

# HIGH CORRELATION BETWEEN CLINICAL RESPONSES TO FIRST LINE AML PATIENTS TREATED WITH CYTARABINE AND IDARUBICIN AND THEIR PHARMACOLOGICAL PROFILES IN PATIENT SAMPLES MEASURED BY EXVITECH

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## ABSTRACT

**Background:** Complete remission (CR) after induction therapy is the first treatment goal in acute myeloid leukemia (AML) patients. The aim of this study is to determine the ability of the Vivia's novel ex vivo drug sensitivity platform Exvitech to predict the CR rates after induction chemotherapy with cytarabine (Ara-C) and idarubicin (Ida) in 1<sup>st</sup> line AML.

**Material and Methods:** Bone marrow samples from adult patients diagnosed with de novo AML in Spanish centers from the PETHEMA group were included. Whole marrow samples were incubated for 48h in well plates containing Ara-C, Ida, or their combination. Pharmacological responses are calculated using pharmacokinetic population models. Induction response was assessed according to the Cheson criteria (2003). Patients attaining a CR/CRI were classified as responders and the remaining as resistant.

**Results:** 180 patient samples were used to calculate the dose response (DR) curves for Ara-C alone, Ida alone, and their synergism. For clinical correlation we used 77 patients with a median age of 55 years. Many samples had a significant number (>20%) of resistant cells to Ara-C. This is a strong clinical predictor of resistance because in the patient the drug will never be present at these high doses for 48h. The second variable that is a good predictor of response is the synergism between these 2 drugs. The generalized additive model identified an algebraic combination of these 2 variables that yielded the best marker to separate both groups of patients. The probability density functions had minimal overlap. The area under the corresponding ROC curve was 0.935 (0.872, 0.997), and the classification probabilities for the optimal cut point, were 87% (68% to 95%) and 91% (80% to 96%) for sensitivity and specificity, respectively. 54 patients (70.1%) achieved CR after Ida+Ara-C, and the remaining 23 (29.9%) were resistant. 20 of the 23 (86.9%) patients who fail to achieve CR were predicted as resistance in the ex vivo test. 49 of the 54 patients (90.74%) who achieved CR showed good ex vivo sensitivity to Ida+Ara-C predicting for CR. When the ex vivo test predicted a patient as sensitive it was correct in 49/52 cases (94.23%), and when it predicted resistant it was correct 20/25 cases (80%). Overall, 69/77 patients (89.61%) had an accurate prediction of their response to treatment.

## RESULTS

Figure 1 Objectives & Study Design

- Background & Objectives
  - Complete remission (CR) after induction is the first treatment goal in AML patients
  - Response to chemotherapy is the main prognostic factor
  - There is no test accurately predicting the response to specific drug schedules.
  - The aim is to determine the ability of an ex-vivo drug sensitivity test to predict the clinical response to Ida+Ara-C (3+7) induction

Study Design

- Non-interventional and prospective study
- Samples from adult patients diagnosed with de novo AML in centers from the PETHEMA group
- CR/CRI were classified as responders (vs. PR/resistance)
- Induction death → non-evaluable
- 180 patient samples to calculate the dose response curves for Ara-C alone, Ida alone, and Ara-C plus Ida
- For clinical correlation, 77 patients (median age 55 years)

