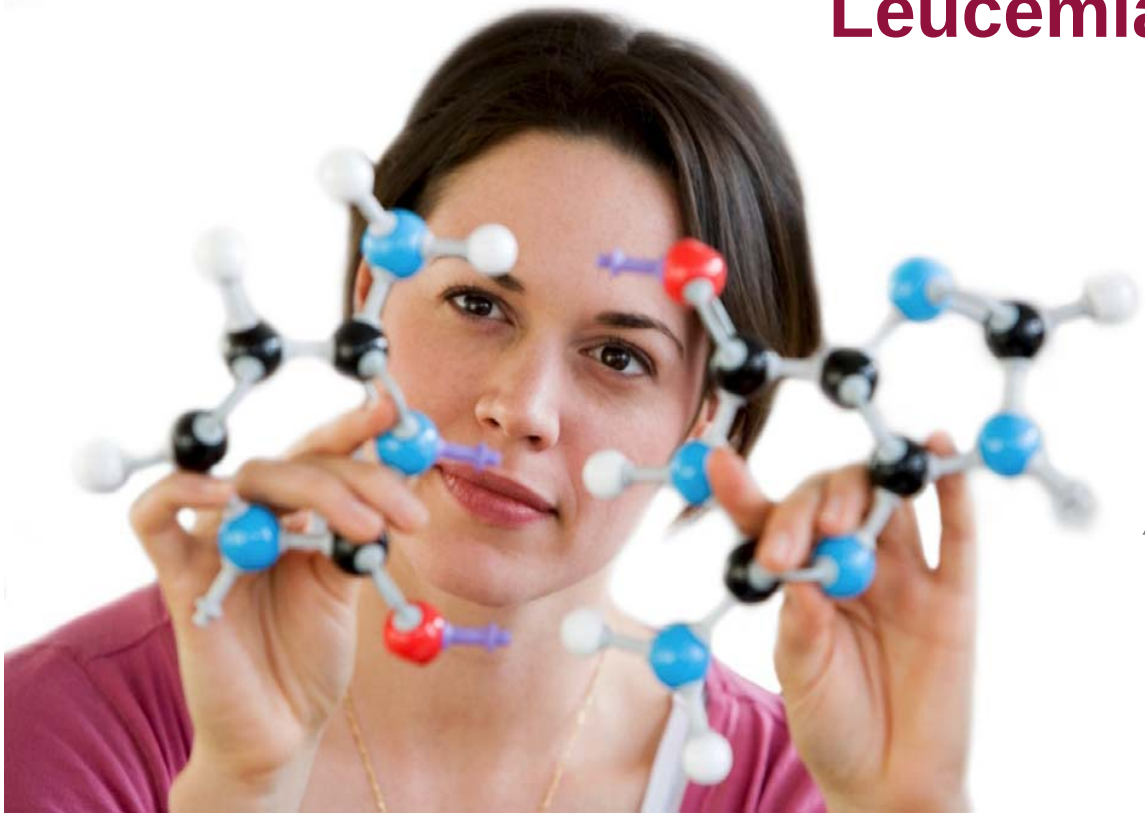
Vivia Test AML:
Test de Medicina Personalizada para el tratamiento de la Leucemia Mieloide Aguda



