GRAND ROUNDS CLINICI DEL MERCOLEDÌ
con il Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

Fondazione IRCCS Policlinico San Matteo

ATS Pavia

Aula Magna "C. Golgi"
& WEBINAR

11-05-2022

Chiara Elena

Systemic Mastocytosis: a multidisciplinar precision approach

Female, 58 y.o.

Medical history:

- Left annessiectomy (1978), histerectomy (1990)
- Laparoscopic cholecistectomy (2000)
- Roux-en-Y gastric bypass (2012), weight loss 80 Kg, actual body weight 73 Kg
- HP-related gastritis (2015)
- Anxiety disorder

Drug allergies: antifungal azoles (itraconazole and posaconazole), allopurinol, amoxicillin-clavulanic acid

2015, September (53 y.o.) (Cremona)

Diagnosis of **Acute Myeloid Leukemia, NOS**
Intermediate-I genetic risk (normal karyotype, wt NPM1, no FLT3-ITD) (ELN 2010)
Induction chemotherapy '3+7' => NR
Salvage chemoterapy FLAG-IDA => CR

2016, February (Bergamo): Allogeneic Hematopoietic Stem Cell Transplant
(Marrow Unrelated Donor, male sex), myeloablative conditioning, no acute or chronic GvHD

2017, November: **AML relapse** (FISH XY 59% donor)
Salvage therapy (Dec2017 – Dec2018):
DLI + 5-Azacitidine (6 cycles)=> NR
Azacitidine + Venetoclax (3 cycles) => **2019, Jan** CRi (complete remission with incomplete hematological recovery)

During follow-up persistence of moderate cytopenias, no transfusion need

ELN 2010, Dohner et al, Blood. 2010

2019, October (57 y.o.)

Traumatic left femur fracture, treated with osteosynthesis
Bone biopsy: suspected systemic mastocytosis

The patient was then referred to our Division **(2020, May)**

- no B symptoms, no skin symptoms, no gastrointestinal symptoms, no bone pain

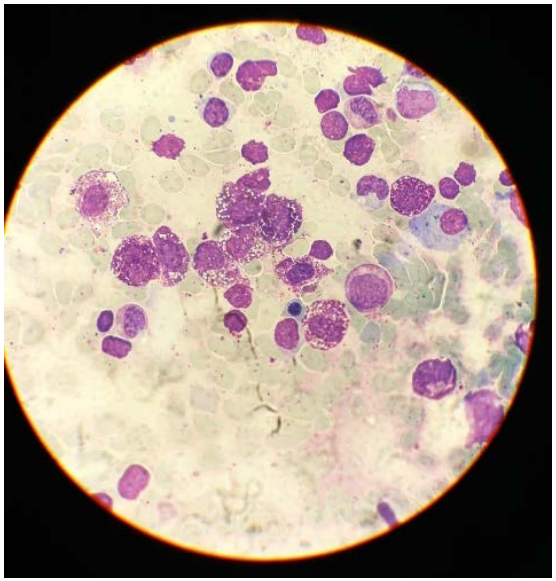
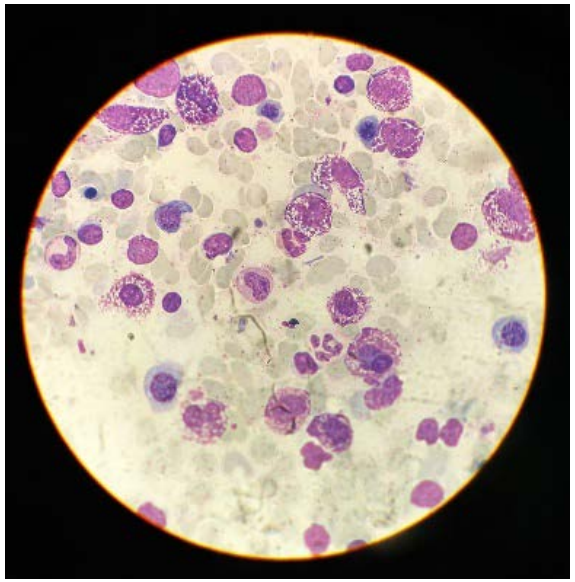
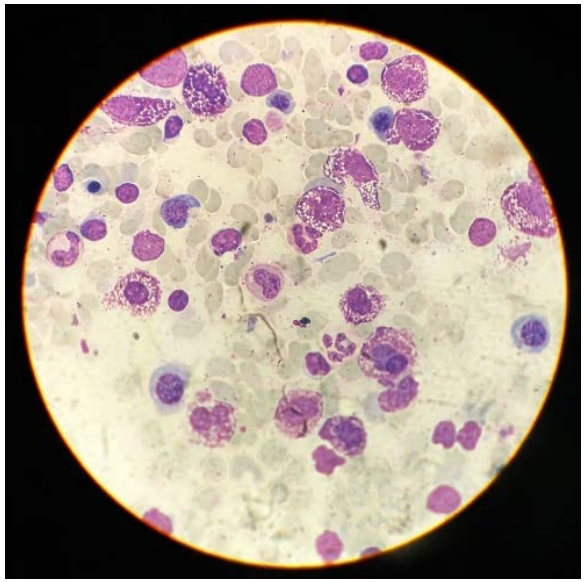
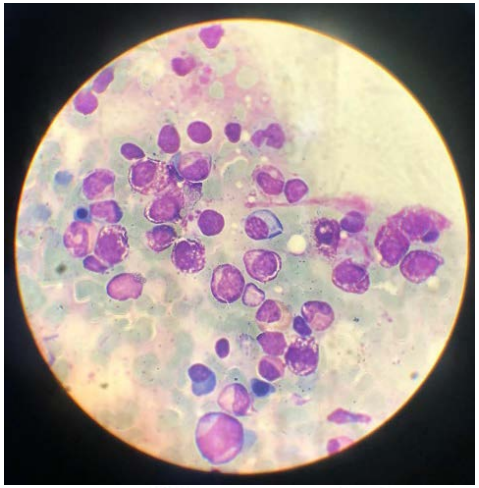
- palpable hepatomegaly 2 cm from CM, no splenomegaly, no superficial lymphnodes, no skin lesions (UP)

- ***CBC count***:
WBC 2,29 x10^9/L (N 1,24, Ly 0,79, Mo 0,19, Eo 0,1), Hb 10,7 g/dl, MCV 131,6 fl, PLT 68 x10^9/L

- ***Peripheral blood smear***: no circulating blasts or mast cells

- ***Blood examinations:*** serum tryptase 283 mcg/l, ALP 312 U/L, folic acid deficiency

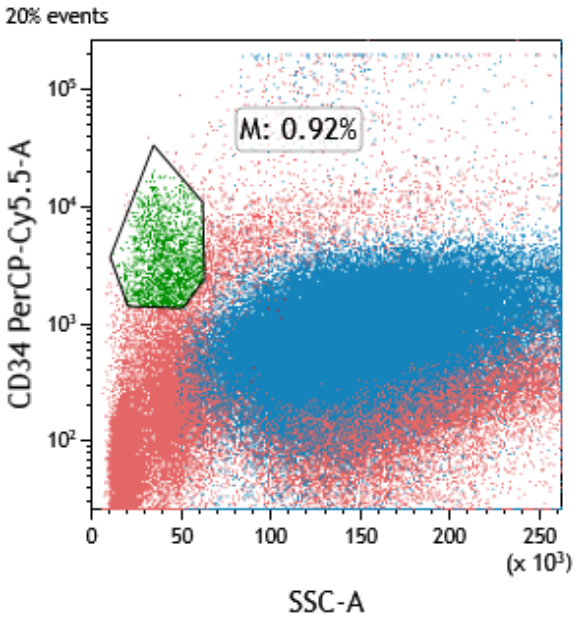
BM aspirate: increased cellularity, dysplastic features, increased atypical mast cells Type I and Type II up to 40% ; ***no increased blast cells***

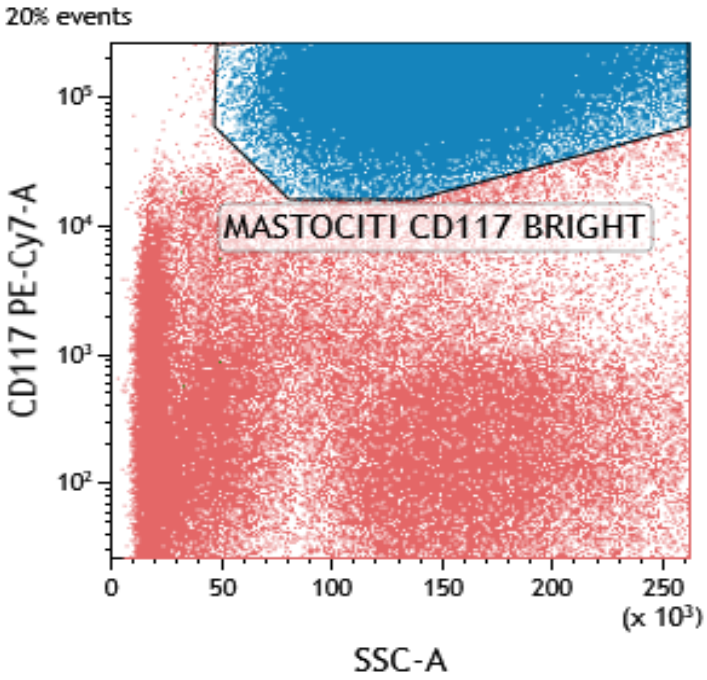





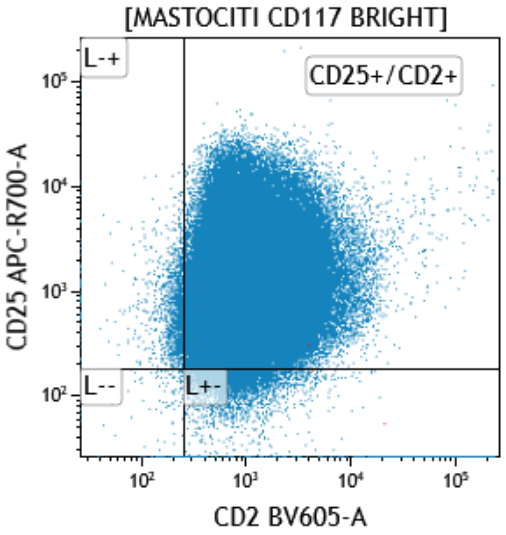
BM flow cytometry:

mast cells CD34-, CD117+, CD2+, CD25+ 42%;