Figure 2 Pharmacological ex vivo Data: Single drugs & Synergism

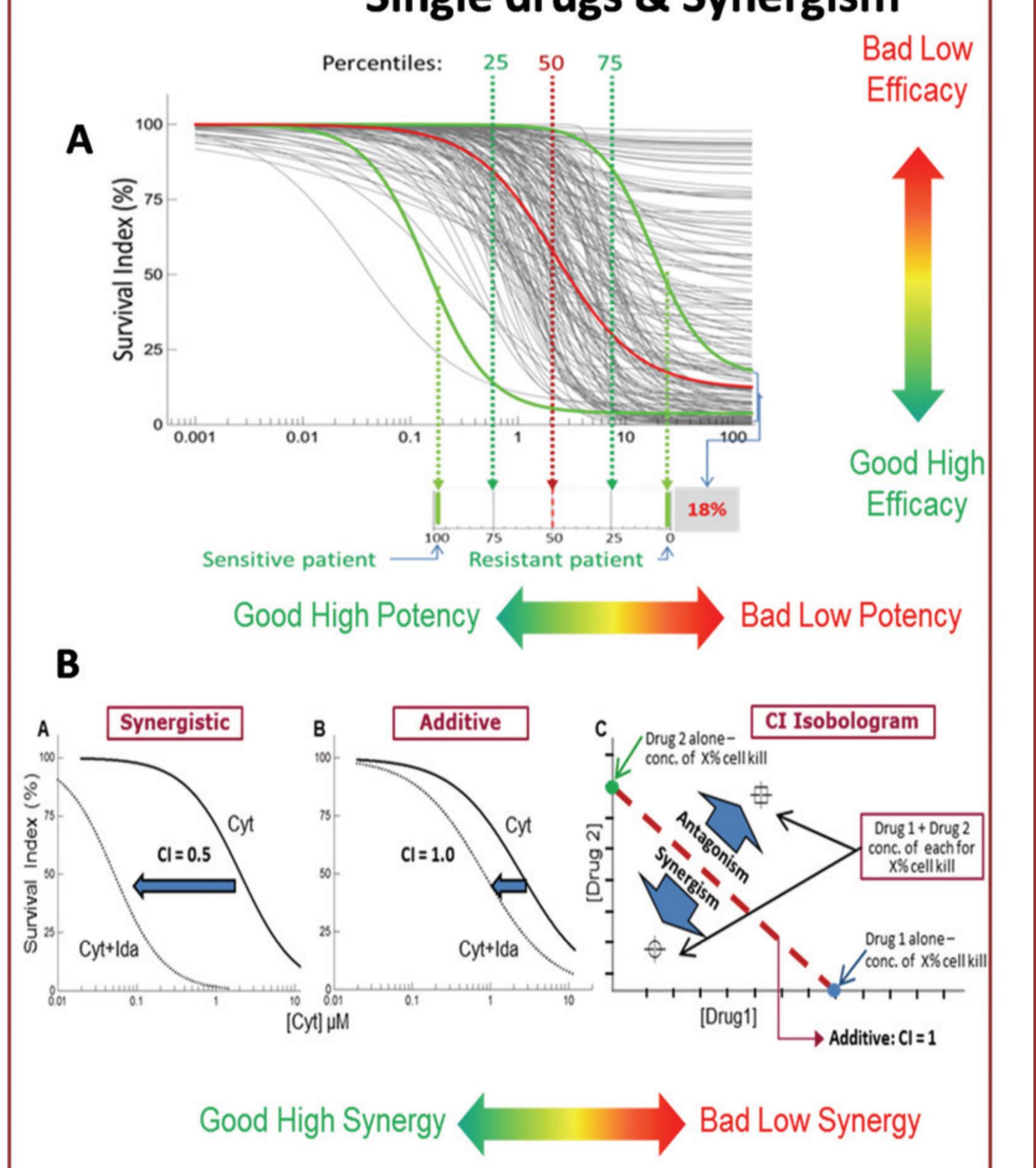
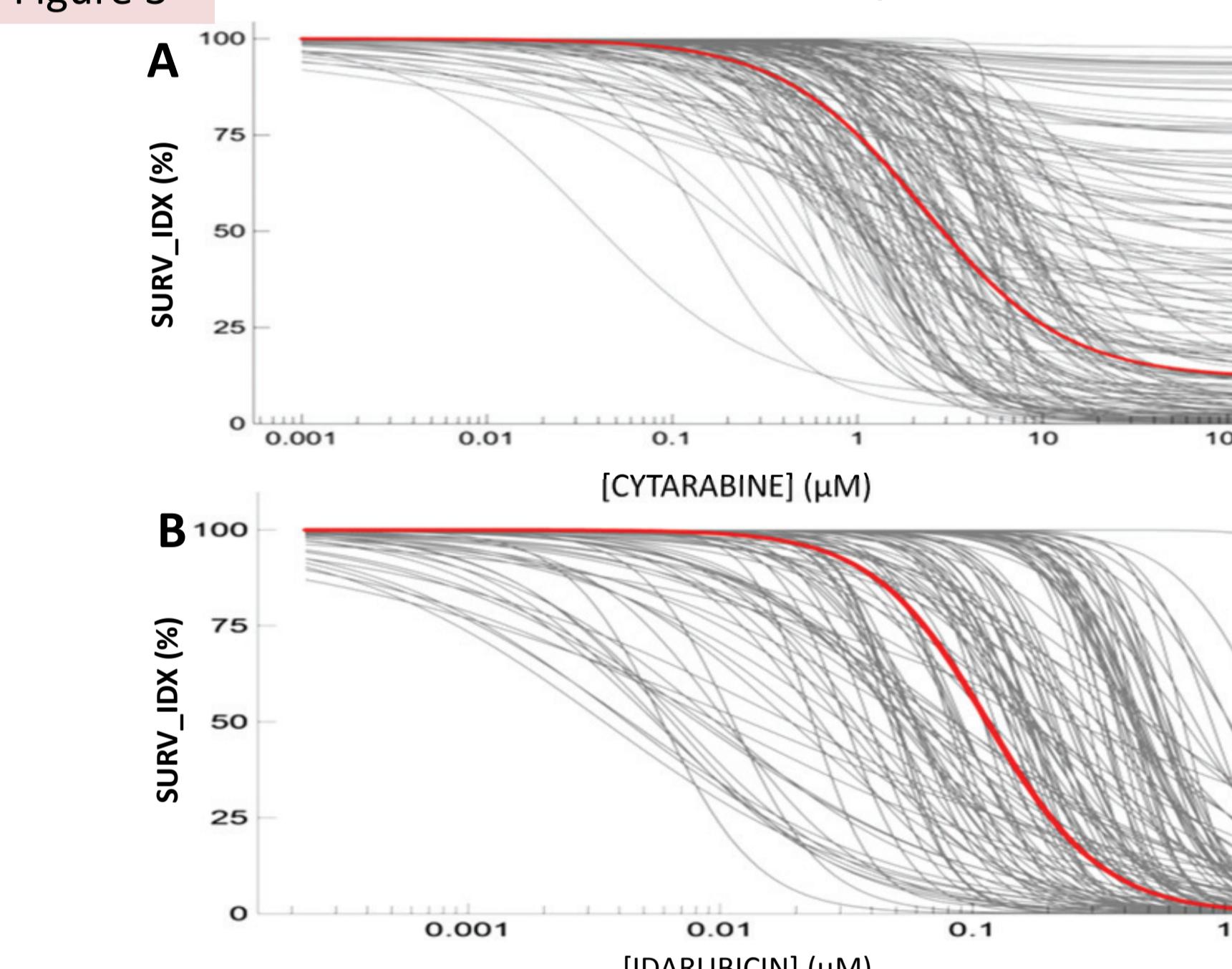


