soho2023
ELEVENTH ANNUAL MEETING

THE LD-VENEX PHASE II CLINICAL TRIAL: AN *EX VIVO* FLOW CYTOMETRY BASED-DRUG SCREENING OF AML PATIENT SAMPLES

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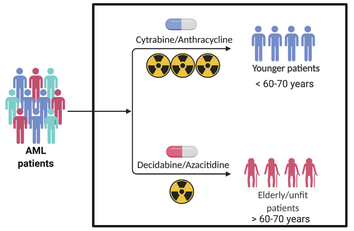
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INTRODUCTION

Acute Myeloid Leukemia (AML) is a haematological malignancy distinguished by the accumulation of clonal, proliferative, poorly differentiated cells in bone marrow (BM) and peripheral blood (PB) (Döhner et al., 2015; 2017). AML is an aggressive cancer in adults with an over survival rate of five years (25%). Patients with refractory/relapse (R/R) and elderly/unfit AML Patients display low survival rate (10%) and clinical outcome with 5 year. The clinical trial exploring therapeutic efficacy and safety of combination drugs will help to improve the clinical outcome of AML patients.

AML STANDARD TREATMENT

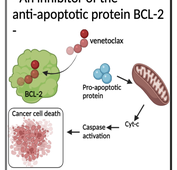


- Current average survival rate of <60 years adult AML patient is only 35% to 40% and 5% to 15% patients >60 years (Döhner et al., 2015; 2017)
- Elderly/unfit and R/R AML patients rarely survive beyond two years

SINGLE/COMBINATION DRUG TREATMENT

Venetoclax (VEN)

- An inhibitor of the anti-apoptotic protein BCL-2



- No biomarkers have been validated in clinical setting yet

Azacitidine (AZA)

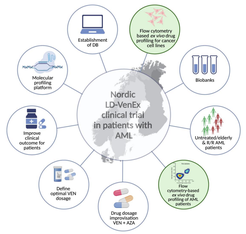
- Hypomethylating agent
- Inhibit DNA methyltransferases at low doses thereby supressing tumor supressor genes (Pleyer and Greil, 2015; Schuh et al., 2017)
- Approved in EU for treatment of AML patients with >30% bone marrow blasts (Schuh et al., 2017)

VEN + AZA

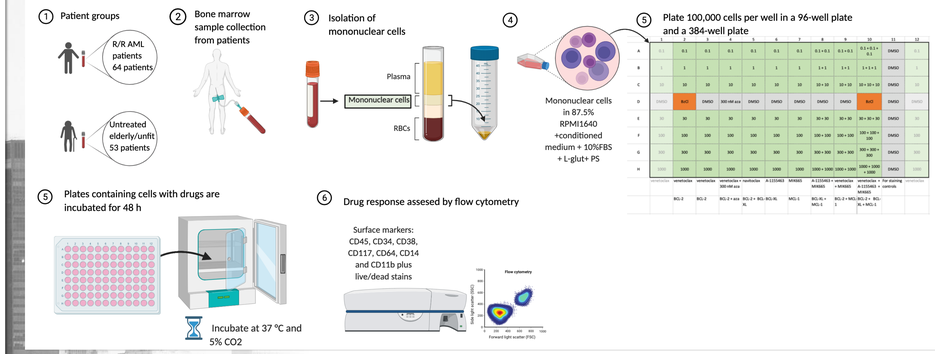
- VEN + AZA induce high remission rates and extend survival of newly diagnosed elderly and unfit AML patients
- currently approved for use in the US since 2018
- showed substantial improvement of response rates (OS 14.7 months) as compared to AZA alone (9.6 months) (one-third did not achieve the response; DiNardo et al., 2020)

PROJECT GOALS

- Identify the *ex vivo* drug response profiling (sensitivity/resistance) to AML between the three Nordic testing sites by flow cytometry
- Investigate AZA in combination with low-dose of VEN (LD-VEN) can improve quality of life and reducing the toxicity while maintaining therapeutic efficacy/survival for R/R and unfit/elderly AML patients
- Determine the optimal VEN dosage and potential efficacy of drug combinations

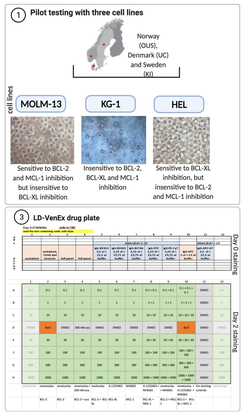


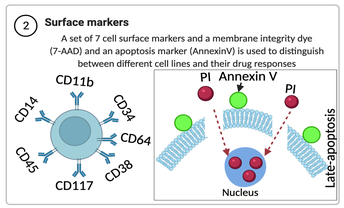
DRUG RESPONSE PROFILING OF PATIENT SAMPLES FROM THE LD-VENEX TRIAL

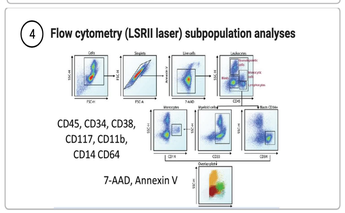


- 96-well plates contains the drugs like, VEN (0.1-1000 nM), VEN (0.1-1000 nM) with a fixed concentration of AZA (300 nM and 1000 nM); the MCL-1 inhibitor MIK665 (0.1-1000 nM), the BCL-2/BCL-XL inhibitor navitoclax (0.1-1000 nM) and the BCL-XL inhibitor A-1331852 (0.1-1000 nM). The drug responses were assessed after 48 h by flow cytometry using the markers CD45, CD34, CD38, CD117, CD64, CD14 and CD11b.

VALIDATION OF CELL POPULATION SPECIFIC DRUG RESPONSE







EXPECTED OUTCOME

- Pilot testing on cell lines will be used to calibrate the experimental approach and reagents, data acquisition equipment, and data analysis between all the three centres
- The flow cytometric analysis from AML patient samples will allow us to measure total live cell counts, total blasts, CD34+, CD34+/CD38-, CD117+ as well as degree of myeloid differentiation (CD14+ and/or CD11b+) in response to drugs/drug combinations
- The combination treatment will help to identify novel treatment for future clinical trials for the R/R patients from VEN/AZA treatment
- Identify predictive biomarkers for VEN response in AML
- Detect and validate the efficacy of low-dose VEN treatment of AML

REFERENCES

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ACKNOWLEDGEMENTS

I would like to take this opportunity to recognize and thank our fellow Nordic partners involved in this project and AML patients recruited for the Nordic clinical trial

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