Joan Ballesteros, PhD

Chief Scientific Officer

Joaquin Martinez

Medical Director

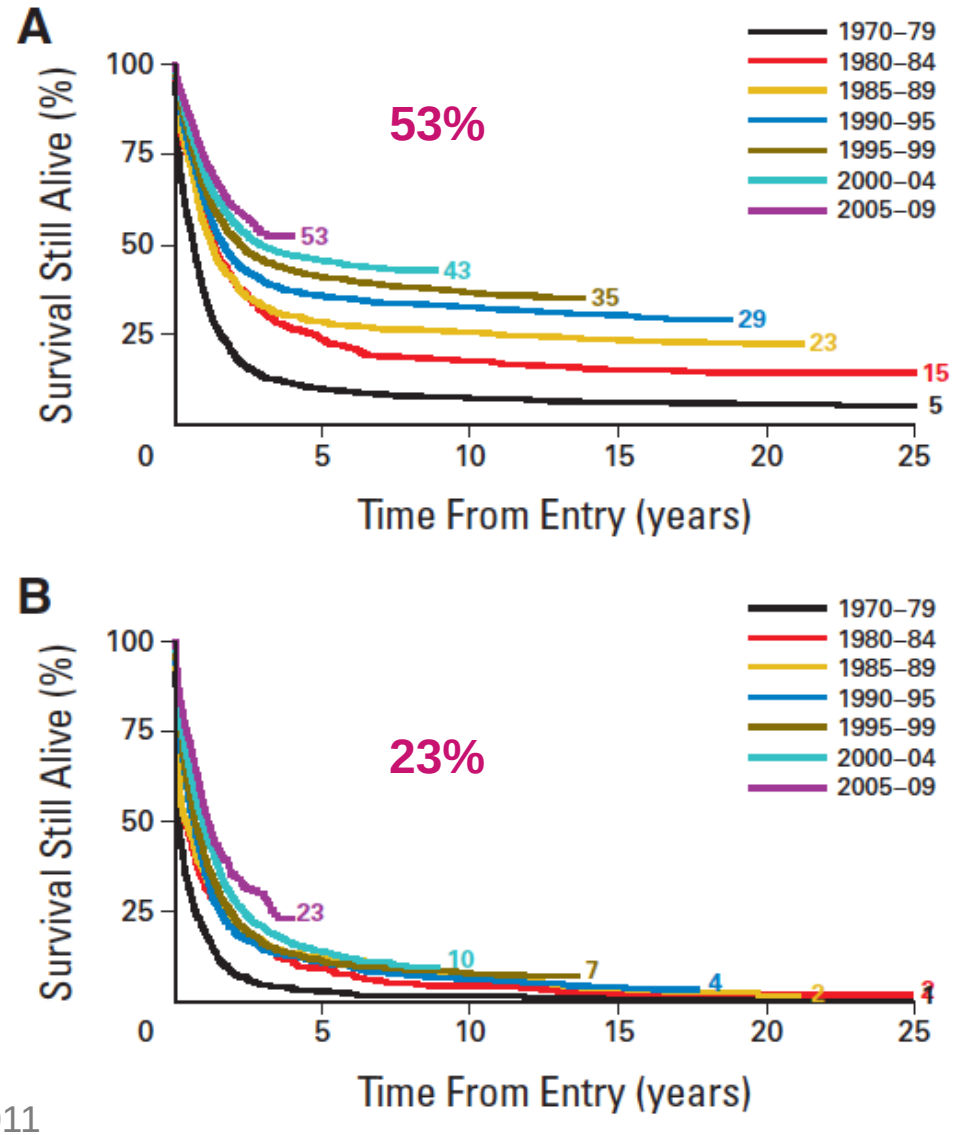
Andres Ballesteros, CEO

In collaboration with

PETHEMA Spain,

PI: Pau Montesinos

AML survival along the last 30 years



Young
< 65 years old

Elderly
> 65 years old

B Lowenberg et al JCO 2011

Vivia's Innovative Research Model: Screening 1000s Drugs in Patient Samples

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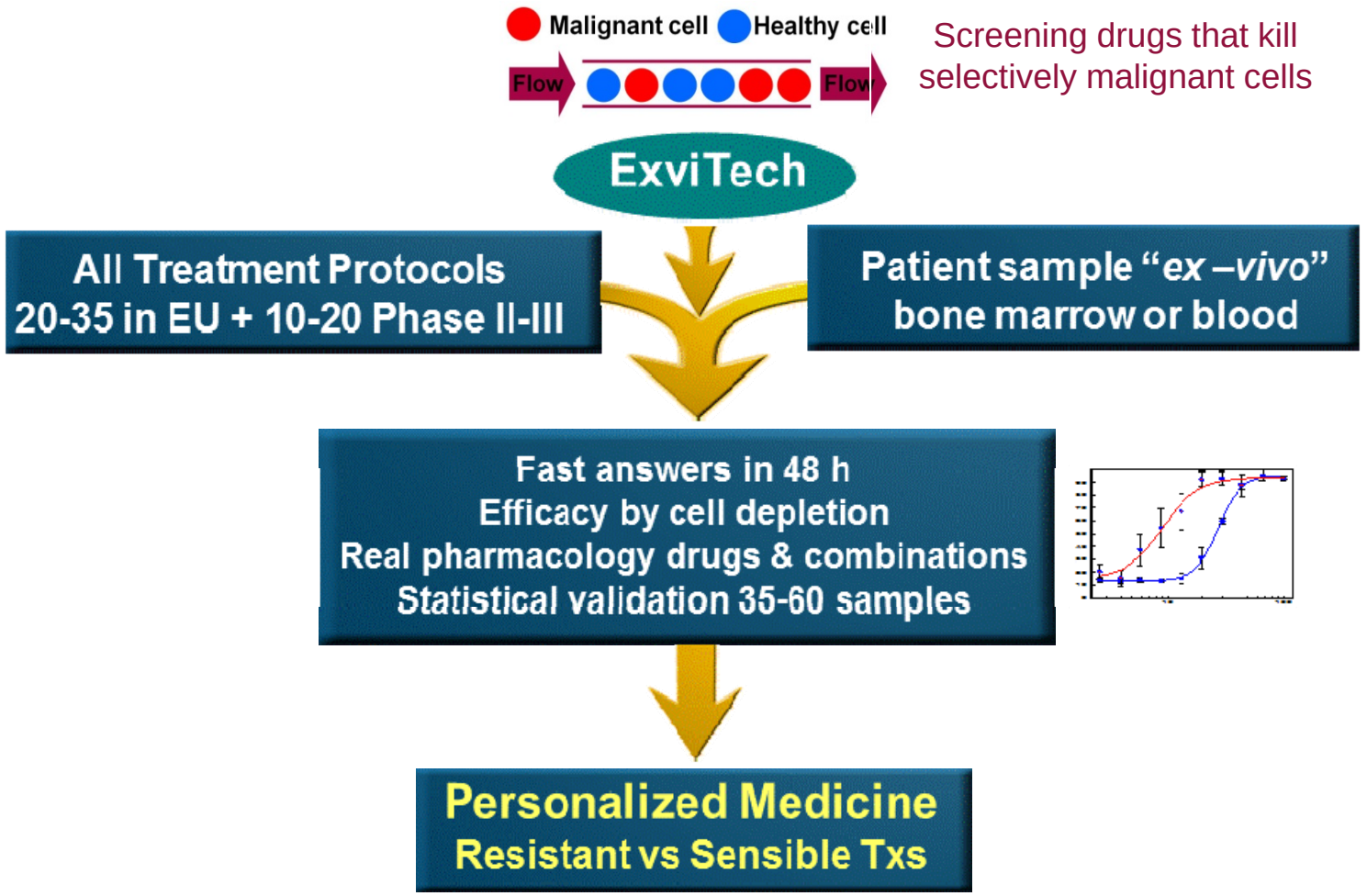

