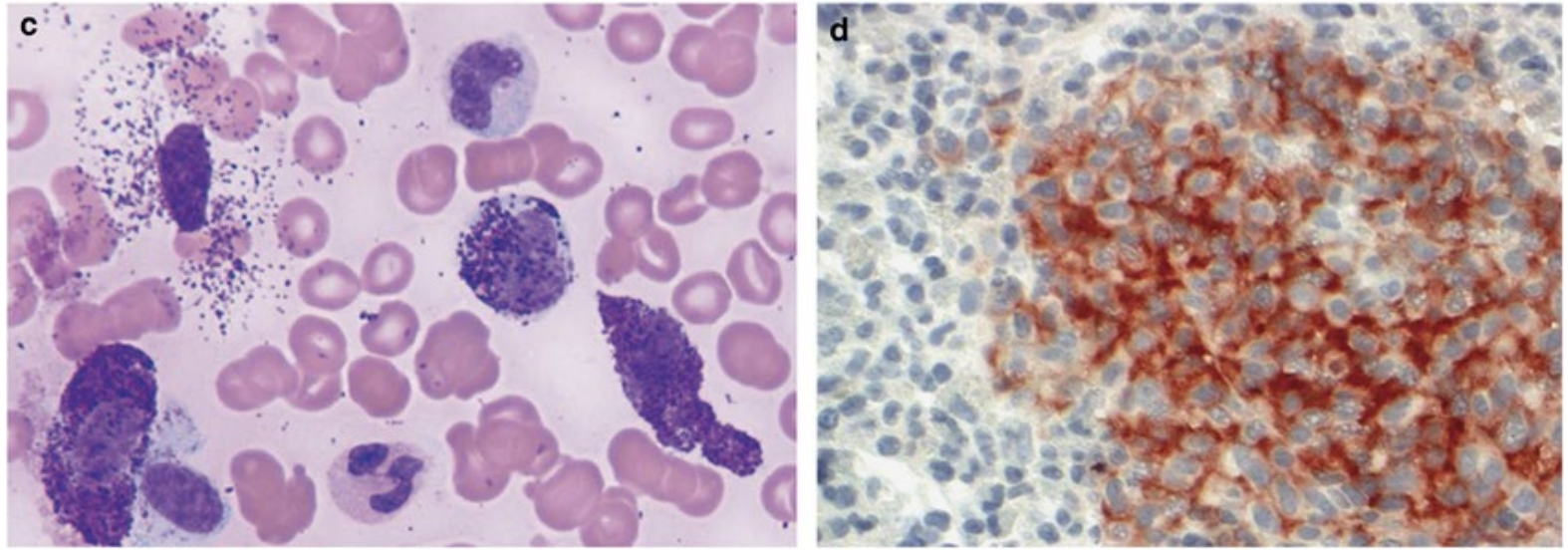
Bone marrow biopsy:
multifocal aggregates
of ≥15 mast cells
(**major diagnostic criterion**)

Minor criteria

1. *KIT*D816V mutation
2. Serum tryptase >20 ng/mL
3. >25% of mast cells are atypical
4. CD25 mast cell expression



Bone marrow biopsy:
Tryptase immunostain



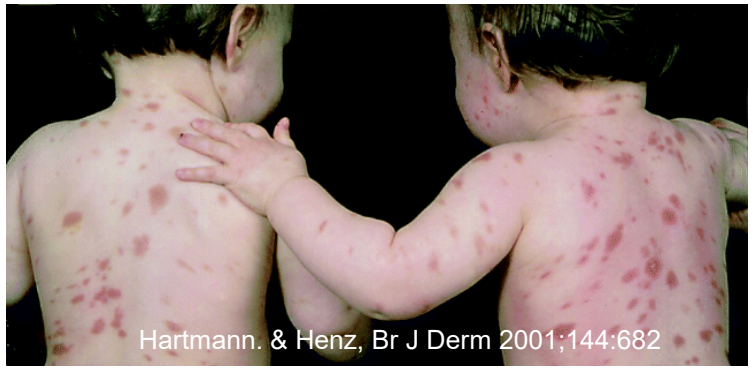
Bone marrow aspirate:
Spindle-shaped and
degranulated and
hypogranulated
mast cells

Bone marrow biopsy:
CD25 immunostain

Johnson et al. *Modern Pathology* (2009) 22, 50

Practical classification of mast cell disease

1 **Cutaneous mastocytosis (skin-only disease)**



Both can manifest mast cell mediator release symptoms

2 **Systemic mastocytosis (SM)**

i **Indolent SM**

No associated hematological neoplasm
No organopathy (i.e., no "C" findings)
("C" findings = ≥1 cytopenia, large osteolytic lesions, or palpable organomegaly with consequences, MC infiltrate-induced malabsorption with weight loss)
±Urticaria pigmentosa
±Mast cell mediator symptoms

