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## Machine-learning based prediction of Germinal Center, MYC/BCL2 Double Protein Expressor status, and MYC rearrangement from Whole Slide Images in DLBCL patients

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be augmented upon binding to CLL1 and expanded our study to various AML cell lines and blasts from AML patients.

**Methods:** To determine CLL1 binding-dependent CD3 binding of ABL602, T cell binding was measured by flow cytometry in the presence of CLL1-spiked beads. ABL602-mediated antitumor activity and T cell activation were tested in CLL1 expressing AML cell lines and AML blasts from patients. In vivo antitumor activity was determined in humanized mice bearing AML tumors.

**Results:** ABL602 (2+1), with its CD3 binding arm sterically hindered by CLL1 binding arm, binds to CD3 with a lower affinity compared with 1+1 format in the absence of CLL1-expressing cells. By incubating T cells with beads spiked with various amounts of CLL1 in the presence of ABL602, we proved that ABL602's binding affinity to CD3 was increased in a CLL1-dependent manner, reaching comparable level to that of 1+1. ABL602 induced superior tumor cell killing than 1+1 reference antibody JNJ-67571244. Moreover, ABL602 showed a dose-dependent anti-tumor activity with tumor regression in OCIAML2 xenograft and HL-60 orthotopic model. In AML patient blasts, CLL1 was highly expressed and ABL602 exhibited a strong T cell activation and tumor killing activity on CLL1<sup>+</sup> AML blasts.

**Conclusions:** This study supports the target-specific T cell activation and tumor killing activity of 2+1 heterodimeric structure of ABL602 on both AML cell lines and patient-originated AML blasts and warrants further pre-clinical development.

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### 623MO Machine learning-based prediction of germinal center, MYC/BCL2 double protein expressor status, and MYC rearrangement from whole slide images in DLBCL patients

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**Background:** Diffuse Large B-Cells Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma in adults (30-40%). In the 2016 World Health Organization (WHO), DLBCL are classified into 3 molecular subtypes according to cell of origin (COO), germinal-center, activated B-cell like and unclassified, based on gene-expression profiling (GEP). In daily routine, COO classification is replaced by immunohistochemistry (IHC) stains using the Hans algorithm based on the expression of CD10, BCL6 and MUM1 proteins. In addition, co-expression of BCL2 and MYC proteins is of prognostic value and defines the double-protein expressors (DPE) subtypes, associated with worse prognosis. Fluorescent In Situ Hybridization (FISH) is mandatory in the workup of DLBCL to detect MYC and BCL2 and/or BCL6 rearrangements.

**Methods:** 565 whole-slide images (WSI) stained with hematoxylin/eosin from the LYSA trial "GHEDI" (Deciphering the Genetic Heterogeneity of Diffuse large B-cell lymphoma in the rituximab era) dataset were analyzed. A Deep Learning (DL) model was trained to predict COO and DPE status, the presence of MYC rearrangements (no MYC rearrangement/MYC-Single Hit or HGBL-Double Hit/Triple Hit) and expression of BCL6, CD10 and MUM1 proteins from WSI. Performance was evaluated using several repetitions of stratified five-fold cross-validation.

**Results:** The DL model achieved a ROC AUC of 0.624 for GC, 0.687 for DPE, and 0.675 for MYC rearrangement. Using Cox proportional hazard model, predictions of DPE status (HR=0.38, P=.016), and MYC rearrangements (HR=5.23, P<.001) and MUM1 expression (HR=2.80, P=.027) were associated with worse overall survival.

**Conclusions:** Our study demonstrates the predictive power of DL applied to WSI to predict DLBCL subtypes. Such predictive models could be used to augment pathologists analysis capacities, especially when IHC staining or FISH are not available.

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### 624MO Retrospective analysis of clinical value of ctDNA in newly diagnosed diffuse large B cell lymphoma

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**Background:** Diffuse Large B Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma with high incidence, strong clinical and genetic heterogeneity. Current clinical characteristics are insufficient for the prognostic stratification of DLBCL. In recently, circulating tumor DNA (ctDNA) emerging as a biomarker for DLBCL prognostic stratification. However, whether it could use ctDNA as a biomarker to detect mutated genes in samples from Chinese DLBCL patients is uncertain.