Centralized Lab Workflow
ExviTech Platform Automating Flow Cytometry

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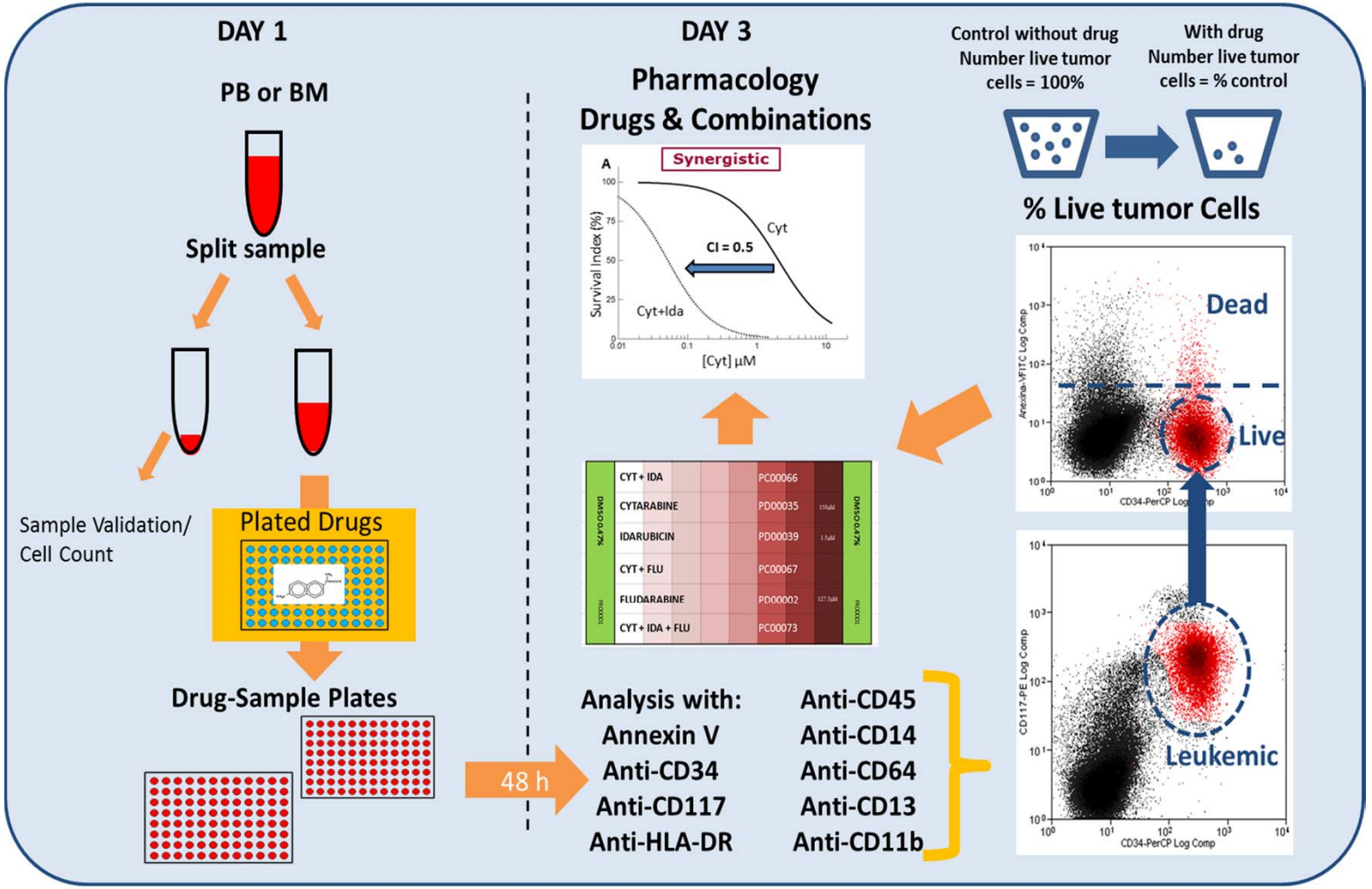

Pioneers Drug ex vivo Pharmacology in Whole Sample, Not Isolated Leukocytes

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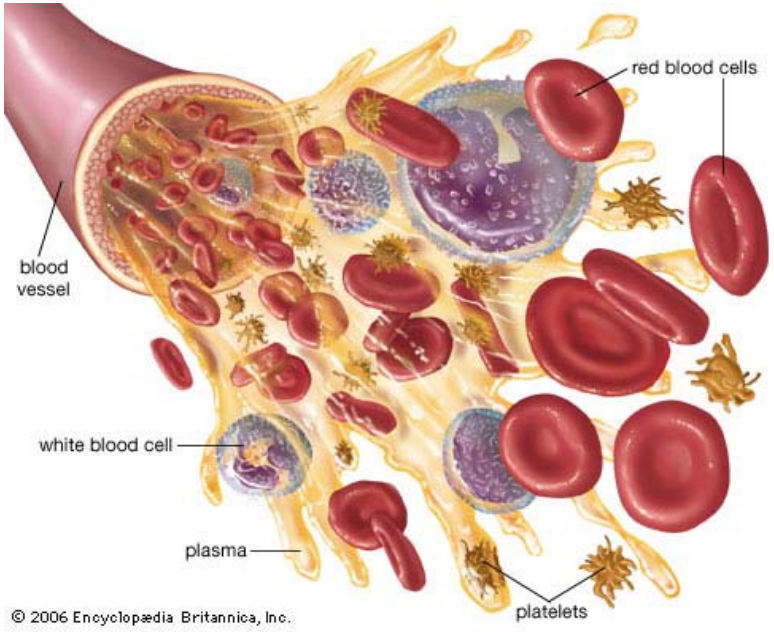
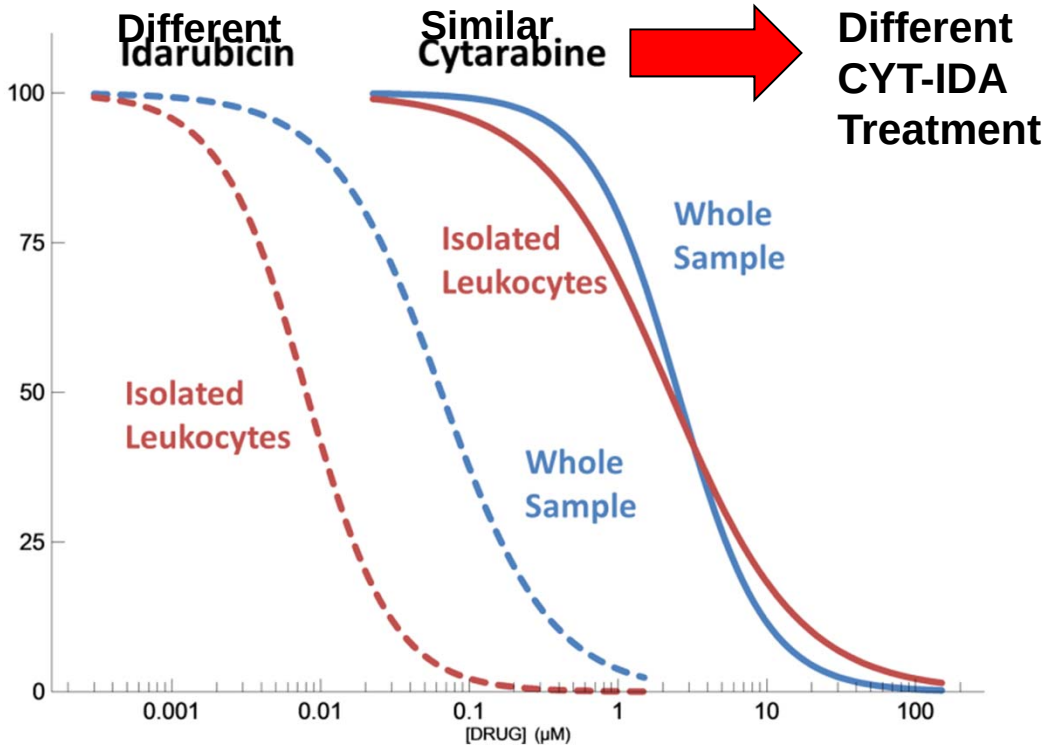




