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ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Involvement of the JAK-STAT Pathway in the Molecular Landscape of Fusion-Free Myeloid Neoplasms with Eosinophilia

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Introduction. Gene fusions leading to the constitutive activation of tyrosine kinases (TK) such as *PDGFRA, PDGFRB* or *FGFR1* have been the first recurrent genetic defects involved in myeloid hypereosinophilic syndromes (HES). Although activation of the Janus kinase (JAK)/Signal Transducer and Activator of Transcription(STAT) pathway is critical for eosinophil production and survival, genes involved in the JAK/STAT pathway are not included in most next-generation sequencing (NGS) panels used for the etiological workup of hypereosinophilia (HE).
Methods. A custom 149-gene NGS panel including subunits of the IL3/IL5/GM-CSF receptors, TK (*PDGFRA/B, FGFR1, ABL1, FLT3, KIT*), intracellular proteins of the JAK-STAT and RAS-MAPK pathways was performed in 64 consecutive adult patients (experimental group) referred between March 2012 to June 2023 to the French Reference Center for Hypereosinophilic Syndromes (CEREO) for HE/HES displaying at least one clinic-biological feature suggestive of myeloid neoplasm (*i.e.* splenomegaly, other unexplained CBC abnormality besides HE, increased serum tryptase and/or vitamin B12 levels, corticosteroid-refractory HE and/or sensitivity to either TK inhibitors or JAK inhibitors). All of them were negative by PCR and/or FISH analyses for gene rearrangements involving *PDGFRA, PDGFRB* or *FGFR1*. Patients with lymphocytic HES (n=7), idiopathic HES (n=26) and HE of undetermined significance (n=11) were used as controls (total, n=44).
Results. Concordant with the latest recommendations of the international cooperative working group on eosinophil-associated disorders, at least one mutation was reported in 50/64 (78%) patients of the experimental group versus 8/44 (18%) patients in the control group ($p<0.001$) when applying a threshold of at least 3% of variant allele frequency (VAF). Mutations in the control group implied genes involved in age-related clonal hematopoiesis (*e.g. DNMT3A, TET2*), with low VAF in almost all cases. All 35 patients with at least one mutation involving the JAK/STAT pathway belonged to the experimental group, among whom all 22 patients treated with steroids were refractory to therapy. Eighteen patients had *STAT5B* mutations, including 13 (72%) with the somatic N642H mutational hotspot. Two patients harbored *JAK2* ^{Ex13InDel} mutations, including one with eosinophilia and erythrocytosis. Previously unreported molecular alterations were also evidenced, including seven patients with *JAK1* mutations and three *STAT5A*-mutated patients who shared common features *i.e.* the co-occurrence of *BCOR* mutations, high hemoglobin levels and eosinophil hyperplasia. Of note, the latter mutations were not reported both in a public database (GnomAD) as well as in a second cohort of 613 samples referred for suspicion of myeloid malignancies (yet without HE) studied with the same NGS workflow, thereby strongly supporting their association with myeloid HES. Deciphering the data from bulk sequencing also suggests that JAK-STAT mutations were frequently preceded by (or associated with) myelodysplasia-related gene mutations, with *SF3B1* (12/36) and *ASXL1* (10/36) mutations being the most common. Overall, both *KIT* D816V (n=2) and RAS/MAPK pathway activation mutations (n=3) were rare. No mutation of either *PDGFRA/B*, *FGFR1* or *IL3/IL5/GM-CSF*-receptor genes was evidenced.In the experimental group, 17/18 (94%) patients (including 12 with JAK-STAT mutations) treated with ruxolitinib and with > 3 months of follow-up responded to treatment (12 complete and 5 partial hematological responses).
Discussion. These dataemphasize the usefulness of NGS in daily practice for the workup of fusion-free HES patients harboring features suggestive of myeloid neoplasms. In such patients, druggable mutations involving the JAK-STAT pathway (including yet unidentified *STAT5A* mutations) are frequent. Most JAK/STAT mutations occur in the setting of a preexisting myelodysplastic or myelodysplastic/myeloproliferative disease harboring mutations in RNA-splicing genes or chromatin modifiers. These findings provide a rationale for refining treatment algorithms in fusion-free myeloid HES patients, supporting the use of JAK inhibitors as frontline therapy. More data are warranted to assess whether JAK inhibition enables sustained molecular remission in all disease subtypes.