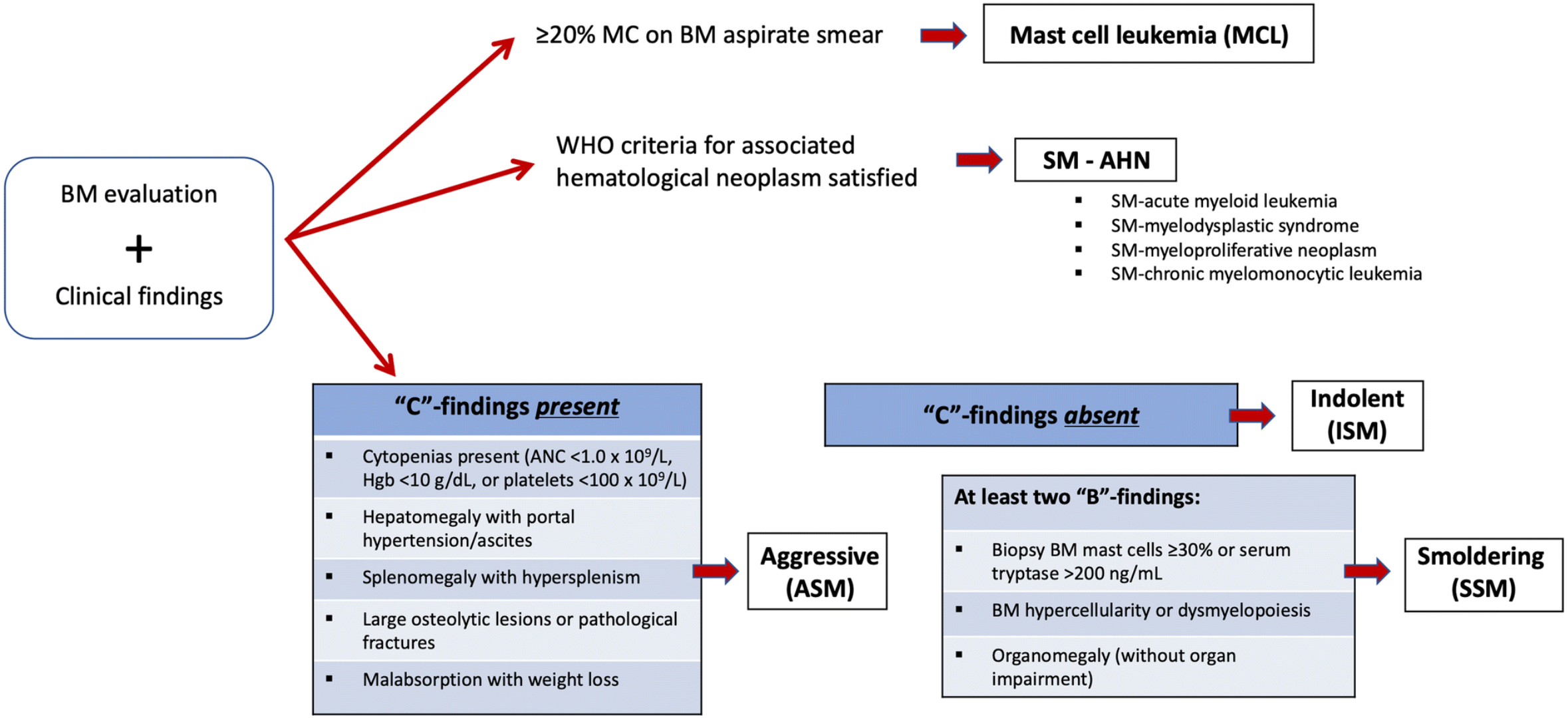
ii **Advanced SM**

1. Aggressive SM (≥1 "C" finding)
2. SM associated hematological neoplasm (SM-AHN)
3. Mast cell leukemia (BM aspirate ≥20% mast cells) → *PB often with >10% mast cells*

iii **Smouldering SM**

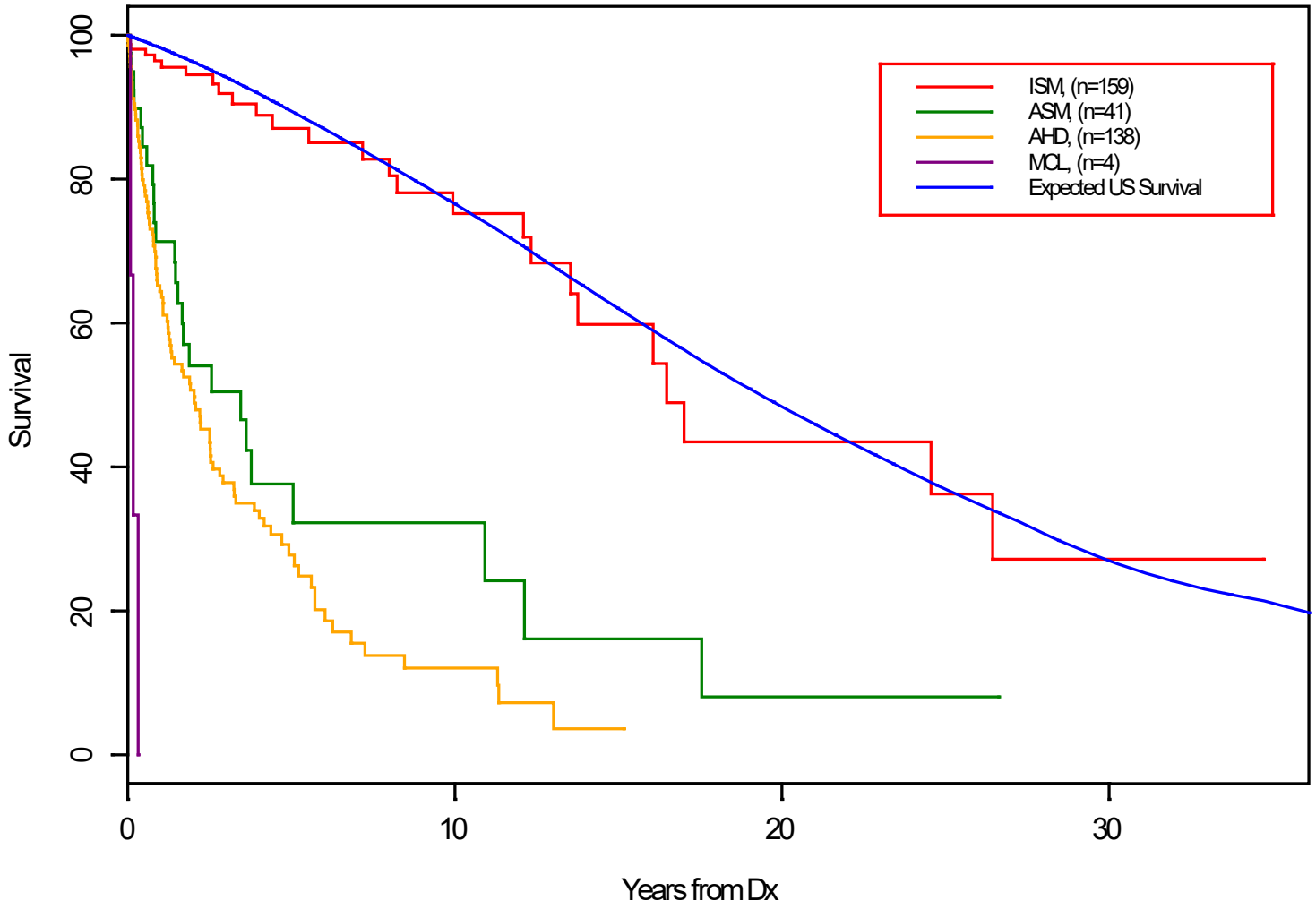
Like indolent but with higher mast cell burden, i.e., ≥2 "B" findings
("B" findings = >30% BM biopsy MC infiltrate or serum tryptase >200 ng/mL; organomegaly without consequences or lymphadenopathy; features of myeloid neoplasm not otherwise classified)