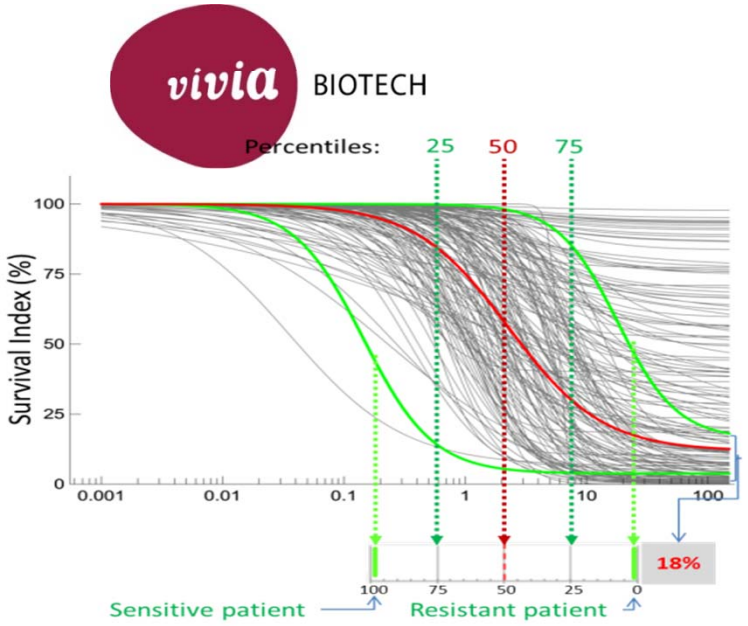
- Difference is no Ficol separation before incubation, only afterwards
- Maintains microenvironment, stromal cells etc avoiding long cultures
- Biologic drugs big artifacts
- If artifacts in 1 drug → artifact in the combination treatment

STANDARD
Isolated leukocytes (white cells), 1%

→

VIVIA
Whole blood

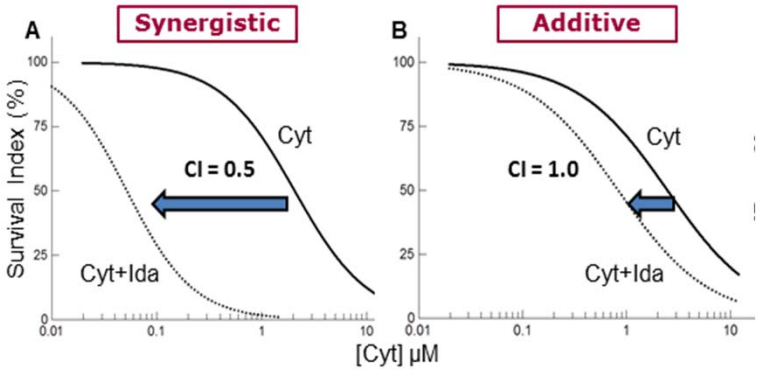
How To Interpret Pharmacology Data For Individual Patients



Bad Low Efficacy

Good High Efficacy

Good High Potency ⟷ Bad Low Potency



Good High Synergy ⟷ Bad Low Synergy

- **Activity assessed relative to the population of patient samples, ranking in percentiles best 100% worst 0%**
- **Analysis divided into single drugs (top) and combination synergy (lower)**
- **Single drugs (top): Potency & Efficacy.**
  - Potency (EC50) represented by dose that kills 50% cells (left-right shifts) ranking 100 best-left to 0 worst-right.
  - Efficacy (Emax): % tumor cells killed, 0% survival is good (bottom), lesser is bad.
- **Combination treatment synergy: Additive is bad (left) and synergism is good (right), converted to 100-0 ranking.**
- **Integrating both sets of data determines tumor responsiveness for treatments.**

Interpatient Variability In AML Supports The Need For Individualized Treatment & Companion Diagnostics

