Financial diclosures: Dr. Pau Montesinos

No financial disclosures

A Personalized Medicine ex vivo test to predict clinical response to first line induction therapy with idarubicin and cytarabine in patients with acute myeloid leukemia

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On behalf of the PETHEMA group

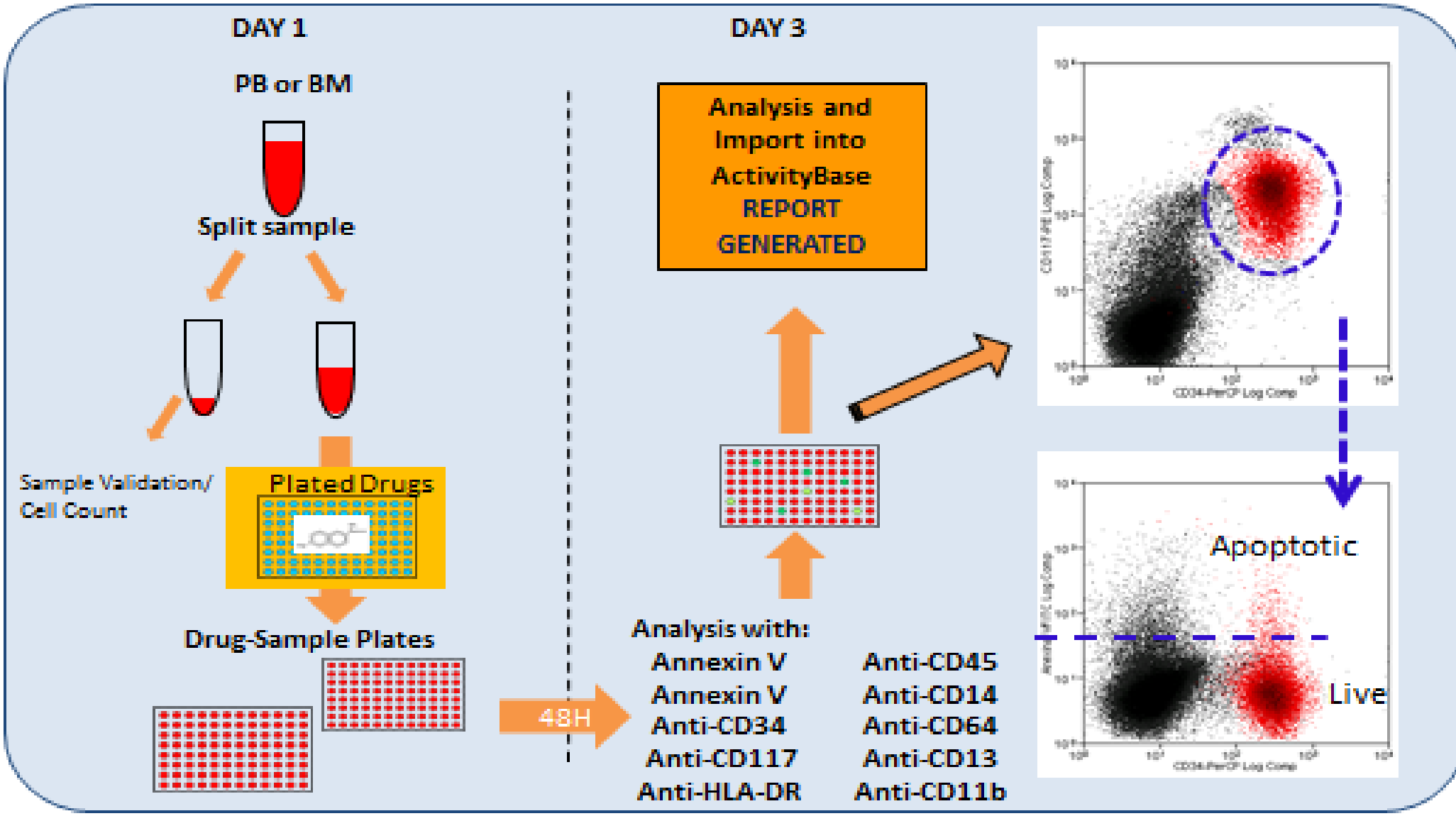
Background & objectives

- 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

