LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

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AIL President: P. Toro
Coordinators: A.M. Carella, S. Amadori

AIL
ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

SIES Società Italiana Ematologia Sperimentale

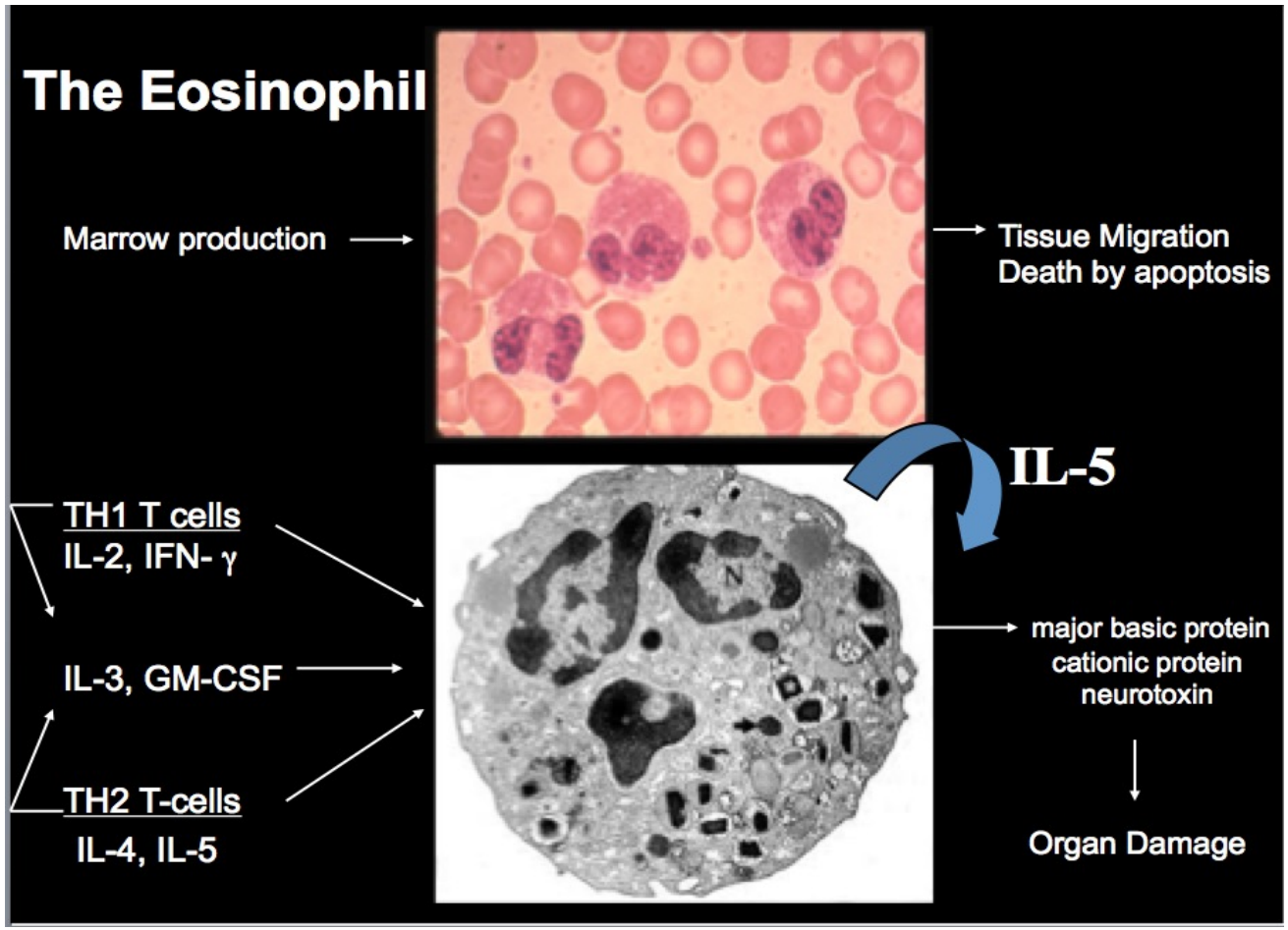
SIE - Società Italiana di Ematologia

Hypereosinophilias with and without genetic rearrangement

Francesco Mannelli, MD

CRIMM – AOU Careggi, Florence, Italy

Eosinophil Biology and Definition of Hypereosinophilia

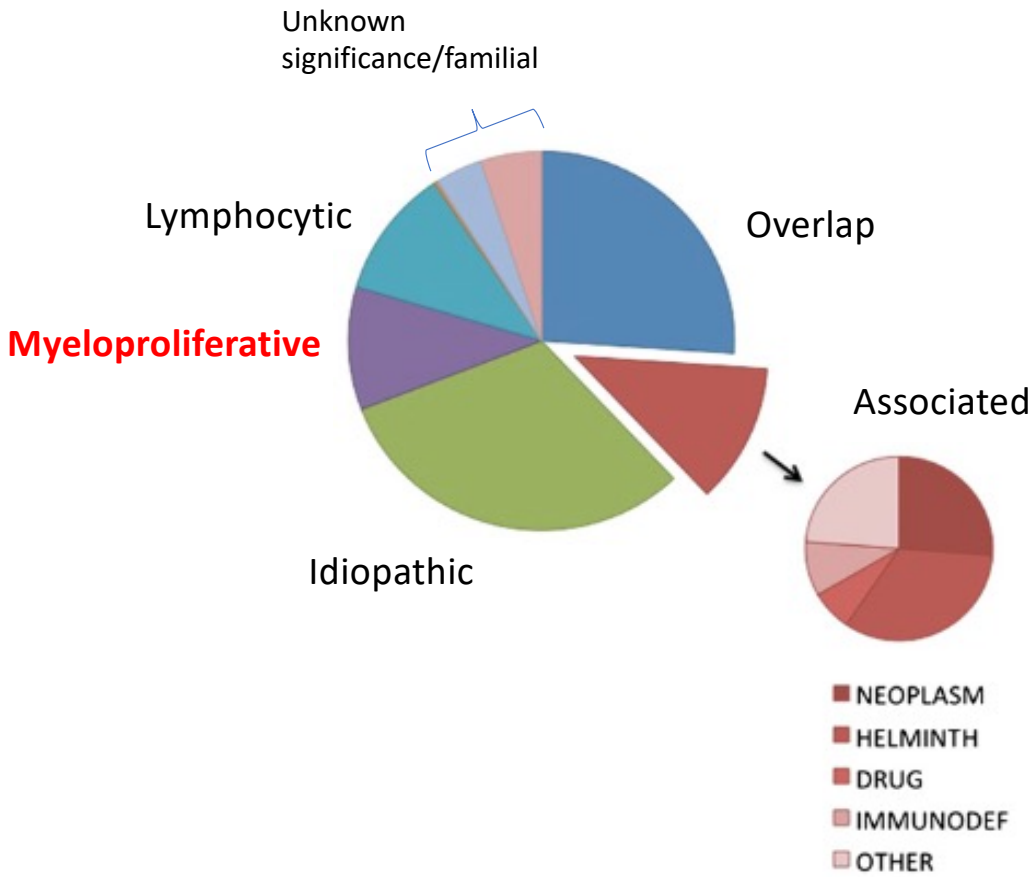


Normal: <5%, < 500/mm^3

[Hyper] eosinophilia

Mild:	**500-1500/mm^3**
Moderate:	**1500-5000/mm^3**
Severe:	**>5000/mm^3**

Eosinophilia: clonal vs. reactive



Eosinophilic disorders

Diagnosis and clinical assessment

- ***DIAGNOSTIC WORKOUT:***

Selected molecular tests *BCR-ABL1, JAK2, KIT*

NGS/ Myeloid gene panel

Flow Cytometry

T-cell clonality

BM biopsy

Standard Karyotyping

FISH for *FIP1L1-PDGFRA, PDGFRB, FGFR1*

- ***EVALUATION OF ORGAN INVOLVEMENT***

ECHO/ Cardiac MRI

US/CT/MRI Abdomen & Pelvis

Endoscopy

Organ-directed Biopsy

Pathogenesis

CLONAL, MYELOID

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*, or *PCM1-JAK2*

WHO-defined myeloid neoplasm associated with eosinophilia

Chronic Eosinophilic Leukemia, NOS

CLONAL, LYMPHOID

Lymphocytic-variant eosinophilia

UNKNOWN

Idiopathic Hypereosinophilic Syndrome (HES)

