Programa Cooperación Farma-Biotech

Jornada IIb: **Oncología**

Vivia-009 for the treatment of blood cancers

vivia BIOTECH

Madrid, 12 de mayo de 2011

CataloniaBIO
Associació catalana d'empreses de biotecnologia

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

farmaindustria

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US Biotech 2000-2006 → team & technology to Spain 2007

Pioneers screening 1000s drugs directly in patient samples

Access to patient samples competitive advantage Spain vs US

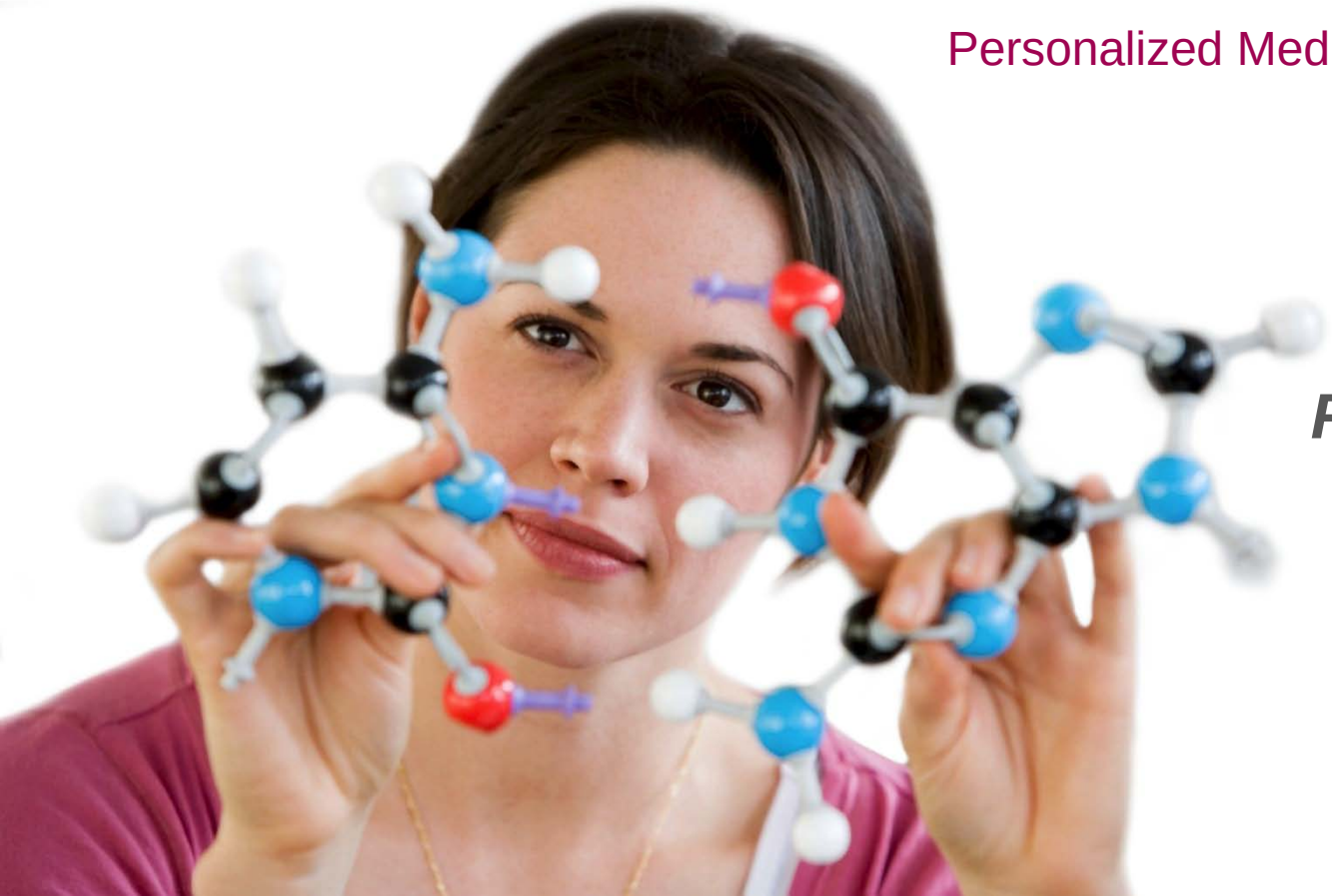
Focused on blood cancers & recently Autoimmune

Agreements with 2 Big Pharmas in US

Starp-up funding €4M 2007 & €17M Grants 2007-2011

Candidate Vivia009 for NHL Phase I in Q4-1011

Personalized Medicine T\test blood cancers sales 2012



Real Translational Research

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

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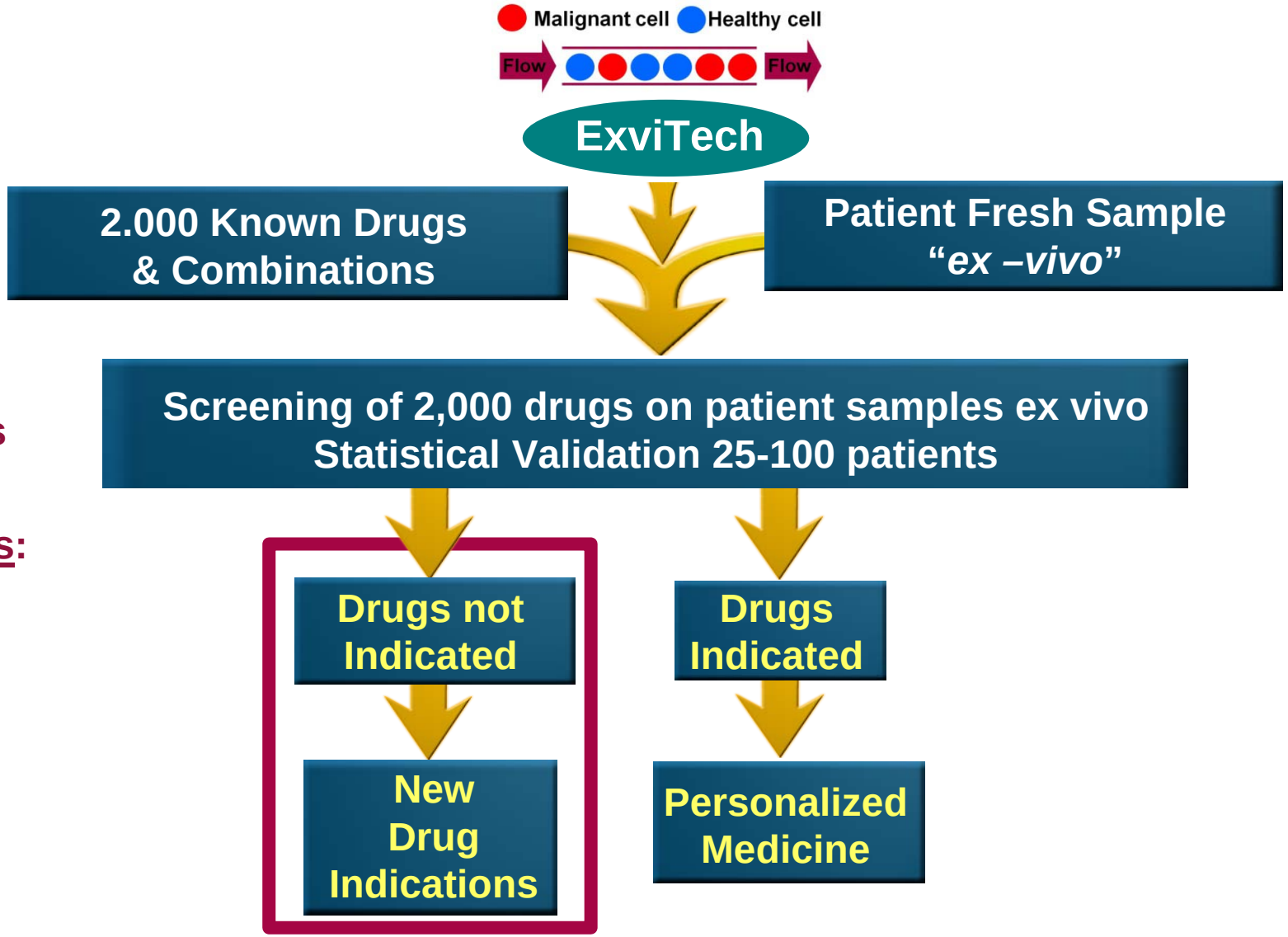
Screening drugs that kill selectively malignant cells

<u>Same Process, Two Results</u>:

