

Translating "proof-of-the-concept" in approved medicines

Operational challenges; Opportunities for partnerships

Convertir un concept en une nouvelle approche thérapeutique

Obstacles opérationnels; Opportunités de partenariat

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Disclaimer

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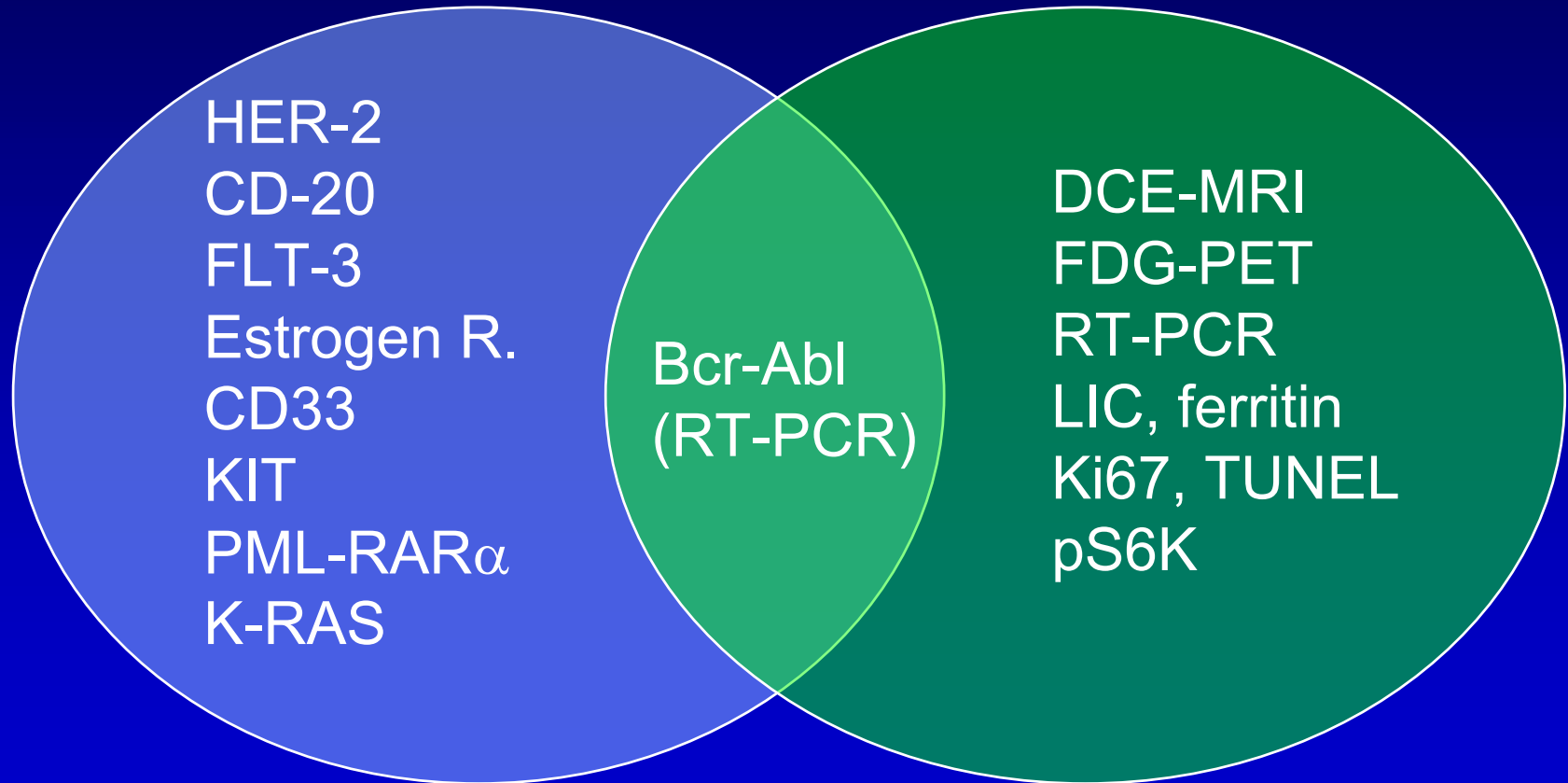
... Oncologists probably know all about the concept of targeted therapy

- Prescribe the **right** treatment
- For the **right** patient
- At the **right** time
- For the **right** reason
- And with a **predictable** outcome

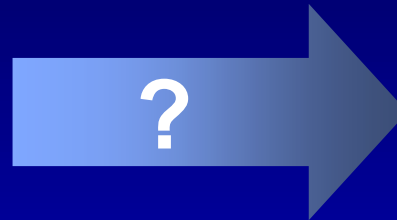
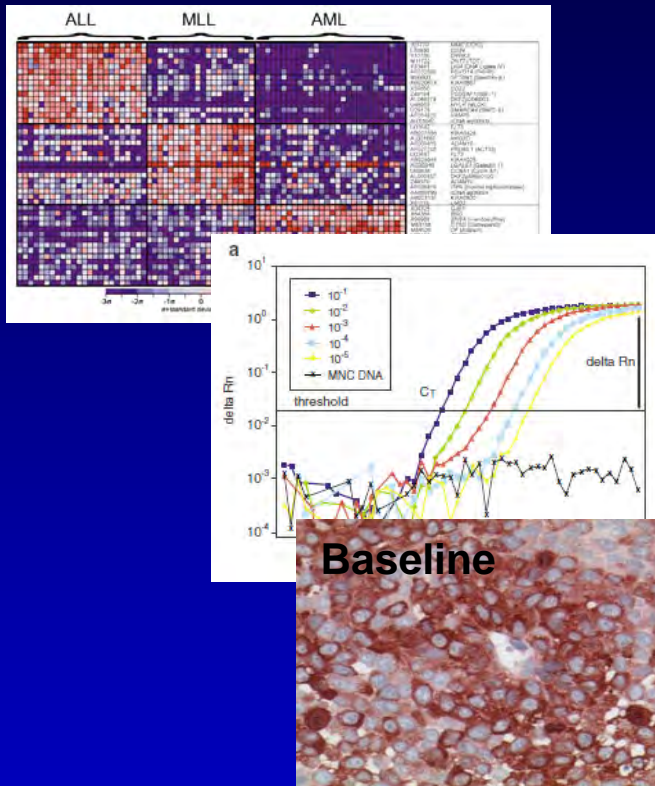
Conceptually, biomarkers can be used...

...to select patients

...to measure drug effect



Question



Mostly used to establish "proof of the concept"