WHO 2016 Classification



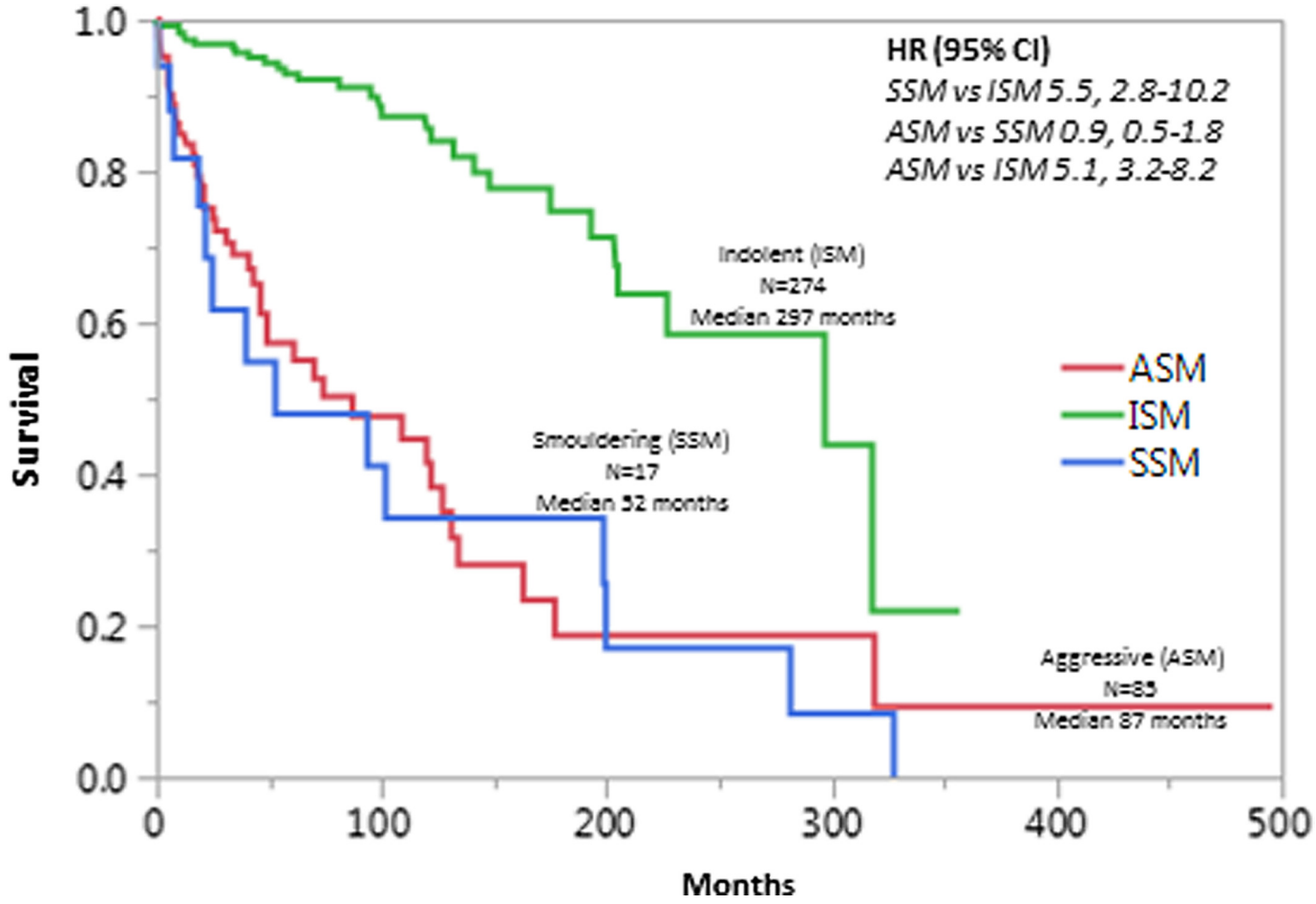
Pardanani algorithm
Mannelli F. *Annals of Hematology.* volume 100, pages337–344 (2021)

Survival for 342 Mayo Clinic patients with systemic mastocytosis classified by disease type and compared with the expected age and gender matched US population



Lim et al. Blood 2009;113:5727.