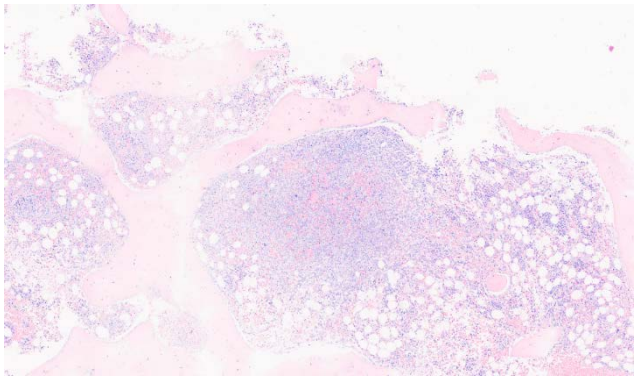
myeloid blasts CD34+ CD117+ CD13+ CD33+ 0,9%

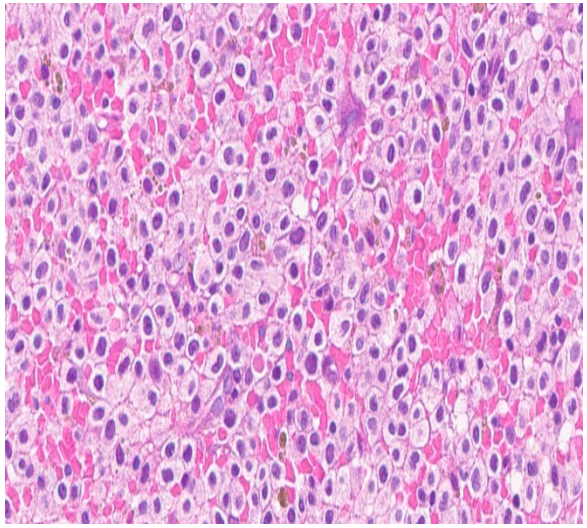


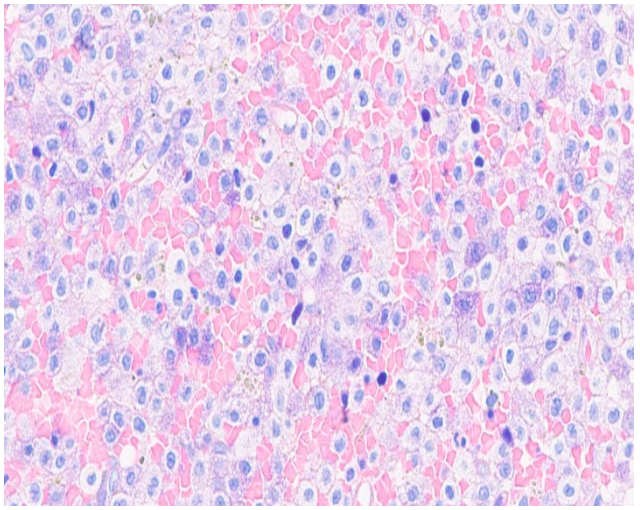


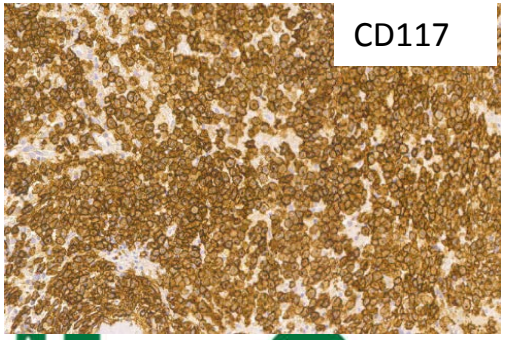


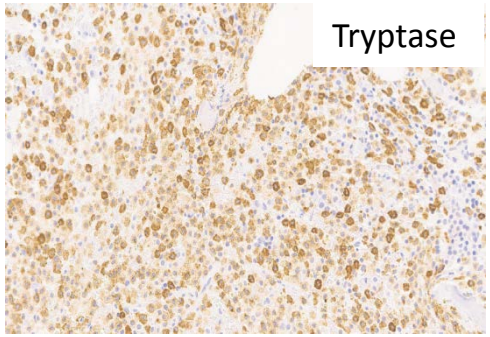
BM biopsy

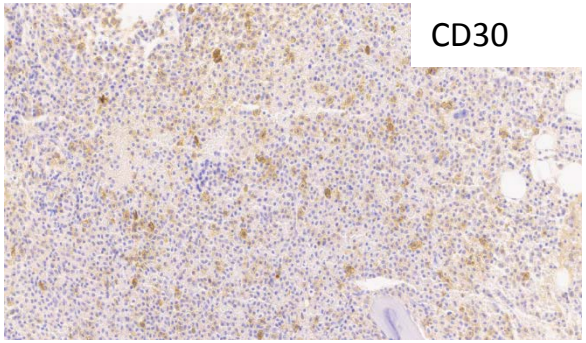




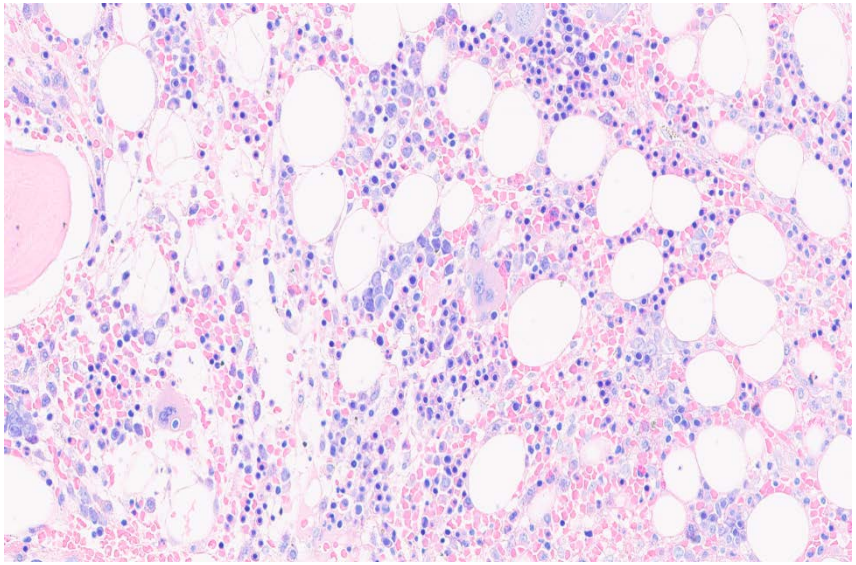


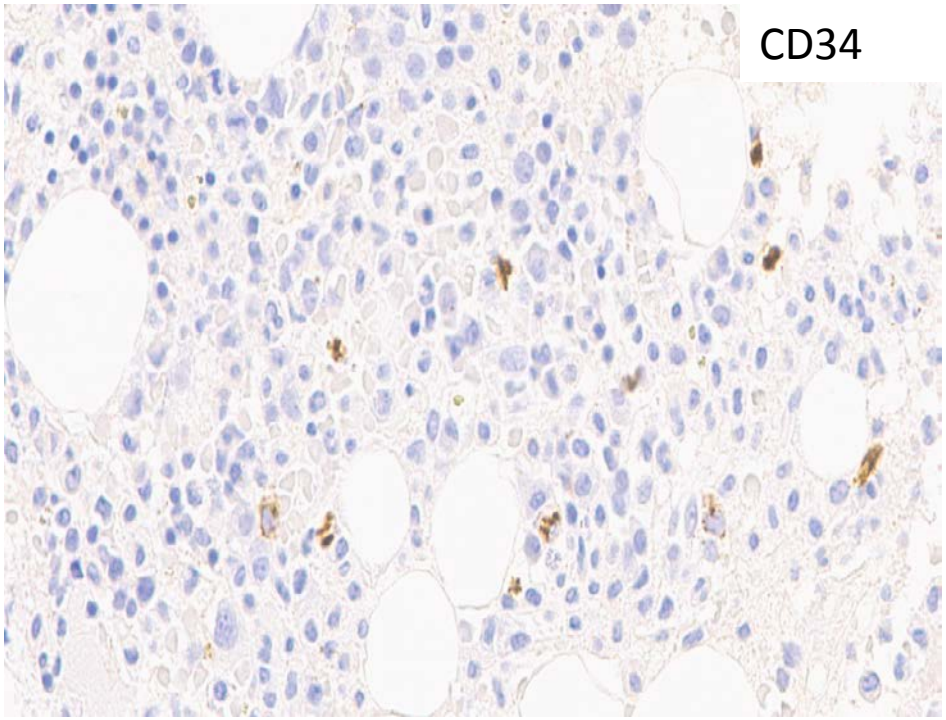






BM biopsy





CD34

Genetic tests

BM Karyotype: 46, XY [8]

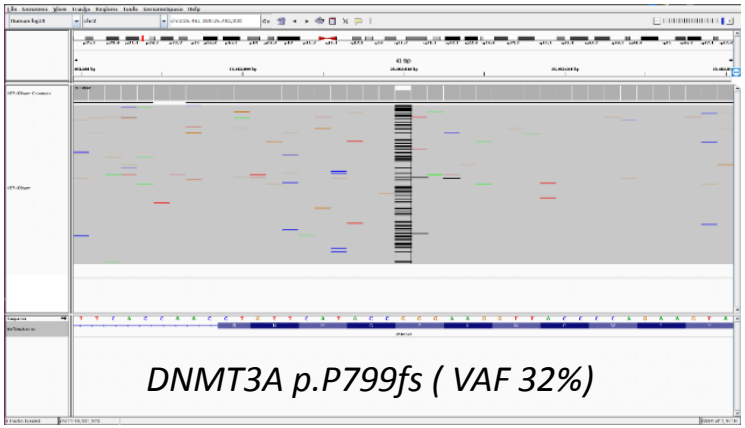
PB molecular tests:
ASO-PCR *CKIT* D816V: wt