Phase III trials & Patients care

3 Examples

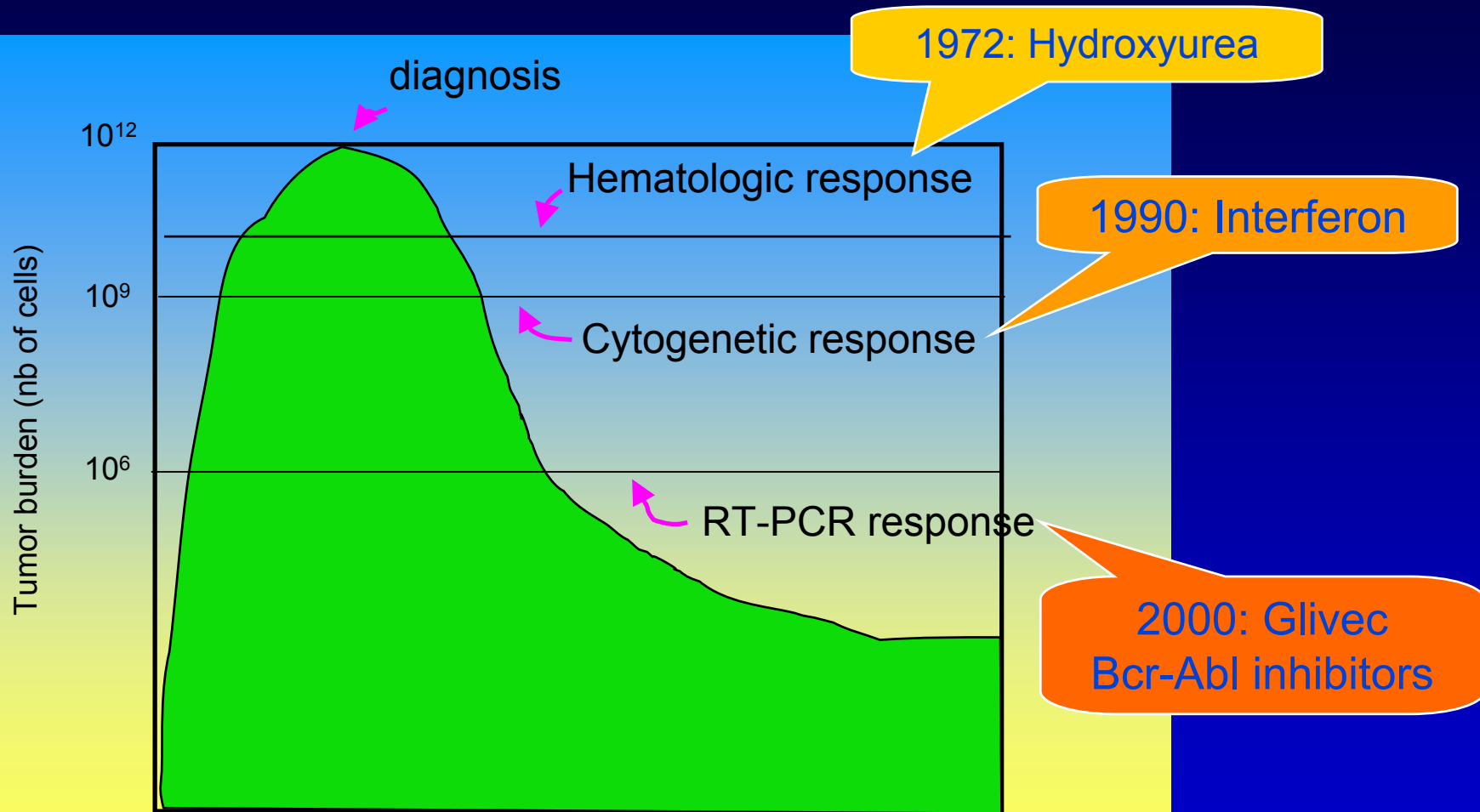
- Glivec/Tasigna (BCR-ABL inhibitors)
- Everolimus (mTOR inhibitor)
- Midostaurin (FLT3 inhibitor)

3 Examples

- Glivec/Tasigna (BCR-ABL inhibitors)
 - ➡ PCR-based molecular response as primary trial endpoint
- Everolimus (mTOR inhibitor)
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"Response" is a moving target

Example of CML



Adapted from Frei III et al.

The Philadelphia Chromosome in CML

BCR gene on Chromosome 22



c-abl gene on Chromosome 9



↑ CML Breakpoints ↑ ALL Breakpoints

↑ mRNA / Protein:



→ RT-PCR: Measure in peripheral blood cells the ratio of the Bcr-Abl mRNA transcript over a control housekeeping gene

The success of Glivec prompted worldwide collaborations to set international PCR standards

Review in translational hematology

Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting *BCR-ABL* transcripts and kinase domain mutations and for expressing results

Timothy Hughes, Michael Deininger, Andreas Hochhaus, Susan Branford, Jerald Radich, Jaspal Kaeda, Michele Baccarani, Jorge Cortes, Nicholas C. P. Cross, Brian J. Druker, Jean Gabert, David Grimwade, Rüdiger Hehlmann, Suzanne Kamel-Reid, Jeffrey H. Lipton, Janina Longtine, Giovanni Martinelli, Giuseppe Saglio, Simona Soverini, Wendy Stock, and John M. Goldman

- Major Molecular Response (MMR)
 - Definition of original IRIS phase III trial: 3-log reduction in RT-PCR *BCR-ABL* transcripts from a standardized baseline
 - International scale definition: *BCR-ABL* transcripts $<0.10\%$ using a conversion factor derived from local baseline reference standards

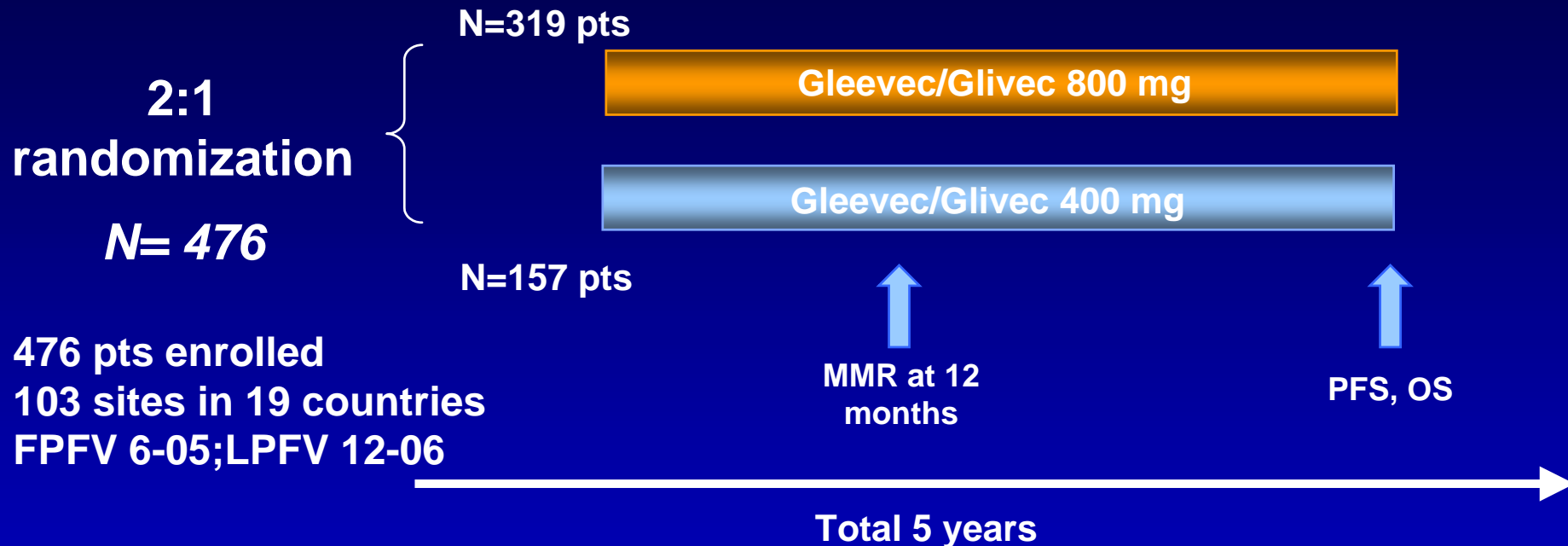
Hughes et al., NEJM, 2003, 349: 1421-30
Hughes et al., Blood, 2006, 108: 28-37
Druker et al., NEJM, 2006, 355: 2408-17

A Phase III, randomized, open-label study of 400 mg versus 800 mg of imatinib mesylate in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular endpoints – TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) Study

Cortes J, Baccarani M, Guilhot F, Druker B, Yu R,
Rudoltz M, Krahne T, Hughes T
on Behalf of the TOPS Study Group

[EHA, Copenhagen, 14 June 2008, abstract #402]