Smoldering systemic mastocytosis: Survival comparisons with indolent and aggressive mastocytosis

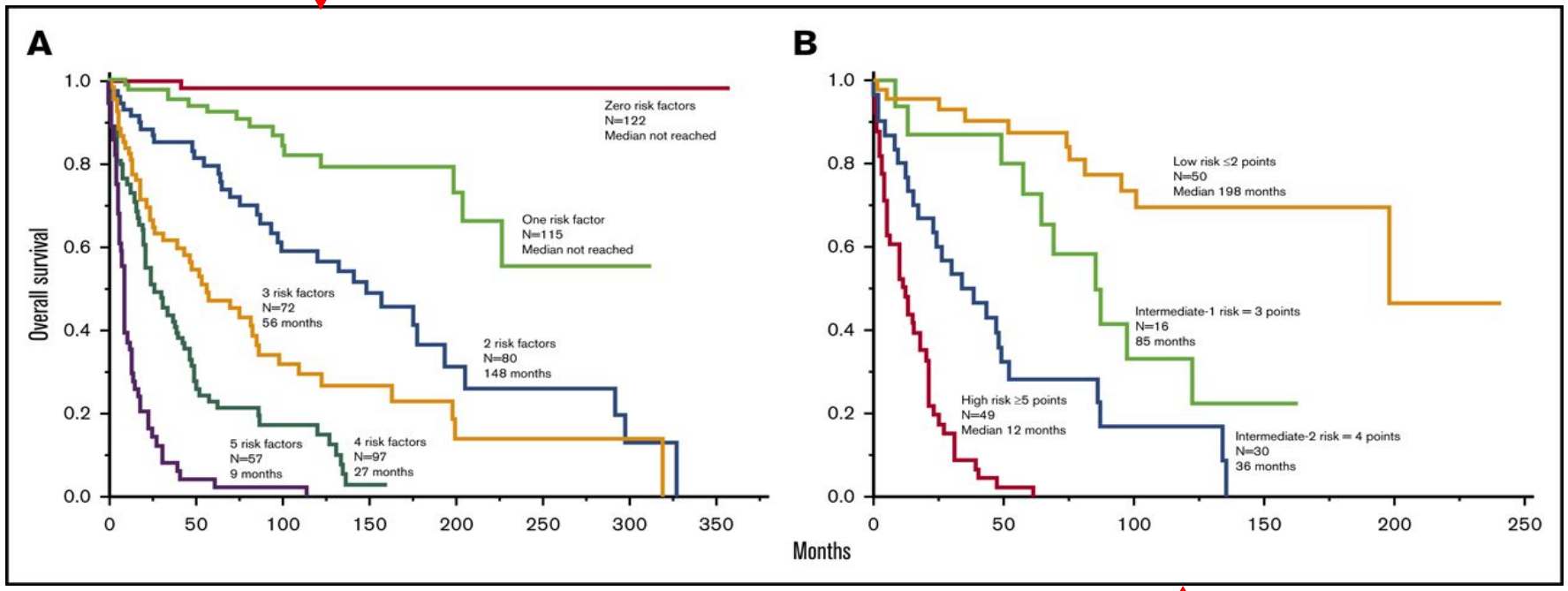


Tefferi et al. American Journal of Hematology, Volume: 94, Issue: 1, Pages: E1-E2, First published: 03 October 2018, DOI: (10.1002/ajh.25302)

New risk models for mastocytosis

A "clinical" risk model for systemic mastocytosis (SM) that is based on number of risk factors:

i) advanced SM vs indolent/smouldering SM
ii) age >60 years
iii) platelets <150 x 10^9/l
iv) anemia below sex-adjusted normal
v) serum alkaline phosphatase above normal range



A "clinical-molecular" hybrid risk model for SM

i) Adverse mutations (*ASXL1*, *RUNX1*, *NRAS*) (1 point)
ii) advanced SM vs indolent/smouldering (2 points)
iii) age >60 years (1 point)
iv) platelets <150 x 10^9/l (1 point)
v) serum alkaline phosphatase above normal range (1 point)

blood advances

Pardanani et al. *Blood Adv* 2018;2:2964-2972

Advanced Systemic Mastocytosis Treatment

Aggressive SM

SM associated with another hematologic neoplasm (SM-AHN)

Mast cell leukemia

	Cladribine 5 mg/m2 2-hr infusion daily x 5 every 4 weeks; N=32 *Barete et al. Blood 2015 126:1009*	**Cladribine 5 mg/m2 2-hr infusion daily x 5 every 4 weeks; N=22** *Tefferi et al. ASH 2021*	**Midostaurin 100 mg PO BID N=89** *Gotlib et al. NEJM.* 2016;374:2530	**Avapritinib 300 mg PO QD N=39** *Radia et al. HemaSphere. 2019;3(Suppl 1)*
Response	OR/MR/PR 50%/38%/13%	OR/MR/PR 77%/45%/32%	OR/MR/PR 60%/45%/15%	OR/CR/CRh/PR/CI 77%/8%/15%/46%/8%
Grade 3/4 neutropenia	47%	Not reported	24%	10%
Grade 3/4 thrombocytopenia	Not reported	32%	29%	23%
Nausea/Vomiting/diarrhea	Not reported	None documented	79%/66%/54%	38/32/41
Periorbital/peripheral edema	Not reported	None documented	Not reported/31%	75%/33%
CNS bleed/cognitive effects/ hair color changes	Not reported	None documented	Not reported	10%/32%/29%

Indolent Systemic Mastocytosis Treatment

H1 and H2 blockers
Leukotriene antagonist
Cromolyn
Phototherapy
Topical steroids

Cetrizine 5-10 mg QD
Fexofenadine 60 mg BID
Hydroxyzine 25 mg q 6 hours

Ranitidine 150 mg BID
Famotidine 10 mg BID
Cimetidine 400 mg BID

Montelukast 10 mg QD
Zafirlucast 20 mg BID

Sodium cromolyn 100-200 mg QID

Osteoporosis prevention
Alendronate 70 mg weekly
Risedronate 35 mg weekly
Pamidronate IV 90 mg q-4 weeks
Zolendronic acid 4 mg IV q 4 weeks

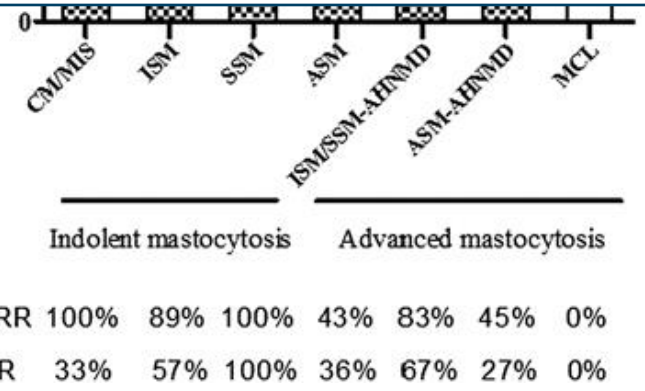
Refractory cases

Cladribine 5 mg/m2; 2-hr infusion daily x 5 every 4 weeks; N=20
Tefferi et al. ASH 2021