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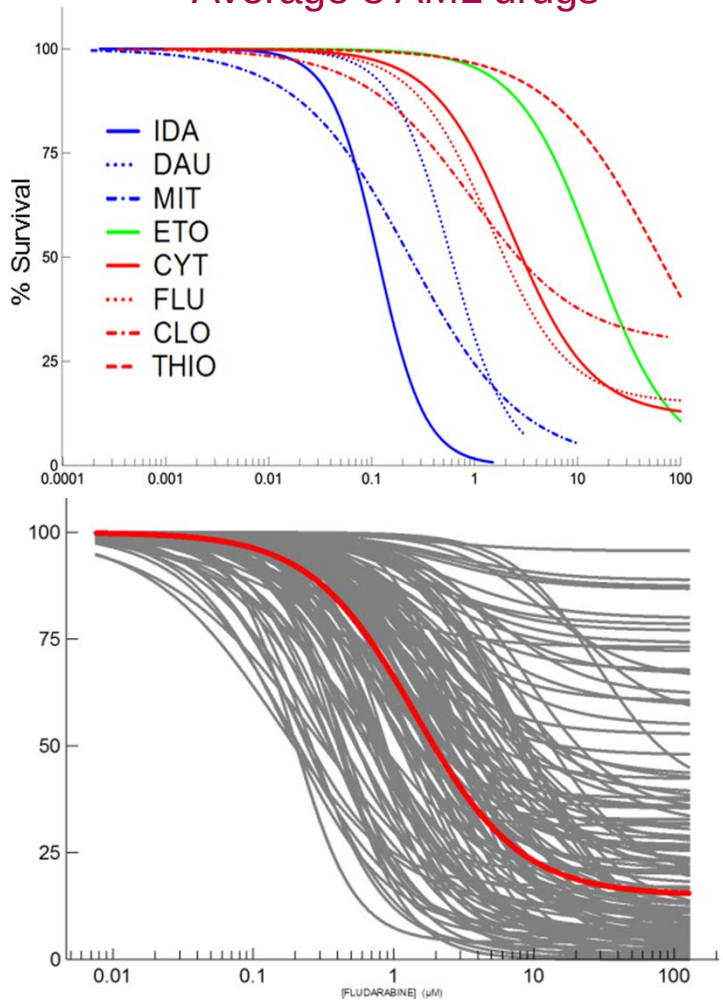
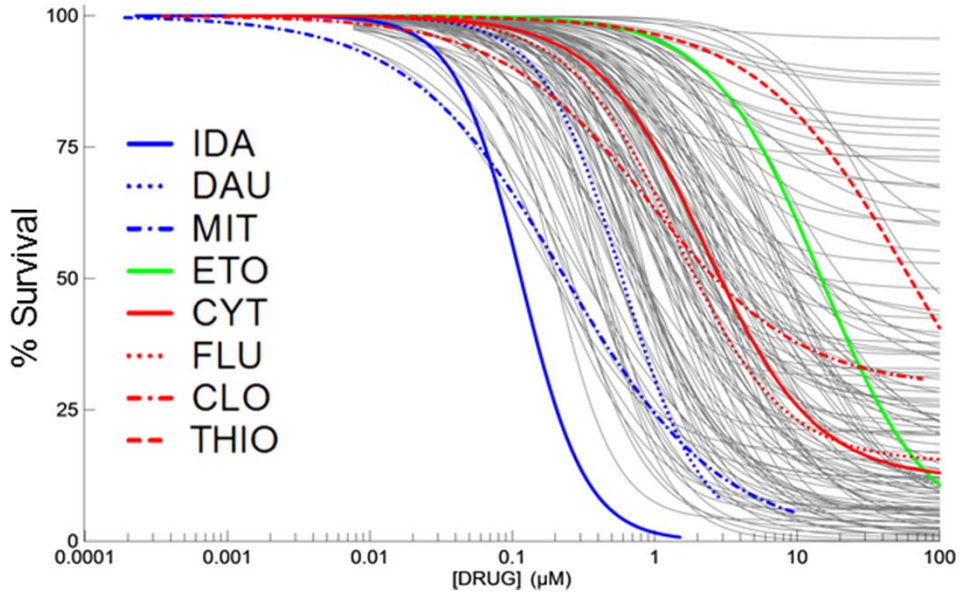
Average 8 AML drugs