Figure 3 Individual Dose Response Curves



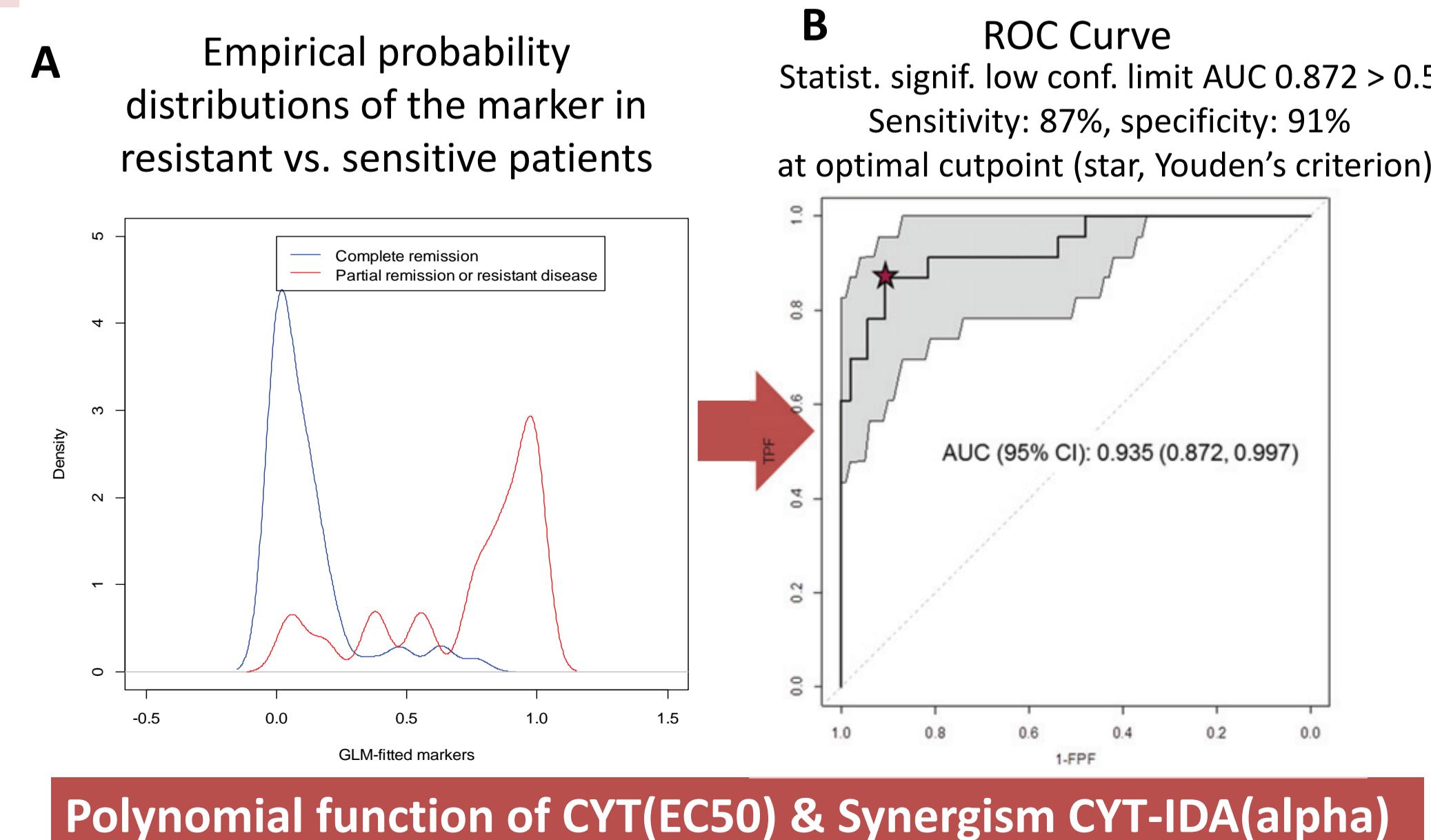
Dose-responses from 180 patient samples. The Survival Index (y-axis) ranges from 100% to 0 displaying the selective AML cell depletion calculated with PKPD Population Models. Median response shown in red. For CYT 40% patient samples have resistant cells left alive at 48 h. IDA eliminates all cells within this timeframe.

C Pharmacological Population Parameters

SINGLE DRUG ex vivo PHARMACOLOGY					
DRUG	N	Efficacy <sub>EC50</sub>	Potency <sub>EC50</sub>	IPV <sub>EC50</sub>	IPV <sub>EC50</sub>
IDA	125	0	0.0105	0.016	NE
CYT	125	11.8	2.28	0.13	32

Individual drug typical and random error values (left). Inter-patient variability (IPV) expressed as CV(%); Synergism (right) using the CI, \*, estimate not significantly different from 0; ne, not estimated