If organ damage present

Eosinophilic disorders

➢ **Primary, clonal underlying disease** and the **presence of organ damage** represent the basis for clinical management

CLONAL, MYELOID

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*, or *PCM1-JAK2*

Chronic Eosinophilic Leukemia, NOS

✓A **myeloid malignancy bearing specific rearrangements** sustains initiation of treatment depending on **availability of effective therapies**

✓**CEL NOS** mandates for initiation of therapy because of **poor prognosis** and risk of clonal progression

Eosinophilic disorders – Neoplasms with recurrent abnormalities

CLONAL, MYELOID

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*, or *PCM1-JAK2*

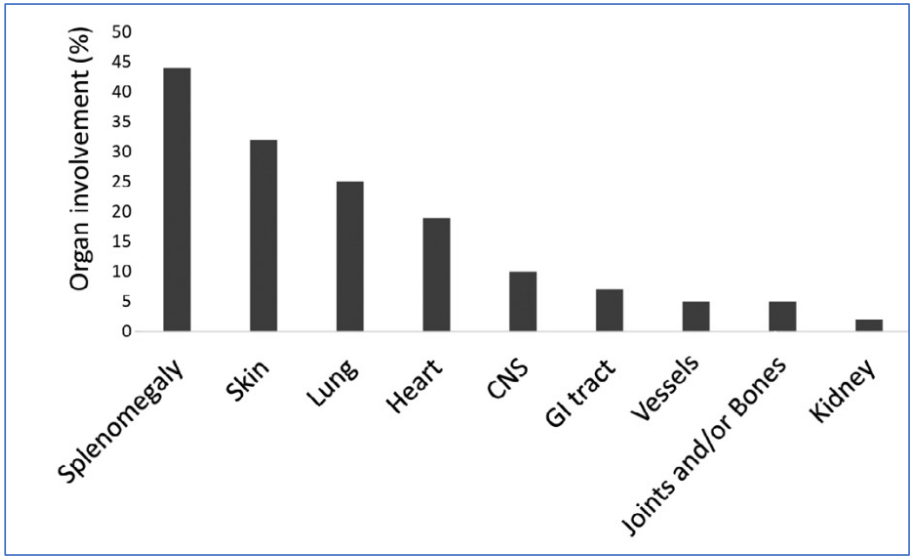
Breakpoint	Gene
4q12	*PDGFRA*
5q33	*PDGFRB*
8p11	*FGFR1*
9p24	*JAK2*

- ***FIP1L1-PDGFRA+*** Myeloid Neoplasms

  - ✓ Not visible with standard cytogenetics (Detectable by FISH or RT-PCR)
  - ✓ Elevated serum tryptase