100 patient samples FLU

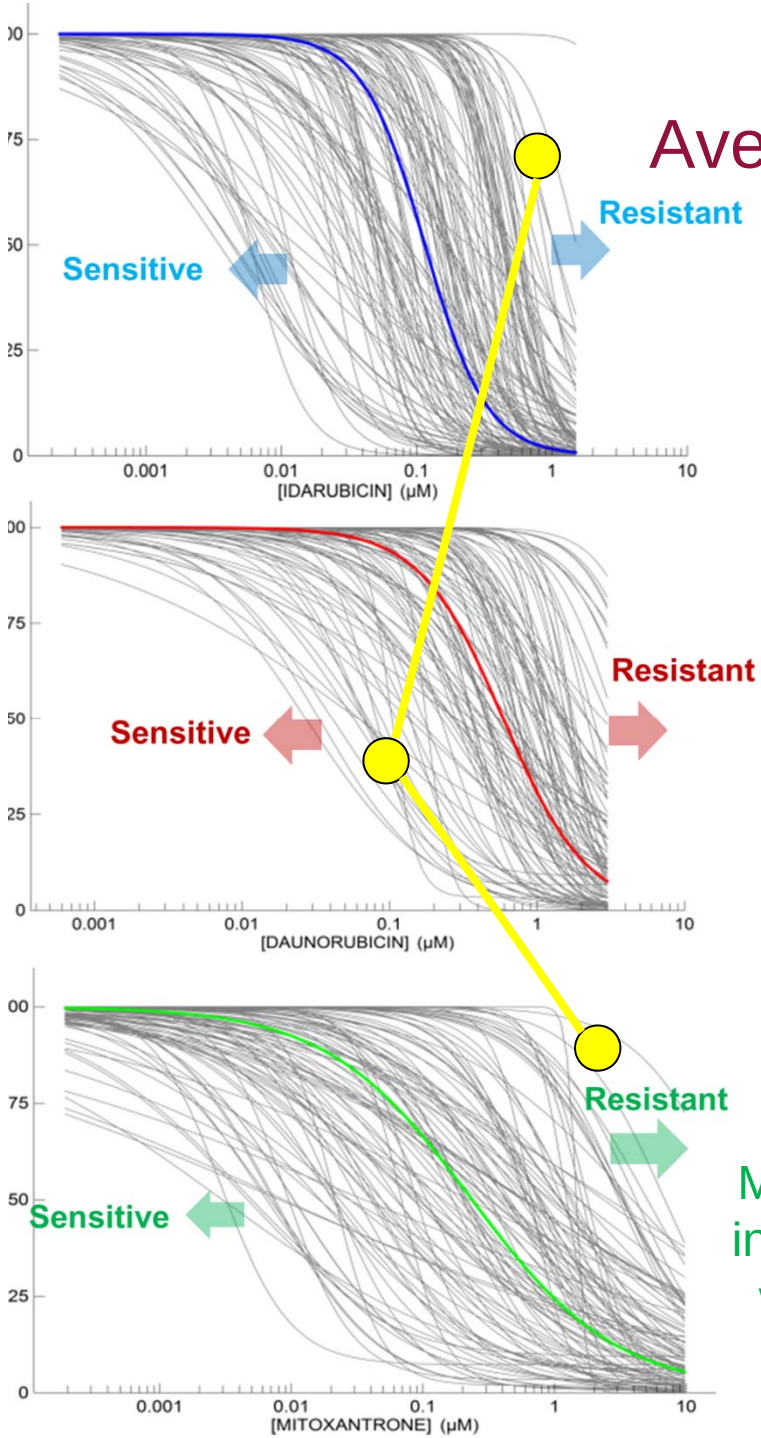


100 Samples FLU cover the same range as the average 8 AML drugs

Documento Confidencial

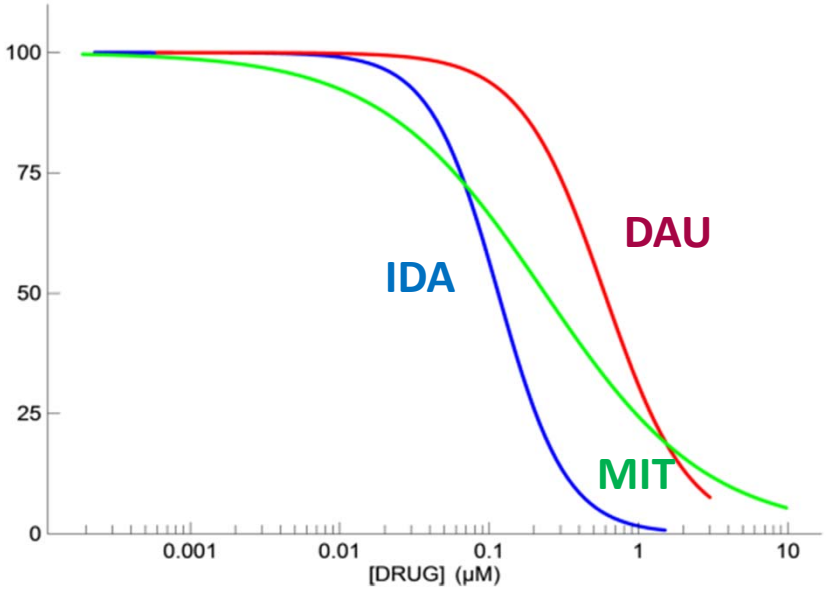
T Bennett. Clin Lymphoma Myeloma Leuk. 2013

1ST Line CYT + (IDA-DAU-MIT)
Average vs Individual Patient Responses



MIT higher inter-patient variability

CYT + IDA-DAU-MIT common 1st line Tx
Average dose responses are similar
Just as clinical trial results are similar



Are individual responses similar?
dose responses 180 patient samples
Could a patient be sensitive to 1 anthracyclin and resistant to another ?

Which % patients samples show selective sensitivity IDA-DAU-MIT

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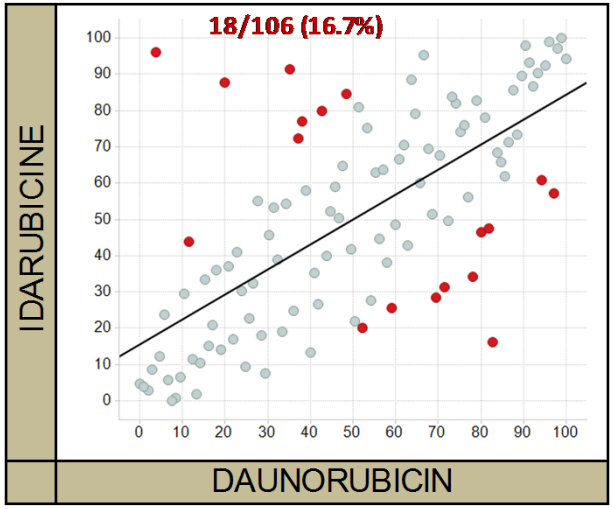
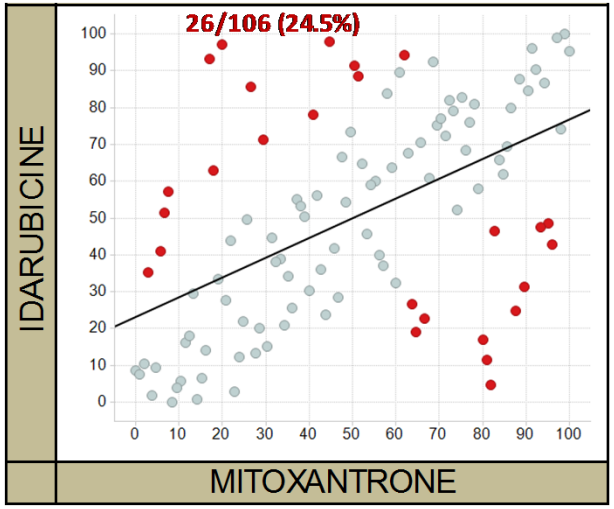
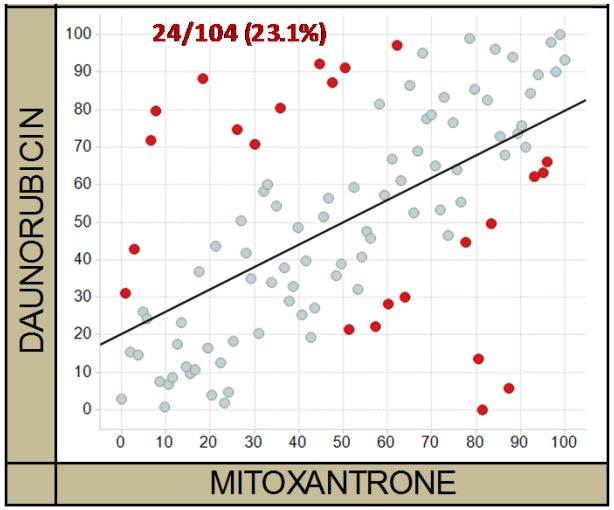
Pairwise IDA-DAU-MIT EC50 differences > 30% red dots (population ranking)