<u>New Drug Indications</u>:
License after Fase IIa

<u>Personalized Medicine</u>:
Diagnostic Service



ExviTech (Ex vivo Technology) Escalates Known Clinical Data

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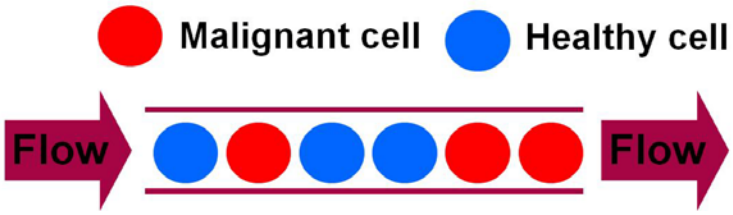
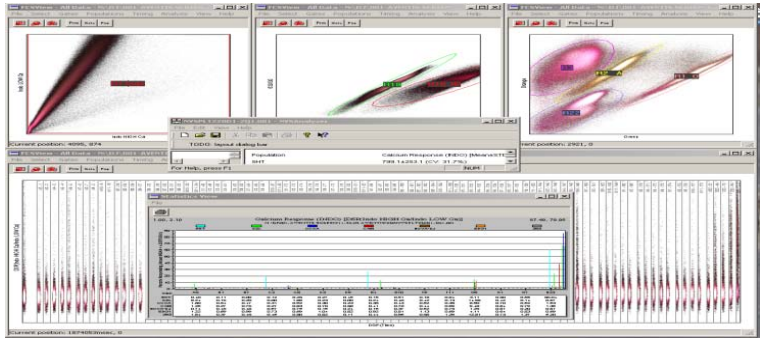
Pioneering Automated Flow Cytometry platform Evaluates if drugs kills selectively malignant cells

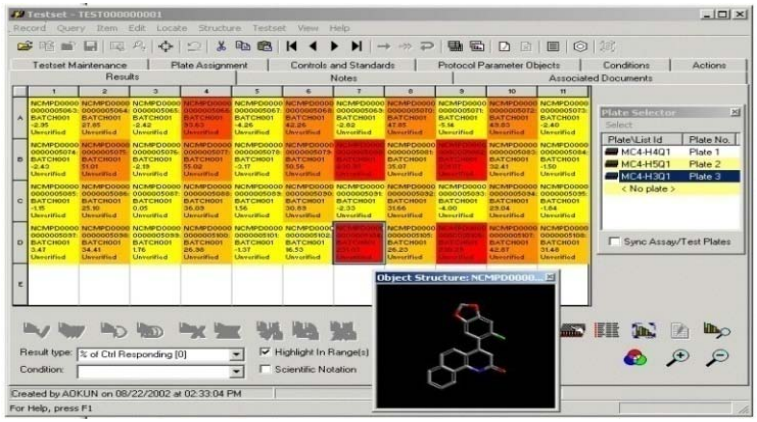
Sterilized preparation

Screening Drugs on Samples



Bioinformatics (FDA/EMEA)





Screening 2,000 drugs ex vivo per day

Access to Patient Samples for Biotechs Competitive Advantage Spain vs USA

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The Economist, October 2008

Spain, champion of the dead-donor league and pioneer of the opt-out approach, has more than doubled its rate (from 14 to 34) in the past 20 years. But that is not merely the result of an opt-out system; at least as much of Spain's success reflects an excellent network of organ-transplant teams in every hospital, which routinely screen patients' records to find potential donors. The recent British inquiry found that mainly by copying Spain's efficiency, donation could be boosted by 50%, enough to cover Britain's needs. Another factor is that Spain's media have helped allay public fears. Even so, Spain

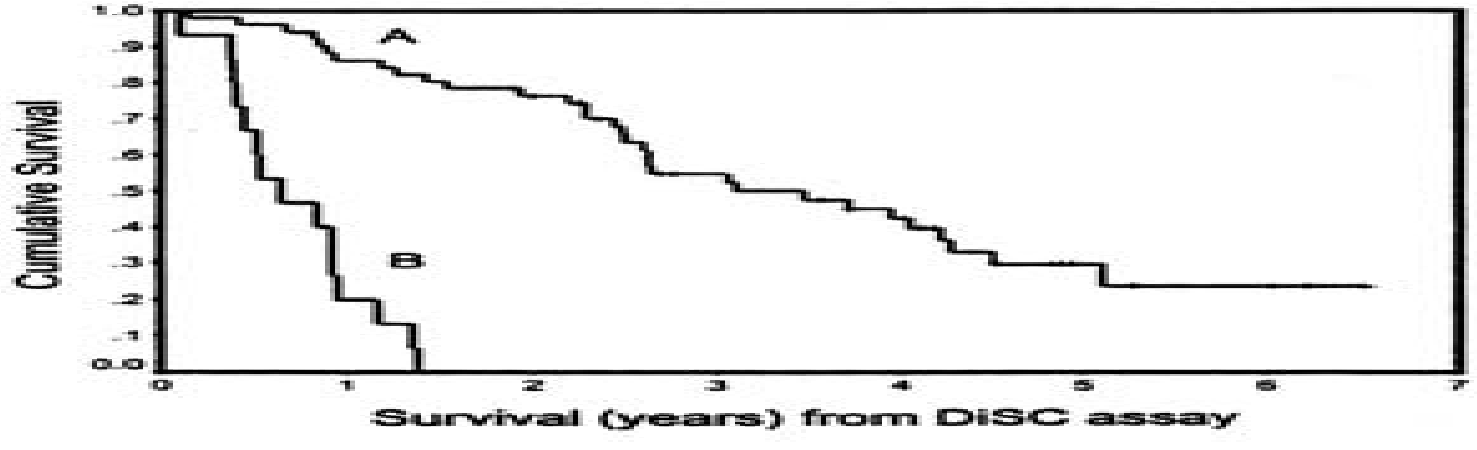
Differential Factor Spain vs. USA in Biotech

Spain is world leader in organ and samples donation for research

Potential of Combination ExviTech Platform & Access to Patient Samples

Focus on Hematological Malignancies

- **Validated clinical correlation of "*ex-vivo*" test ("ITRT")**
- **Has generated new non cytotoxic drugs (Methylprednisolone 1990s)**
- **Dr. Bosanquet (Bath, GB): Pioneer test in Europe, collaborator USA biotechs, performed clinical trial to validate ex vivo tests (CLL4 GB)**
  - **Principal consultant for Personalized Medicine**



*Correlations of In Vitro Test Results with Patient Response**

Assay Type	Total N	TP	TN	FP	FN	% Negative Predictive Accuracy	% Sensitivity
Disc Assay	510	247	175	72	16	92	94

Pioneers System´s Biology Screening
Whole Blood Not Isolated Cells

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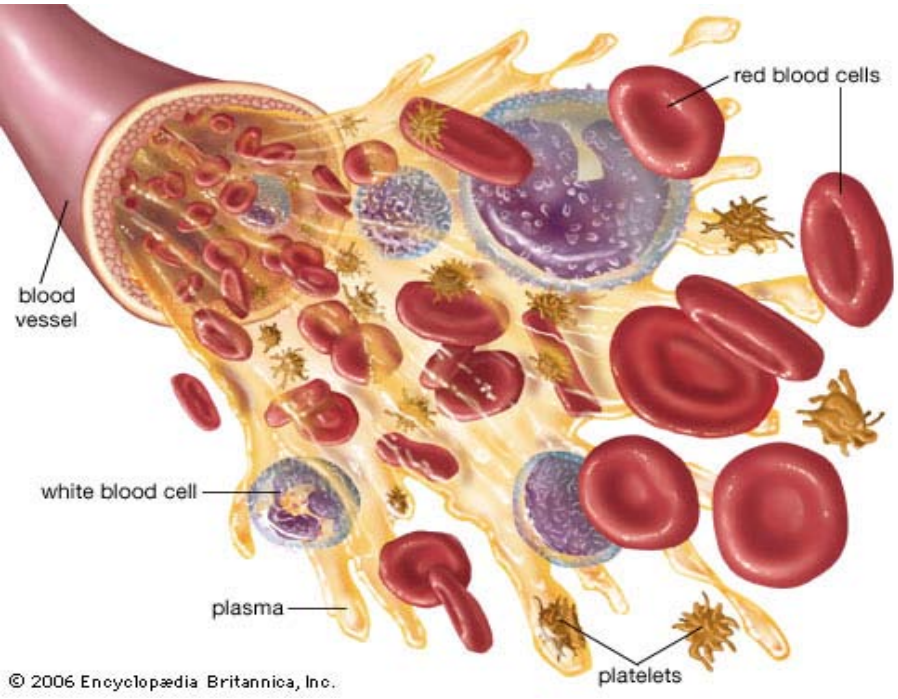
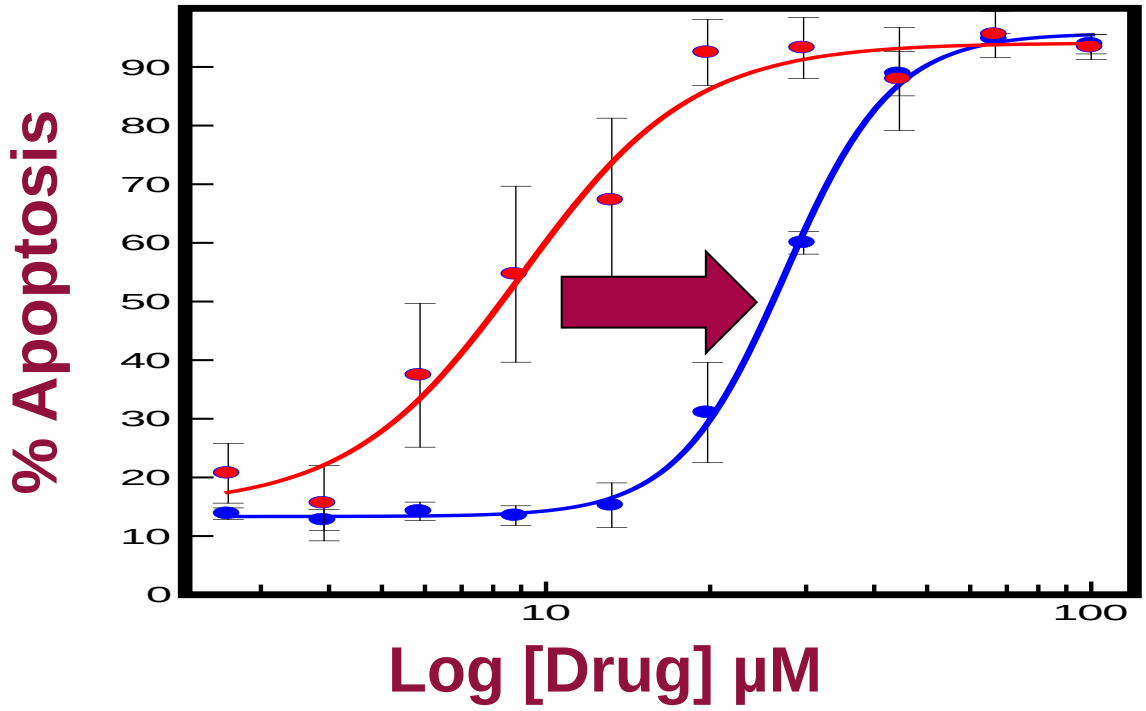