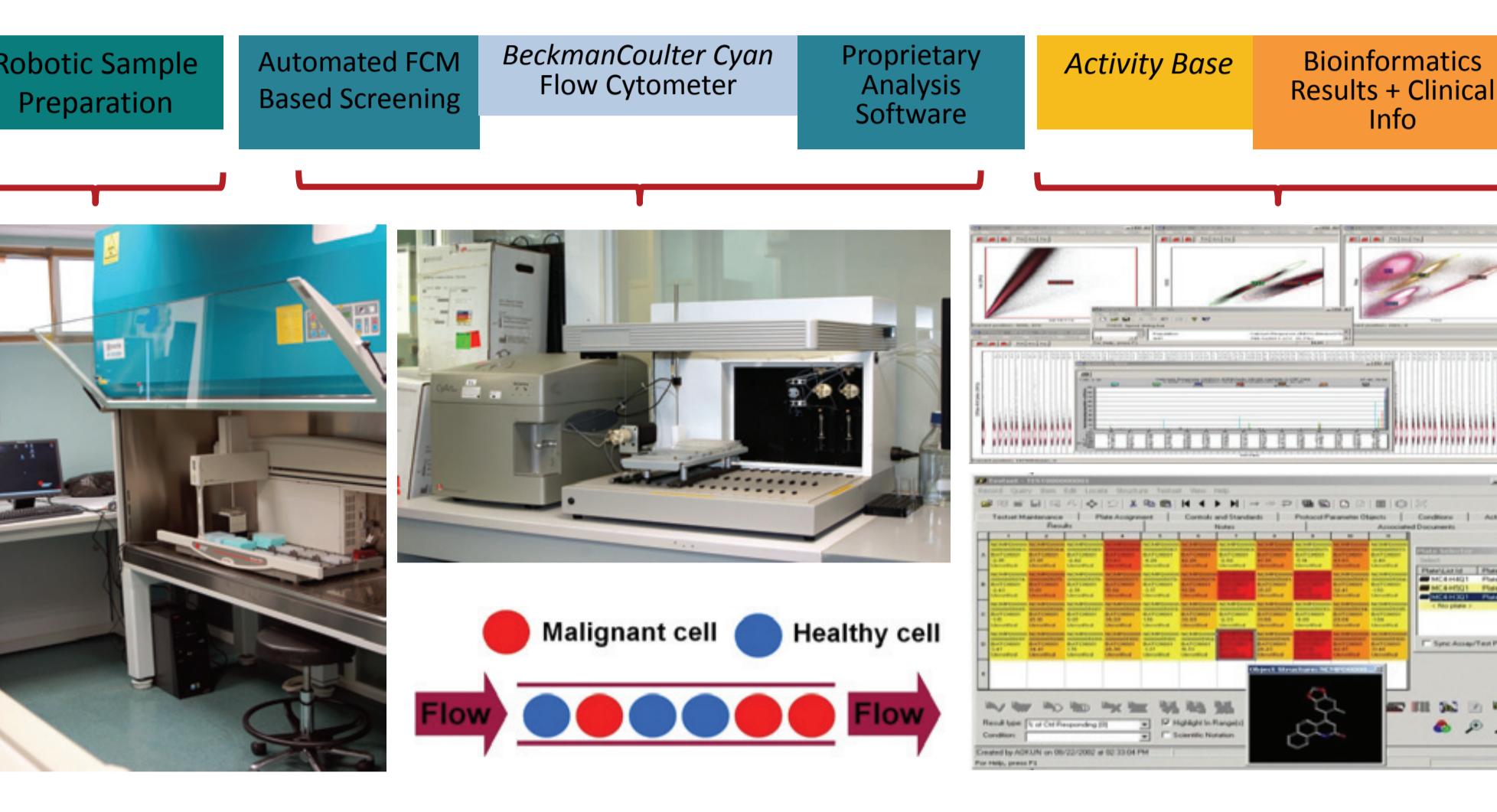
Figure 5 Logistic additive model of ex vivo CYT-IDA vs Clinical Outcome



Polynomial function of CYT(EC50) & Synergism CYT-IDA(alpha)