BM molecular tests:

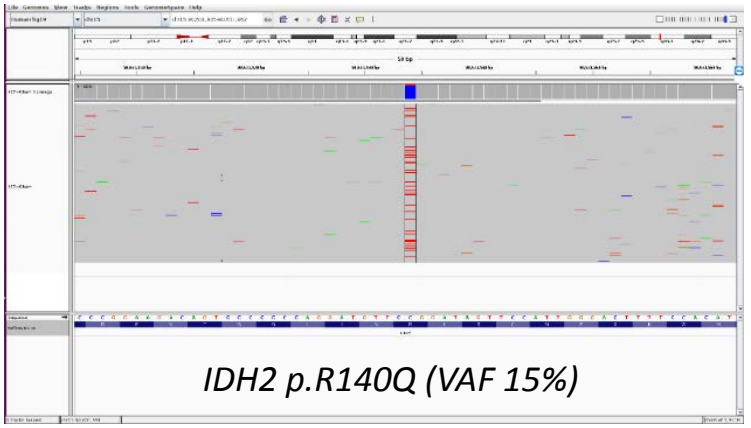
ASO-PCR *CKIT* D816V: wt

Sanger Sequencing exon 9-11-13-17 *cKIT*: wt

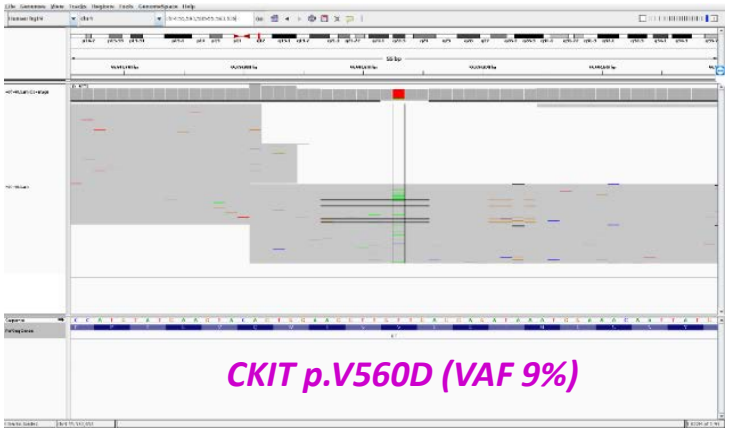
NGS (Myeloid panel, Illumina): oncogenic somatic mutations identified in



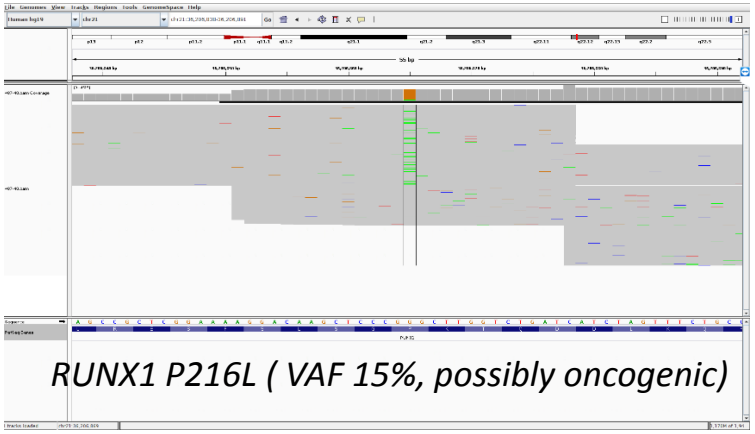
DNMT3A p.P799fs (VAF 32%)



IDH2 p.R140Q (VAF 15%)



CKIT p.V560D (VAF 9%)

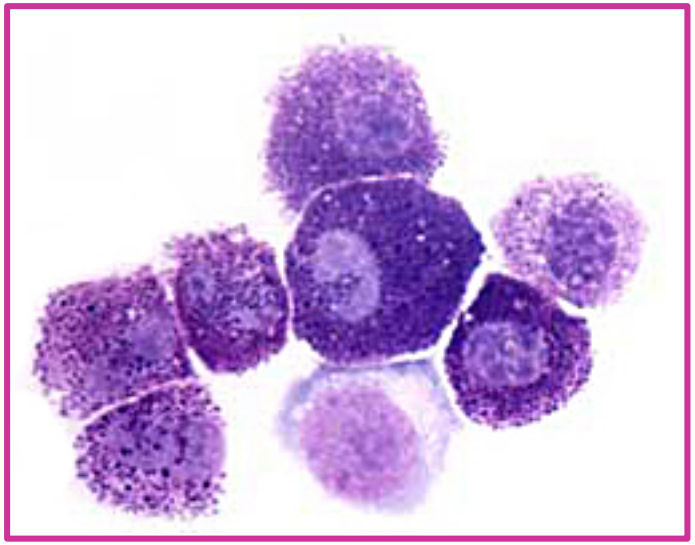


RUNX1 P216L (VAF 15%, possibly oncogenic)

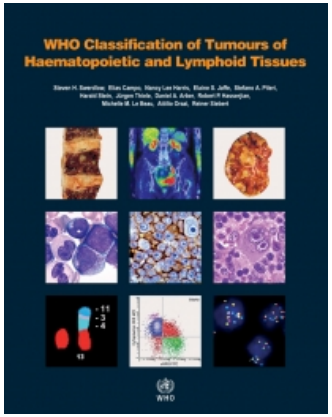
ID	LIBRARY		FUNCTION	CHR	POSITION START	POSITION STOP	WT	MT	% AB	TUMOR DEPTH READ	GENE	TRANSCRIPT	CCDS	EXON	C.	P.	TAG
487-40	MYELOID	exonic	frameshift deletion	2	25462010	25462010	G	-	0,3219	4995	DNMT3A	NM_175629	CCDS33157.1	exon20	c.2397delC	p.P799fs	oncogenic
487-40	MYELOID	exonic	nonsynonymous SNV	15	90631934	90631934	C	T	0,152	3955	IDH2	NM_002168	CCDS10359.1	exon4	c.G419A	p.R140Q	oncogenic
487-40	MYELOID	exonic	nonsynonymous SNV	4	55593613	55593613	T	A	0,09	3089	KIT	NM_000222	CCDS3496.1	exon11	c.T1679A	p.V560D	oncogenic
487-40	MYELOID	exonic	nonsynonymous SNV	21	36206865	36206865	G	A	0,1595	909	RUNX1	NM_001754	CCDS13639.1	exon7	c.C647T	p.P216L	possibly oncogenic

MASTOCYTOSIS: DEFINITION

- Rare disease characterized by abnormal proliferation and accumulation of neoplastic clonal mast cells in various organ systems, including skin, bone marrow, spleen and gastrointestinal tract
- Multidisciplinary disease



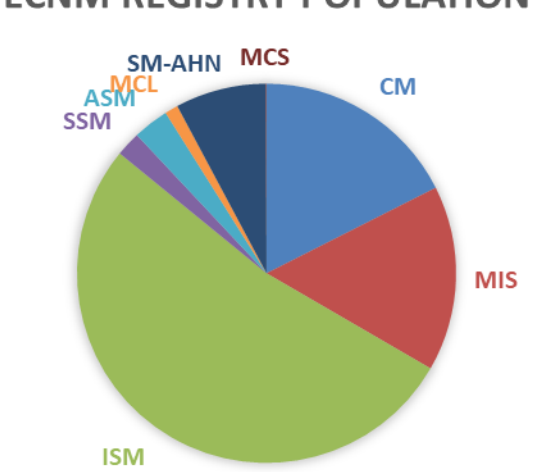
WHO 2016 CLASSIFICATION



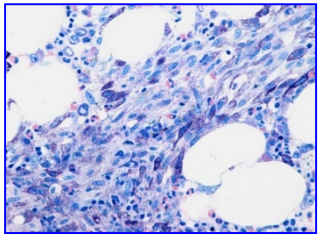
1. Cutaneous Mastocytosis (CM)
   - Urticaria pigmentosa (UP)/Maculopapular cutaneous mastocytosis (MPCM)
   - Diffuse cutaneous mastocytosis
   - Solitary mastocytoma of skin

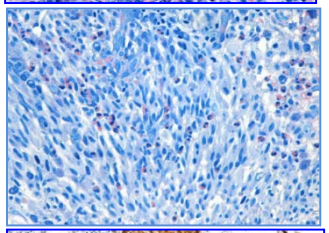
2. Systemic mastocytosis (SM)
   - Indolent systemic mastocytosis (ISM) (including BMM)
   - Smouldering systemic mastocytosis (SSM)
   - SM with an associated haematological neoplasm (SM-AHN)
   - Aggressive SM (ASM)
   - MC leukemia (MCL)

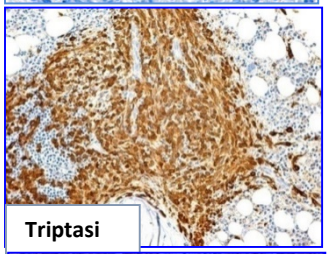
3. Mast cell sarcoma

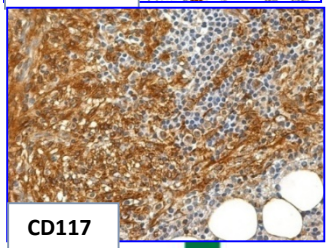


WHO DIAGNOSTIC CRITERIA









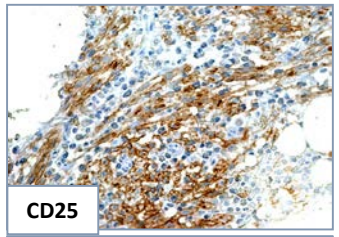
MAJOR CRITERION:

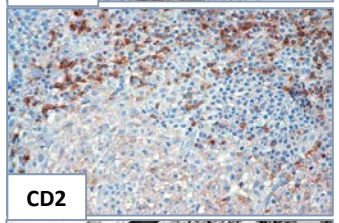
1. Multifocal dense infiltrates of MCs (> 15 MCs in aggregates) in BM sections or other extracutaneuos organ(s)