OR/MR
70%/60%
UP response 69%; 23% complete response
Mediator symptom response 70%; 20% complete response

15% grade 3 or 4 myeloid cytopenia

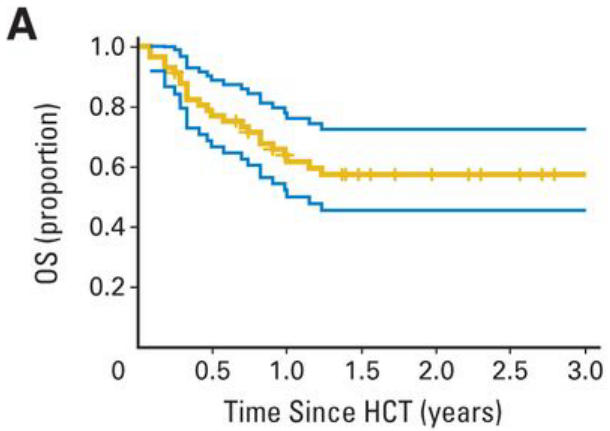
30% grade 3 or 4 lymphopenia

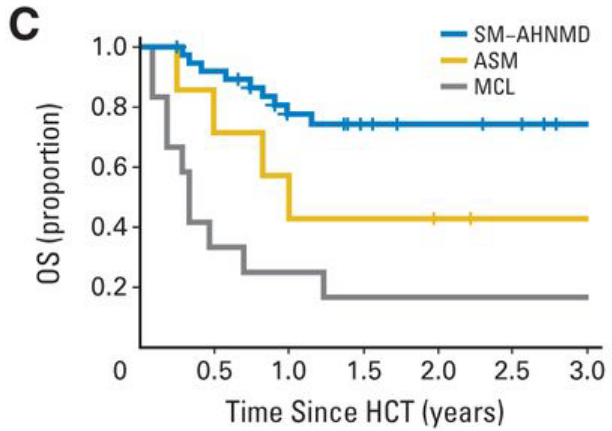


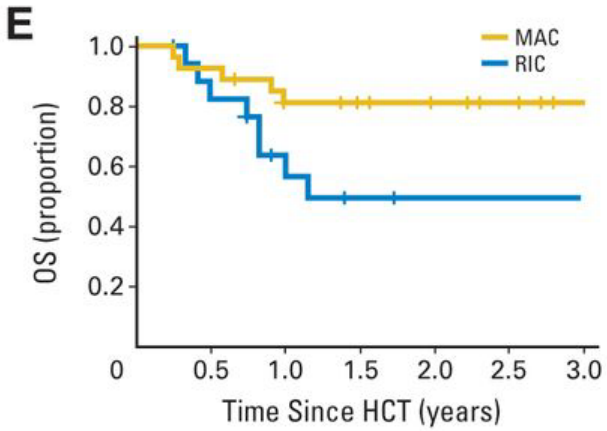
ORR	100%	89%	100%	43%	83%	45%	0%
MR	33%	57%	100%	36%	67%	27%	0%

Barete et al. Blood 2015 126:1009
ISM/SSM = 30 patients

Allogeneic hematopoietic stem-cell transplantation (HCT) in 57 patients with advanced systemic mastocytosis (SM): 38 SM-AHNMD; 12 MCL and 7 aggressive SM