Disclosures Groh: *AstraZeneca:* Consultancy; *GlaxoSmithKline:* Consultancy, Honoraria. **Forcade:** *Astellas:* Speakers Bureau; *Alexion:* Other: Travel support, Speakers Bureau; *Novartis:* Consultancy, Other: Travel support, Speakers Bureau; *Gilead Sciences:* Other: Travel support, Speakers Bureau; *GSK:* Speakers Bureau; *Sanofi:* Speakers Bureau; *MSD:* Other: Travel support. **Nicolini:** *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *SUN pharma:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *INCYTE BIOSCIENCES:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Rousselot:** *Incyte:* Consultancy; *Pfizer:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Novartis:* Consultancy; *Takeda:* Consultancy. **Viallard:** *EUSAPHARMA:* Consultancy. **Kahn:** *AstraZeneca:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *GlaxoSmithKline:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Lefèvre:** *AstraZeneca:* Consultancy, Membership on an entity's Board of Directors

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OffLabel Disclosure: Ruxolitinib in fusion-free patients with features of myeloid neoplasms and eosinophilia, harbouring mutations of the JAK-STAT pathway.

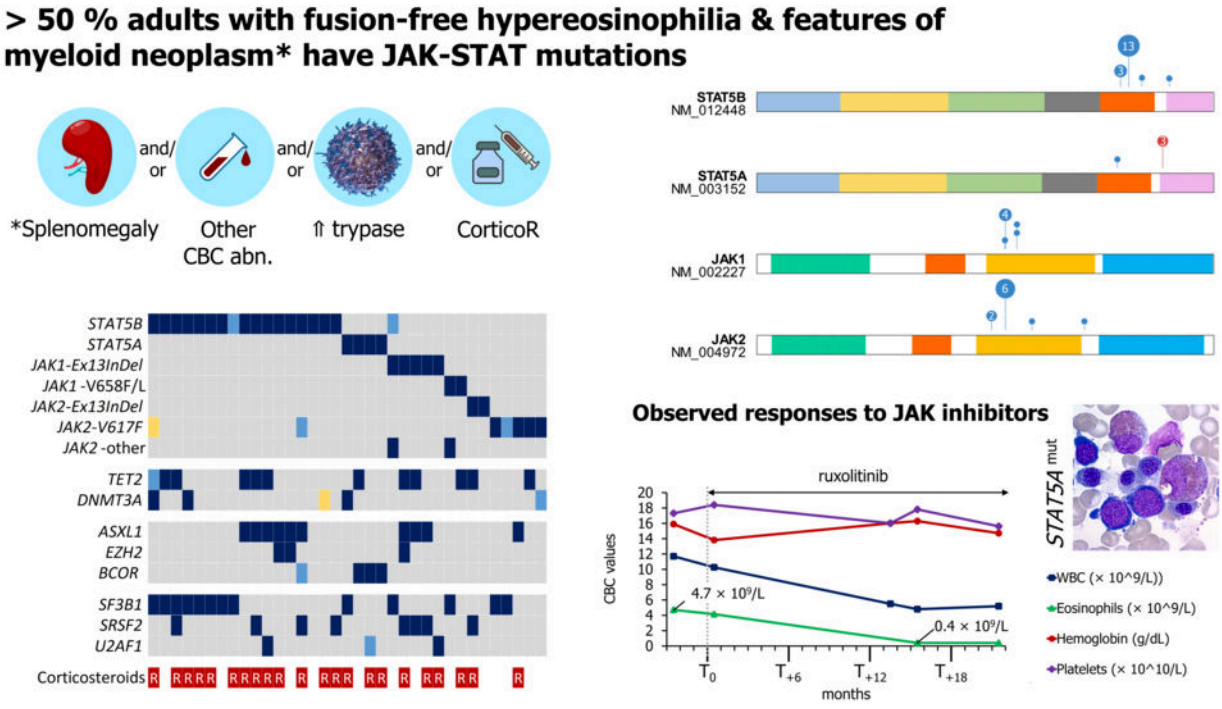

Figure 1

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