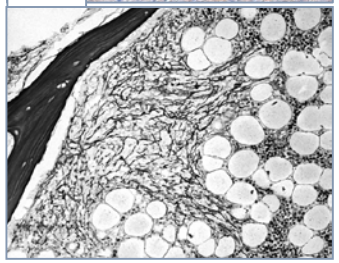
MINOR CRITERIA:

1. > 25% MCs in the infiltrate (BM or other extracutaneous organ) are spindle-shaped or have atypical morphology or > 25% MCs in BM aspirate smears are immature or atypical
2. Detection of KIT mutation at codon 816 in the BM, blood or extracutaneous organ(s)
3. MCs express CD2 and/or CD25 by flow or IHC
4. Serum total tryptase > 20 ng/ml (not valid if concomitant AHN)

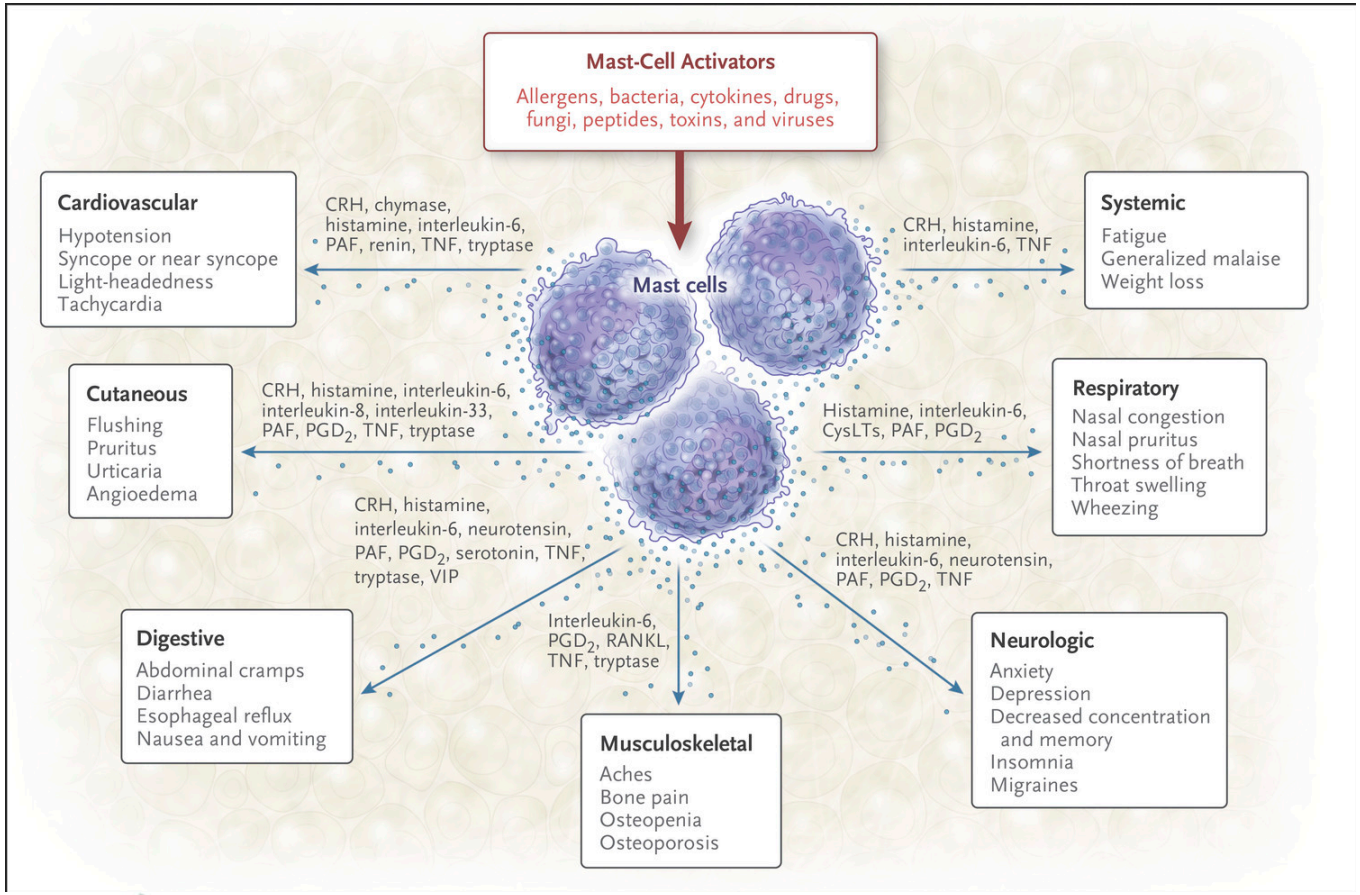
1 major and at least 1 minor criteria, or ≥ 3 minor criteria are required for SM diagnosis





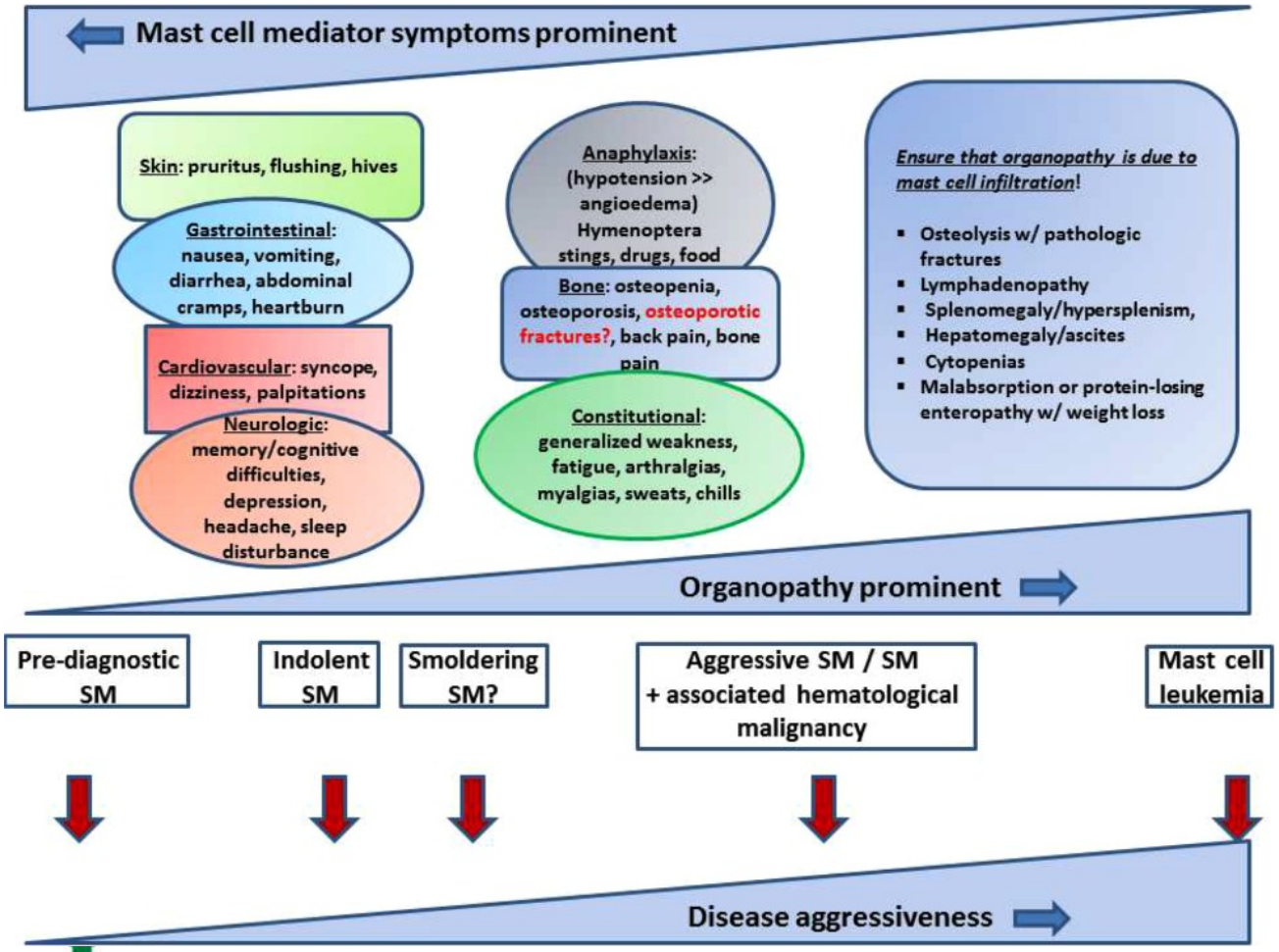


CLINICAL PRESENTATION



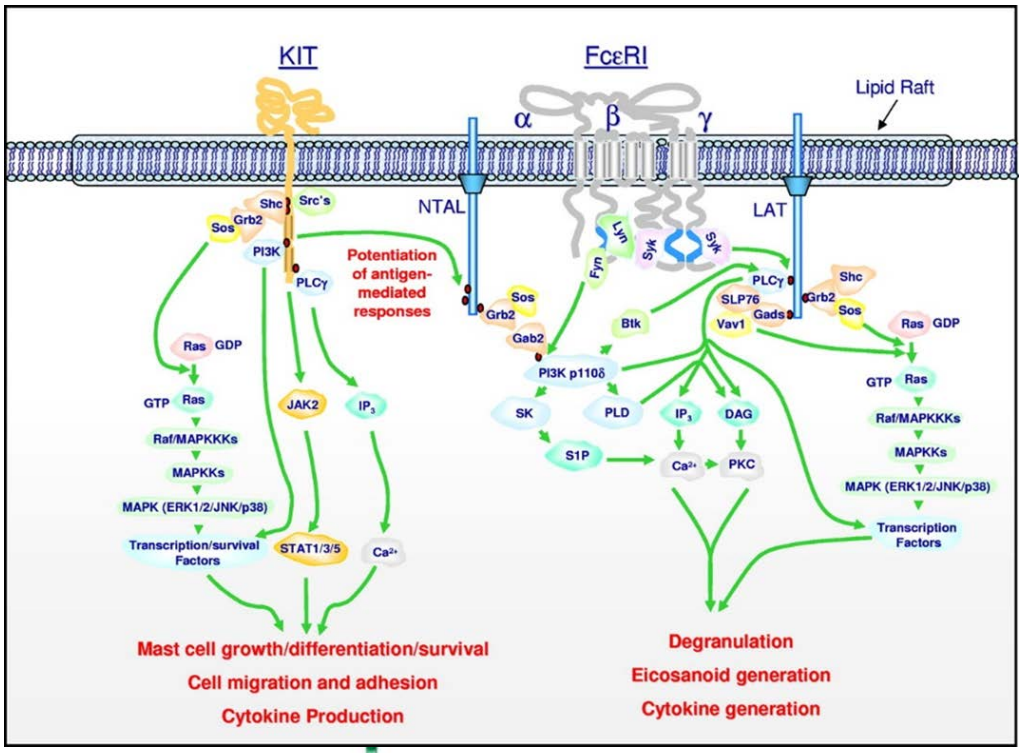
Theoharides TC et al. N Engl J Med 2015;373:163-172.