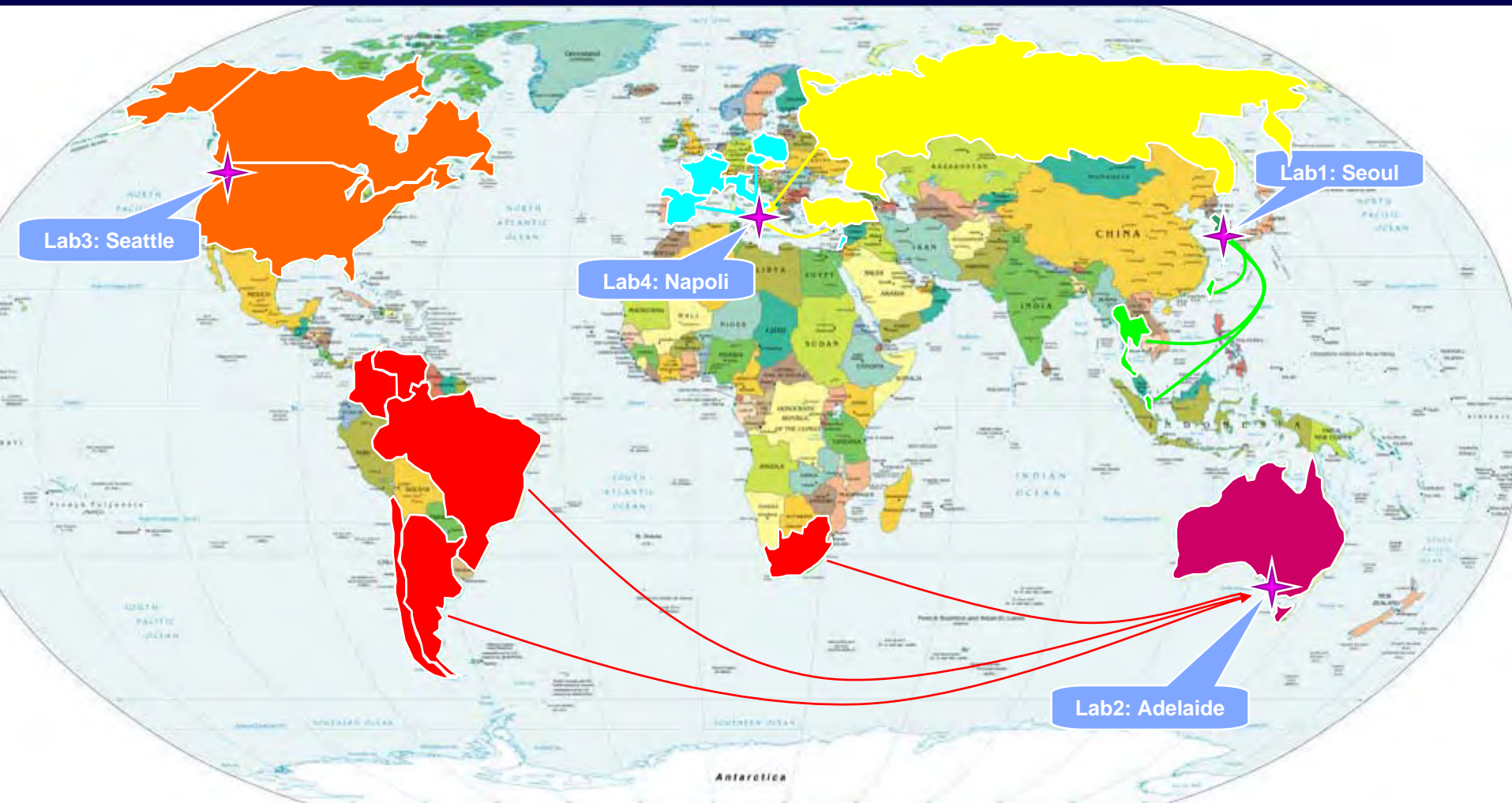
Study Design



Detect a difference of 20% for the MMR rate at 12 months (i.e., from 40% to 60% with a 90% power)

- Cytogenetic analysis every 6 months until CCyR, then every 12 months
- Molecular analysis by PCR every month x 3, then every 3 months

Setting a truly global network



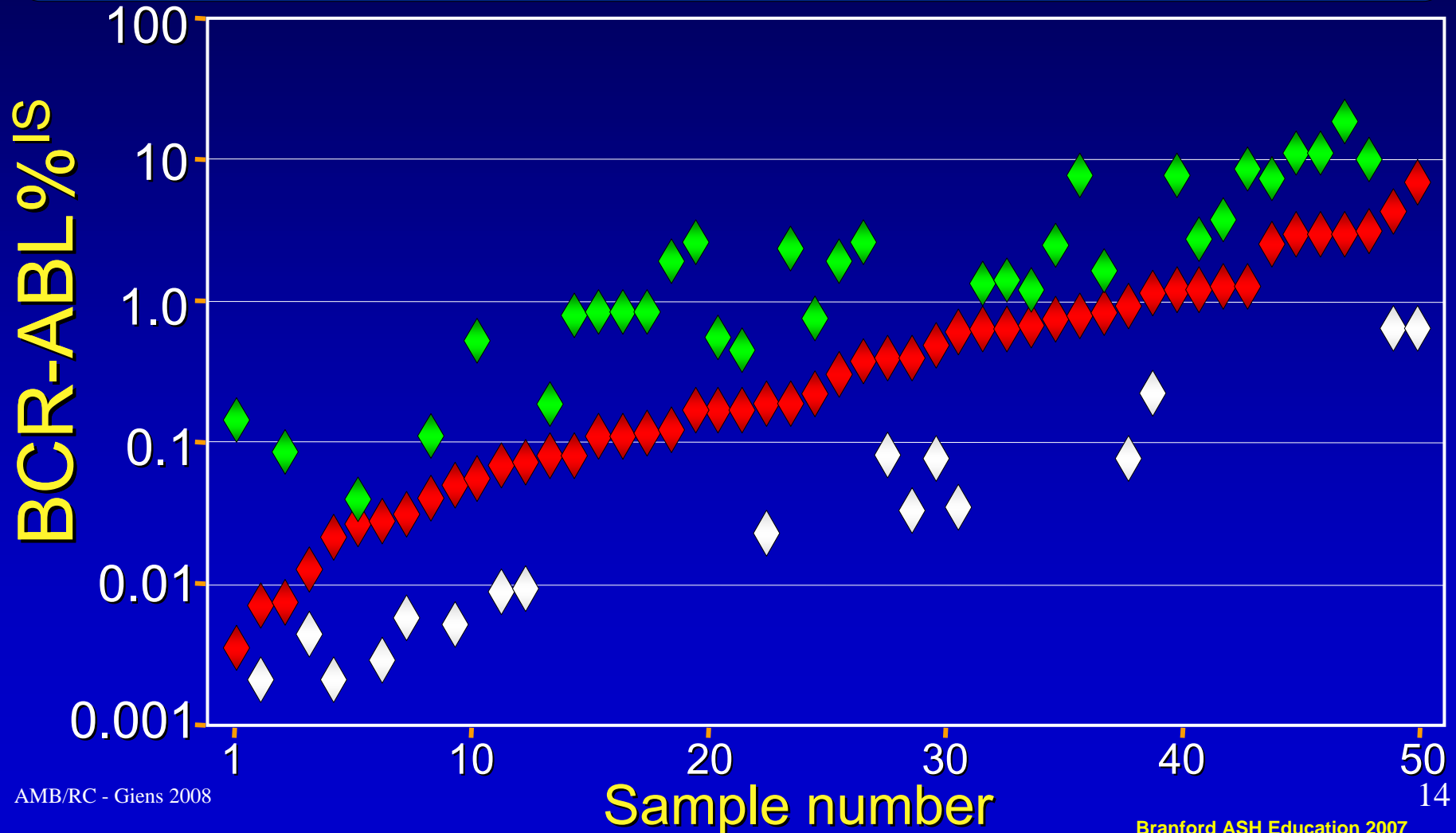
   Sample fixed at site before -70°C shipping     Ambient sample shipped directly to lab

