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# POSTER ABSTRACTS

## 622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

### A Digital Gene-Expression Signature Supports Mediastinal Gray Zone Lymphoma Stratification within Classical Hodgkin or Primary Mediastinal B-Cell Lymphoma

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**Abstract** Mediastinal non-Hodgkin Lymphomas with intermediate features between Primary Mediastinal Large B-cell Lymphoma (PMBCL) and classical Hodgkin Lymphoma (cHL) - also known as mediastinal Gray Zone Lymphomas (mGZL) - represent a unique, diagnostically challenging entity (Khoury et al., Leukemia 2022). They typically exhibit discordant morpho-phenotypical characteristics between cHL and PMBCL, a high rate of diagnostic reclassification and consequent poor therapeutic outcomes. While a comprehensive biological picture of this entity remains to be fully deciphered, recent gene expression profiling of mGZL confirmed their molecular straddling between cHL and PMBCL (Pittaluga et al., Blood Cancer Discov., 2020; Sarkozy et al., BLOOD ADVANCES, 2020). However, the diagnosis of mGZL is still challenging and largely based on the satisfaction of morphological and immunophenotypic criteria. Therefore, there is an urgent need of practical tools exploiting deeper molecular traits of mGZL to facilitate their pathological boundaries between cHL or PMBCL and selection of proper treatment. We applied CIBERSORTx (Newman et al., Nat. Biotechnol., 2019) to public Gene Expression Profiling (GEP) data of a training set comprising 50 cHL (GSE17920) and 31 PMBCL (GSE11318). Such approach purified GEP of both tumor and microenvironment (TME) origin, followed by a Nonnegative Matrix Factorization (NMF)-based selection of 2,913 genes with high discriminating capacity between the two lymphoma subtypes. After a fine-tuned feature selection, a final signature of 168 genes was verified on the training cohort, tested *in silico* on an independent series of 34 cHL (GSE17920) and 20 PMBCL (GSE87371), and finally validated by NanoString technology on a real-life (RL) cohort including ten cHL and twelve PMBCL to which were added ten mGZL samples. Although we initially gathered 20 GZL, only the mediastinal were included in the study ($n$=14). Finally, we selected only the ten mGZL that successfully passed Quality Control. The signature produced a successful clustering of cHL or PMBCL cases in all the series analyzed from different technology platforms. Notably, the mGZL broke down into the two clusters, either cHL or PMBCL subtypes on a transcriptomic ground (Figure 1). Moreover, to assess the specificity of the signature in categorizing mGZL within the cHL/PMBCL spectrum, we tested it on ten Follicular Lymphoma samples which, as expected, segregated in a stand-alone subgroup.
In conclusion, we provided a proof of concept of a NanoString-based gene signature enabling a transcriptomic stratification of mGZL, adding up to their morpho-phenotypical categorization. If validated on larger cohorts, our approach might prompt the design of a useful molecular assay easily transferable to routine clinical practice.

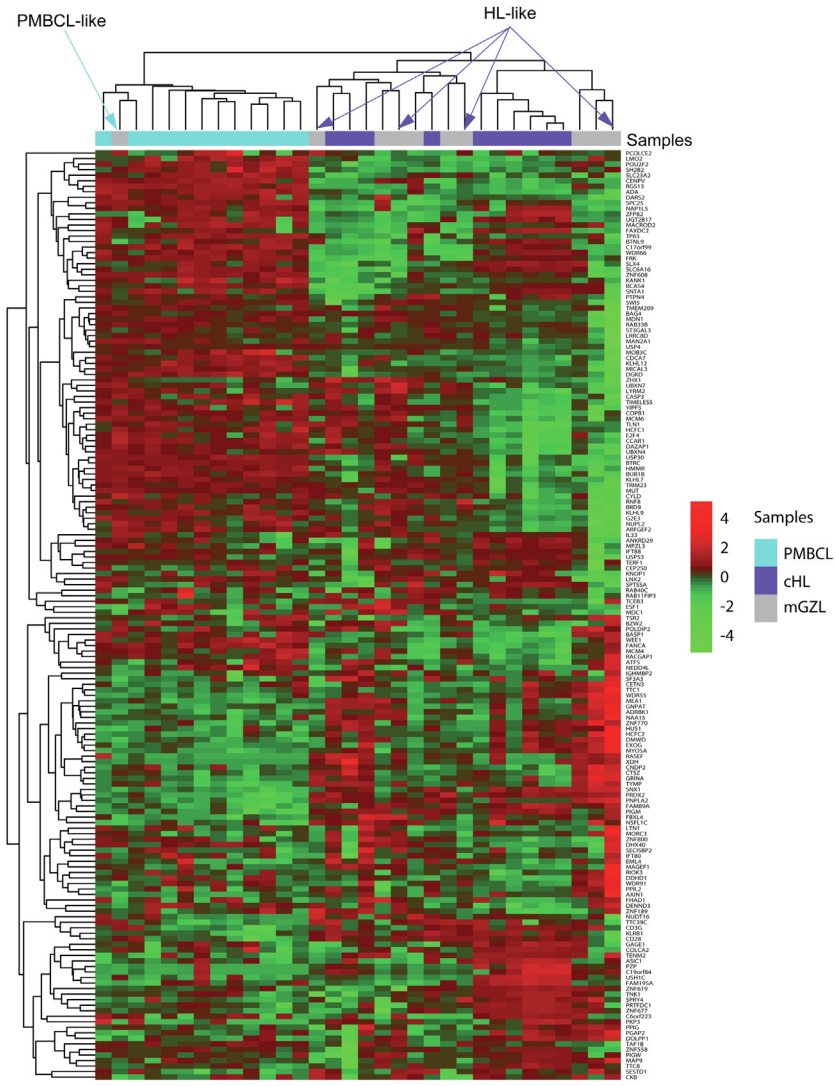


**Figure 1**: Heatmap showing the clustering analysis of the 168-gene signature in the real-life cohort including 10 cHL, 12 PMBCL and 10 mGZL. Arrows show the morphological subtypes.

**Figure 1.**

**Disclosures Sabattini:** *Novartis:* Speakers Bureau; *EUSA Pharma:* Consultancy, Speakers Bureau. **Nassi:** *Roche:* Membership on an entity's Board of Directors or advisory committees; *Takeda:* Membership on an entity's Board of Directors or advisory committees; *Incyte:* Membership on an entity's Board of Directors or advisory committees; *Kyowa Kirin:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees.

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