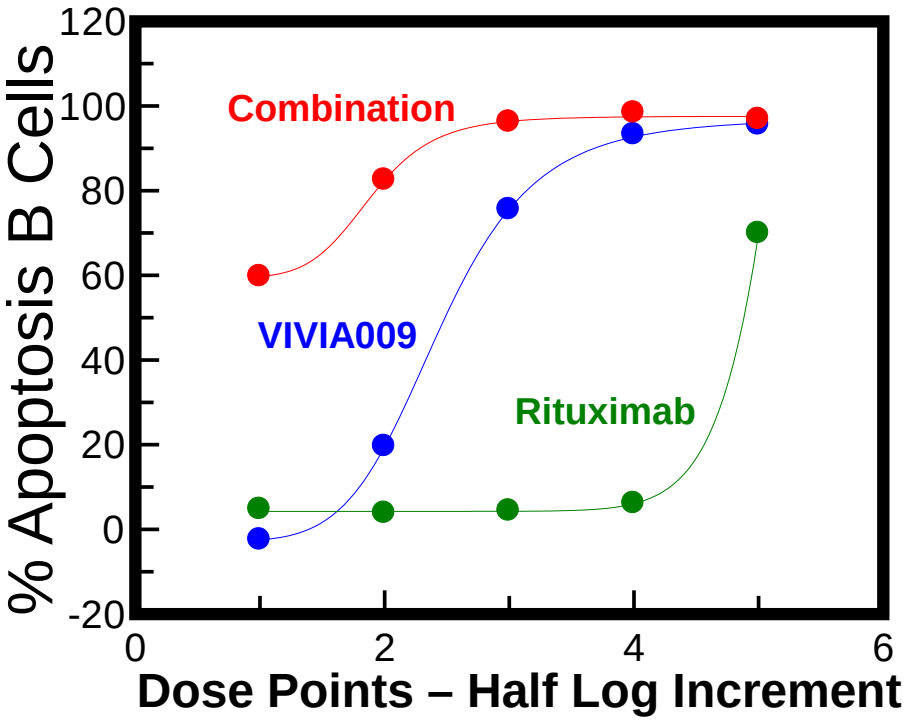


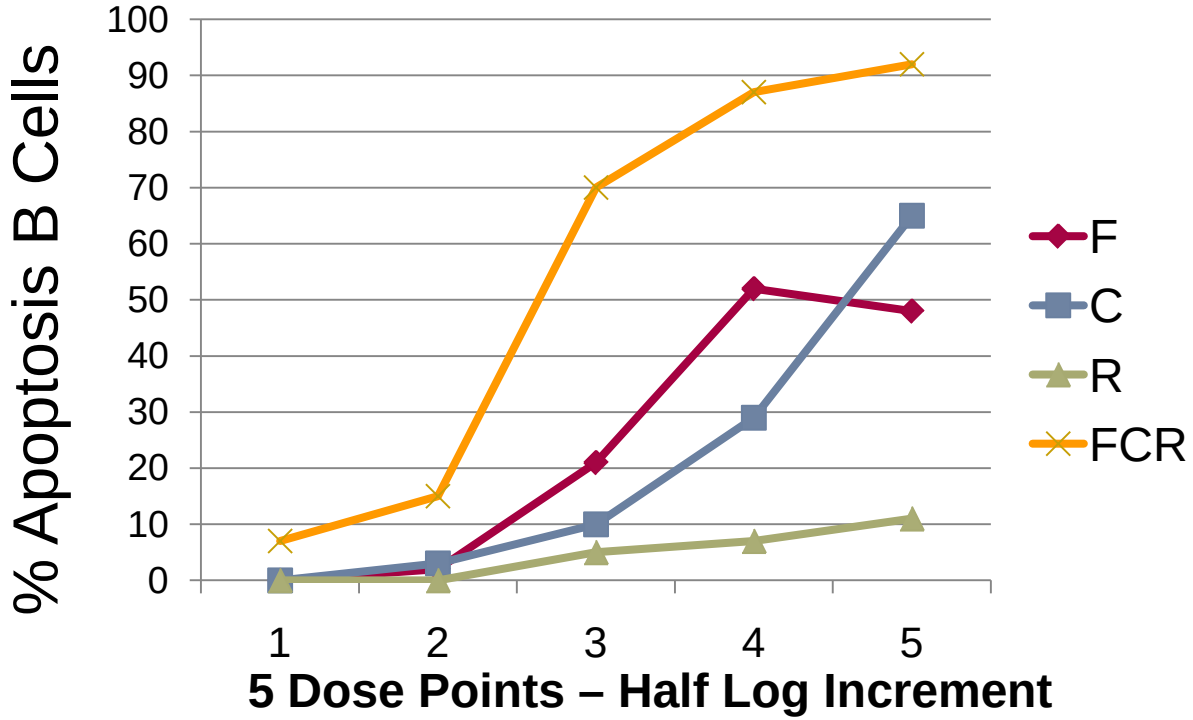
Enables ex vivo efficacy combinations small molecules & antibodies

STANDARD
Isolated leucocytes (white cells), 1%

VIVIA
Whole blood
Different > reliable

Combination of Biologics & Small Molecule Drugs in CLL Samples





Offering service to pharmas: Market Positioning of your Drug Candidates Identifying synergistic combinations with approved & Phase II-III drugs for blood cancers & Autoimmune

1st To Screen 2.000 drugs on Patient Samples Identifies Best Noncytotoxic Candidates

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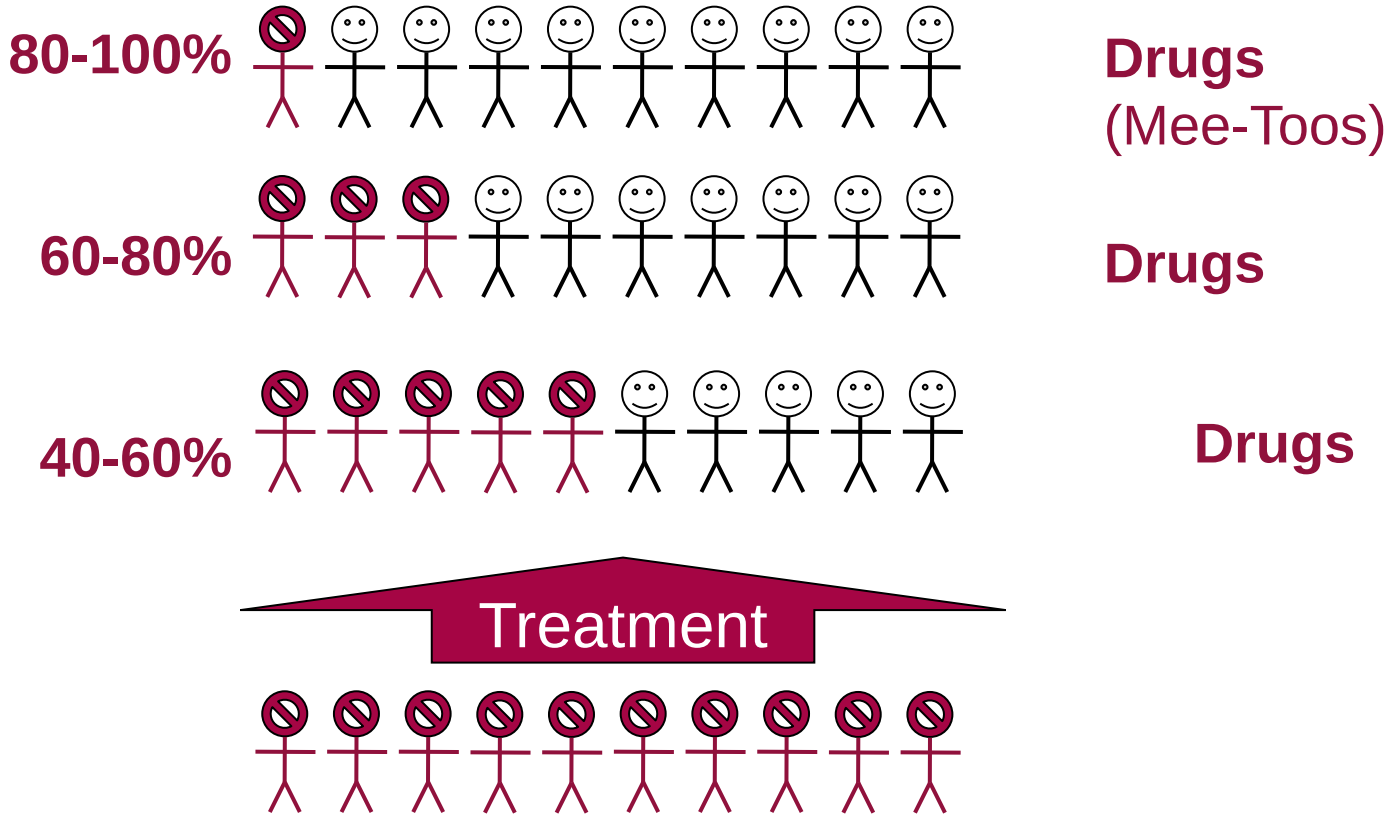
- 2.000 drugs on 25 samples
- Candidate drug if it kills >80% tumor cells
- Most drugs effective in patient subpopulations
- Only 3 Mee-Too drugs are candidates for >80% patients
- Our candidate is Vivia009