Red dots from 3 pairwise comparisons represent

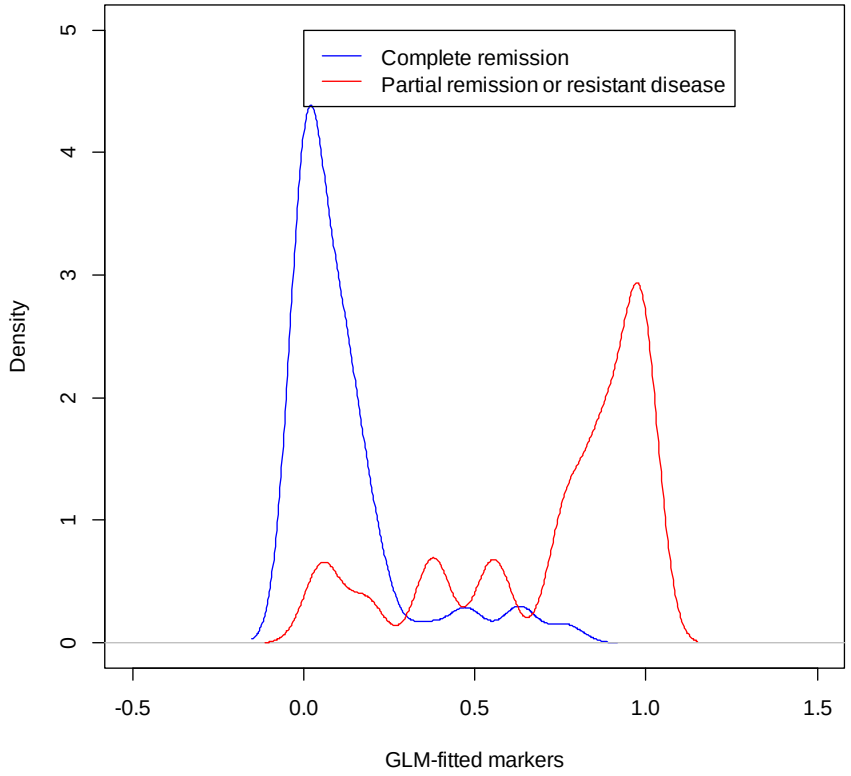
<u>40% of all patients</u>,

With significant preference IDA vs DAU vs MIT ex vivo

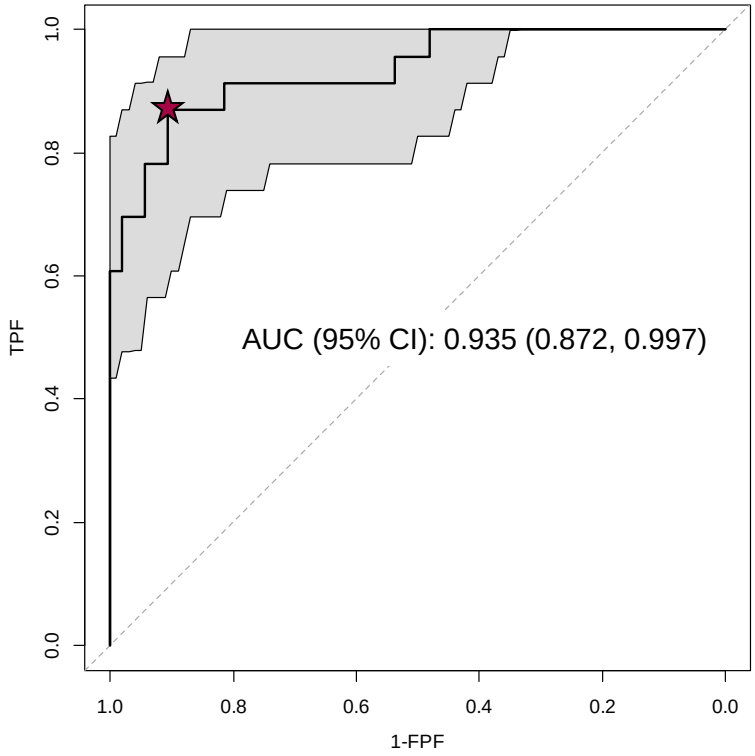
2nd prize best poster MD Anderson Texas SOHO Meeting 2013

Logistic Regression 1st Line CYT-IDA N=77 *ex vivo* vs Clinical Outcome

Empirical probability distributions of the marker in resistant vs. sensitive patients



ROC Curve
Statistically signif. low conf. limit AUC 0.872 > 0.5
Sensitivity: 87%, specificity: 91%
at optimal cutpoint (star, Youden's criterion)



Correlation Results 1st Line CYT-IDA 90% Correct Prediction N=77

- **Key value NPV 94% in clinical practice defines how well (%) test predicts resistant patients.**
- **Regulatory key diagnostic performance values sensitivity 87% & specificity 91%**
- **Launched implementation test in few hospitals 2014**
- **PETHEMA when N > 100 if correlation > 80% then launch interventional trial relapse-refractory AML**

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

	Estimate	Selected CI: 95% Lo	Hi
Sensitivity (Se):	87%	68%	95%
Specificity (Sp):	91%	80%	96%
Positive predictive value (PV+):	80%	63%	90%
Negative predictive value (PV−):	94%	85%	98%
Positive likelihood ratio (LR+):	9.39	4.01	21.97
Negative likelihood ratio (LR−):	0.14	0.05	0.41
Prevalence (res):	30%		

P Montesinos PP ASH 2013

Relapse? Extend concept to Extreme Pharmacologic Profiles
Interpret only extreme sensitivity or resistance