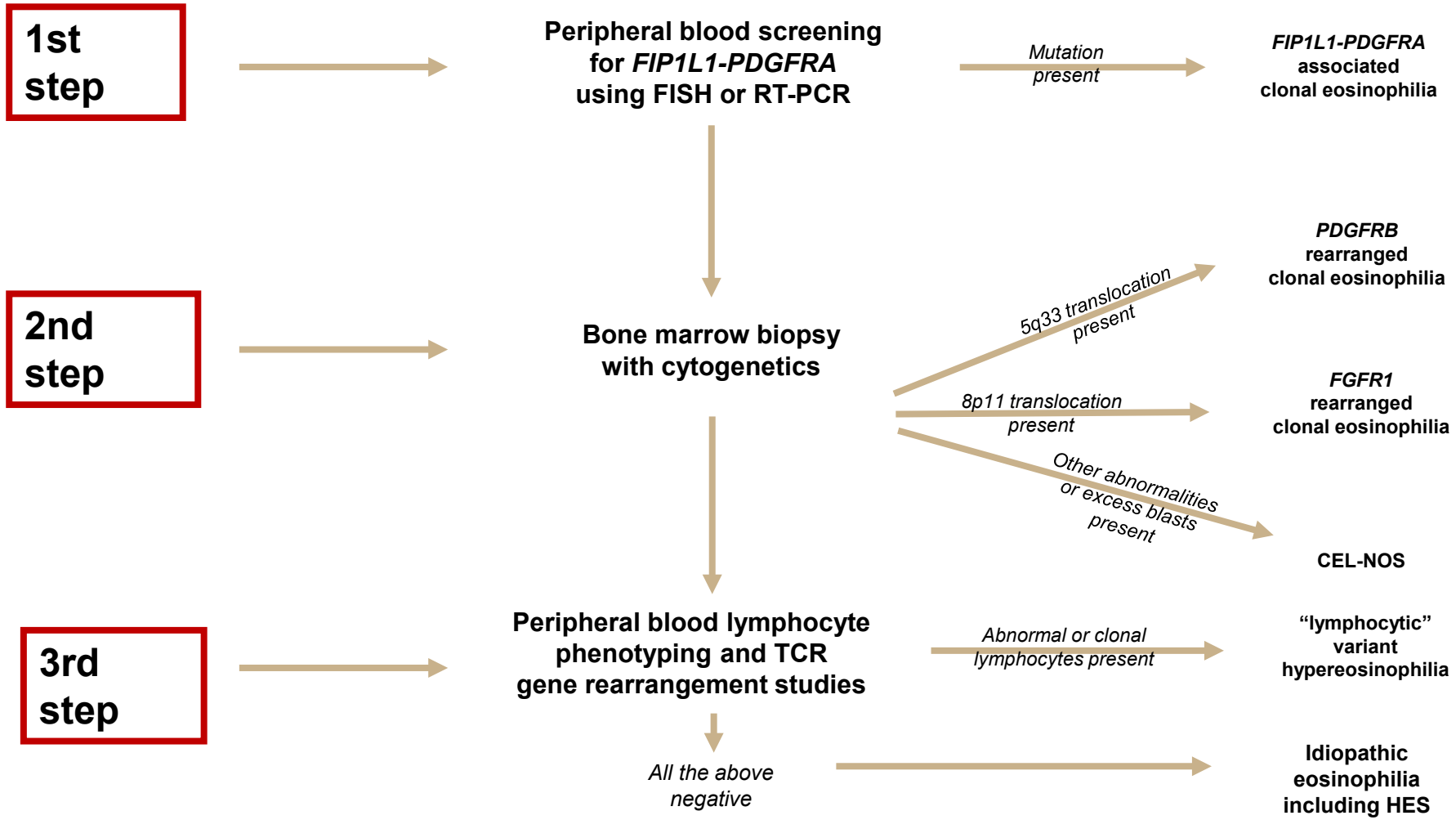
JCO 2014;32:3264

Take home message in systemic mastocytosis (SM)

- Diagnosis of SM is unlikely in the absence of overt BM mast cell clusters, KIT D816V mutation or abnormal mast cell flow (CD25 expression)
- Start by distinguishing indolent vs advanced SM
- Mayo alliance model for SM is easy to use and is based on five easily accessible risk factors: advanced vs indolent; age >60; anemia; thrombocytopenia; and increased ALP
- Cladribine could be considered first cytoreductive drug of choice for both indolent and advanced SM
- Side effects of midostaurin and avapritinib are more concerning than those of cladribine
- In SM-AHN, mast cell-directed treatment might not be enough