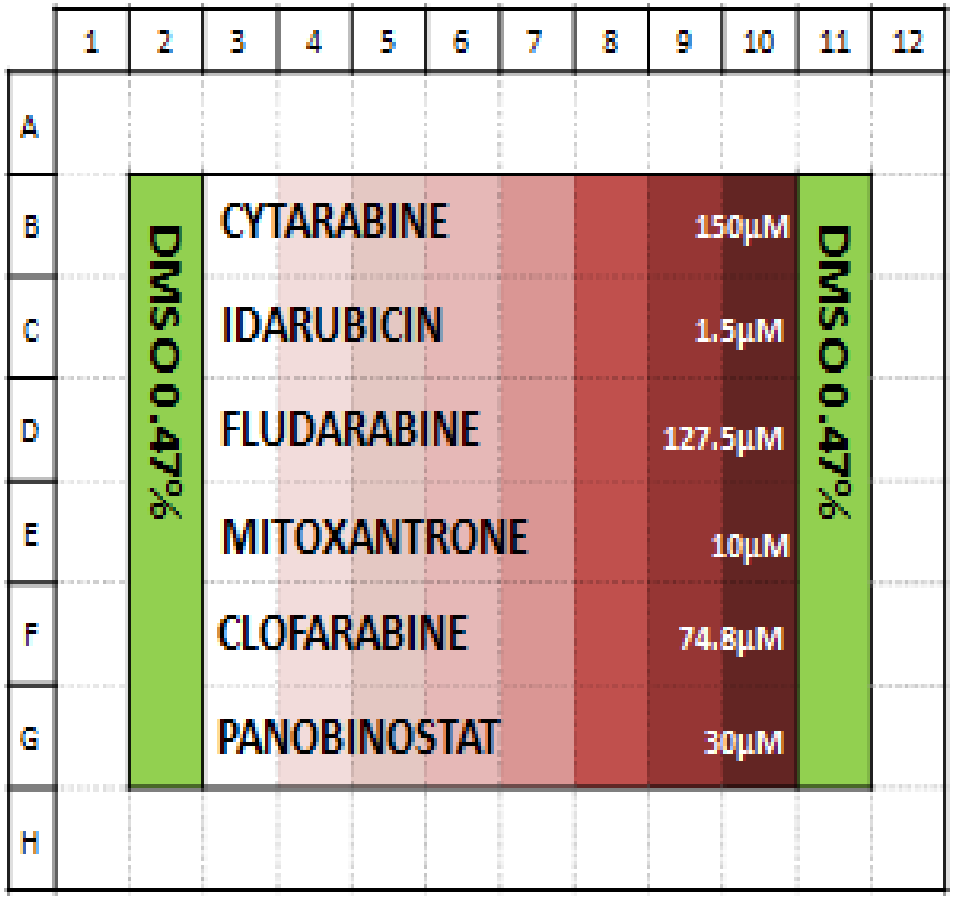
- Non-interventional and prospective study
- Samples from adult patients diagnosed with de novo AML in centres from the PETHEMA group
- CR/CRi were classified as responders (vs. PR/resistance)
- Induction death → non-evaluable
- 91 patient samples to calculate the dose response curves for Ara-C alone, Ida alone, and Ara-C plus Ida
- For clinical correlation, 37 patients (median age 53 years)