Each value multiplied by assay specific CF

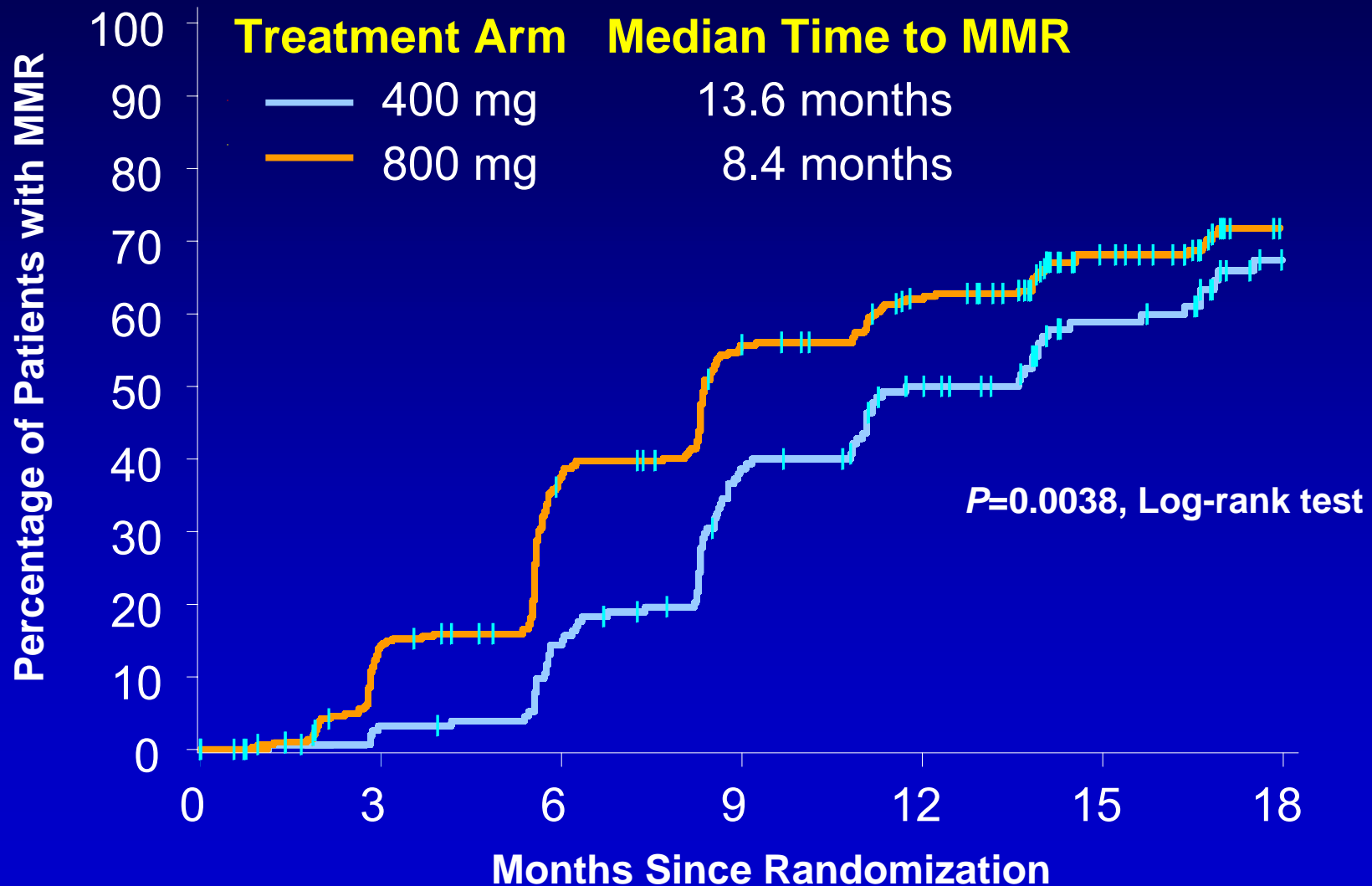
◆ Ref Lab / BCR
CF = 5025

◆ Korea / ABL
CF = 0323

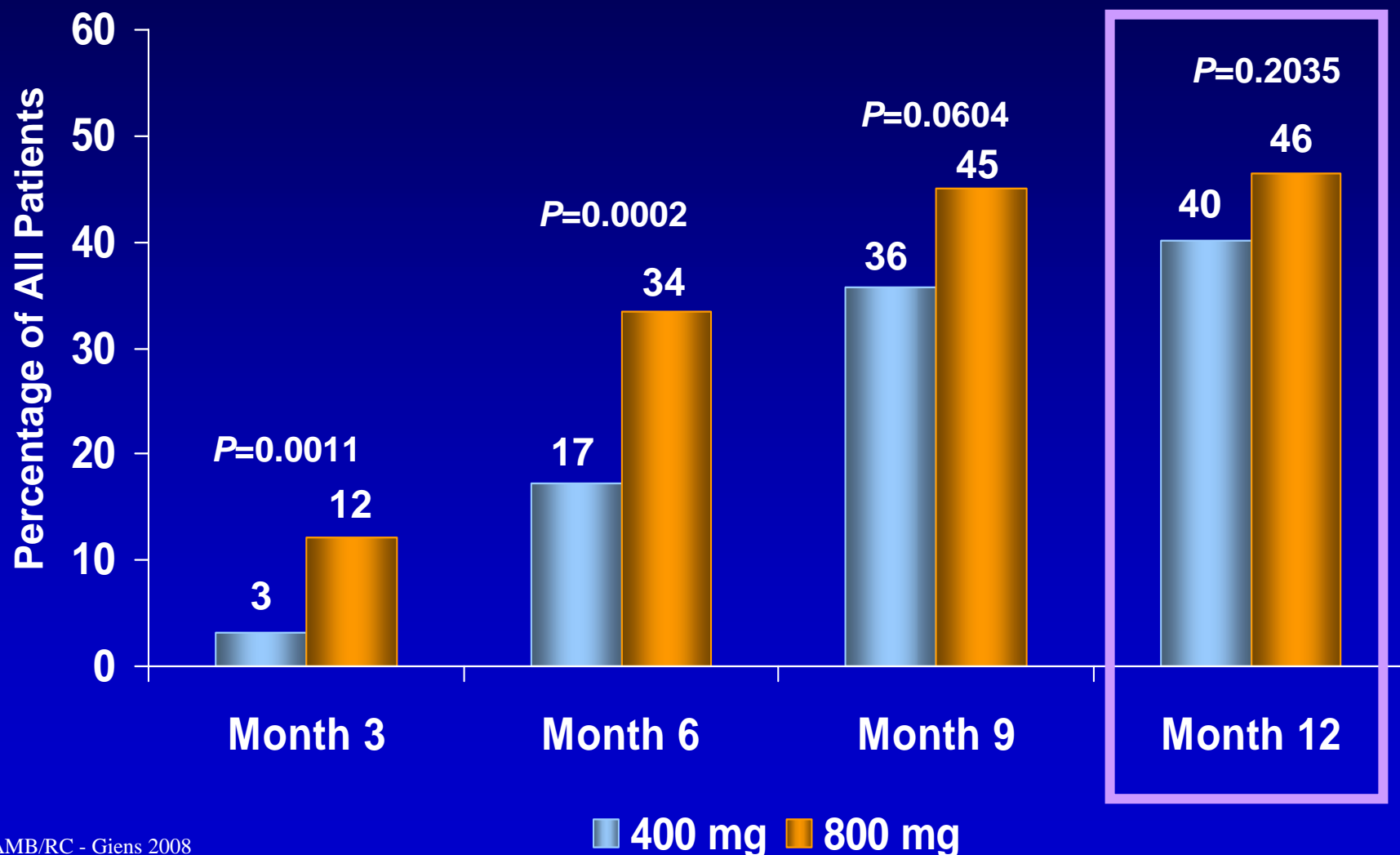
◆ USA / β 2M
CF = 0.7



Imatinib 400 mg vs 800 mg in CML-CP: Time to First MMR by Treatment Arm



Imatinib 400 mg vs 800 mg in CML-CP: MMR Rates Over Time (ITT)



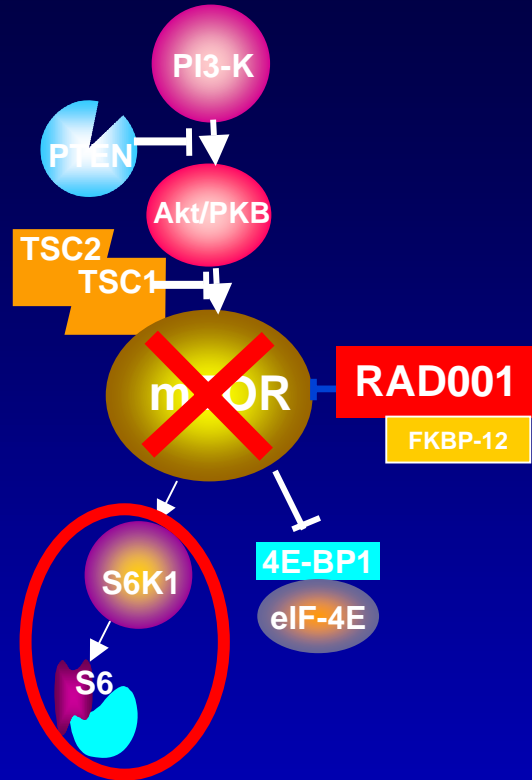
3 Examples

- Glivec/Tasigna (BCR-ABL inhibitors)
 - ➡ PCR-based molecular response as primary trial endpoint
- Everolimus (mTOR inhibitor)
 - ➡ multiparametric biomarker data to guide dose selection and decision making
- Midostaurin (FLT3 inhibitor)

