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POSTER ABSTRACTS

802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

Indicators of Response to the Wee1 Inhibitor Adavosertib in Acute Myeloid Leukemia

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Wee1 is a nuclear kinase that regulates cell cycle progression by inhibiting Cdk1, which is essential for G2 to M phase transition. Inhibition of Wee1 leads to high Cdk1 activity, causing cells to bypass proper DNA repair at the G2/M checkpoint, resulting in mitotic catastrophe and cell death, plus increased Cdk2 activity, causing abnormal DNA replication and DNA double-stranded breaks. Inhibitors of Wee1 are being investigated for the treatment of a variety of cancers including AML. In this study, we aimed to identify biomarkers for Wee1 inhibitor (Wee1i) response in AML using *ex vivo* drug sensitivity data, bulk RNA sequence, exome sequence, and associated clinical data for a large set of primary AML samples tested against the Wee1i adavosertib.

Mononuclear cells from bone marrow aspirates (n=136) or peripheral blood samples (n=11) were collected from AML patients using approved protocols and after informed consent. 101 samples were collected at the time of diagnosis and 35 samples were from relapsed/refractory (R/R) patients. For *ex vivo* drug-sensitivity testing, freshly isolated cells were tested against a library of up to 634 oncology drugs (215 approved drugs) including adavosertib. The drugs were pre-plated in 5 concentrations in a 10,000-fold concentration range and incubated with cells for 72h. Cell viability was assessed using the CellTiter Glo (CTG) assay, and a drug sensitivity score (DSS) calculated based on the area under the dose response curve. Somatic alterations of the drug tested samples were identified via exome sequencing of DNA from the AML samples and matched skin biopsy controls. Gene expression data were obtained from bulk RNA sequence data of the AML samples.

Out of 136 samples analyzed, the median DSS for adavosertib was 8.45. We found positive and significant correlations between sensitivity to adavosertib and two factors: 1) malignant cell percentage (R= 0.31, p-value= 0.0097), and 2) final relative viability percentage (R=0.58, p-value= 4.3e-13). Correlation analysis between the DSS of adavosertib and 633 other drugs revealed several strong positive and significant correlations. These included drugs with specific mechanisms of actions including HSP90 inhibitors (n=5), JAK2 inhibitors (n=4), topoisomerase II inhibitors (n=4), CDK4/6 inhibitors (n=3), mitotic inhibitors, vinca alkaloid microtubule depolymerizers (n=3), and PLK1 inhibitors (n=3). Since adavosertib also targets PLK1 in addition to Wee1, the correlation with PLK1 inhibitor activity confirms the similar target profiles.

Based on the specific adavosertib DSS thresholds, the samples were separated in two groups. Samples sensitive to adavosertib (n=35) had DSS between 21.3 (max) and 11.9 (3rd quartile). Samples resistant to adavosertib (n=34) had DSS between 0.0 (min) and 5.65 (1st quartile). Differential gene expression analysis between the sensitive vs resistant samples showed that multiple isoforms of the *PCDH* and *HOXB* genes were upregulated in adavosertib sensitive samples. The *GLI2*, *PI15*, and *SKIDA1* genes were also upregulated in the sensitive samples (Figure A). In contrast, genes such *DNTT*, *PF4V1*, *TRH*, *CD1B*, *S100A16*, and *CD34* were overexpressed in resistant samples (Figure B). Gene set enrichment analysis revealed positive enrichment of pathways related to MYC targets v2 in the sensitive samples. On the other hand, hallmark pathways associated with cell cycle, apoptosis, RAS signaling, and p53 showed significant negative enrichment scores in the sensitive samples. No

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statistically significant associations were observed between drug response and frequently occuring somatic mutations in our dataset. However, genetic abberations related MLLT4-MLL/MLL-fusions were only observed in sensitive samples.
Collectively, our current findings show that there may be specific gene expression signatures associated with Wee1i sensitivity such high expression of *PCDH* and *HOXB*. Also, the positive enrichment of the MYC target v2 pathway in adavosertib sensitive samples suggests that highly proliferating tumor cells might be more sensitive to Wee1i. In addition, high *CD34* expression in resistant samples suggests that immature stem and progenitor cells may be less susceptible to Wee1i. In summary, targeting of Wee1 in AML - as studied in NCT05682170 azenosertib study - may be effective for a molecularly defined subset of patients.

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Figure

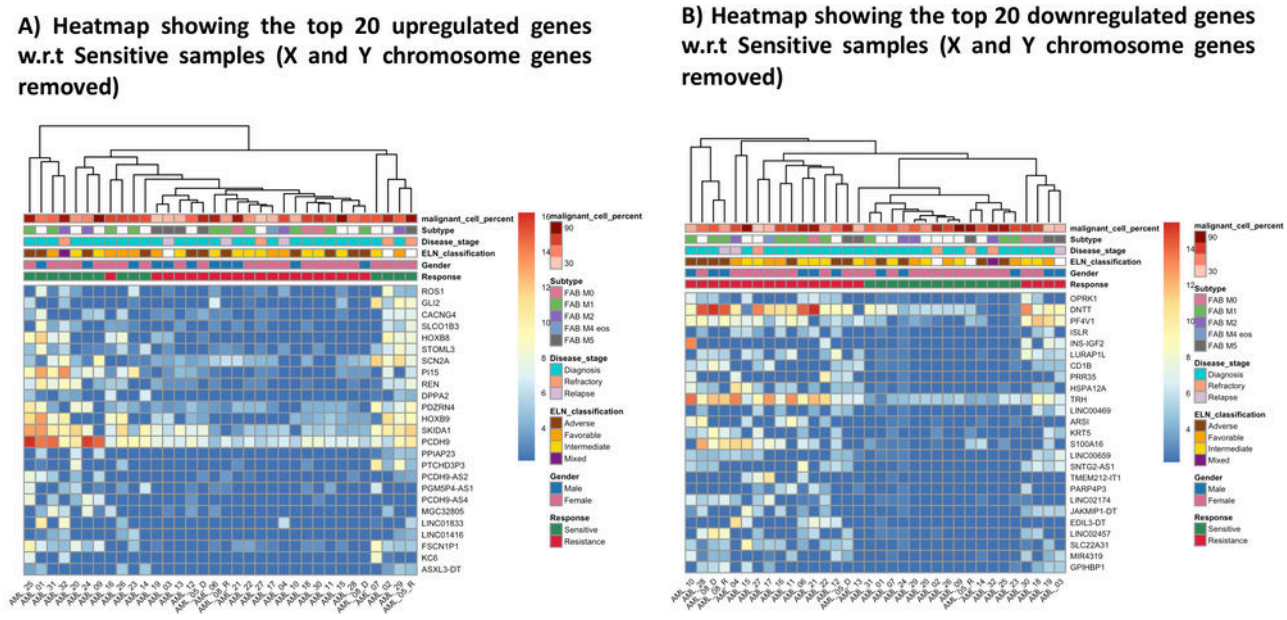

Figure 1

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