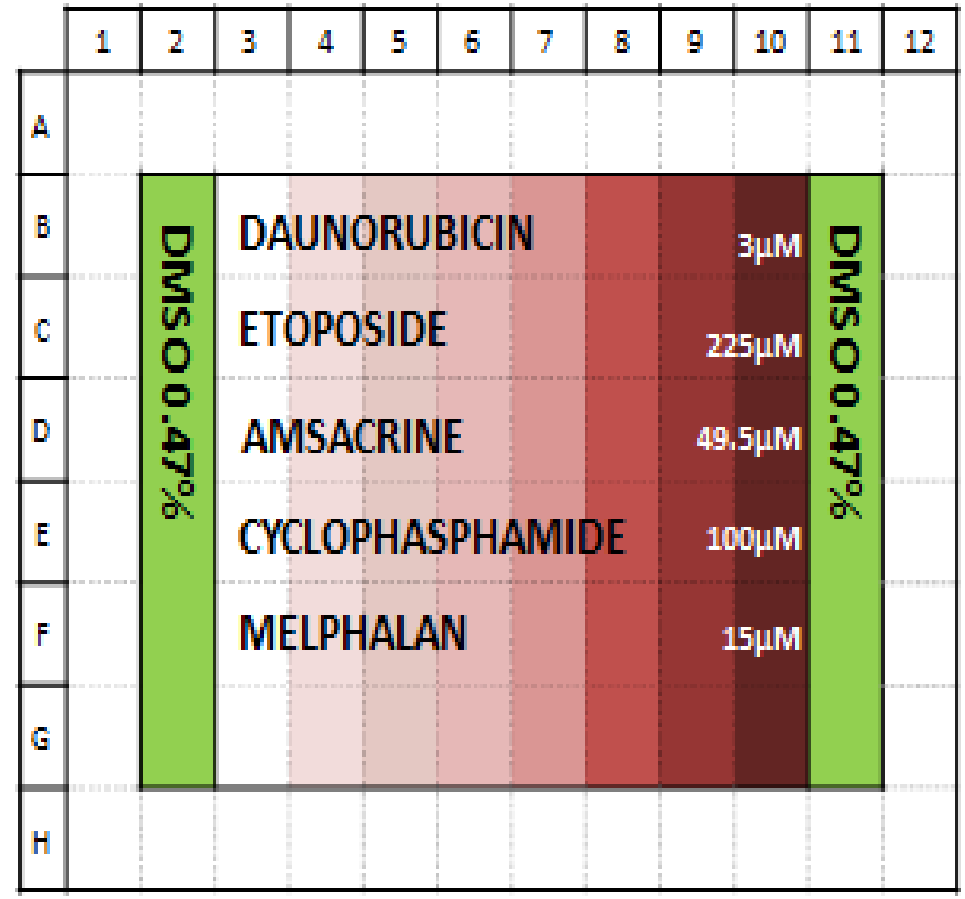
Screening Setup and Workflow



- Phenotypic analysis by flow cytometry to identify AML blast population and viability using Annexin V-FITC.