CLINICAL SPECTRUM OF PATIENTS WITH CLONAL MAST CELLS DISORDERS

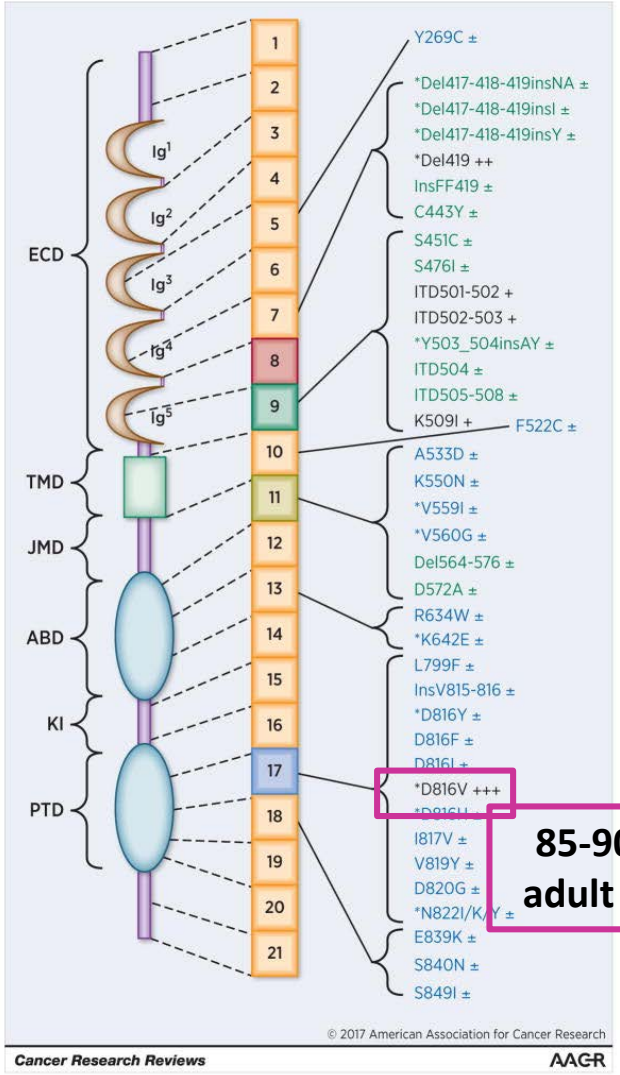


Pardanani, AJH 2016

SOMATIC C-KIT MUTATIONS IN MASTOCYTOSIS

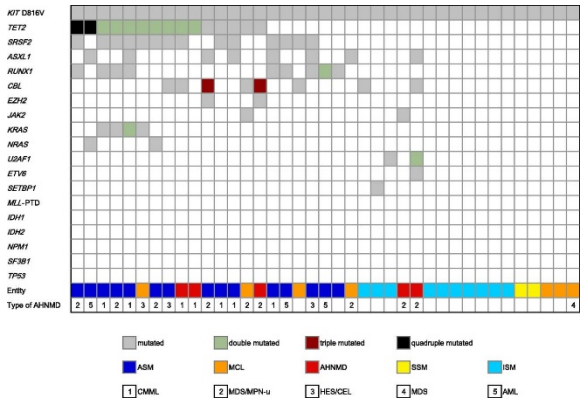


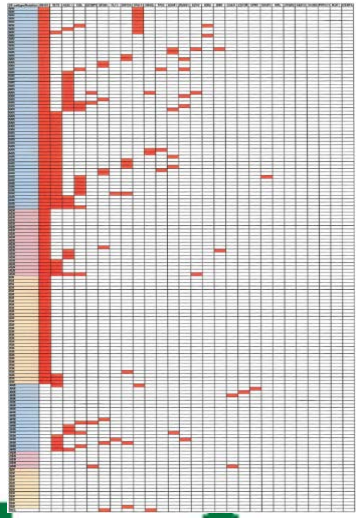
Valent et al, Cancer Res. 2017 Mar 15;77(6):1261-1270

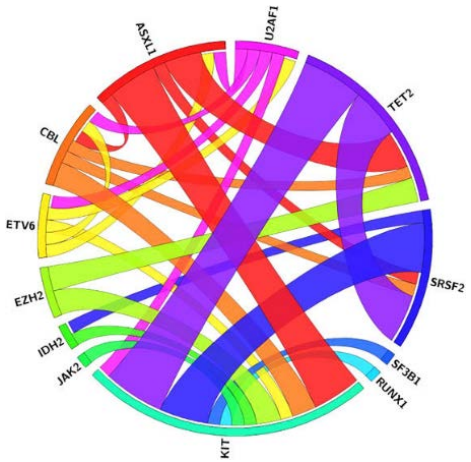


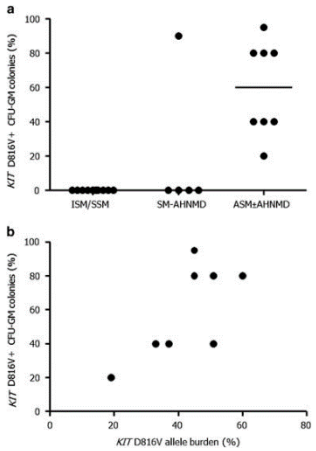
85-90% adult pts

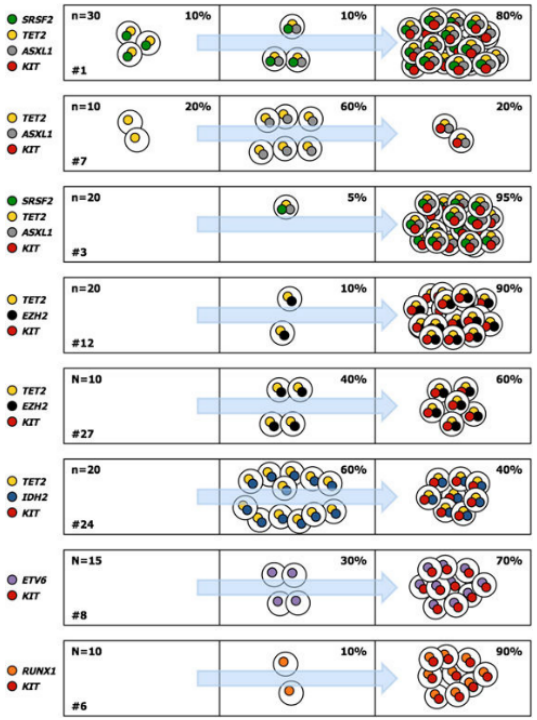
SOMATIC MUTATIONS OTHER THAN C-KIT IN SM











Schwaab et al. Blood 2013;122:2460-2466; Pardanani et al, Am J Hematol. 2016 Sep;91(9):888-93; Jawhar M et al, Leukemia. 2015 May;29(5):1115-22

NCCN Guidelines Version 2.2019
Systemic Mastocytosis

NCCN Guidelines Index
Table of Contents
Discussion

WORKUP FOR SUSPECTED SYSTEMIC MASTOCYTOSIS[i]

General Diagnostic Studies

- H&P, including, prior history of mast cell activation symptoms; potential triggers; examination for MIS; spleen and liver size by palpation; documentation of medications, transfusion history, and weight loss
- Comprehensive metabolic panel with uric acid, lactate dehydrogenase (LDH), and liver function tests (LFTs)
- Serum tryptase level
- CBC with differential
- Examination of blood smear (eg, monocytosis, eosinophilia, dysplasia)[j]
- Bone marrow aspirate and biopsy with[j]:
  - Flow cytometry: CD34, CD117, CD25, CD2; CD30 (optional)
  - Immunohistochemistry: CD117, CD25, tryptase; CD30 (optional)
- Cytogenetics
- FISH as needed for associated hematologic neoplasm (AHN)-related abnormalities[j]
- Molecular testing for *KIT* D816V by allele-specific PCR or alternative high-sensitivity method[j,k,l]
- Myeloid mutation panel (eg, containing *SRSF2, ASXL1, RUNX1*)[j,l]

Evaluation of B- and C-Findings and Organ Involvement[d]

- CT/MRI or ultrasound of the abdomen/pelvis
- DEXA scan to evaluate for osteopenia/osteoporosis
- Metastatic skeletal survey to evaluate for osteolytic lesions
- Organ-directed biopsy (eg, endoscopy, liver biopsy) as needed with immunohistochemistry (CD117, CD25, tryptase, and CD3 as a control T-cell marker)