Candidate Vivia-009:
Non Cytotoxic Drug Taken by Millions of Patients

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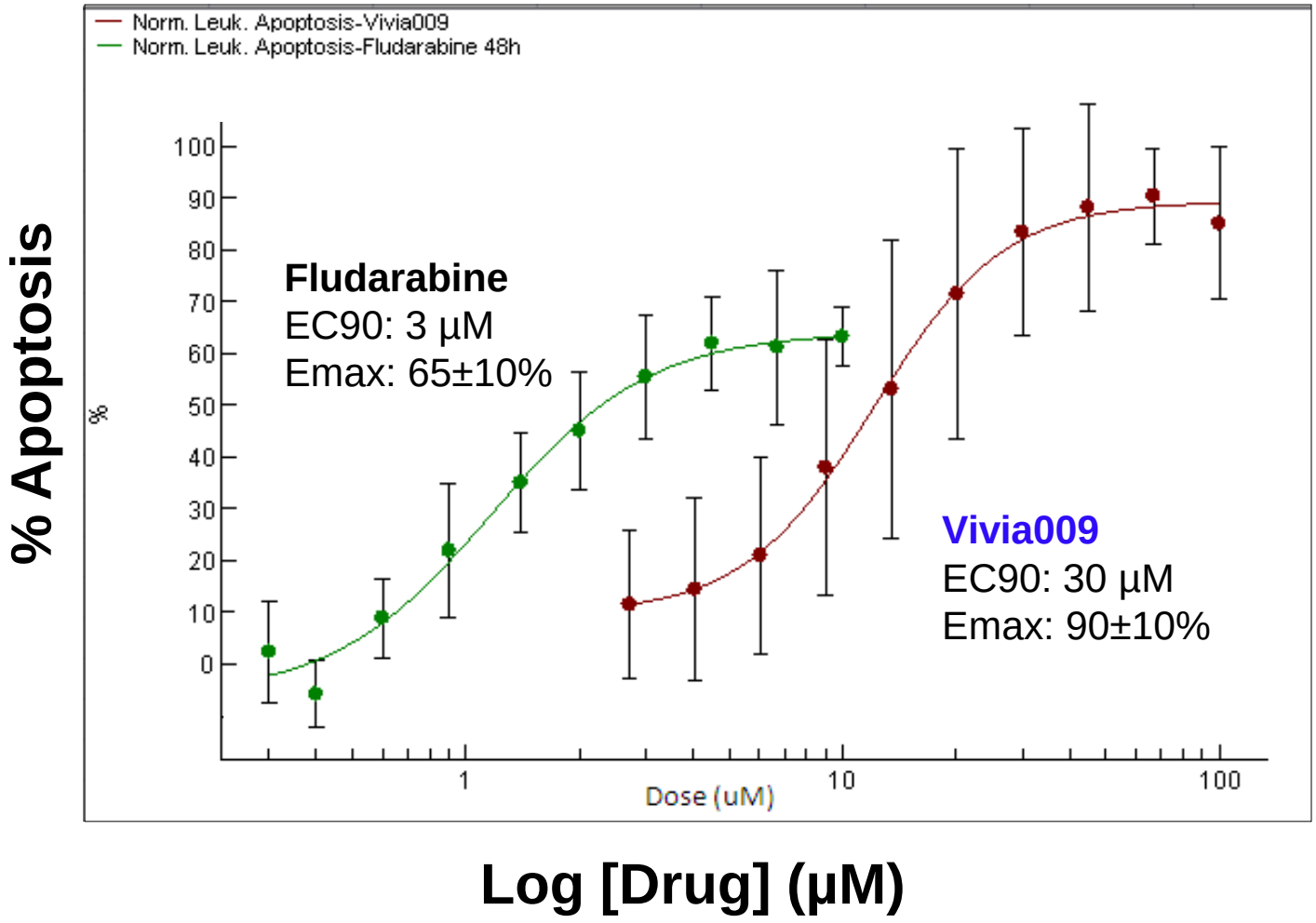
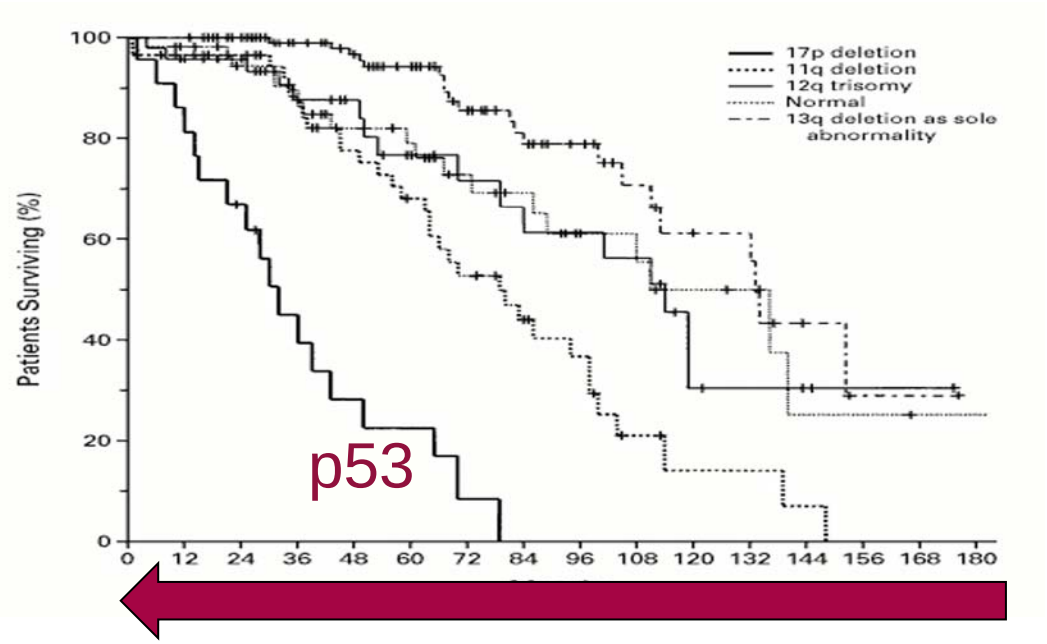
- Non cytotoxic generic drug, good safety profile
- Needs reformulation from approved oral to IV for clinical efficacy in HM
- Better efficacy than Fludarabine in killing CLL tumor cells, at higher doses:
  - EC90 30 vs. 3 μM but not cytotoxic
  - Emax 90% vs. 65%
  - 24 h vs. 48 h
- Validated B-Cell HM samples