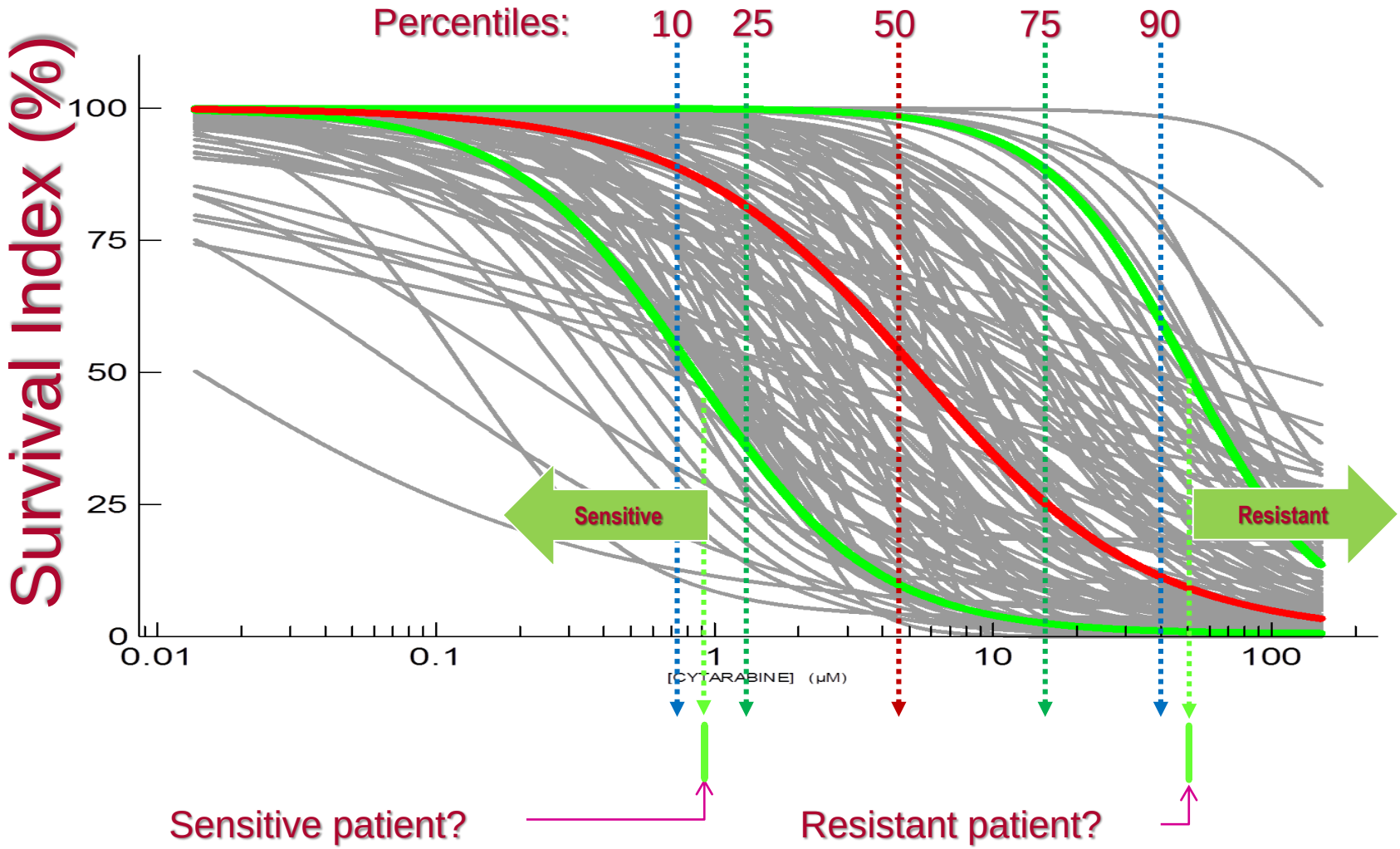
PLATE SETUP

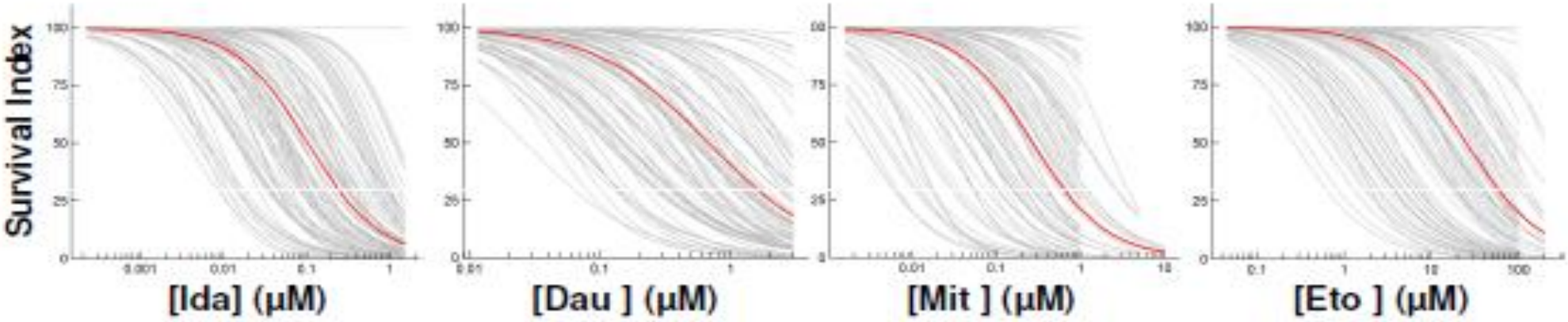




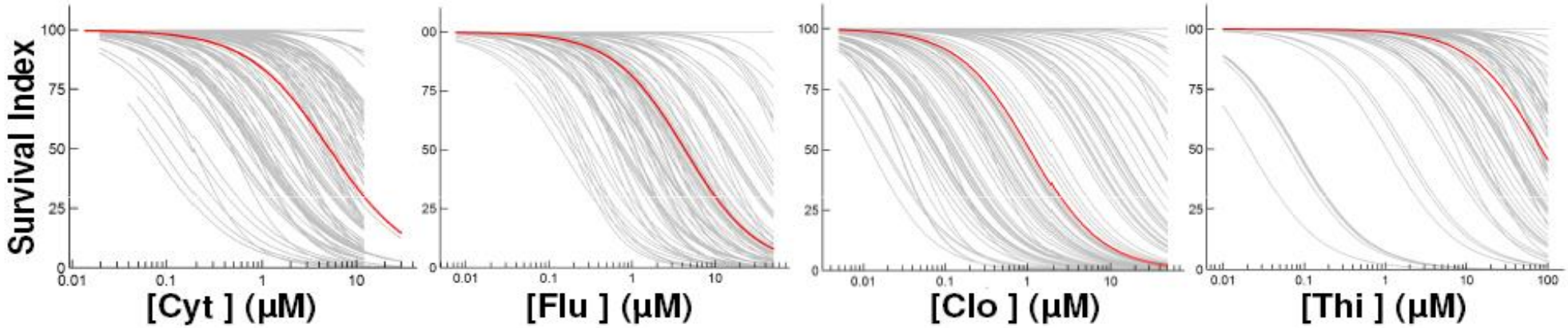
Eight different concentrations of each drug or drug combination is run for the used treatment protocols. The max concentration used is listed

Conversion dose-response analysis to a pharmacologic profile of potential ex-vivo response to each drug