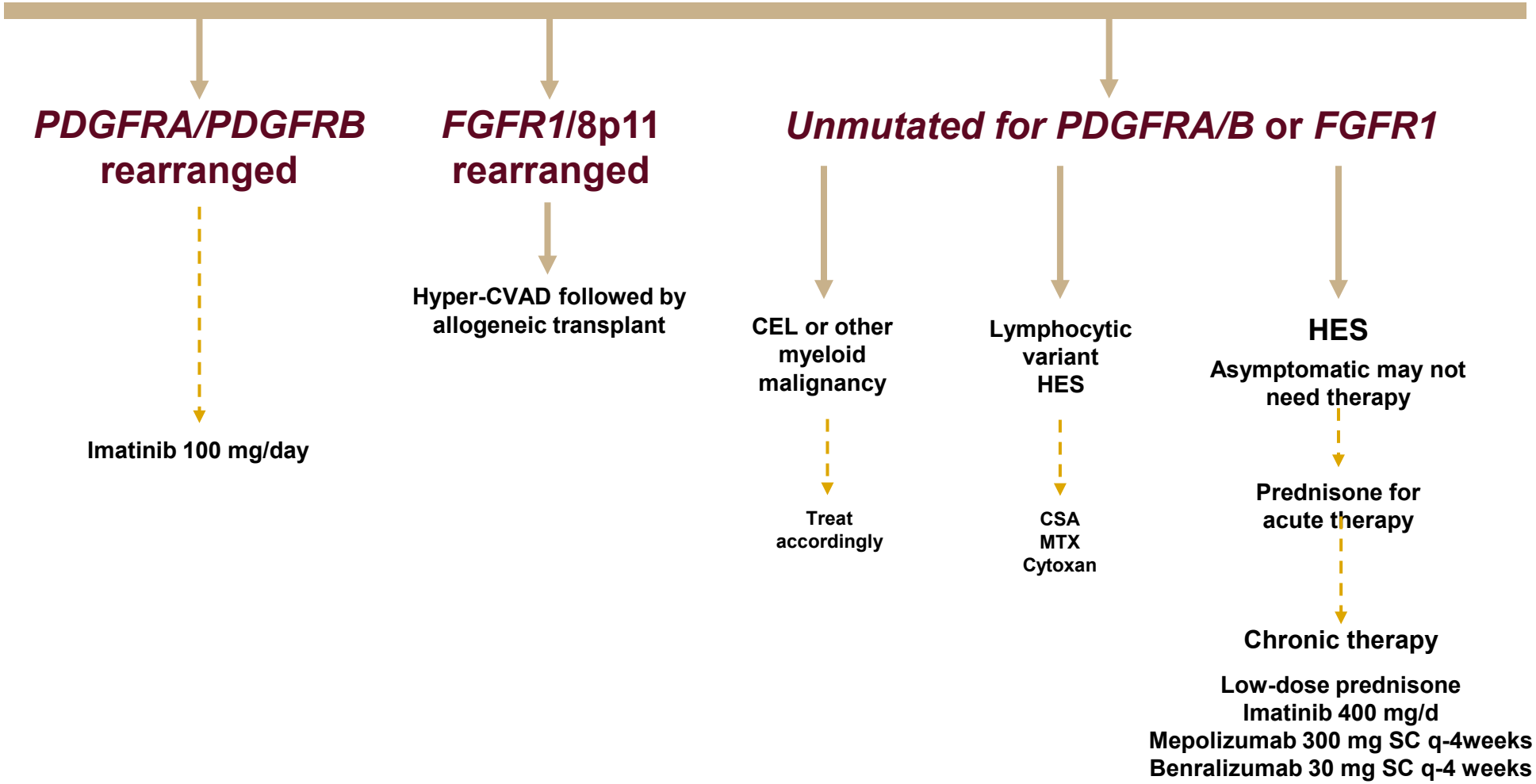
Primary eosinophilia

Diagnostic algorithm



Mayo Clin Proc 85:158, 2010

Management approach to HES or HES-like eosinophilic disorders

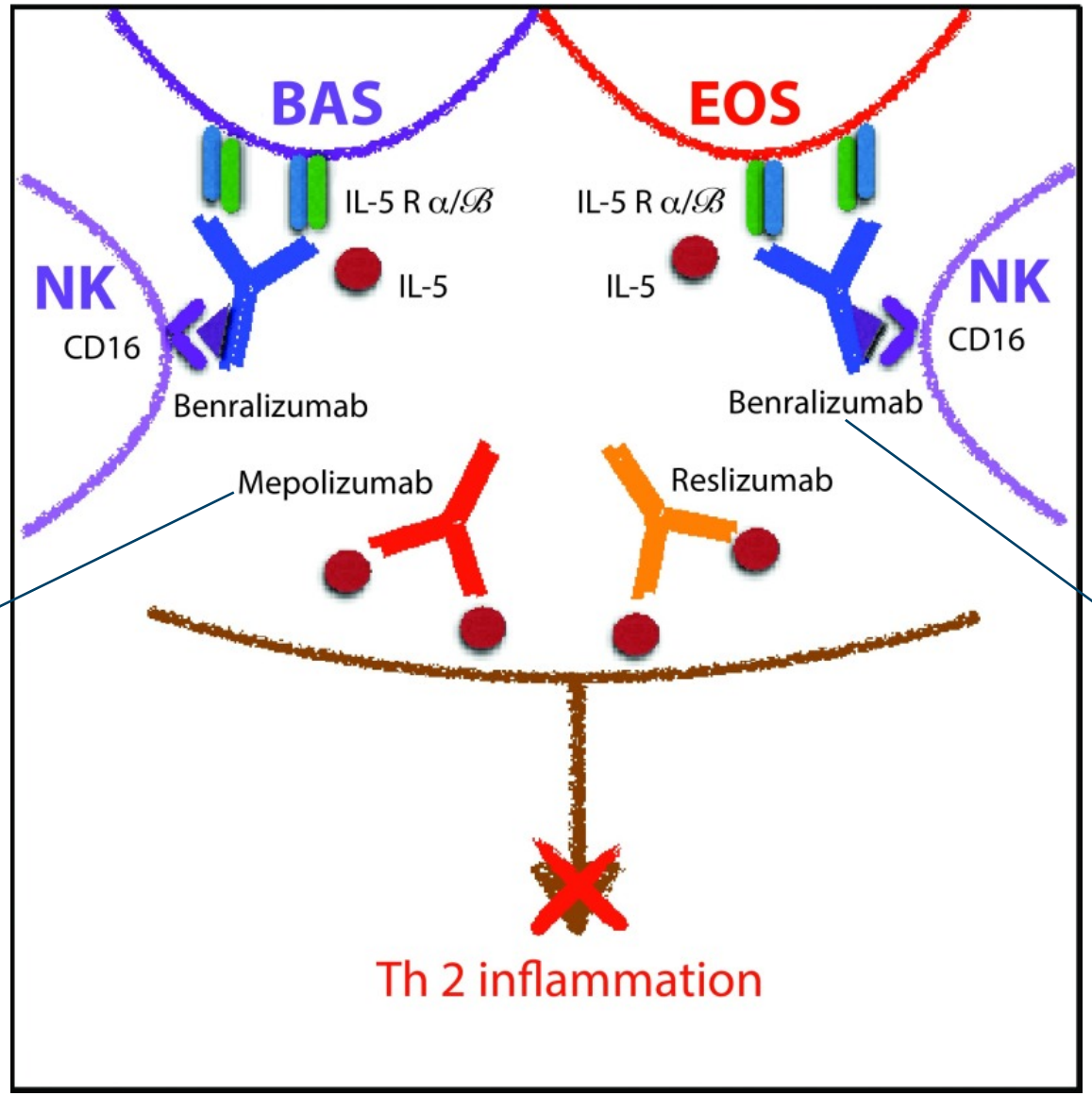


Tefferi A. 2021

T helper type 2 (Th2) cells secrete IL-5, IL-4, and IL-13, responsible for eosinophil proliferation, activation, and tissue recruitment.

Dupilumab targets IL-4 receptor

Omalizumab targets IgE

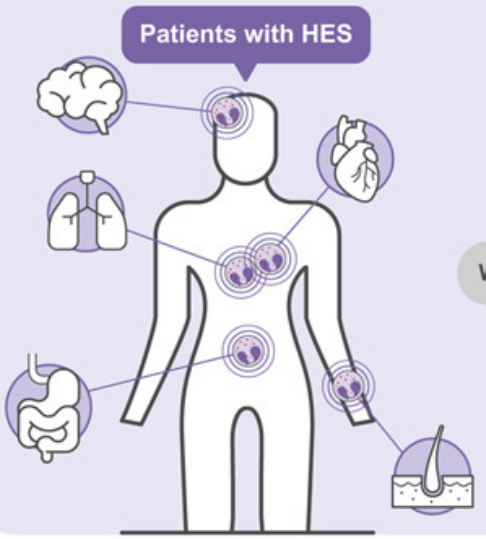


Mepolizumab and reslizumab are humanized monoclonal antibodies targeting circulating IL-5 (mepolizumab 300 mg SC q 4 wks)

Benralizumab targets the α-subunit of the IL-5 receptor (IL-5Rα) and its Fc region increases affinity to NK cells, basophils, and mast cells (30 mg SC q 4 weeks)

Caminati et al. Drugs Context. 2019; 8: 212587

Efficacy and safety of mepolizumab in hypereosinophilic syndrome: a Phase III, randomized, placebo-controlled trial



Patients received **placebo (n=54)** or **mepolizumab 300 mg SC (n=54)** plus existing HES therapy.