  <u>40 CLL, 7 NHL, 7 MM, 6 ALL</u>

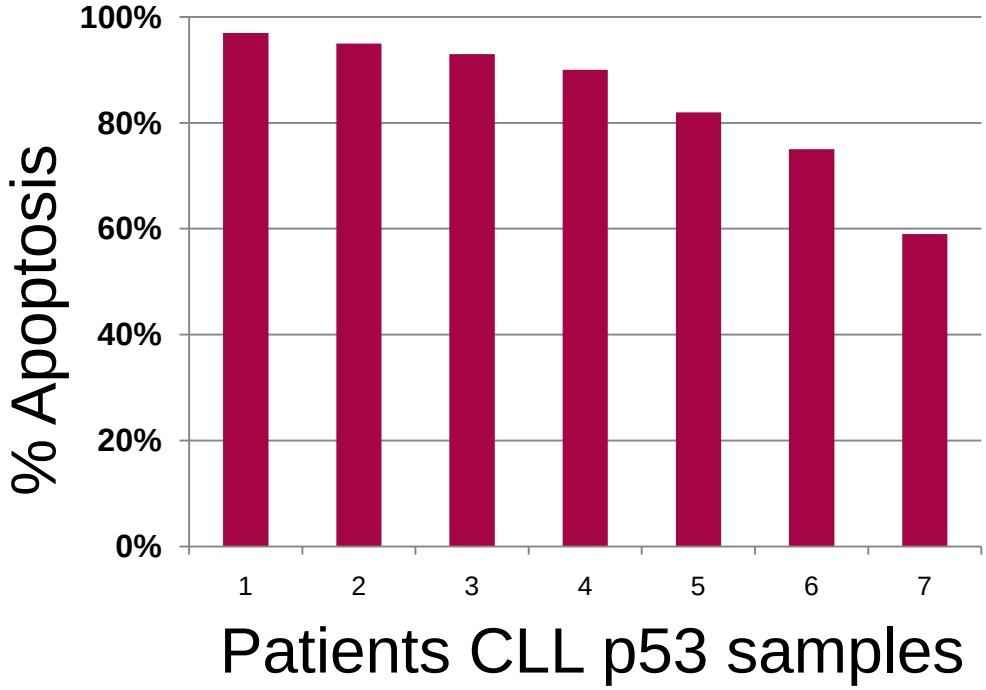


Vivia009

Effective CLL Resistant Patients (p53) with Worst Prognosis



Mortality in # months

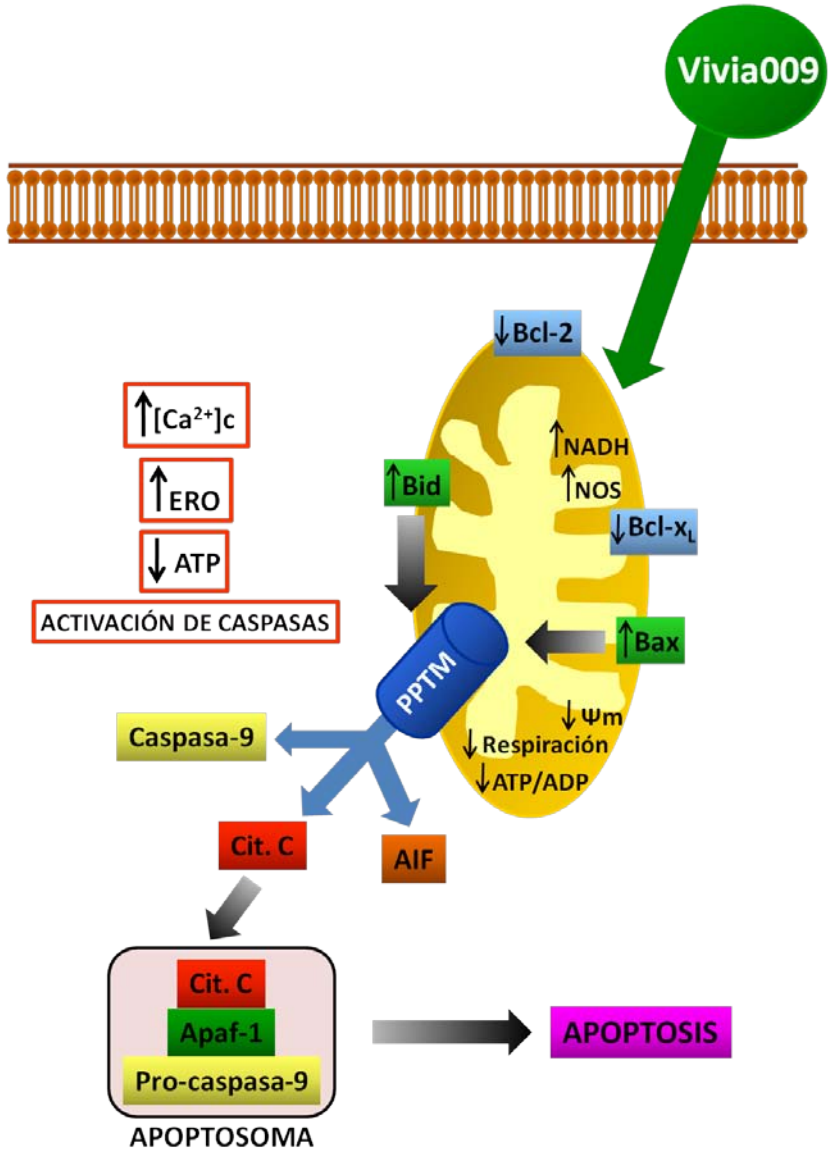


- **No effective treatment alternative (Campath too toxic)**
- **10% CLL patients, higher % in Phase I-II trials CLL & NHL**
- **NHL increasing evidence altered p53 signaling → bad prognosis**

Vivia009

Mechanism of Action

- **Vivia009 accumulates in <u>mitochondria</u>**
- **Induces apoptosis from mitochondria skipping p53**
- **Explains selectivity neoplasic cells metabolically more active**
- **Explains fast kinetics**
  - 24 h vs 48 h Fludarabine
  - only 30 min incubation
- **Mechanism unclear**
- **Could induce opening of Transient Mitochondrial Permeability Pore (MEPP), initiating release of pro-apoptotic molecules**



Intravenous (IV.) Vivia-009 Does Not Induce Myelotoxicity in Rats

- Doesn´t induce neutropenia or thrombocytopenia.
- To be validated in Phase I trials.
- Could be considered a non cytotoxic drug.
- Suitable for fragile geriatric patients.
- Could be added to existing treatment protocols.
- Maintenance therapy?

Neutrophils

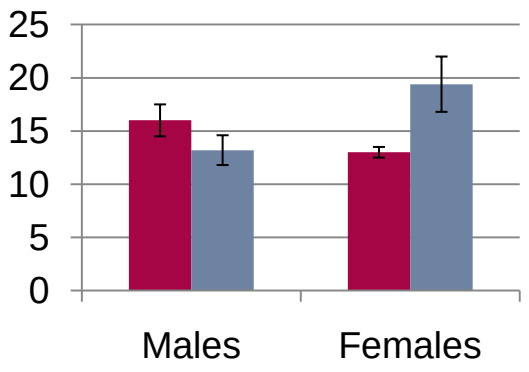
% Cells

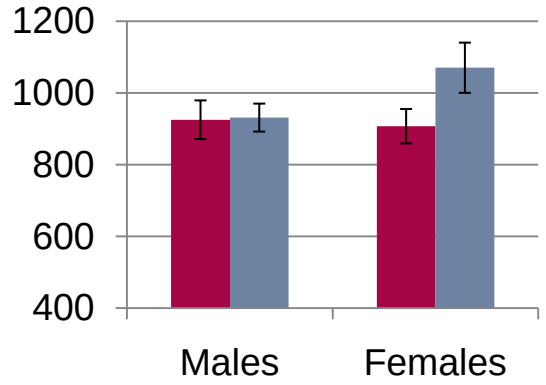
Platelets

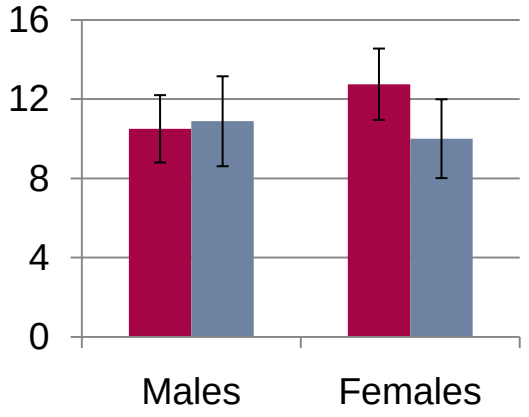
Cell number 10^3/µl

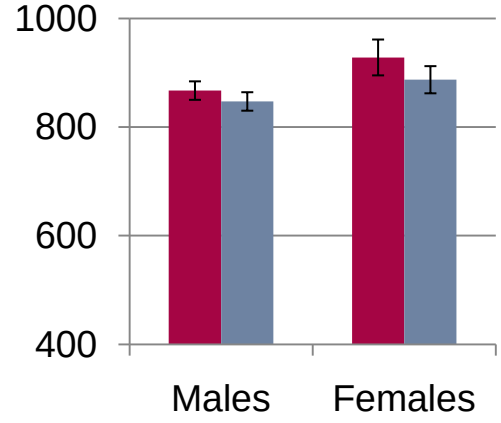
Vivia009 Control

7 days @ 5 mg/Kg1 dose @ 20 mg/Kg









Formulated Vivia-009 IV.