- **Anthracyclins + Eto**

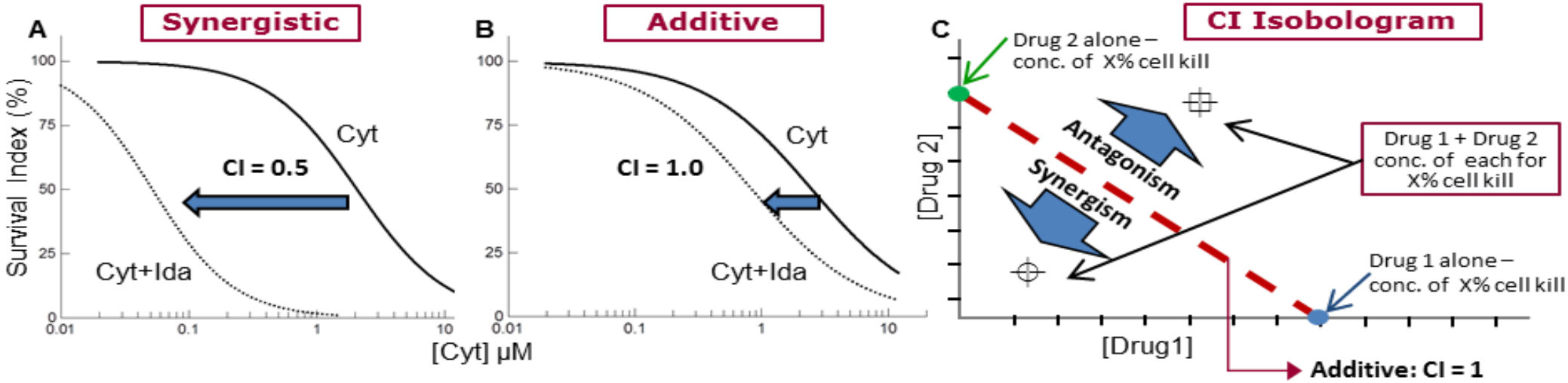


- **Nucleosides**

Median drug concentrations to kill 50% of blasts ex-vivo

DRUG	N	Median EC50 (µM)
IDARUBICIN	91	0.08
MITOXANTRONE	82	0.24
DAUNORUBICIN	82	0.53
CYTARABINE	91	4.95
FLUDARABINE	92	3.37
CLOFARABINE	93	0.84
6-THIOGUANINE	79	79.32
ETOPOSIDE	83	14.66
PANOBINOSTAT	71	0.04
5-AZACYTIDINE	95	6.70
DECITABINE	83	512.78