Selection of Dose and Schedule: The RAD001 Experience

RAD001 Preclinical pharmacology

- CA20948 syngeneic rat pancreas tumor model
- Anti-tumor activity
- PD effect of RAD in target pathway in normal tissues and tumor
- PK studies at effective doses
- IC50 levels *in vitro*



RAD001 Phase Experience: Two Clinical Trials

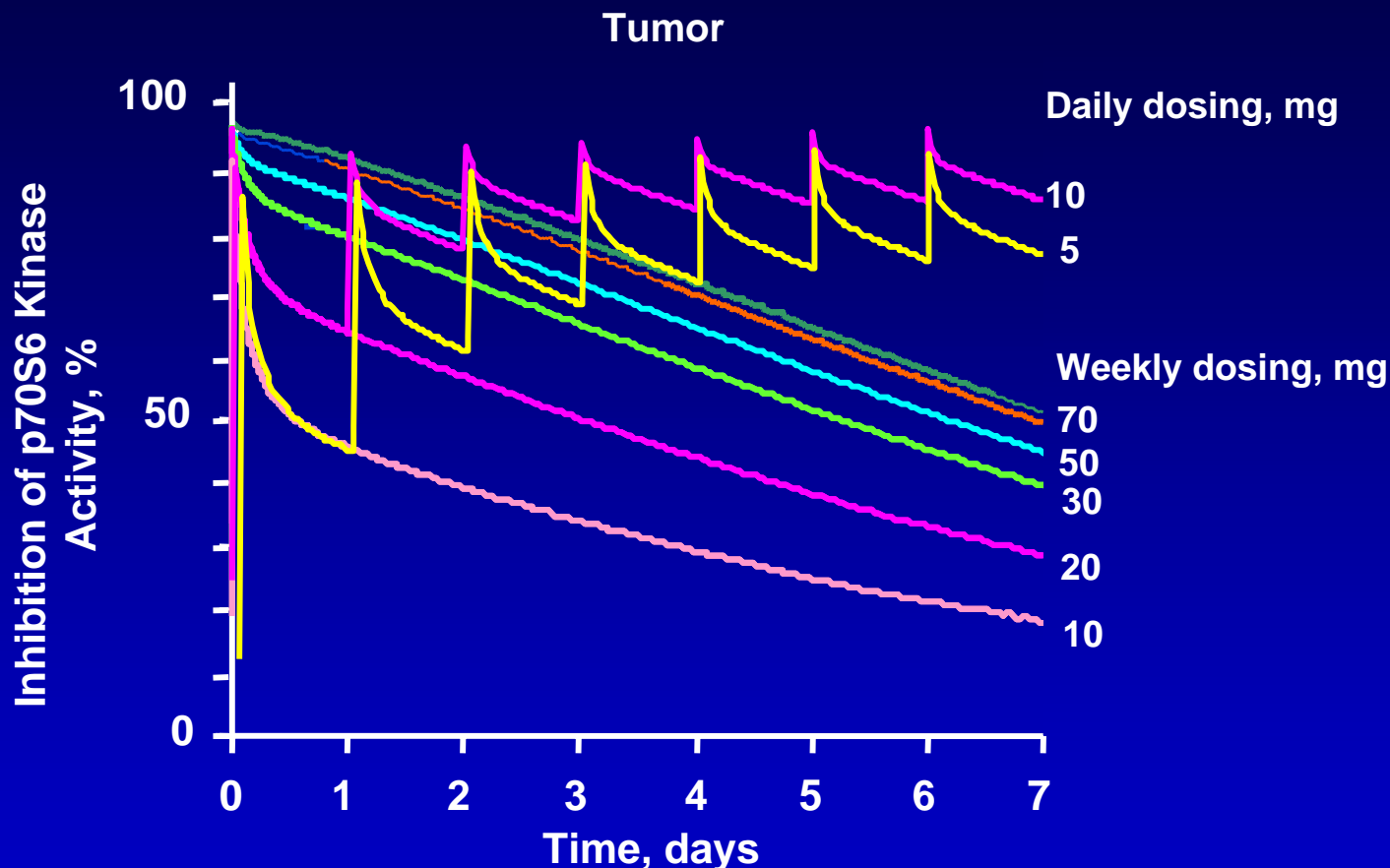
- Daily and weekly schedules
- Safety at increasing doses in sequential cohorts of pts
- PK studies
- Anti-tumor activity
- PD effect of RAD in target pathway in normal tissues and tumors
- **Define Optimal Biological Dose**

PK/PD modeling linking

- dose-concentration relationship
- concentration-effect relationship

Selection optimal dose/schedule

PK/PD modeling of inhibition of S6K1 in patients



Continuous, optimal, target inhibition is predicted to be achievable through the use of daily dosing schedules

Improved Clinical and Cell Cycle Response With an mTOR Inhibitor, Daily Oral RAD001 (Everolimus) Plus Letrozole Versus Placebo Plus Letrozole in a Randomized Phase II Neoadjuvant Trial in ER⁺ Breast Cancer

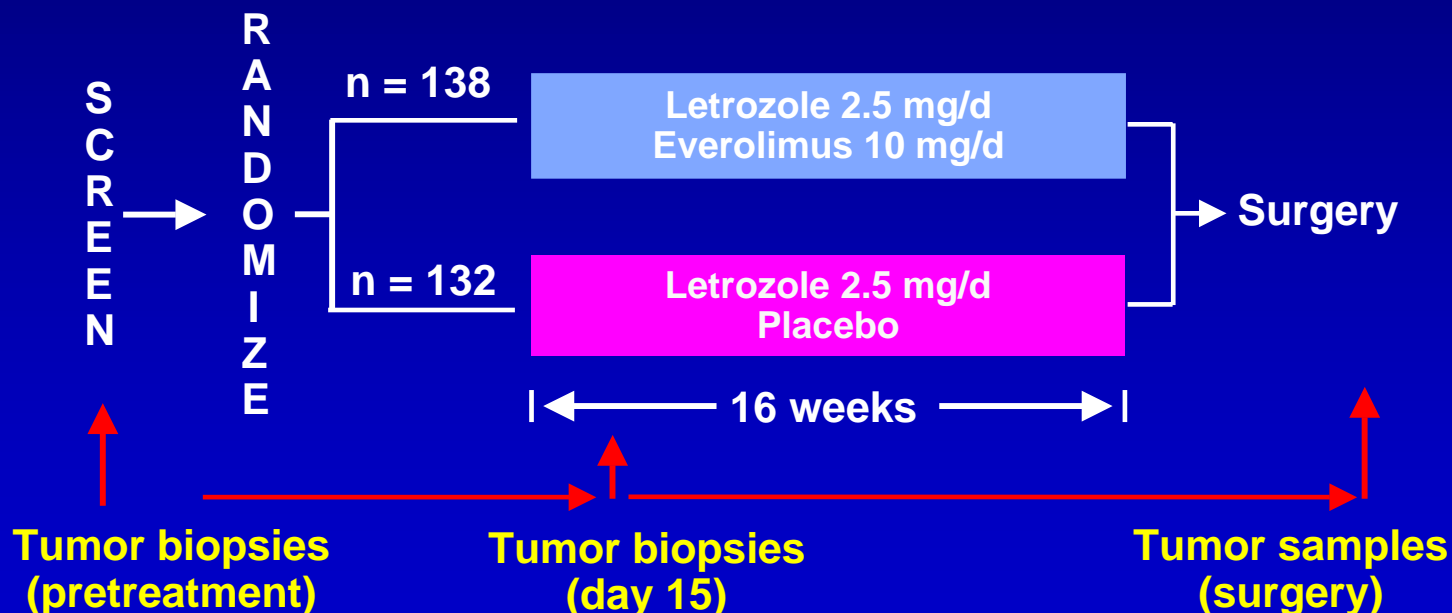
J. Baselga,¹ P. van Dam,² R. Greil,³ H. Gardner,⁴ R. Bandaru,⁴
B. Molloy,⁵ J. Steinseifer,⁵ P. Phillips,⁶ J. M. Dixon,⁷ H. S. Rugo⁸