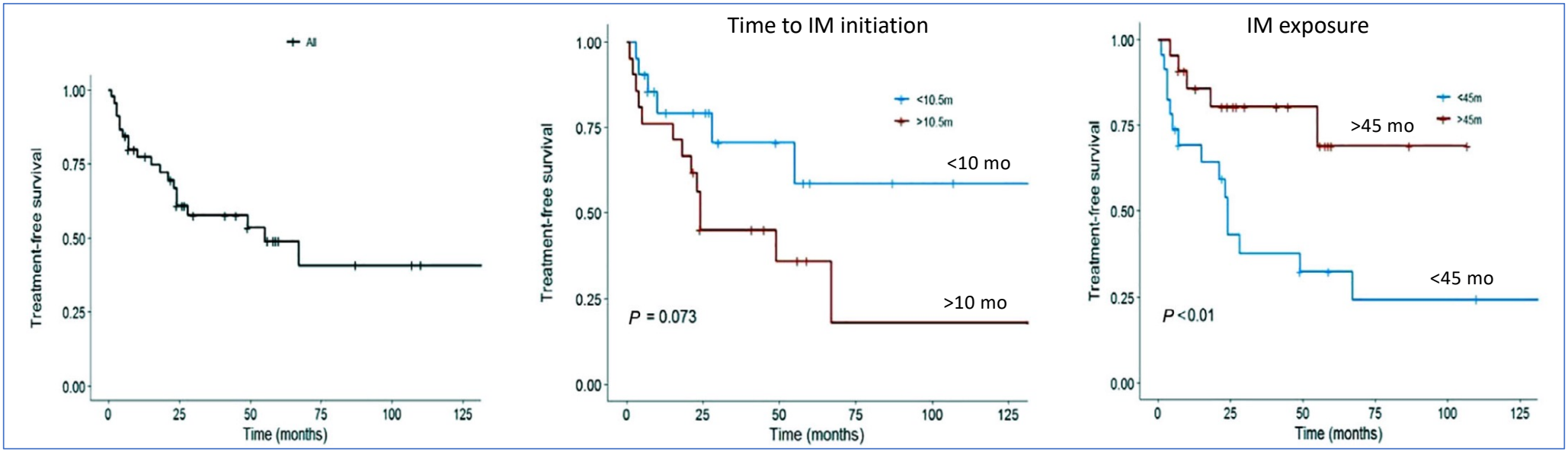
<u>Exquisite sensitivity to IMATINIB 100 mg daily</u>

- Complete molecular **remissions** achieved **rapidly** (e.g. 3 months). **Steroids** should be added in the first days of therapy with evidence of cardiac involvement



FIP1L1-PDGFRA+ Myeloid Neoplasms - treatment discontinuation

- **Imatinib discontinuation** is debated also due to scarcity of data (about 200 cases reported overall); the rate of **relapse sets around 50%** with frequent obtainment of response after re-exposure to Imatinib
- **Maintenance** dosing of 100 mg/week is feasible in some patients achieving CMR (*Helbig et al, Br J Haematol, 2008*)
- Role for **time of exposure** to Imatinib



Rohmer, AJH 2021

Eosinophilic disorders – Neoplasms with recurrent abnormalities

CLONAL, MYELOID

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*, or *PCM1-JAK2*

Breakpoint	Gene
4q12	*PDGFRA*
5q33	***PDGFRB***
8p11	*FGFR1*
9p24	*JAK2*

- ***PDGFRB***-rearranged Myeloid Neoplasms

PDGFRB-Rearranged Myeloid Neoplasms

- Prototypic *ETV6 (TEL)-PDGFRB* fusion described by Golub *et al* in 1994; **> 25 fusion partners described**
- **Phenotype:** Usually an MDS/MPN overlap (e.g. CMML or atypical CML) with eosinophilia; myeloid blast phase and B/T-cell lymphoblastic leukemia/lymphoma less common
- **Diagnosis:** Standard karyotyping usually exhibits a reciprocal translocation involving 5q31~q33; complex karyotypes observed
  - FISH probes can be used to confirm involvement of *PDGFRB*
  - PCR required to confirm fusion partners
- **Treatment**: Imatinib 400 mg daily recommended; doses of 100 mg/d have been used