Synergism Key Clinical Predictor
Combination Index (CI) from Chou & Talalay

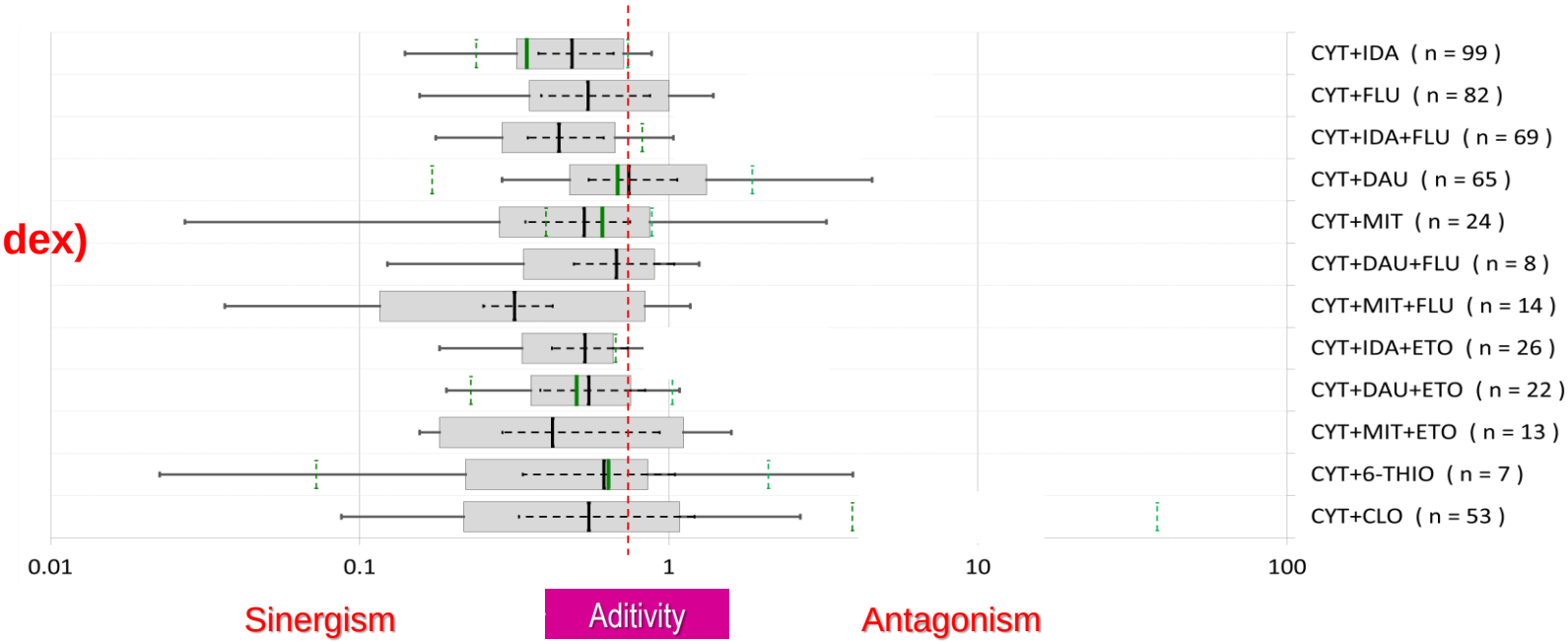


Sinergy (Combination Index)