## METHODS

### Exvitech® Platform



### Screening Setup and Workflow

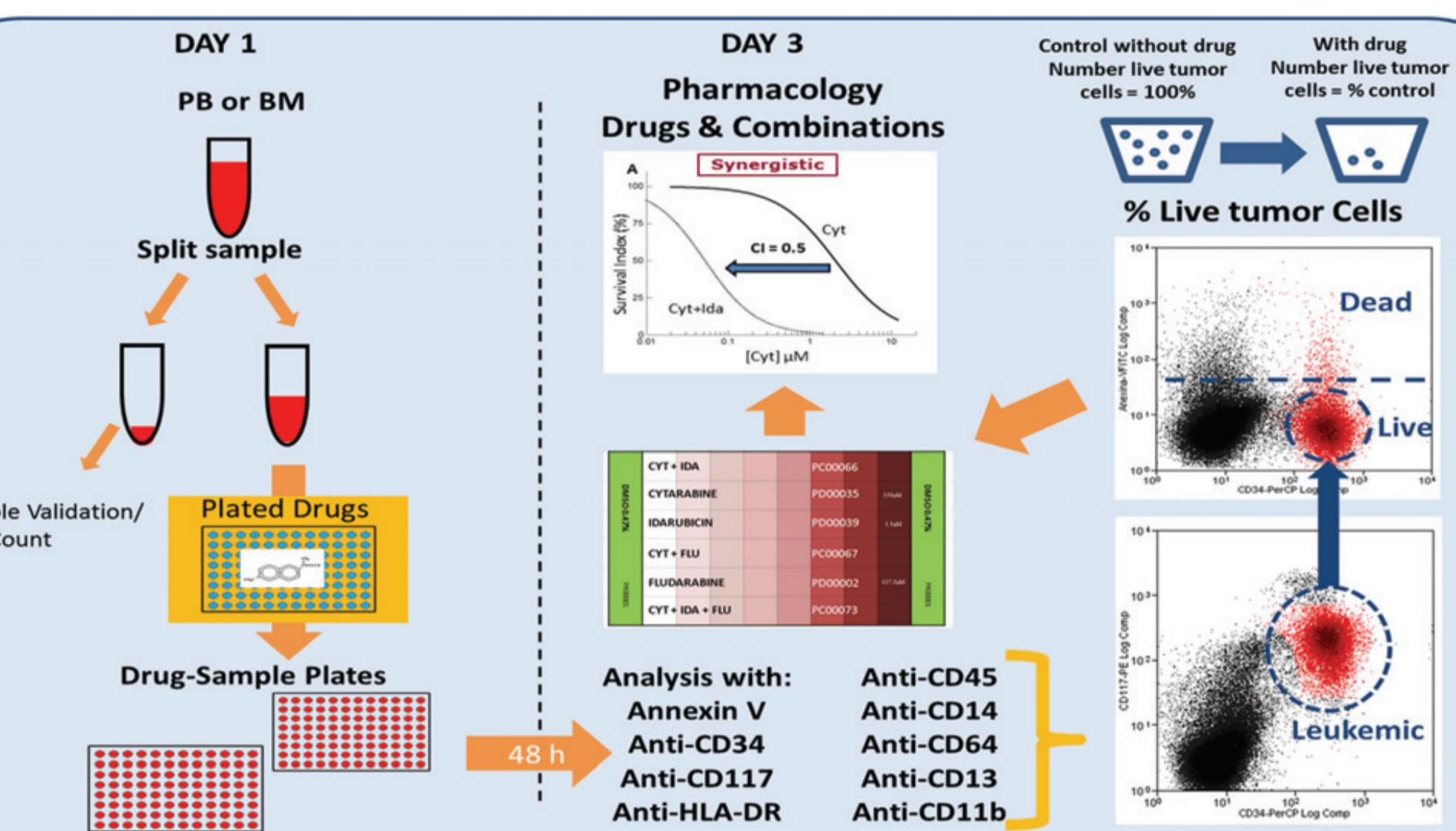


Figure 4

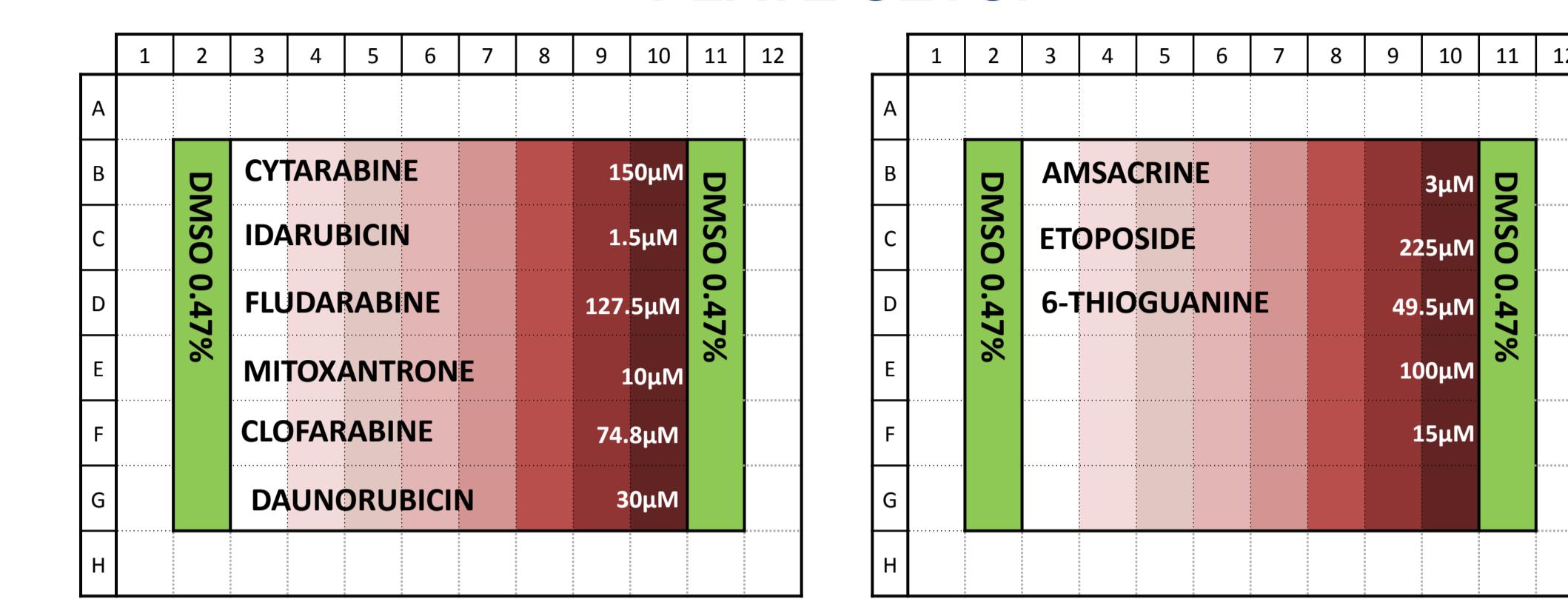
### 90% Prediction ex vivo Personalized Medicine Test

Clinical outcome		Ex vivo response		Subtotal
RESISTANT	SENSITIVE	RESISTANT	SENSITIVE	
20	5	26.0%	6.5%	25 32.5%
3	49	3.9%	63.6%	52 67.5%
Positive predictive value %		Negative predictive value %		
80.00		94.23		
Sensitivity %		Specificity %		
86.96		90.74		
Prediction rate %		89.61		
Subtotal		23 29.9%		
N		54 70.1%		
77		100.0%		

## CONCLUSIONS

- This novel personalized medicine test may be able to predict the clinical response to Ida+Ara-C.
- Potency(EC50) of CYT and synergism CYT-IDA are the predictive ex vivo variables in final algorithm. Though Efficacy (Emax) CYT also shows predictive value.
- Validation cohort is ongoing and could achieve earliest validation by year end at N=100
- Clinical trials demonstrating clinical benefits by using a personalized medicine test-adapted therapy are needed
- We are planning a personalized medicine test-adapted Clinical Trial.

