Background: We have overcome the limitations of 40 years of ex vivo testing with our novel Native Environment Precision Medicine approach. The aim of this study is to determine the ability of Vivia’s novel test to predict the complete remission (CR) rates after induction chemotherapy with cytarabine (Ara-C) and idarubicin (Ida) in 1st line AML.

Material and Methods: Bone marrow samples from adult patients diagnosed with de novo AML in Spanish centers from the PETHENA group were included. While marrow samples mature the patients’ Native Environment was preserved for 48h in well plates containing Ara-C, Ida, or their combination. Pharmacological responses were calculated using pharmacodynamic population Hill-based dose-effect models and drugs surface interaction analysis. Induction response was assessed according to the chemotherapy protocol (Os), while overall survival was followed using Kaplan-Meier chart. Patients a CVR were classified as responders and the remaining as resistant.

Results: 377 patient samples were used to fit the dose response (DR) curves for Ara-C alone, Ida alone, and their interaction. For clinical correlation we used 142 patients with median 66 years. The strongest clinical predictions were the Area Under the Curve (AUC) of the DR of Ara-C, and the AUC of Ida. Additional prediction capabilities associated were the sensitivity to the drug combination parameter. Results are summarized in Figure 7 in a table showing the correlation between the estimated cut points (lines). From a diagnostic criteria (columns), clinically resistant patients (1st column) are not well predicted with a Sensitivity of 50%, while clinically sensitive patients (2nd column) are well predicted with a Specificity of 95%. From a Precision Medicine criteria (rows) patients predicted resistant (1st line) and well predicted with 80.7% positive predictive value, similar to patients predicted sensitive (2nd line) with 84.3% negative predictive value. Very significant difference (P<0.0002) was observed in the overall survival analysis between the group of patients predicted as responders from those predicted as non-responders (Figure 8).

Distribution of the interaction index calculated for the samples in the study. The central tendency was towards an additive or weak synergistic behavior although clear synergetic occurred in many cases.

Key Clinical Indicators: Overall prediction 81.7% vs 81.9%

Clinical positives: 74.8µM, 150µM

Clinical negatives: 30µM, 74.8µM

Figure 3 Individual Dose Response Curves

Figure 4 Interaction index

Figure 5 Pharmacological Population Parameters

Figure 6 Logistic additive model of ex vivo Cyt-IDA vs Clinical Outcome

Figure 7 Correlation results summary

Figure 8 Overall survival analysis

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This novel test is able to predict the clinical response to Ida+Ara-C induction with 80.7%, significantly higher than the current clinical response rate of 66.7%. The test did not properly identify 21/142 that were clinically resistant and the test predicted as sensitive. This mismatch highlights the current clinical restrictions where a resistant clone present in a minority of leukemic cells cannot be detected yet drives the patient response. However, this group mismatch does not present a good correlation with the test predicted outcome.

Good predictive capabilities were identified for dose-effect area under the curve variables.

No statistical significance was found in the surface interaction analysis of the drugs combination analysis.

Very significant separation was found in the overall survival analysis between the two branches of responsive and resistant cases according to the test results.

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