¹Hospital Vall D'Hebron, Barcelona, Spain; ²Onc Centrum St Augustinus, Wilrijk, Belgium; ³University Hospital, Salzburg, Austria; ⁴Novartis Institutes for Biomedical Research, Cambridge, MA; ⁵Novartis Pharma AG, Basel, Switzerland; ⁶Novartis Pharmaceuticals Corporation, East Hanover, NJ; ⁷Western General Hospital, Edinburgh, United Kingdom; ⁸University of CA SF, San Francisco, CA

Patients and Methods

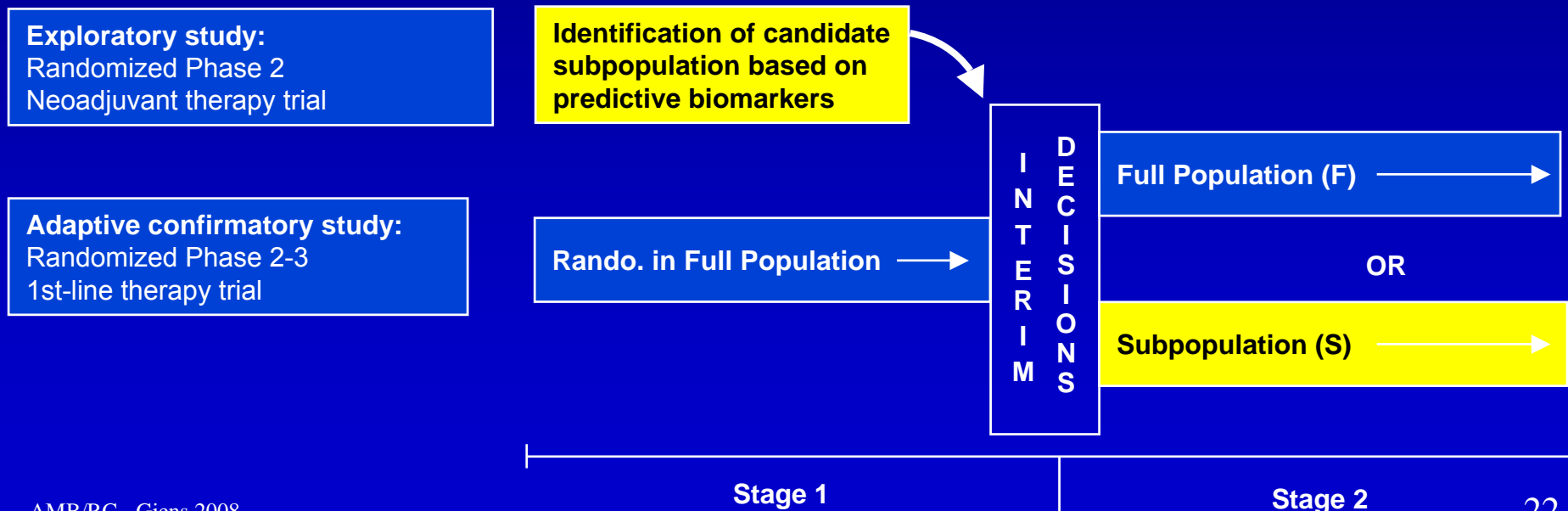
- Study design

- Phase II, randomized double-blind placebo-controlled trial conducted at 68 sites in Europe and the United States



Integration of biomarkers in future confirmatory phase III adaptive design (1)

- Adaptive trial: **two stages, with an interim analysis, to simultaneously meet**
 - **Phase II objectives**
 - to confirm greater benefit in independently identified subpopulation
 - to decide whether or not to adapt trial to focus on that subpopulation
 - **Phase III objective**
 - to demonstrate superiority on time to event (phase III) endpoint



Analytes and Reagents

● Prototype pharmacodiagnostic antibodies

- | | |
|--------------------------|--|
| – Phospho S6 Ser 240/244 | Clone DAK-S6-240, Dako prototype assay |
| – Phospho Akt Ser 473 | Clone 14-5, Dako prototype assay |
| – Cyclin D1 | Clone DCS-6 Dako prototype assay |
| – PTEN | Clone 6H2.1 Dako prototype assay |

● Other assays

- | | |
|--------------------------|---|
| – Phospho S6 Ser 235/236 | Clone 1B2, Cell Signaling Technologies, product 4857 |
| – Estrogen receptor | Clone SP1, Rabbit, Ventana, product 790-4324 |
| – Progesterone receptor | Clone 1E2 Rabbit, Ventana, product 790-2223 |
| – Ki67 | Clone 30-9 Rabbit Ventana, product 790-4288 |
| – AIB1 | BD Transduction Laboratories, product 61105 |
| – p53 | Clone DO-7 Mouse Dako, product M 7001 |
| – Total S6 | Clone 156.17.41, Novartis |
| – Total Akt | Clone E45 1085-1, Rabbit, Epitomics |
| – Her2 FISH | Her2/ <i>neu</i> , Ventana, product 780-2840 |
| – PIK3CA mutation | Surveyor/Wave and direct sequencing of exons 9 and 20 |
| – TP53 mutation | Surveyor/Wave and direct sequencing of exons 5-8 |

Results

Efficacy Summary

Overall Response (CR + PR), %

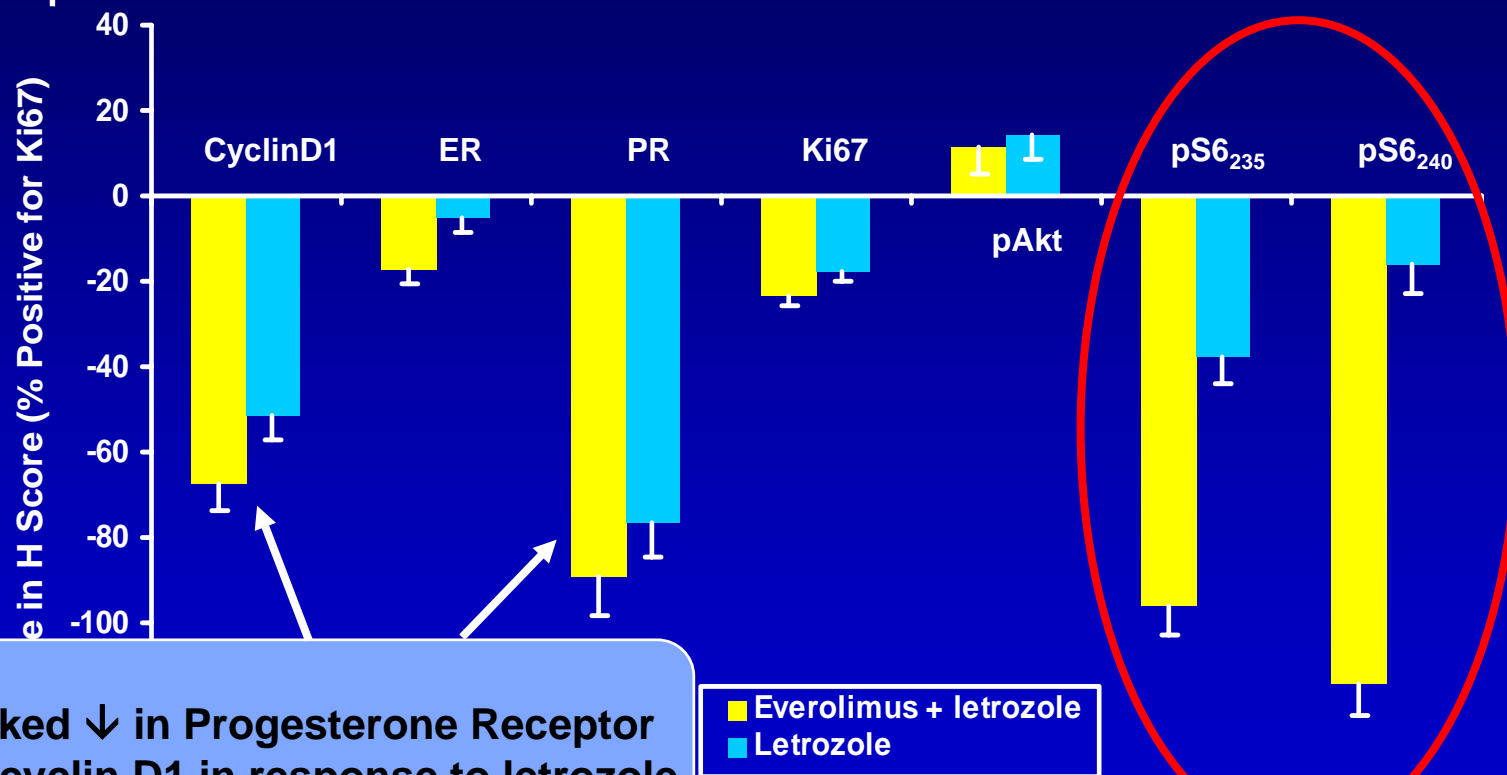
	Everolimus + Letrozole n = 138	Placebo + Letrozole n = 132	<i>P</i>
Palpation (primary end point)	68.1	59.1	.062*
Ultrasound	58.0	47.0	.035*