Eosinophilic disorders – Neoplasms with recurrent abnormalities

CLONAL, MYELOID

Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*, or *PCM1-JAK2*

Breakpoint	Gene
4q12	*PDGFRA*
5q33	*PDGFRB*
8p11	***FGFR1***
9p24	*JAK2*

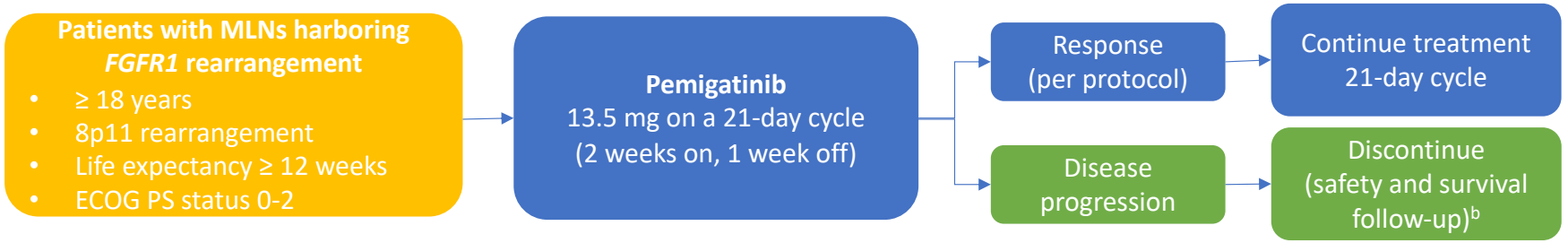
- ***FGFR1***-rearranged Myeloid/Lymphoid Neoplasms

FGFR1-Rearranged Neoplasms

- First described in 1995; 13 fusion partners since described
- **Phenotype**: MPN or AML, usually with eosinophilia; B/T-cell lymphoma; trilineage disease; rare cases with atypical mast cells / mastocytosis
- **Diagnosis:** Cytogenetically visible reciprocal translocations involving chromosome breakpoint 8p11-12; additional cytogenetic abnormalities
  - *Historically referred to as stem cell leukemia/lymphoma or 8p11 myeloproliferative syndrome*
- **Biology:** Arises in a multipotent hematopoietic progenitor
- **Clinical course**: Aggressive; often terminates in AML in 1-2 yrs
- **Therapy**: Intensive AML/ALL **chemotherapy** followed by transplant; transient responses with **Ponatinib**; selective and potent inhibitors of *FGFR1* such as **PEMIGATINIB**

FGFR1-Rearranged Neoplasms

FIGHT-203: A Phase 2, Open-label Study Evaluating the Efficacy and Safety of Pemigatinib in Patients With MLN Harboring *FGFR1* Rearrangement: Study Design



34 pts enrolled

	CR, n (%)		CCyR, n (%)	
	Investigator	CRC	Investigator	CRC
Responses, N=31 for CR and N=33 for CCyR	20 (64.5)	24 (77.4)	24 (72.7)	25 (75.8)
CP disease only, N=18 (CP without EMD)	15 (83.3)	16 (88.9)	14 (77.8)	16 (88.9)
Any BP component, N=13 (BP with or without EMD; CP with EMD; EMD only)	5 (38.5)	8 (61.5)	8 (61.5)	7 (53.8)
Treated MLN with no morphologic evidence of disease but persistent cytogenetic abnormality, N=2	NE	NE	2 (100)	2 (100)

The most common treatment-emergent AEs were:
- ✓ hyperphosphatemia (68%)
- ✓ alopecia (59%)
- ✓ diarrhea (50%)
- ✓ stomatitis (44%)
- ✓ anemia (35%)

- Long-term treatment option for pts ineligible for HSCT or bridging strategy to HSCT

Gotlib et al, ASH 2021

Eosinophilic disorders – Neoplasms with recurrent abnormalities

CLONAL, MYELOID

Chronic Eosinophilic Leukemia, NOS

- Chronic Eosinophilic Leukemia, NOS

Key diagnostic criterion: evidence of clonal myeloid involvement (blasts, chromosomal abnormalities)

+ exclusion of other myeloid neoplasms

✓A challenge with **IMATINIB** might be attempted in order to assess potential sensitivity (reported cases with *KIT* M541L somatic mutation)