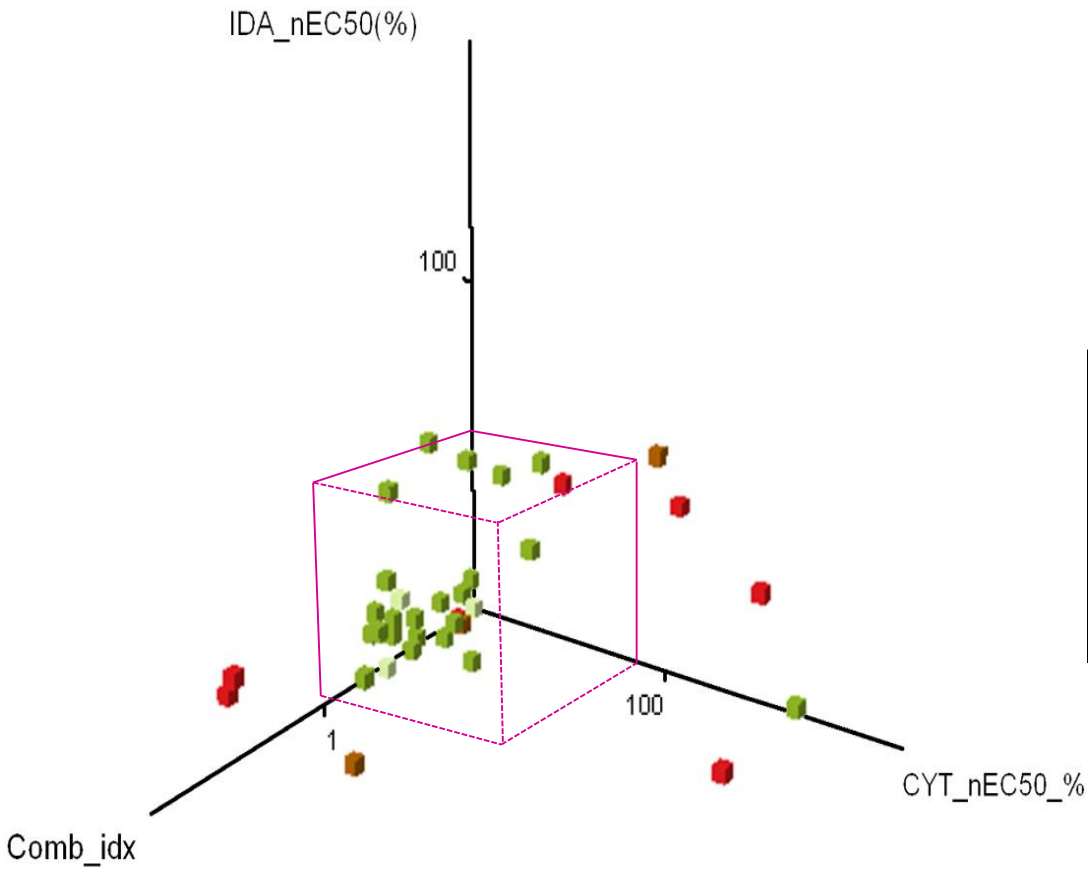
<1: Sinergism

~1: Aditivity response

>1: Antagonism



Correlation results CYT-IDA
92% correct prediction



		Clinical outcome: RESISTANT	Clinical outcome: SENSITIVE		Subtotal
Exvivo response	RESISTANT	8 *21.6%*	1 *2.7%*	Positive predictive value % **88.89**	9 *24.3%*
	SENSITIVE	2 *5.4%*	26 *70.3%*	Negative predictive value % **92.86**	28 *75.7%*
		Sensitivity % **80.00**	Specificity % **96.30**	Prediction rate % **91.89**	
Subtotal		10 *27.0%*	27 *73.0%*		N **37** *100.0%*

Criteria for resistance:

CIT_EC50 > 80% **or**

IDA_EC50 > 70% **or**

CI > 1

- **Sensitive patients towards zero axis (green)**
- **Resistant patients far out zero axis (red-yellow)**