## PLATE SETUP

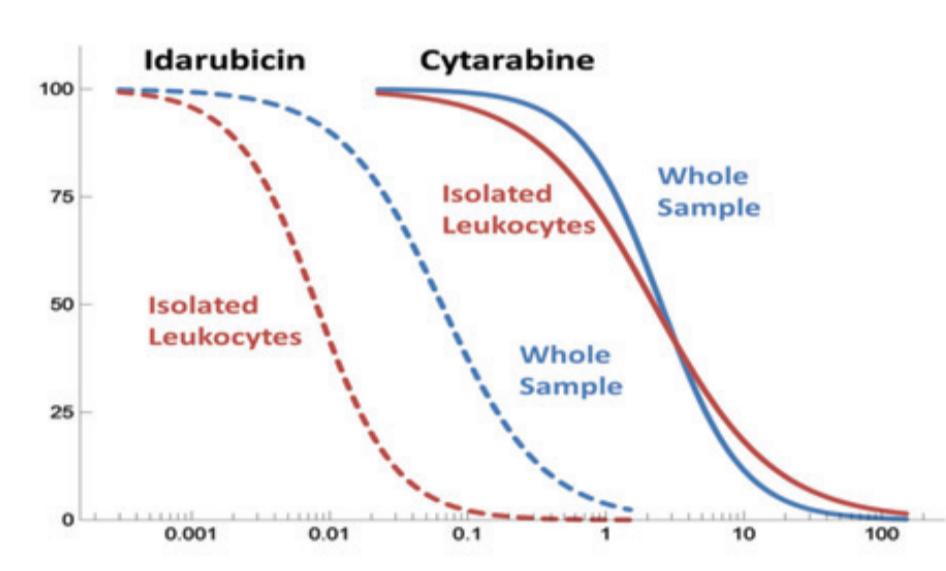


Eight different concentrations of each drug or drug combination is run for the used treatment protocols. The max concentration used is listed

### Whole sample vs. Isolated Leukocytes:

- Dose-response curves for IDA and CYT in isolated leukocytes and whole sample. Data, from sample 6 below, displays a log difference in the EC50s for IDA, but equal results for CYT.
- The EC50 (y-axis) of the whole sample and the isolated leukocyte fraction from 9 patient samples with cytarabine.
- EC50 of the same samples to idarubicin.

Data Analysis: performed using the population approach using NONMEM 7.2.: population PD modelling of the ex vivo response vs. concentration data in monotherapy (fig.2), establishing for each patient the 95% prediction intervals (PI) of the isobogram from each individual parameter (fig.4) computation of the combination index using raw data descriptors from combination experiments. Chou and Talay. 2010. *Cancer Research* 70: 440-446.



## ACKNOWLEDGEMENTS

Special Thanks to the Patients and Hospitals for Providing the Samples (listed alphabetically)

- ❖ Complejo Hospitalario de Jaén
- ❖ Complejo Hospitalario Xeral Cies de Vigo
- ❖ Hospital Carlos Haya, MÁLAGA
- ❖ Hospital Clínico San Carlos, MADRID
- ❖ Hospital de la Santa Creu i Sant Pau, BARCELONA
- ❖ Hospital de Madrid Norte Sanchinarro, MADRID
- ❖ Hospital Doce de Octubre, MADRID
- ❖ Hospital General Universitario de Alicante
- ❖ Hospital Infanta Sofía, MADRID
- ❖ Hospital Moncloa, MADRID
- ❖ Hospital Povisa, PONTEVEDRA
- ❖ Hospital Quirón, MADRID
- ❖ Hospital Ramón y Cajal, MADRID
- ❖ Hospital Universitario Central de Asturias, OVIEDO
- ❖ Hospital Universitario de Canarias Doctor Negrín
- ❖ Hospital Universitario General de Castellón
- ❖ Hospital Universitario Gregorio Marañón, MADRID
- ❖ Hospital Universitari i Politècnic La Fe, VALENCIA
- ❖ Hospital Universitario Infanta Leonor, MADRID
- ❖ Hospital Universitario Lucus Augusti, LUGO
- ❖ Hospital Universitario Príncipe de Asturias, MADRID
- ❖ Hospital Universitario Reina Sofía, CÓRDOBA
- ❖ Hospital Universitario Virgen Macarena, SEVILLA