**Methods:** The present study evaluated ctDNA as prognostic value for clinical diagnosis prior to treatment. We enrolled 172 newly diagnosed DLBCL patients, and all patients underwent targeted NGS-based 59-gene panel. The prognostic value of ctDNA in the context of established risk factors, including the International Prognostic Index, Ann Arbor stage, Lactate Dehydrogenase level (LDH), BULK, and bone marrow involvement (BMI), were evaluated. Finally, effects of pretreatment ctDNA on outcome of DLBCL were assessed.

**Results:** Before therapy, ctDNA was detectable in 74.4% of patients. The most frequently mutated genes were *PCLO* (33.6%) and *PIM1* (32.8%). The mutation frequencies of *KMT2D*, *CREBBP*, *BCL2*, *TP53*, *KLHL6* and *MYC* in GCB were significantly higher than in Non-GCB (p=0.012; 0.011; 0.036; 0.020; 0.0056). Whereas, *CD79B* mutation was more frequent in Non-GCB (p=0.023). The mean of pretreatment ctDNA variant allele frequencies (VAF) was significantly associated with both International Prognostic Index (IPI) and Ann Arbor stages; and we observed a significantly higher VAF mean among patients with abnormal LDH (p<0.0001), with bone marrow involvement (p=0.0277), and with the bulk (p=0.0047). Using 23% threshold of ctDNA VAF mean, patients with high levels had inferior rates of overall survival (OS) and progression-free survival (PFS) than those with low levels, and its association with OS was significant.

**Conclusions:** CtDNA could serve as a prognostic factor and a tumor specific biomarker for DLBCL in China. The most frequently mutated genes were *PCLO*. The level of pretreatment ctDNA VAF mean could predict therapy response and prognosis.

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### 625MO Combination of mitoxantrone hydrochloride liposome with pegaspargase in patients with extranodal NK/T-cell lymphoma: A phase I/II clinical trial

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**Background:** Extranodal NK/T-cell lymphoma (ENKTCL) remains a high unmet clinical need for improving outcome. This trial aimed to explore the safety, pharmacokinetics (PK) and efficacy of mitoxantrone hydrochloride liposome (PLM60) plus pegaspargase in patients (pts) with ENKTCL.

**Methods:** Adult pts with histologically confirmed treatment-naïve or relapsed/refractory ENKTCL were recruited. Phase I was 3+3 dose-escalation design with four dose levels of PLM60 (12, 16, 20 and 24 mg/m<sup>2</sup>) plus pegaspargase 2000 IU/m<sup>2</sup> administered on day 1 of every cycle (21 days) for 4-6 cycles. Phase II was dose expansion at the recommended phase 2 dose (RP2D) in pts with treatment-naïve ENKTCL. The primary endpoints were safety and PK. The secondary endpoint was efficacy including complete response (CR) rate, objective response rate (ORR) as per Lugano 2014.

**Results:** At the cut-off data of February 15, 2022, 31 eligible pts were enrolled (phase I, n = 21 and phase II, n = 10). Phase I included 9 relapsed/refractory pts and 12 treatment-naïve pts. Two dose-limiting toxicities (grade-4 neutropenia in 20 mg/m<sup>2</sup>; grade-3 abdominal pain in 24 mg/m<sup>2</sup>) occurred. RP2D was PLM60 24 mg/m<sup>2</sup> plus pegaspargase 2000 IU/m<sup>2</sup>. Treatment-related adverse events (TRAEs) of any grade occurred in all 31 pts, in which 27 (87.1%) were ≥ grade 3. The most common ≥ grade 3 TRAEs were neutropenia (77.4%), leucopenia (74.2%), anemia (54.8%), thrombocytopenia (45.2%), hypertriglyceridemia (22.6%), infectious pneumonia