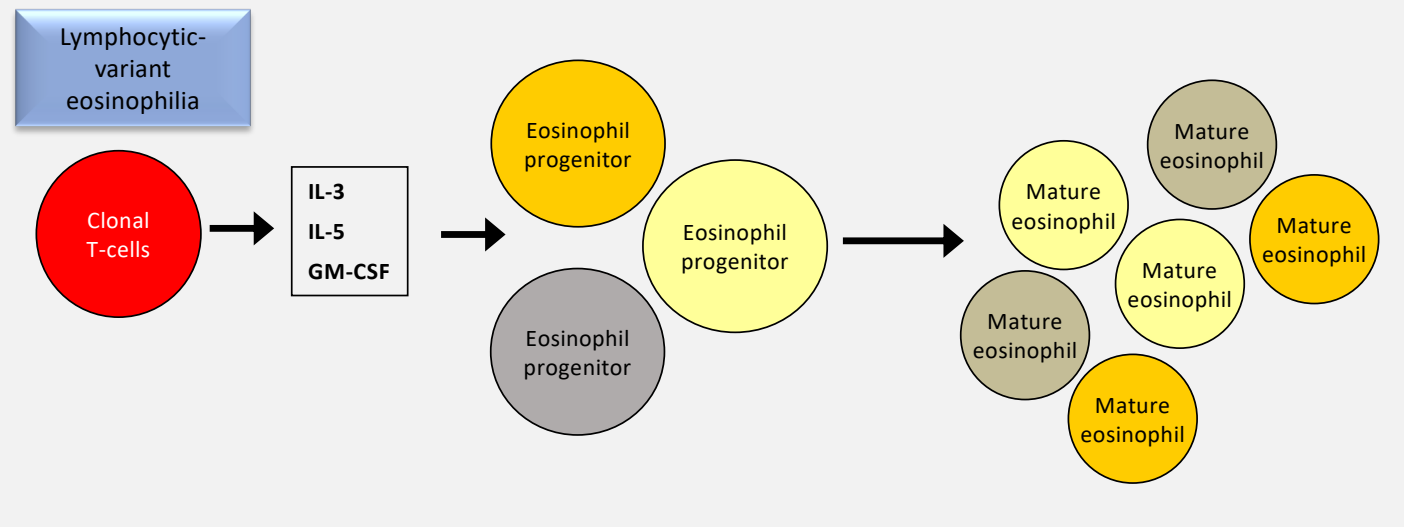
✓**HYDROXYUREA** and **STEROIDS** can be used to control disease manifestations

✓**ALLOGENEIC HSCT** should be considered in selected cases due to poor survival

Iurlo et al, Oncotarget 2014;5(13):4665

Helbig et al, AJH 2012;87(6):643

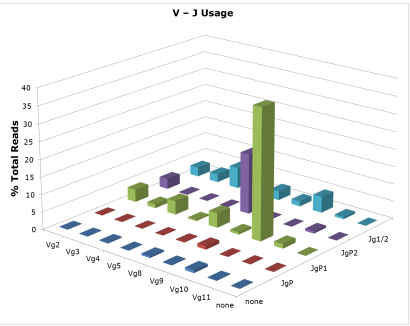
Eosinophilic disorders – lymphocytic variant



Flow cytometry

- Absence of CD3 ($CD3^{-}CD4^{+}$)
- Double-negative immature T-cells ($CD3^{+}CD4^{-}CD8^{-}$)

NGS



Up to 10% of pts tests positive for TCR rearrangement in *FIP1L1/PDGFRA*

- Lymphocytic Variant Hypereosinophilia

✓**STEROIDS** are considered the first-line therapy. Disease control often requires **long-term administration of therapy**

✓The pathogenetic mechanism sustains the application of therapeutic **approaches targeting T-cell clones**:

- **Cyclosporine**
- Anti-CD52 **Alemtuzumab**

Eosinophilic disorders – HES

- Idiopathic Hypereosinophilic Syndrome (HES)

Idiopathic Hypereosinophilic Syndrome (HES)

✓ A **watch-and-wait approach** is acceptable for asymptomatic patients with absolute eosinophil count >1.500/microliter and no evidence of myeloid neoplasm and end-organ manifestations

✓ Pts should be **closely monitored for early organ damage** (echocardiography, serum troponin level, pulmonary function testing)

✓ **STEROIDS** are considered the first-line therapy

Prednisone (PDN) 1 mg/kg for 15 days followed by slow dose-tapering

✓ When long-term treatment (PDN >10 mg daily) is required for disease control, **steroid-sparing therapies** should be used:

- **Hydroxyurea**
- **Interferon-α**
- Monoclonal antibodies vs IL-5/IL-5-receptor (**Mepolizumab**)

✓ **IMATINIB** is a reasonable try, especially with prominent myeloproliferation and/or dysplasia