Useful Under Selected Circumstances

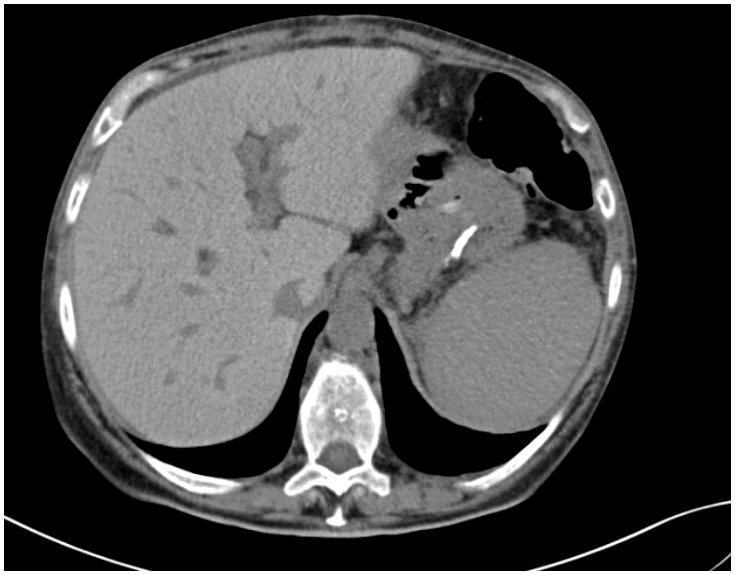
- 24-hour urine studies for biochemical evidence of mast cell activation
  - N-methylhistamine
  - Prostaglandin D2
  - 2,3-Dinor-11beta-prostaglandin F2 alpha
- HLA testing, if considering allogeneic hematopoietic cell transplant (HCT)
- Assessment of symptom burden and quality of life (QOL) using the Mastocytosis Symptom Assessment form (MSAF) and the Mastocytosis Quality of Life Questionnaire (MQLQ)[m]

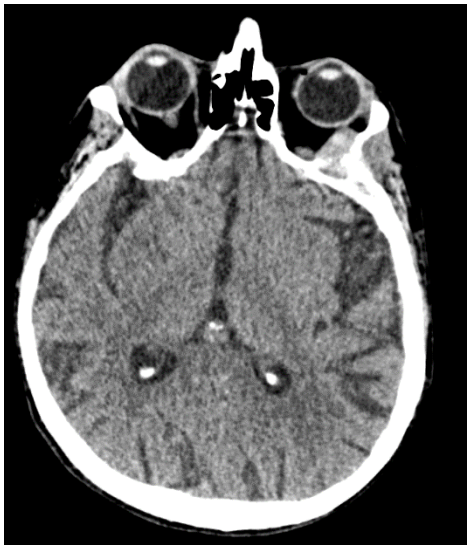
CLASSIFICATION[i]

- Indolent SM (ISM) (SM-3) and (SM-4)
- Smoldering SM (SSM) (SM-3) and (SM-4)
- Aggressive SM (ASM)(SM-5)
- SM with an associated hematologic neoplasm (SM-AHN) (SM-6) and SM-7)
- Mast cell leukemia (MCL) (SM-8)

STAGING

- ***TC WB and brain MRI (contrast medium premedication with antiH1 and steroids)***

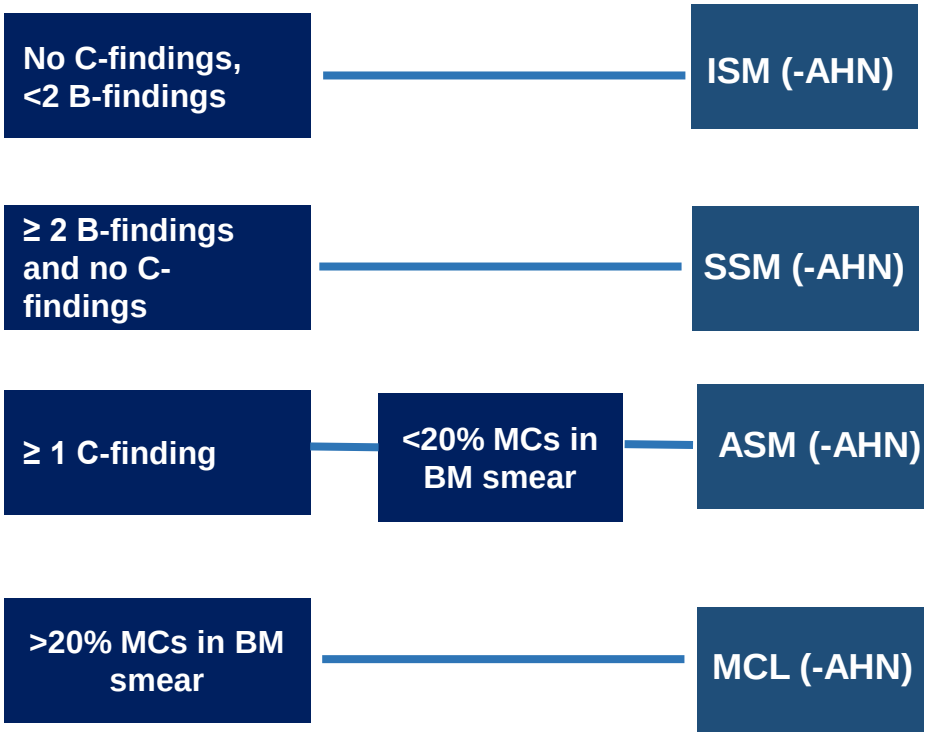




- *Neurosurgical consultation: asymptomatic patient, no diplopia, no exophtalmos, surgical intervention not urgent*
- *Costal lesion biopsy:* ***localization of systemic mastocytosis***

- ***DEXA (2020, Jan):*** ***femoral and lumbar osteoporosis***
  (femoral neck T -2,7, Z -1,5 / L1-L4 T -2,5, Z -0,5)

SM: ALGHORITM FOR CATEGORIZATION



B findings (Borderline Benign/ Be watchful)

- MCs infiltrates in BM > 30% AND sTryptase > 200
- Dysplasia or myeloproliferation
- Organomegaly without impaired function

C findings (Consider Cytoreduction)

- Cytopenias
- Hepatomegaly with ascites, portal hypertension and/or impaired liver function
- Splenomegaly with hypersplenism
- Malabsorption with hypoalbuminemia and weight loss
- Skeletal lesions: large-sized osteolyses (NOT caused by osteoporosis)
- Life-threating organ damage due to MCs infiltrates

Tefferi et al, AJH 2019;94:E1–E41; *Yang et al, Blood 2019, 133:2243*

FINAL DIAGNOSIS

MAST CELL LEUKEMIA (WHO 2017), aleukemic variant

NGS (Myeloid panel, Illumina):

oncogenic somatic mutations identified in
CKIT V560D (VAF 9%)
DNMT3A P799fs (VAF 32%)
IDH2 R140Q (VAF 15%)
RUNX1 P216L (VAF 15%, possibly oncogenic)

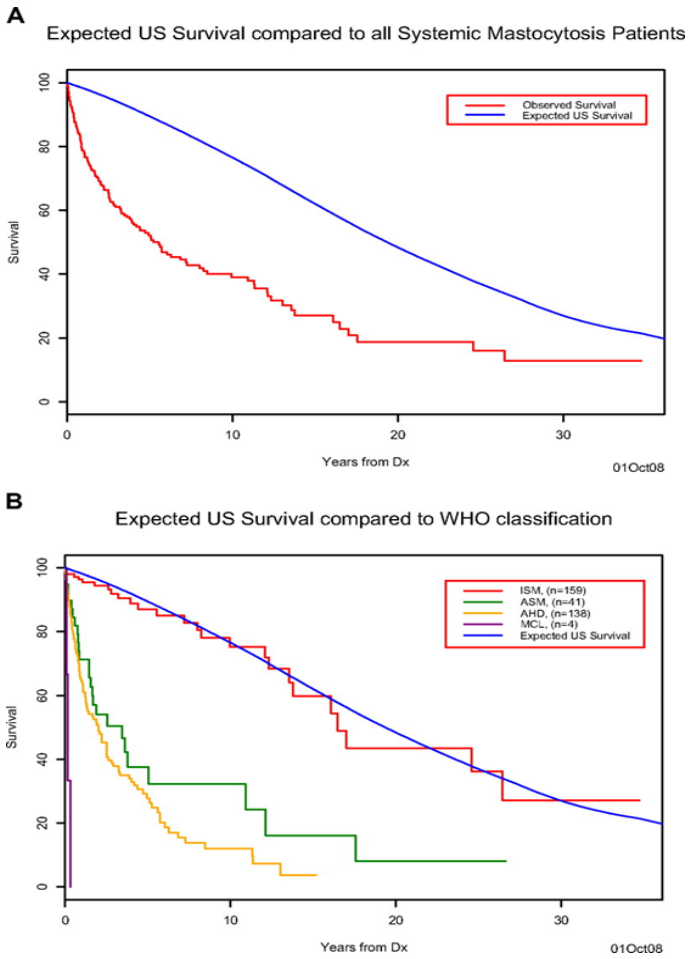
2018, March
NGS

BM FISH XY: donor 203/300 (68%) nuclei, recipient 97/300 (32%) nuclei

SM-AHN

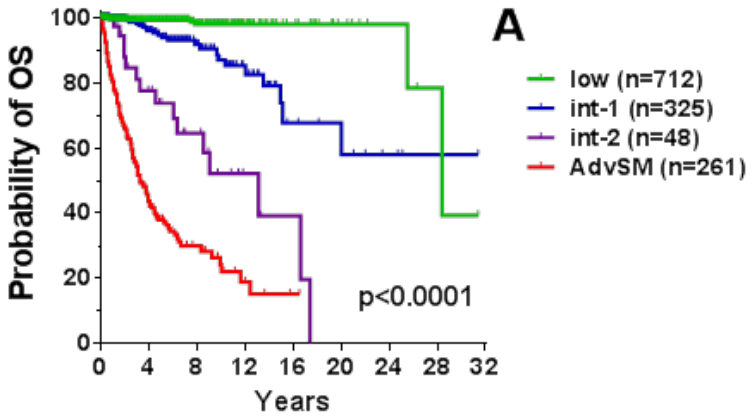
- MAST CELL LEUKEMIA (WHO 2017), aleukemic variant
- AML in CR post HSCT