*1-sided chi-square level of significance is 10%.

Results

Major Pharmacodynamic Changes at Day 15

- Reduction in pS6240 and pS6235 reveals everolimus-treated patients



Marked ↓ in Progesterone Receptor and cyclin D1 in response to letrozole

Phospho. S6 ↓
in response to everolimus

Results

Cell Cycle Response (Ki67)

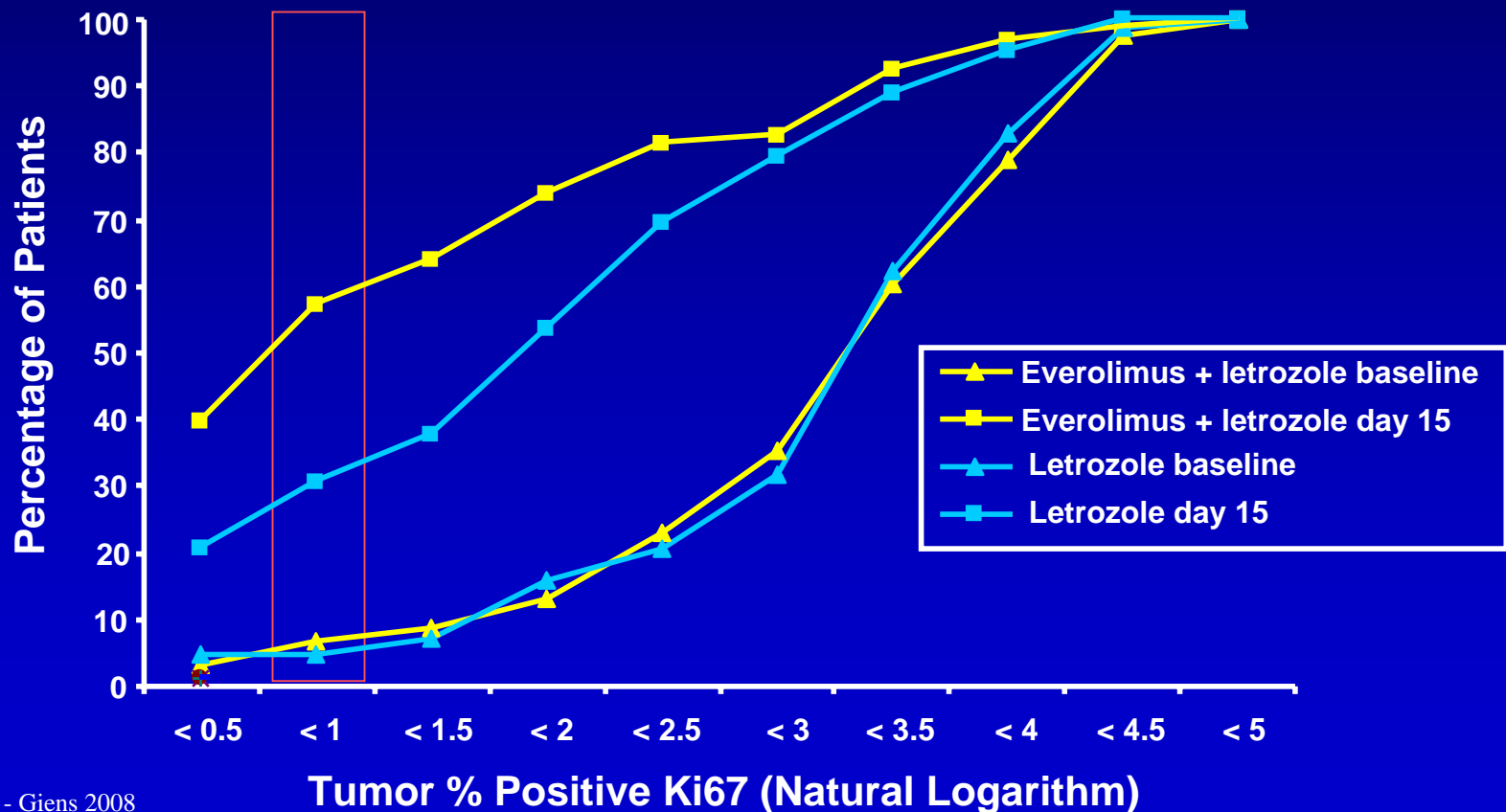
- Ki67 expression was measured in 91 everolimus and 82 placebo patients, from whom an evaluable baseline tumor sample and an evaluable day 15 biopsy were obtained
- Patients with $< 2.7\%$ Ki67⁺ tumor cells (ie, $\ln[\%Ki67^+] < 1$) at day 15 are defined as “cell cycle responders”¹

1. Dowsett et al. *J Natl Cancer Inst.* 2007;99:167-170.

Results

Change in Ki67 Values From Baseline to Day 15

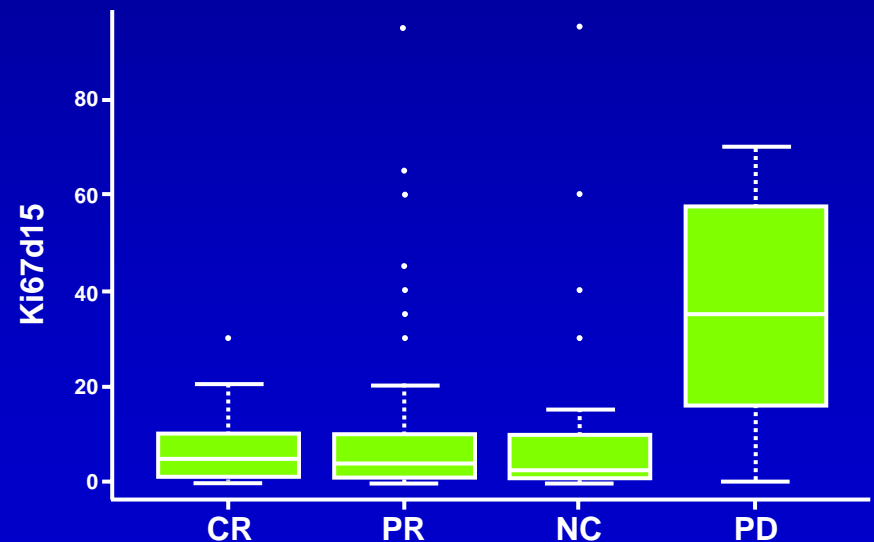
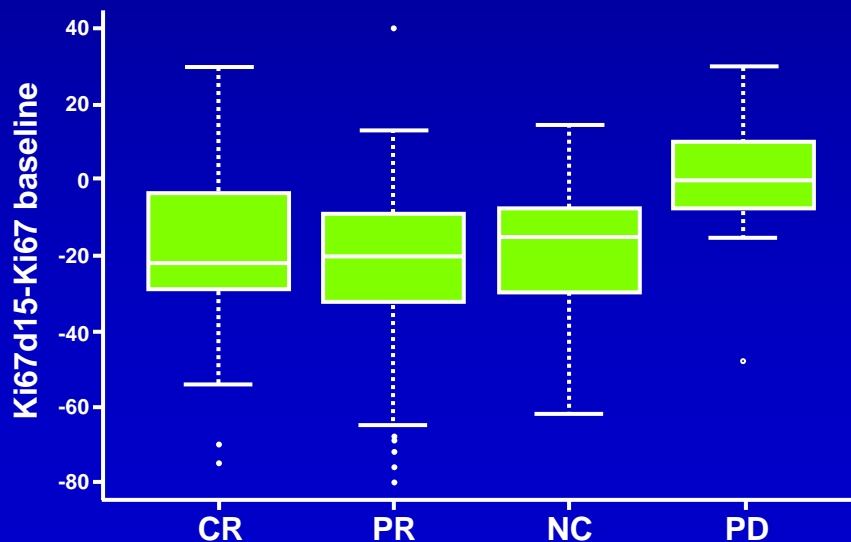
- At day 15, a large difference in Ki67 values is seen between the everolimus + letrozole and the placebo + letrozole arms, which was not seen at baseline