Primary endpoint*
Proportion of patients experiencing a disease flare

HES flare defined as:
(a) an HES-related clinical manifestation
(b) receipt of ≥2 courses of oral corticosteroid add-on

REDUCTION in proportion of patients who experienced a flare or withdrew during study — 50%

REDUCTION in risk of a flare — 66%

REDUCTION in annualized flare rate — 66%

SIMILAR proportions of patients experienced on-treatment adverse events

Placebo Mepolizumab

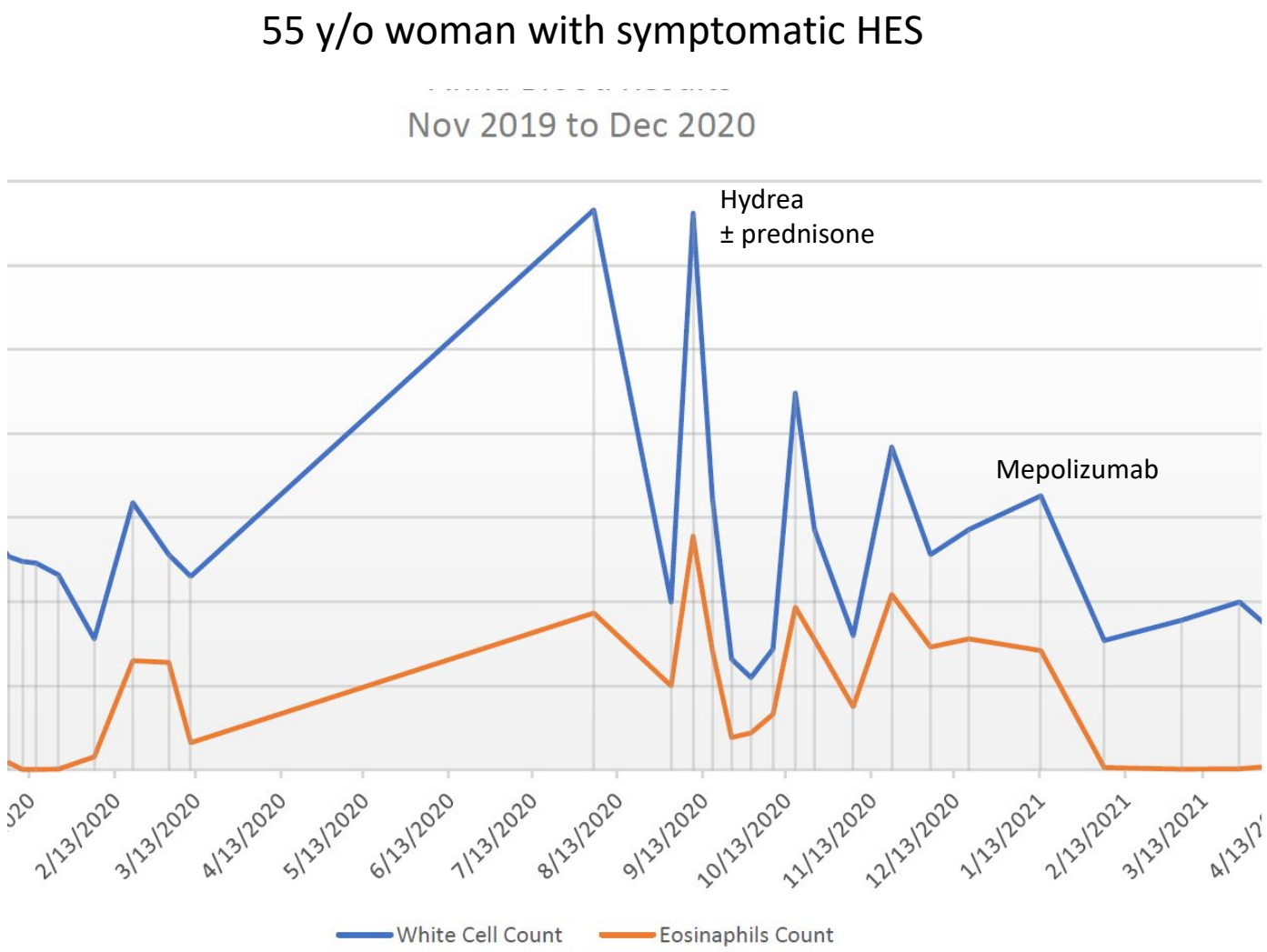
*Secondary endpoints included time to first flare, annualized flare rate, proportion of patients experiencing a flare during Weeks 20-32 and change from baseline at Week 32 in fatigue severity; safety outcomes were also assessed. HES, hypereosinophilic syndrome; SC, subcutaneous.

Roufosse et al. Journal of Allergy and Clinical Immunology
Volume 146, Issue 6, December 2020, Pages 1397-1405

Date	White Cell Count	Eosinaphils Count
11/13/2019	25,800	12771
11/18/2019	27,400	5206
12/2/2019	7600	3192
12/26/2019	15,000	0
1/5/2020	12,700	445
1/10/2020	12,400	37
1/15/2020	12,300	25
1/23/2020	11,600	58
2/5/2020	7800	780
2/19/2020	15,900	6503
3/3/2020	12,800	6400
3/11/2020	11,500	1622
8/4/2020	33,300	9324
9/1/2020	10,000	5000
9/9/2020	33,100	13902
9/16/2020	16100	7084
9/23/2020	6600	1940
9/30/2020	5,500	2200
10/8/2020	7,200	3312
10/16/2020	22,400	9677
10/23/2020	14,300	7765
11/6/2020	8,000	3760
11/20/2020	19,200	10445
12/4/2020	12,800	7308
12/18/2020	14,300	7800
1/13/2021	16,300	7100
2/5/2021	7,700	146
3/5/2021	8,900	53
3/26/2021	10,000	70
4/9/2021	8,000	256
5/11/2021	4,400	480
6/18/2021	7,700	169
7/8/2021	8,700	617

Hydrea
± prednisone

Mepolizumab



Thank You