CLINICAL VALUE OF WHO CLASSIFICATION

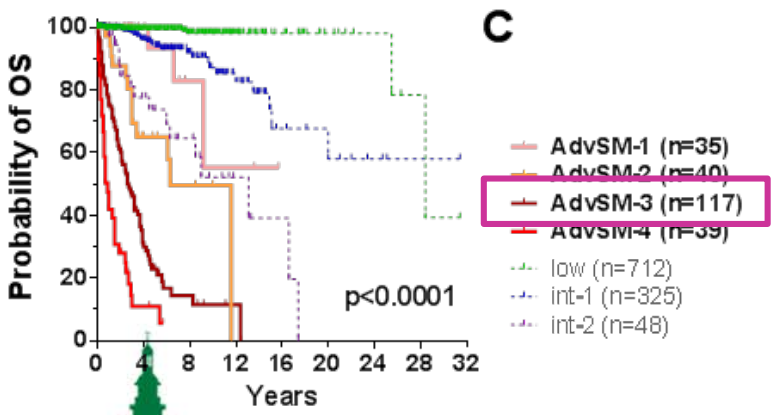


Lim et al, Blood 2009 Jun 4;113(23):5727-36

INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MASTOCYTOSIS (IPSM)



Risk factors:
age ≥60 yrs
ALP ≥100 U/L



Risk factors:
age ≥ 60 yrs
Tryptase ≥125 ng/ml
WBC ≥16x10^9/L
HB ≤11 g/dl
PLT ≤100x10^9/L
Skin involvement

Sperr et al, Lancet Haematol. 2019

TREATMENT OPTIONS IN SYSTEMIC MASTOCYTOSIS

ISM, SSM

- Continued monitoring
- Avoid triggers
- Auto-injectable epinephrine

- Anti-mediator treatment

If refractory

Treatment considerations:
- Referral to specialized centers with expertise in mastocytosis is strongly recommended.
- Counsel patients regarding signs and symptoms of disease[b]
- Avoid known triggers of mast cell activation[b]
- Carry injectable epinephrine (2 auto injectors) to manage anaphylaxis

AdvSM

Cytoreductive treatment

- IFN-α
- 2-CdA
- TKIs (Midostaurin, Imatinib, Avapritinib)
- Clinical trial
- Intensive chemo + allo-SCT

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Systemic Mastocytosis

MIDOSTAURIN

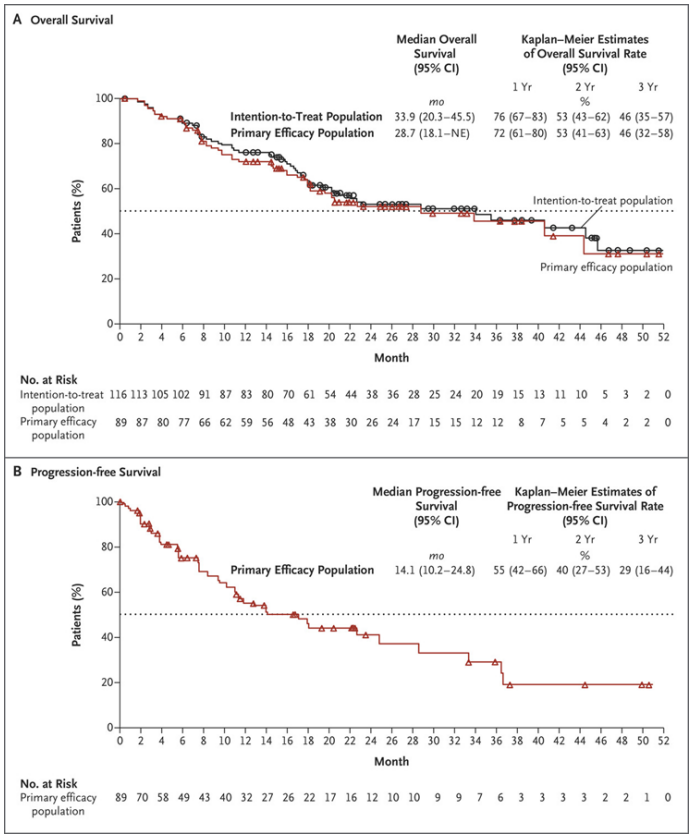
- Oral small molecule inhibitor of KIT, FLT3, VEGFR2, PDGFRα, PDGFR β
- Recommended phase II dose: 100 mg BID
- Hepatically metabolized (CYP3A4)
- Side effects: myelosuppression, diarrhea, nausea, vomiting, headache
- 2017: approved by FDA and EMA as monotherapy in ASM, MCL, SM-AHN

Table 2. Best Overall Response to Midostaurin in the Primary Efficacy Population.*

Variable	Any Subtype of Advanced Systemic Mastocytosis (N=89)	Aggressive Systemic Mastocytosis (N=16)	Systemic Mastocytosis with an AHN (N=57)	Mast-Cell Leukemia (N=16)
Major or partial response as best overall response				
Patients with response — no.	53	12	33	8
Overall response rate (95% CI) — %	60 (49–70)	75 (48–93)	58 (44–71)	50 (25–75)
Duration of response — mo				
Median	24.1	NR	12.7	NR
95% CI	10.8–NE	24.1–NE	7.4–31.4	3.6–NE
Best overall response — no. (%)				
Major response	40 (45)	10 (62)	23 (40)	7 (44)
Complete remission	0	0	0	0
Incomplete remission	19 (21)	6 (38)	9 (16)	4 (25)
Pure clinical response	15 (17)	4 (25)	9 (16)	2 (12)
Unspecified	6 (7)	0	5 (9)	1 (6)
Partial response	13 (15)	2 (12)	10 (18)	1 (6)
Good partial response	11 (12)	1 (6)	10 (18)	0
Minor partial response	2 (2)	1 (6)	0	1 (6)
Stable disease	11 (12)	1 (6)	7 (12)	3 (19)
Progressive disease	10 (11)	1 (6)	6 (11)	3 (19)
Patient could not be evaluated for response†	15 (17)	2 (12)	11 (19)	2 (12)

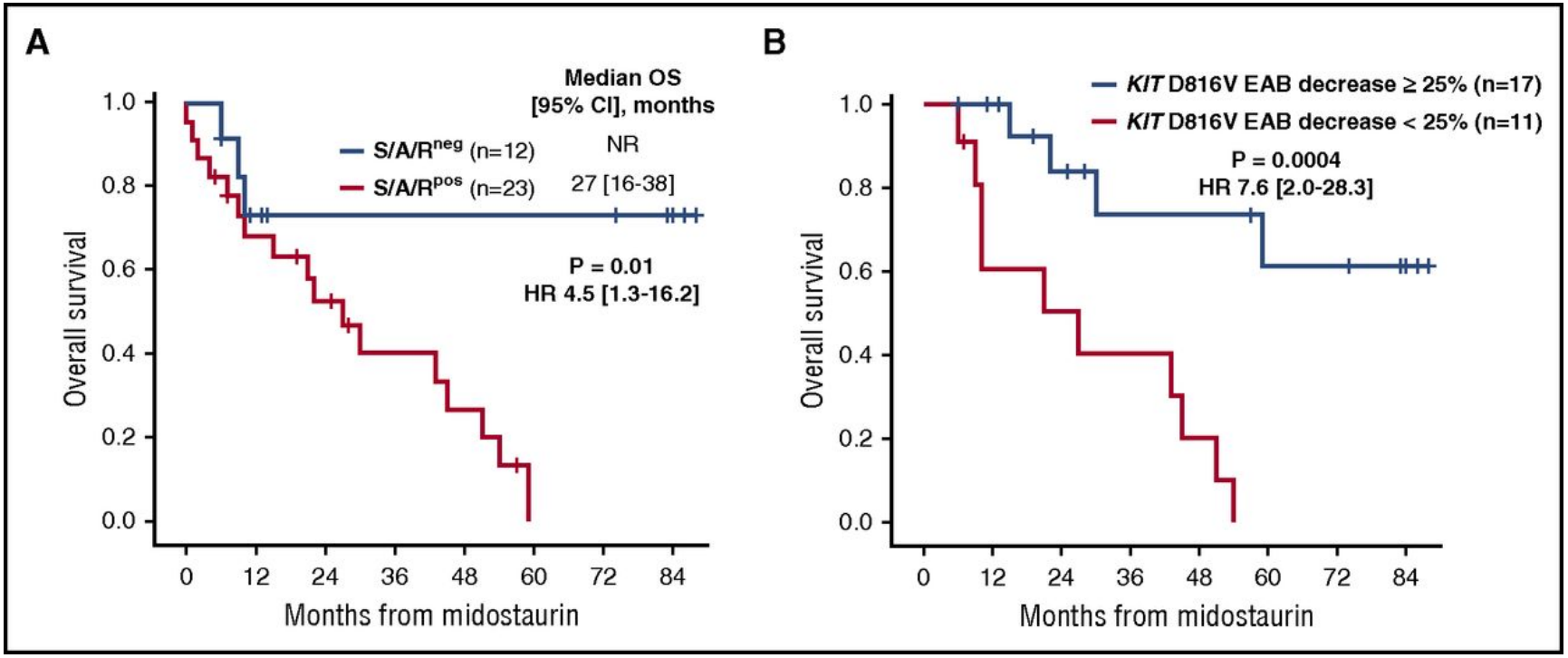
* Responses were evaluated with the use of the modified Valent[1] and Cheson[26,27] criteria; the various types of response are defined in Table S4 in the Supplementary Appendix. AHN denotes associated hematologic neoplasm, CI confidence interval, NE not estimated, and NR not reached.

† Reasons that patients could not be evaluated for response were concurrent use of high-dose glucocorticoids (9 patients), not enough time receiving treatment (3 patients), death (1 patient), red-cell transfusion (1 patient), and neutropenia (1 patient). Patients who could be evaluated for response had an assessment at baseline and at least one postbaseline assessment during the first six cycles of treatment.