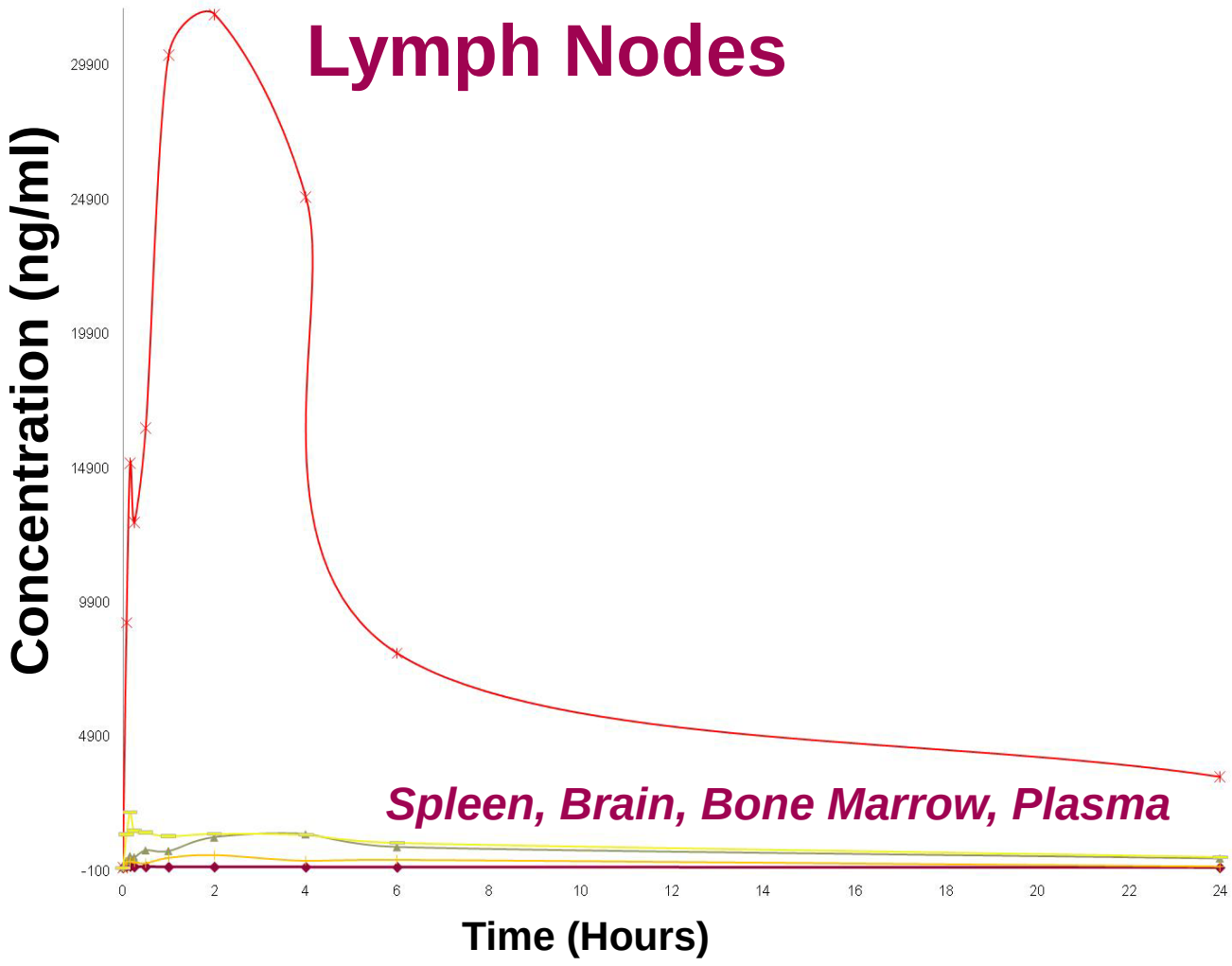
Highly Concentrates in Lymph Nodes

- **Formulated Vivia-009 IV. targets lymph nodes, key organ for B-Cell proliferation & for treating minimal residual disease.**

- **Level in Lymph node is**
  - x65 times bone marrow
  - x600 times plasma
  - x15 times brain

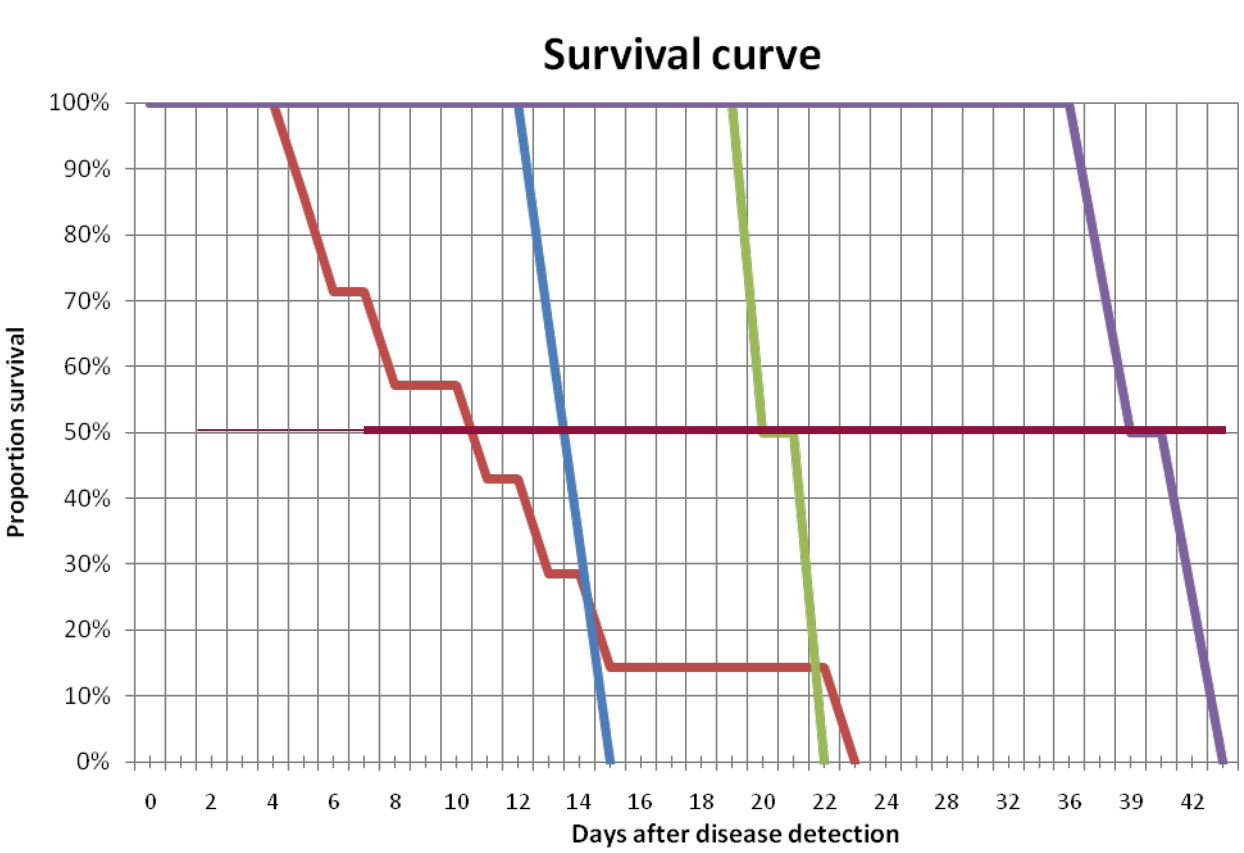
- **Most suitable B-Cell malignancies are Non Hodgkin Lymphomas**

NHL



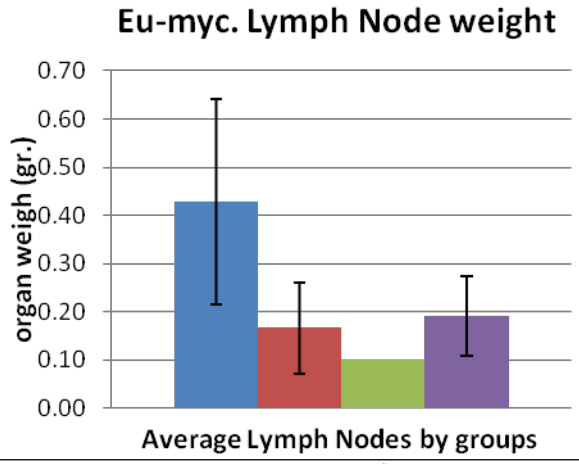
In vivo efficacy of VIVIA009 in Eμ-MYC transgenic mice

Accelerated Lymphomagenesis animal model



Control = No treatment (no vehicle control). N = 6
Treatment 1 = 5d. N = 2
Treatment 2 = 5d + 9 wash out + 5d. N = 2
Treatment 3 = 5d + 9 wash out + 5d + 9 wash out + 5d. N = 4

5d = 5 daily dose 10mg/kg



PK-PD Model Efficacious Dose Is Close to Phase I Starting Dose

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Cmax	10 mg IV 5 days	= 1/18th	180 mg oral Approved
Lymph Node	**30 μM (EC90)**		NA
Plasma	0.04 μM	<	0.3 μM
Brain	0.7 μM	<	6.5 μM

- IV dose is 18 times lower than oral approved dose
- Lower toxicity-related plasma & brain levels than oral approved
- NOAEL in rats (Formulated)→ 15 mg/Kg → 153 mg in humans
- MTD in rats (Formulated)→ 25 mg/Kg → 255 mg in humans

We expect an effective dose of 10 mg = 1/15th of rat MTD
However, microenvironment lymph node may require >30μM