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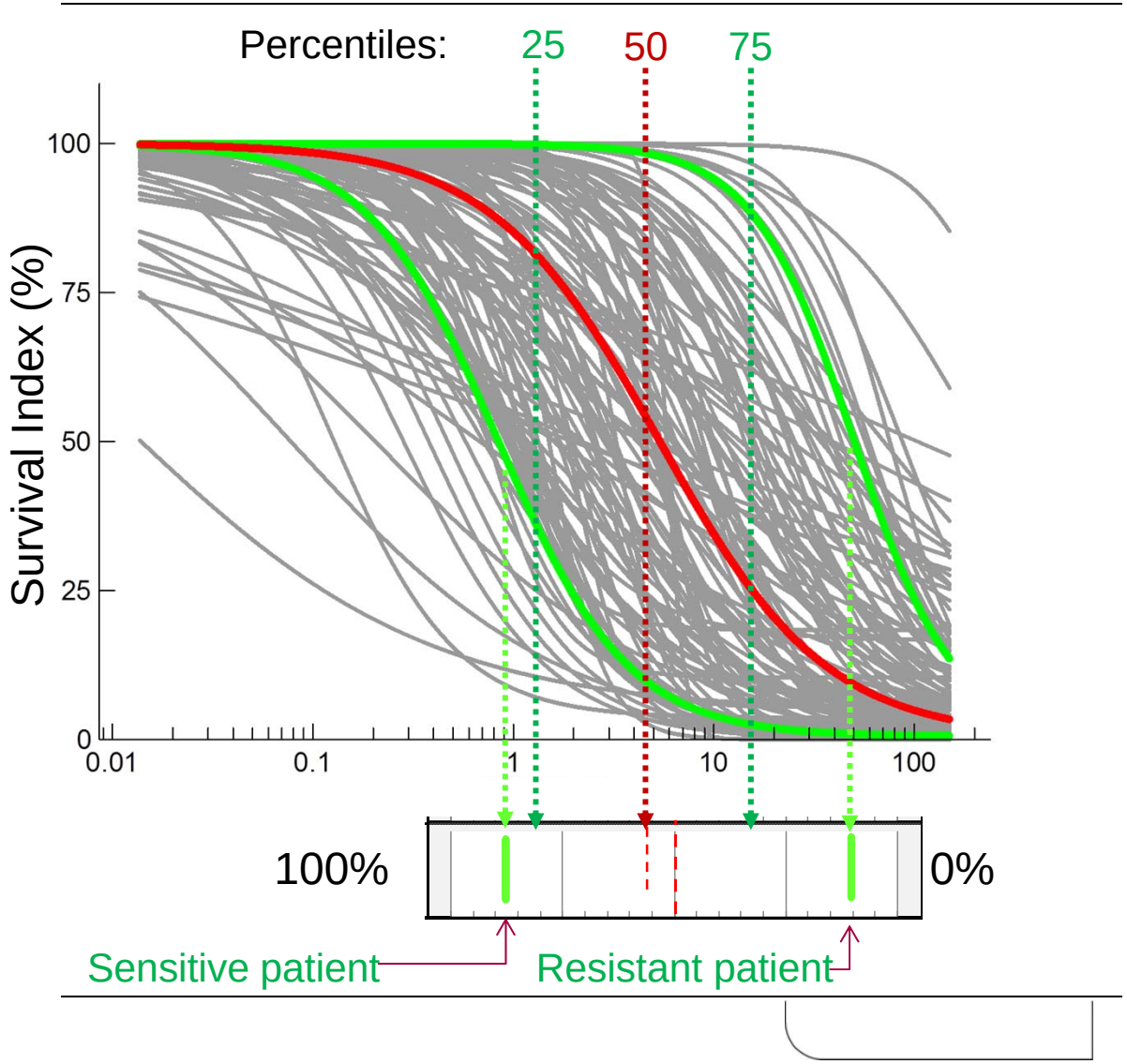
conversion dose-responses to Extreme Pharmacologic Profiles



PM Test Relapse-Refractory ***Extreme*** Pharmacological Profiles Single Drugs (left) & Treatment Synergism (right)

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A.- Valoración de potencia relativa de fármacos individuales.

Farmaco clasificación*	N	Potencia relativa (Percentil)	% Células resistentes
CYT	160		
IDA	159		
FLU	140		
DAU	123		
MIT	153		
ETO	101		
CLO	101		86% (2 - 12)
AMS	153		
THIO	78		
PAN	55		

0 25 50 75 100

B.- Valoración de sinergia entre fármacos en combinación.

Combinación clasificación *	N	Sinergismo relativo (Percentil)	% Células resistentes
CYT+IDA	148		
CYT+FLU	123		
CYT+IDA+FLU	121		
CYT+DAU	133		
CYT+MIT	116		
CYT+DAU+FLU	124		
CYT+MIT+FLU	113		
CYT+IDA+ETO	86		
CYT+DAU+ETO	88		
CYT+MIT+ETO	86		
CYT+AMS	97		
CYT+CLO	97		
CYT+THI	67		

0 25 50 75 100

LEYENDA

***Clasificación**

- Fármacos o combinaciones con mayor sensibilidad en cuanto a la potencia o sinergia.
- Fármacos o combinaciones con mayor probabilidad de resistencia en cuanto a la potencia o sinergia.
- Fármacos o combinaciones no ensayados o con resultados asociados a excesivo error residual (>40%)

Líneas

- Percentil correspondiente al valor estimado del parámetro de potencia (EC50) e intervalo de confianza asociado a su estimación en la muestra de paciente.
- Percentil correspondiente al valor estimado del parámetro de sinergismo (Alpha) e intervalo de confianza asociado a su estimación en la muestra de paciente.
- Límite para resultados extremos asociados a comportamiento resistente.
- Límite para valores extremos propios de respuestas sensibles.

Relapse Patients
PM Test AML VERSION 1.0

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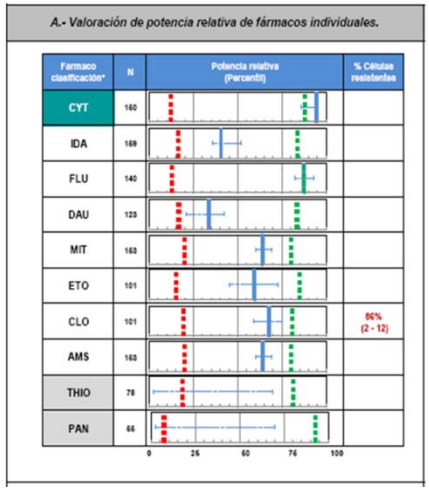
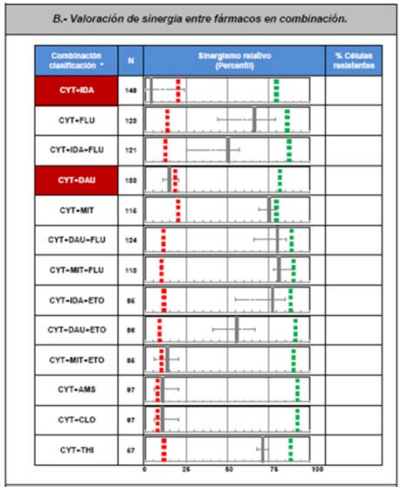
IDA-CYT

Extreme Pharmacological Profiles
10 Drugs & 13 Treatments

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





1. Ensayo clínico Espana PETHEMA 2014
2. Ensayo clínico lideres europeos 2015
3. Ensayo clínico MD Anderson EEUU 2015

Vivia Test AML
Innovación en el sector sanitario privado

- La crisis actual y en especial en el sistema sanitario dificulta la introducción de nuevos productos sanitarios innovadores
- Test MP Vivia aumenta el % de respuesta, ahorrando costes al prevenir tratamientos ineficaces de altos costes hospitalarios
- Hagamos un compromiso de que la innovación sea coste eficiente generando un ahorro neto
- Mediante acuerdos risk-sharing entre empresas innovadoras con Hospitales privados y aseguradoras