Eosinophilic disorders – HES

- Idiopathic Hypereosinophilic Syndrome (HES)

Targeted next-generation sequencing identifies a subset of idiopathic hypereosinophilic syndrome with features similar to chronic eosinophilic leukemia, not otherwise specified

Sa A Wang[1,11], Wayne Tam[2,11], Albert G Tsai[3], Daniel A Arber[3], Robert P Hasserjian[4], Julia T Geyer[2], Tracy I George[5], David R Czuchlewski[5], Kathryn Foucar[5], Heesun J Rogers[6], Eric D Hsi[6], B Bryan Rea[7], Adam Bagg[7], Paola Dal Cin[8], Chong Zhao[1], Todd W Kelley[9], Srdan Verstovsek[10], Carlos Bueso-Ramos[1] and Attilio Orazi[2]

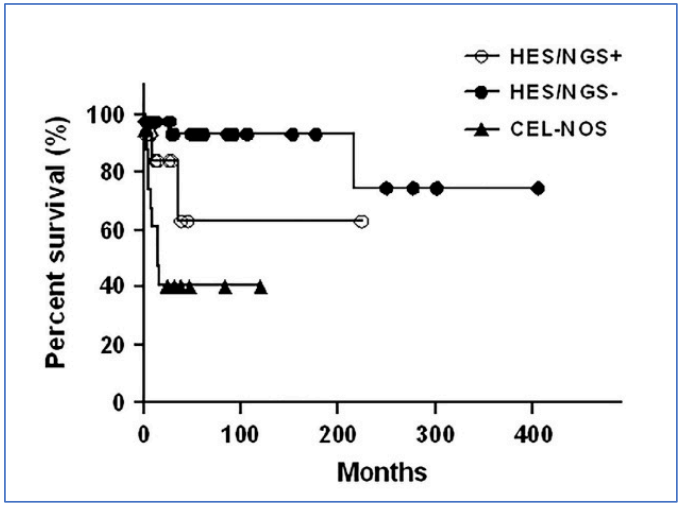
- **NGS** panel: mutations in 14/51 pts (28%)

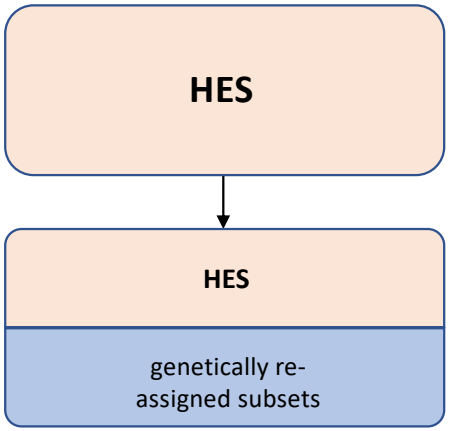
ASXL1	43%
TET2	36%
EZH2	29%
SETBP1	22%
CBL	14%
NOTCH1	14%

Wang et al, Mod Pathology, 2016;29(8):854

- ***STAT5B*** mutations (~ 2% of CEL/HES)

Cross et al, Leukemia, 2019;33:415





Conclusions – Eosinophilic disorders

- The correlation between the extent of eosinophilia and organ damage is uncertain: there are not clear evidences supporting the initiation of therapy merely depending on absolute eosinophil count

- With overriding clinical manifestations prompting immediate initiation of therapy, **adequate sampling for genetic abnormalities** must precede treatment starting

- Identification of **recurrent rearrangements** is the basis for delivery of targeted therapies:
  - *FIP1L1-PDGFRA*+ Myeloid Neoplasms: **Imatinib**
  - *PDGFRB* - rearranged Myeloid Neoplasms: **Imatinib**
  - *FGFR1* - rearranged Myeloid/Lymphoid Neoplasms: **intensive chemotherapy**, **HSCT**; selective **inhibitors** (**Pemigatinib**)

- In **lymphocytic** variant and **idiopathic** hypereosinophilic syndrome, **steroids** are the conventional first-line therapeutic modality. Novel agents are emerging as effective **steroid-sparing** alternatives (**Mepolizumab**)