Vivia-009 IV. PK-PD Model

Double dose 10 to 20 mg @ 5 days

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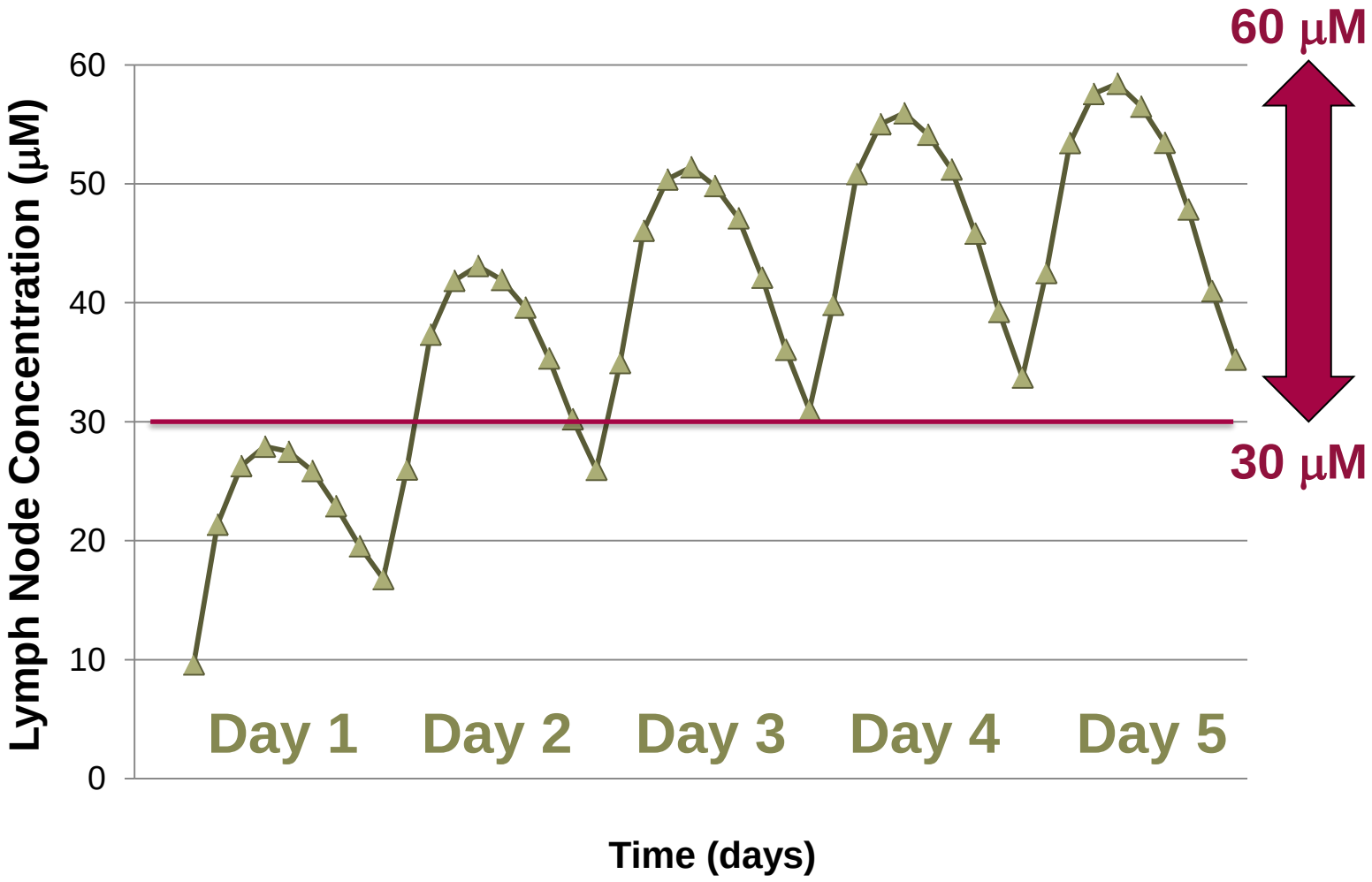
20 mg IV → 30 µM
Lymph Node day 2

ex vivo EC90 = 30 µM
in vivo EC90 > 30µM
for microenvironment

Plateau ~60 µM day 5
→ Low toxic overdose

Restricted lymph node
levels 30-60 µM

Short efficacy margin
may require prolonged
> 1 day exposure



VIVIA009 Phase I-IIa Clinical Protocol Objectives

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PHASE I

Primary- determinate maximum tolerated dose (MTD) and evaluate the safety, tolerability and pharmacokinetics of escalating doses of Vivia009 in the treatment of patients with relapsed or refractory B-cell non-Hodgkin-lymphoma
Secondary- Asses potential Biomarkers

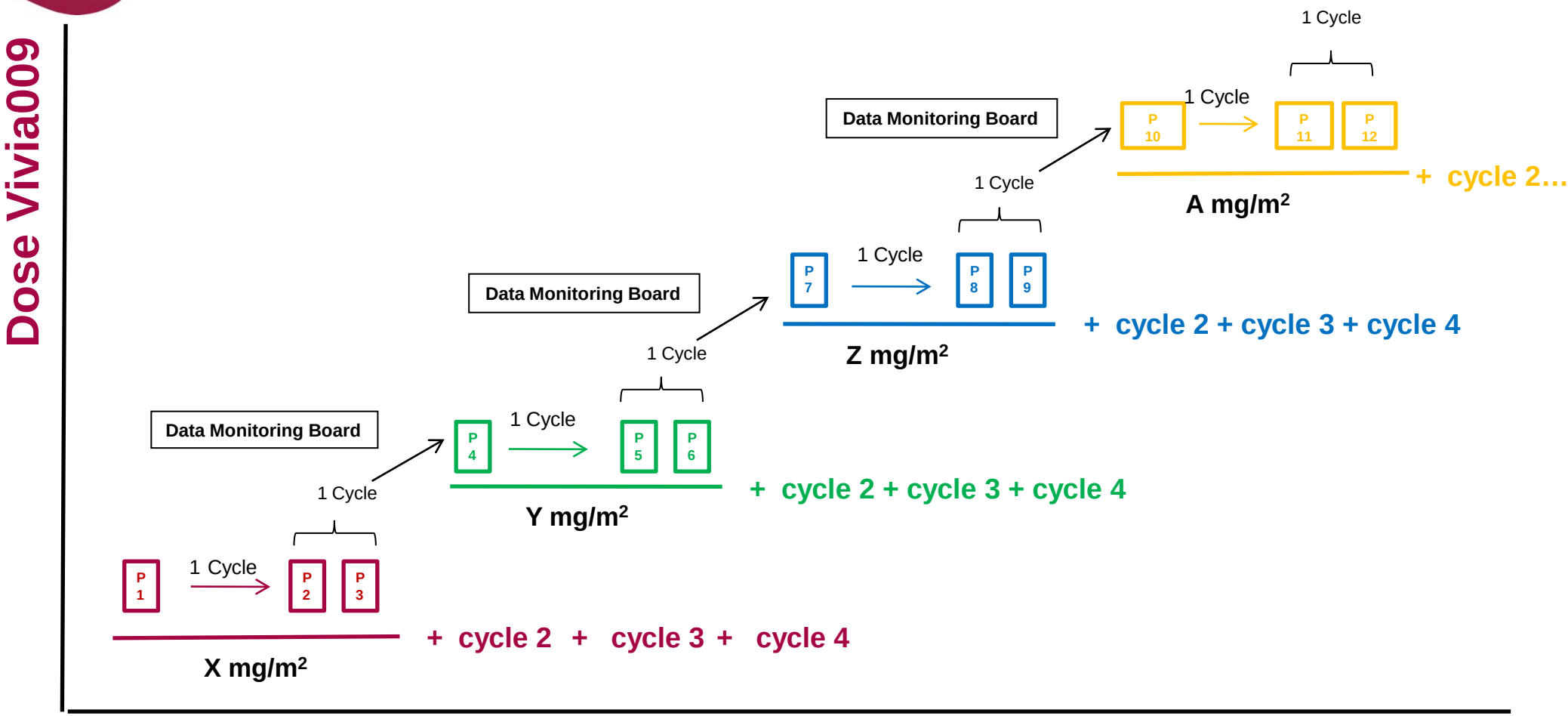
PHASE IIa

Primary- Evaluate the safety, tolerability and pharmacokinetics of Vivia009 + Rituximab in patients with NHL

Secondary- Assess efficacy of Vivia009 in combination therapy with Rituximab in the treatment of NHL

PI Professor Martin Dreyling, Munich, NHL & MCL
CRO Harrison Clinical Research, Munich

Phase I Design



Starting dose : to be determined

Phase I Starting Dose

Starting Dose Selection:

- MTD in rats: 25 mg/Kg
- MTD in dogs (expected): 2 mg/Kg

- Considering 1/10 of the MTD in the most sensible specie (dog):
  - Starting dose will be: 0.2 mg/Kg

This dose correspond to 4 mg/m^2 or 7 mg flat dose

In 12 Months 3rd cohort 15 mg/m^2
= 2.5 x 10 mg expected efficacy dose → fast go/nogo point