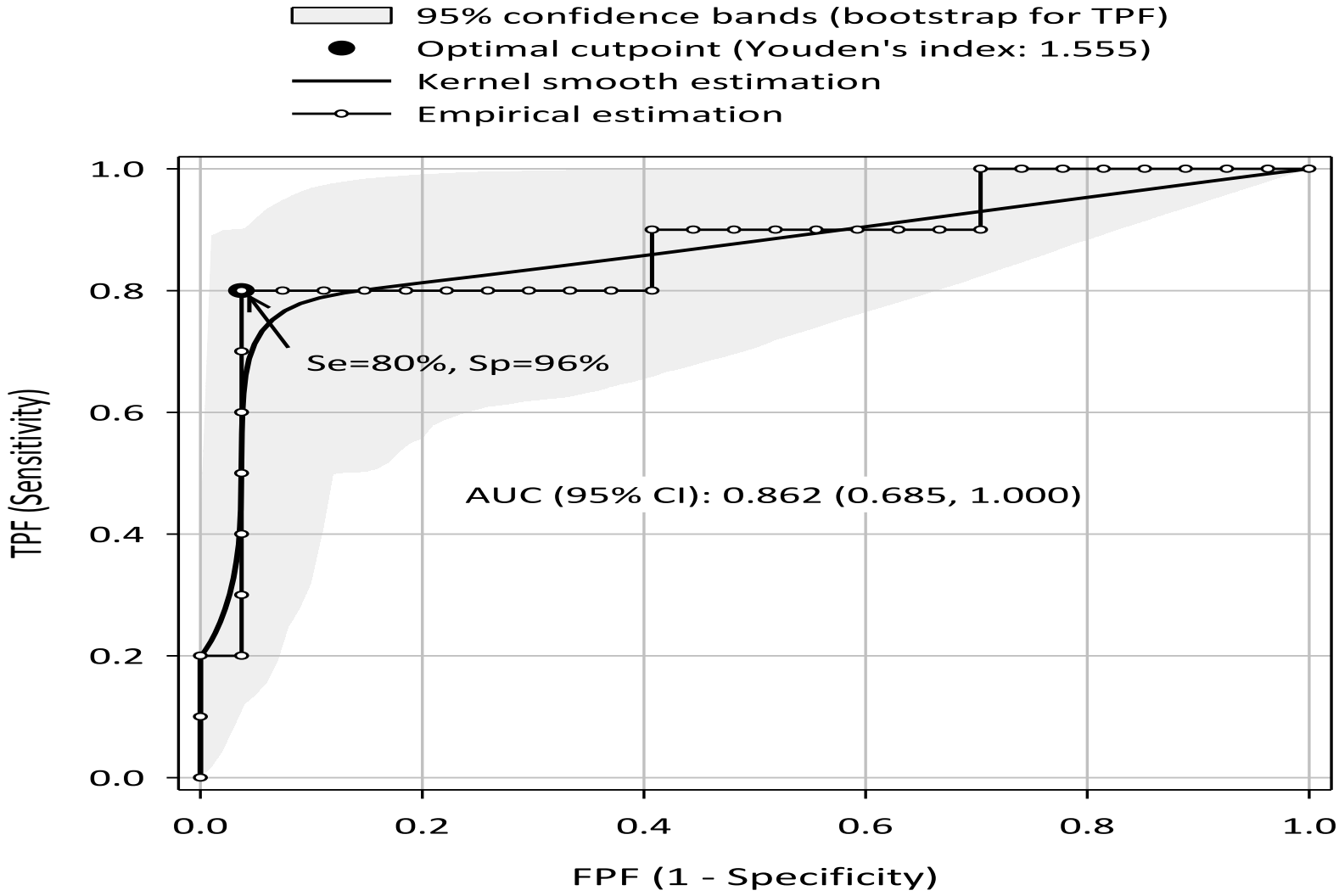
Logistic regression model using pharmacological variables

Run	Model	-2LL	Δ-2LL	p
1	No covariates (base model)	70.782	-	-
2	~ $Cl_{\_80th}$	70.388	-0.394	>0.05
3	~ $Cl_{\_Average}$	67.068	-3.714	>0.05
4	~ $IC_{50\_Idarabine}$	70.478	-0.304	>0.05
5	~ $IC_{50\_cytarabine}$	65.724	-5.058	<0.05
6	~ Baseline (E_0)	68.424	-2.358	>0.05
7	~ $IC_{50\_cytarabine} + Cl_{\_Average}$	61.482	-4.242	<0.05
8	~ $IC_{50\_cytarabine} + Cl_{\_Average} + IC_{50\_Idarabine}$	61.476	-0.006	>0.05
9	~ $IC_{50\_cytarabine}^{\theta} + Cl_{\_Average}^{\theta}$	54.630	-6.852	<0.01
10	~ $IC_{50\_cytarabine} + Cl_{\_Average}^{\theta}$	54.644	-6.838	<0.01

Selected prognostic variable

$0.053 \times IC_{50\_cytarabine} + 0.00725 \times Cl_{\_Average}$

Logistical regression model: smooth ROC curve showing good prediction rate



Conclusions

- This novel personalized medicine test may be able to predict the clinical response to Ida+Ara-C
- Validation cohort is ongoing
- The test will be applied to other induction regimens frequently used by other European study groups
- Clinical trials demonstrating clinical benefits by using a personalized medicine test-adapted therapy are needed

Thanks for your attention