Gotlib et al. NEJM 2016, Jun 30;374(26):2530-41

PROGNOSTIC IMPACT OF MOLECULAR STATUS



Jawhar M et al, Blood. 2017 Jul 13;130(2):137-145

Jul 08, 2020 the patient refused any intensive treatment

She started **MIDOSTAURIN 100 mg BID per os**

+ Zoledronic acid 4 mg ev every month (osteolysis)

Supportive care:
- Loratadine
- PPI
- Injectable epinephrine
- Sertraline, bromazepam, lorazepam

post sleeve gastrectomy
correct absorption

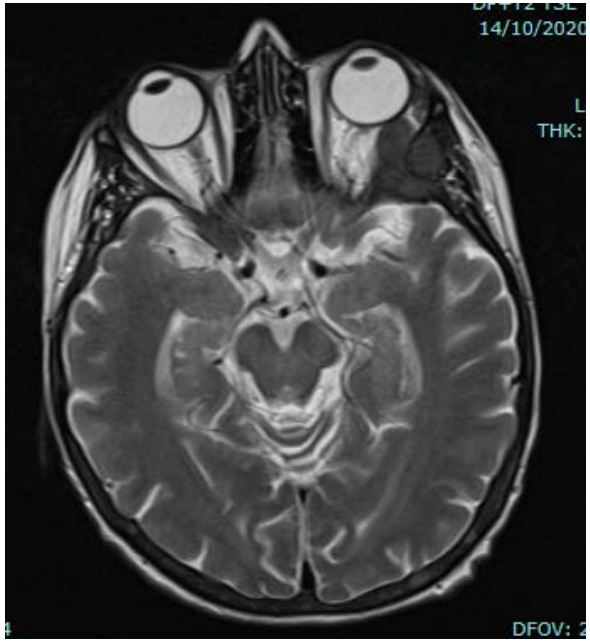
?

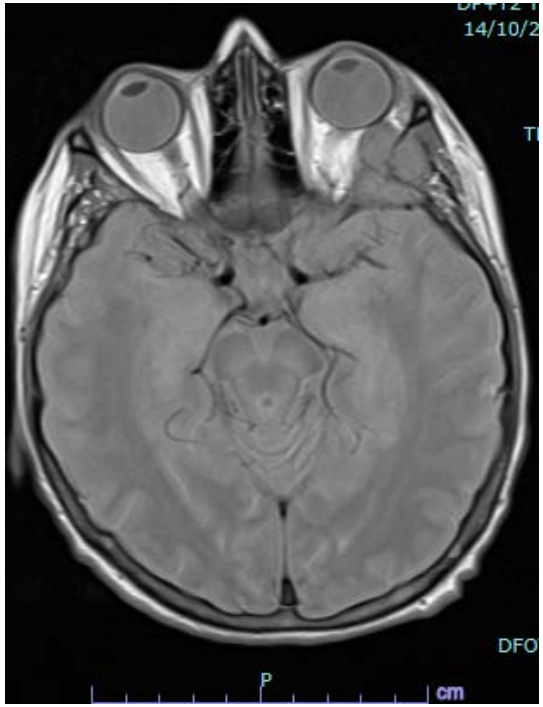
ADVERSE EVENTS AND TOLERABILITY

- Diarrhoea G3
- Nausea G1-2
- Skin rash

=> Dose reduction to 50 mg BID (Jul 28,2020)

Oct 14, 2020: basal brain MRI

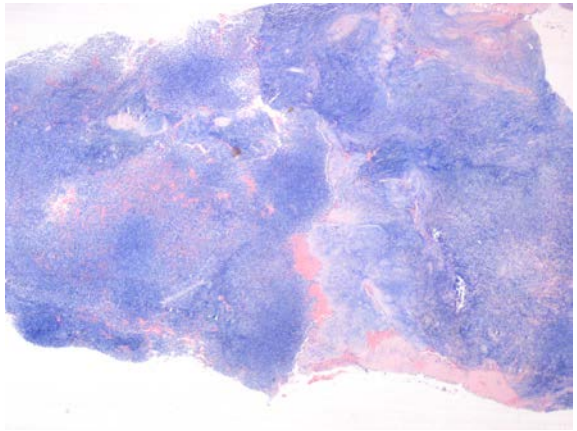


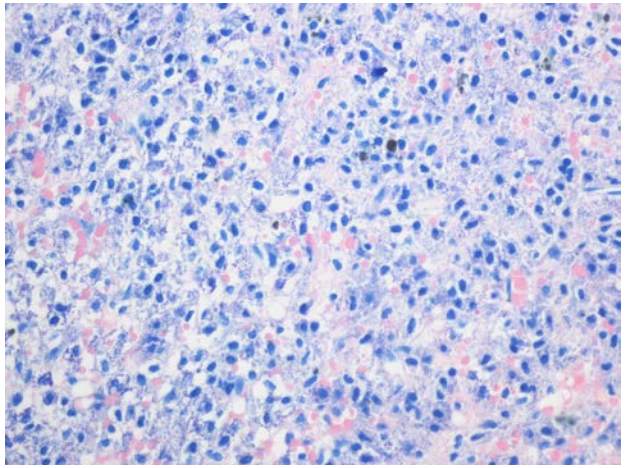


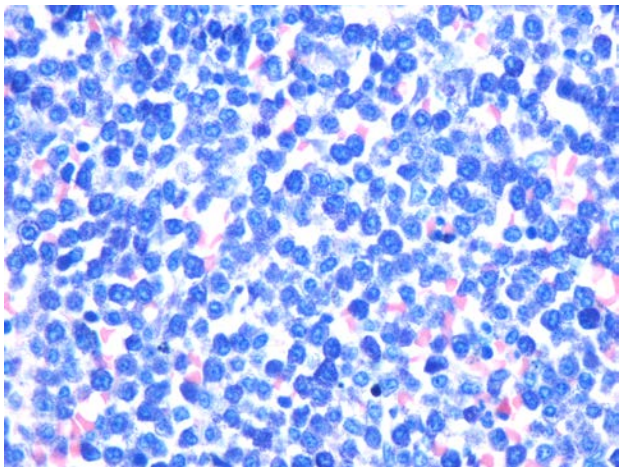
Dec 22, 2020: endoscopic transorbital resection of left spheno-orbital lesion

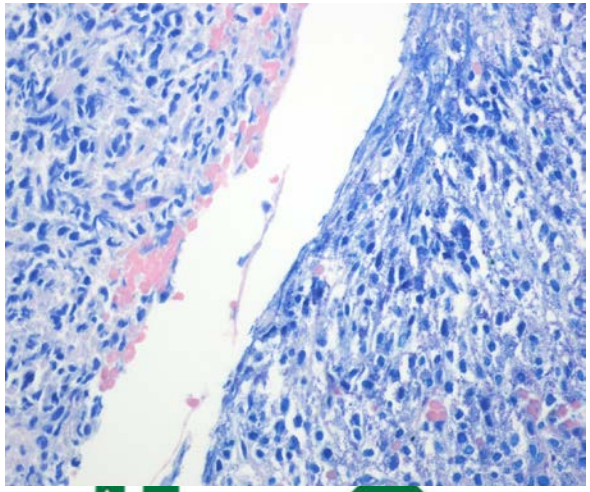
- General anesthesia according to guidelines, anti H1 and antiH2 premedication

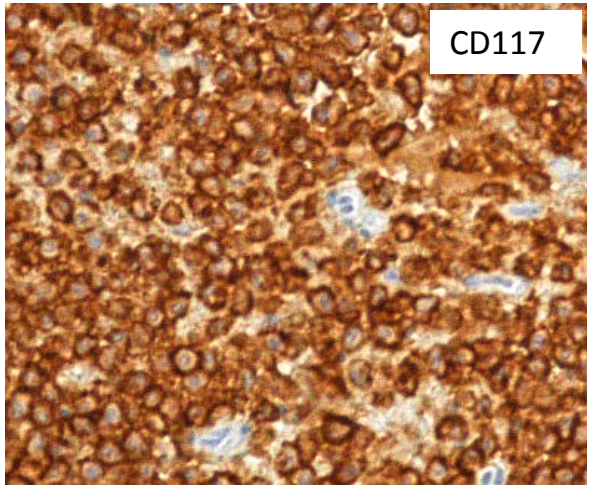
Left latero-orbital neoformation biopsy

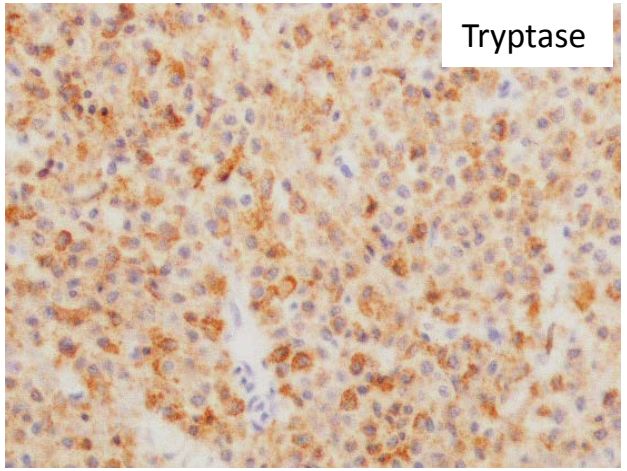












LAST COMPREHENSIVE DISEASE REASSESMENT (Nov 2, 2021), +16 months:

- CBC count: WBC 2,85 x10^9/L (N 1,35), Hb 13,7 g/dl, MCV 110 fl, PLT 85 x10^9/L
- Tryptase 128 mcg/l
- Reduction in BM MC infiltrate (morphological evaluation 11% vs 40%, BM histology 30% vs 60-70%)
- FISH XY on BM: recipient 5%, donor 95%
- Stable hepatosplenomegaly, reduction of mediastinal and abdominal lymphoadenopaty, no ascites, stable bone lesions, no radiological signs of progression
- Improvement of osteoporosis (DEXA scan 2022)
- No new allergic/anaphilactic events
- Slight gastrointestinal toxicity G1-G2 and fatigue
- No other G3-G4 AE

C: ***Clinical improvement of MCL*** according to IWG-ECNM consensus response criteria
AML in CR

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Carlo Maria Rossi
Cesare Zoia

NEW ITALIAN MASTOCYTOSIS REGISTRY


GRAND ROUNDS CLINICI DEL MERCOLEDÌ


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