Phase IIa Design Vivia009 + Rituximab

Complementary tissues Lymph Nodes + Bone Marrow

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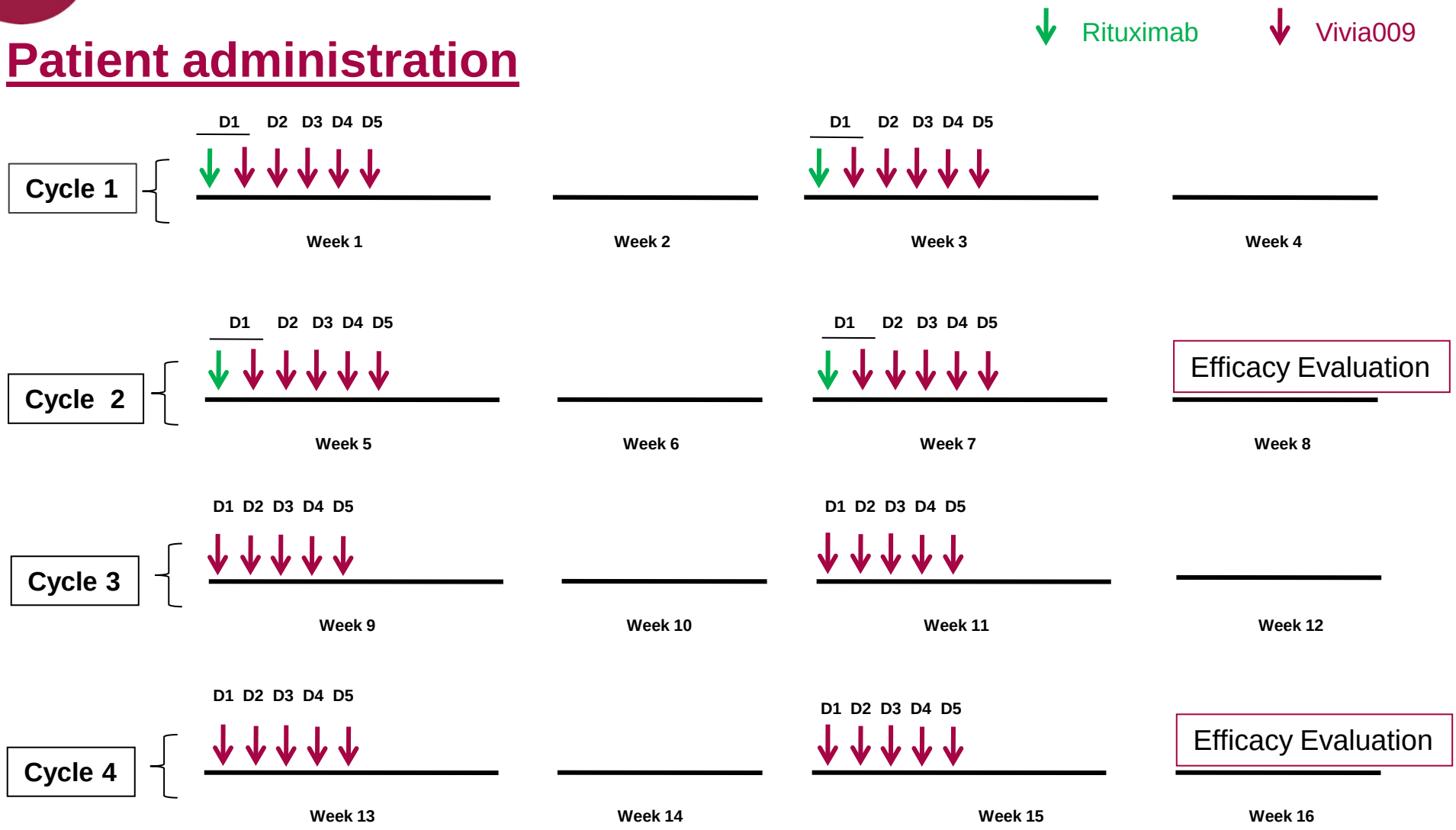
Patient administration



Positioned for Largest Market NHL/CLL Combine with Existing Protocol Treatments

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- **Low toxicity without hematotoxicity & synergistic unique lymph node efficacy → incorporation to most existing protocols**

- **Combination with Rituximab, effective in bone marrow but not in lymph nodes**
  - Low toxicity Rituximab enables intense schedule every other week

- **Combination with chemotherapy too long, for future trials**
  - Standard schedule 6 cycles 28 days
  - Requires independent Phase I combined with chemotherapy using chemotherapy schedule (6 cycles 28 days)

Vivia009 Enantiomer of Metabolite Equally Active, Candidate "NCE-like" Protection & Pricing

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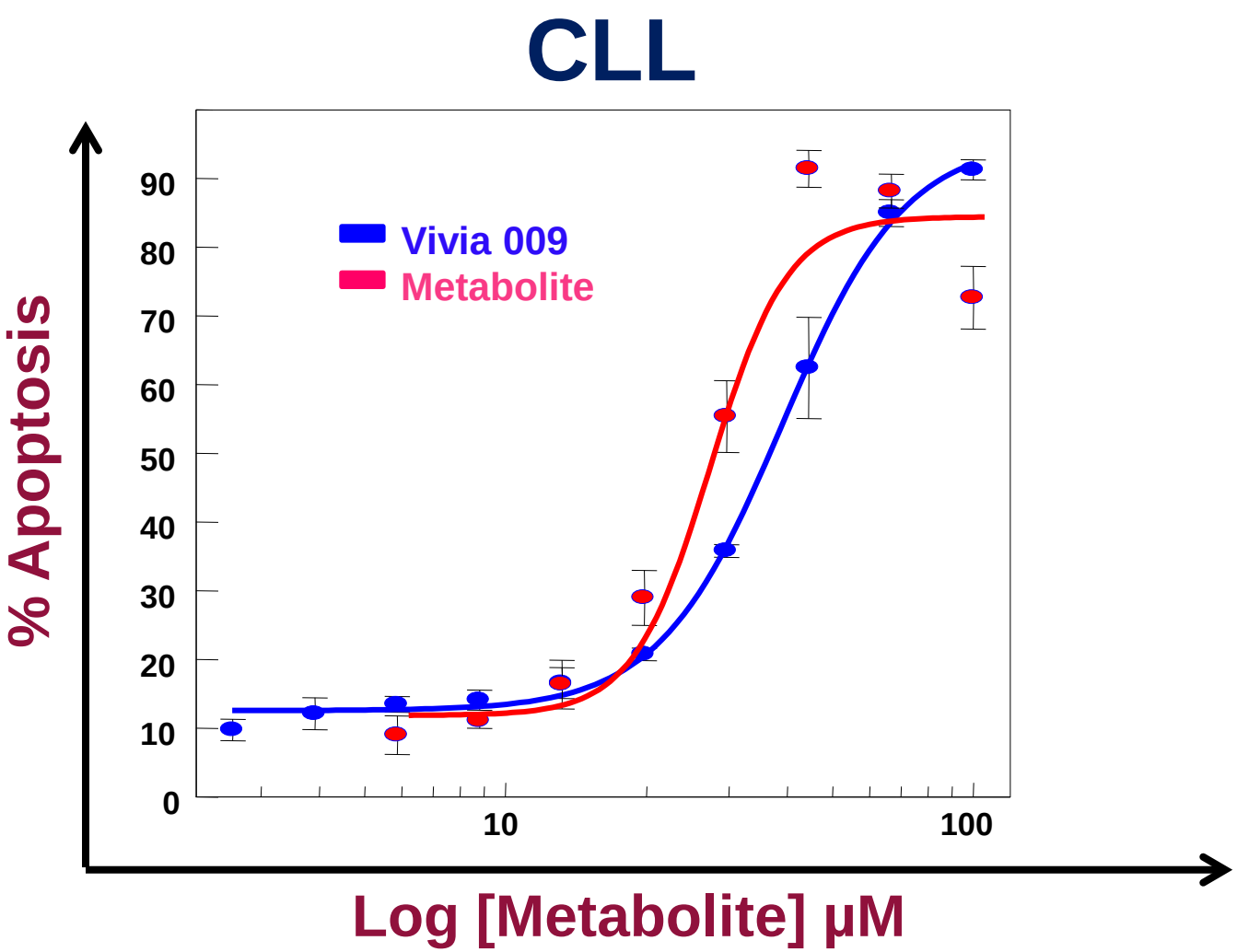
- **Enantiomer of Metabolite** equally active at apoptosis & has proven security as a major metabolite
- Not active on Vivia009 target
- Represents a candidate with stronger protection (Data Protection laws) and free pricing
- Real candidate big pharma?
- Needs 1-2 years additional time to reach clinical trials



Good Commercial Protection & Reimbursement Price

- Generic orally available drug requires reformulation oral to IV for efficacy, preventing use of the generic version and securing reimbursement
- New galenic formulation targeted to lymph nodes enables strong patent (filing for composition of matter)
- Orphan indications (NHL & CLL): 10 years commercial exclusivity
- Metabolite/enantiomer is active and can achieve NCE-like protection & pricing

Key Advantadges
Vivia009 IV for NHL

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1. Most effective drug ex vivo 90%±10%, effective p53 (17p) patients with no treatment options, which can be ~50% Phase I-II clinical trial
2. Safe non cytotoxic drug without myelototoxicity → fragile Pts ~50%
3. Unique Lymph Node biodistribution, key B-Cell reservoir tissue MRD
4. Phase I-II in NHL Q4-2011 with Prof. Dreyling & Harrison Clinical Research
5. **Phase I start dose close efficacy dose→fast clinical validation 12 months**
6. **Positioned for largest market NHL-CLL by incorporation to existing protocols: no tox & synergistic efficacy lymph nodes**
7. **Good commercial protection & reimbursement price**
8. **Metabolite is equally effective, "NCE" alternative candidate, life cycle**

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Management Team

Name	Role	Background
Joan Ballesteros, Ph.D.	Chairman and CSO	16 years in USA, Founder and CSO of Novasite (San Diego, CA) 1999-2006, ExviTech technology
Andrés Ballesteros, JD/LLM & MBA	CEO	MBA & Lawyer for Spain & USA (New York) 8 years experience lawyer New York
Theresa Branchek, PhD	Independent Director	Ex CEO Lundbek USA, ex-founder and CEO of Synaptic. Extensive pharma and biotech experience
Teresa Bennett, PhD	VP Research	Director Research Novasite (San Diego) Developed ExviTech technology
Andrew Saunders, M.D.	VP Clinical Development Hematologist	Hemato-oncology drug development. Led clinical trials of Rituximab at Roche and Clofarabine at Bioenvision
Luis Caveda, PhD	VP Drug Development	CSO ThromboTargets (Spain-USA). Two drugs to IND
Julieta Montejo, MD	CMO, Medical Director	MD Psychiatrist expert Vivia009 candidate

Experienced Pharma/Biotech team + Differential Technological Platform