Results

Cell Cycle Response (Ki67)

- Clinical evaluation of response correlates moderately with extent of reduction in Ki67
- Designation of progressive disease correlates well with high proliferation
- However, clinical categorizations are poor predictors of low Ki67 values

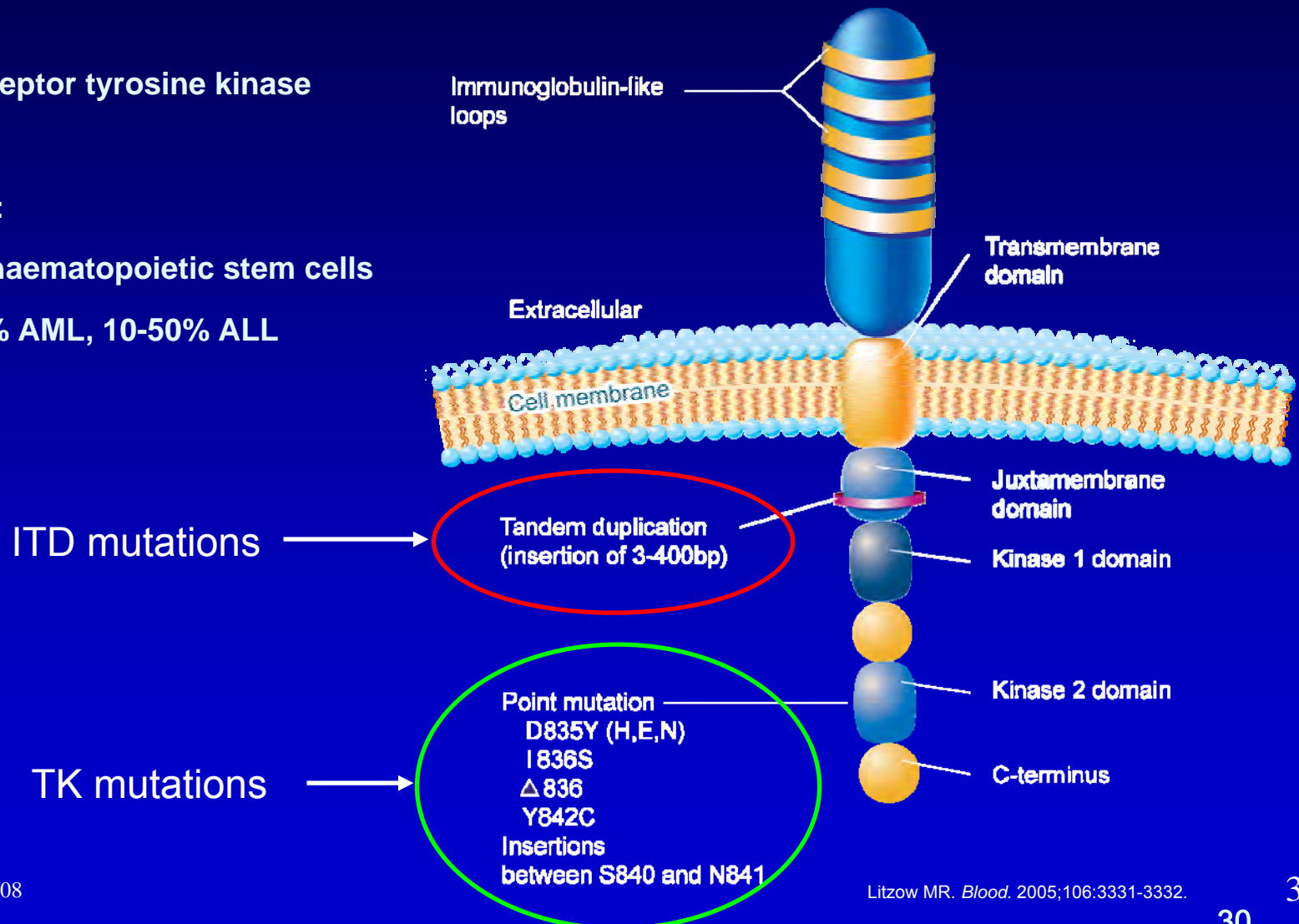


3 Examples

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 - ➡ PCR-based molecular response as primary trial endpoint
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- Midostaurin (FLT3 inhibitor)
 - ➡ FLT3 gene mutations screening to select patients

FLT3 Structure and Activating Mutations

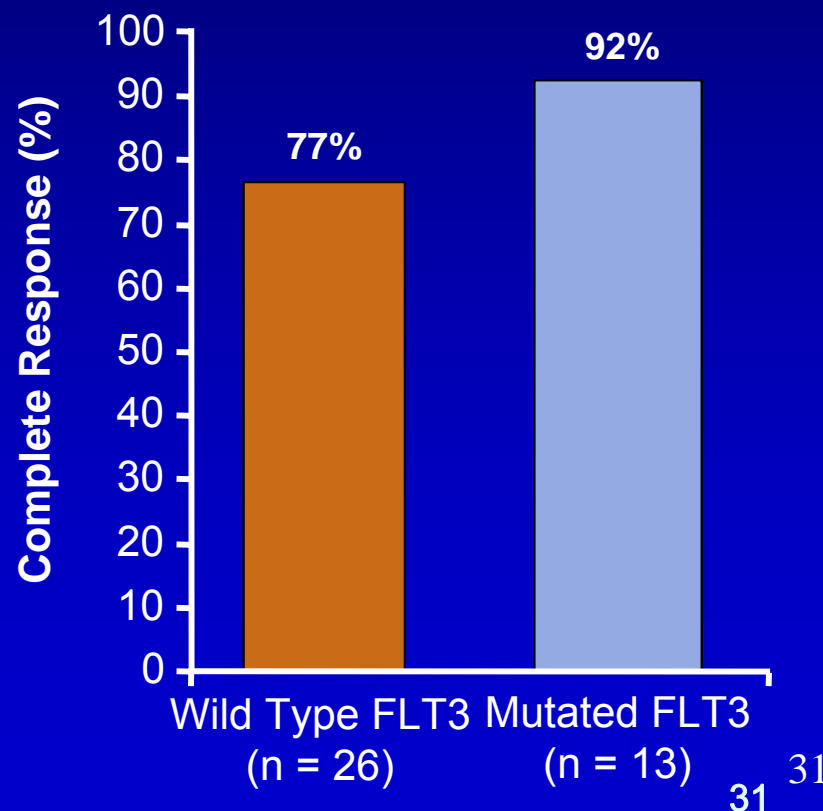
- Class III receptor tyrosine kinase
- Expression:
 - Early haematopoietic stem cells
 - 60-90% AML, 10-50% ALL



Study 2106: Phase 1b Study of Midostaurin (50 mg bid) Plus Chemotherapy: Response

- No significant difference in response rates or duration of remission between the sequential and concomitant schedules
- Midostaurin decreased elimination of daunorubicin but did not appear to interact with cytarabine

Response rate of midostaurin in combination with chemotherapy (N = 39)

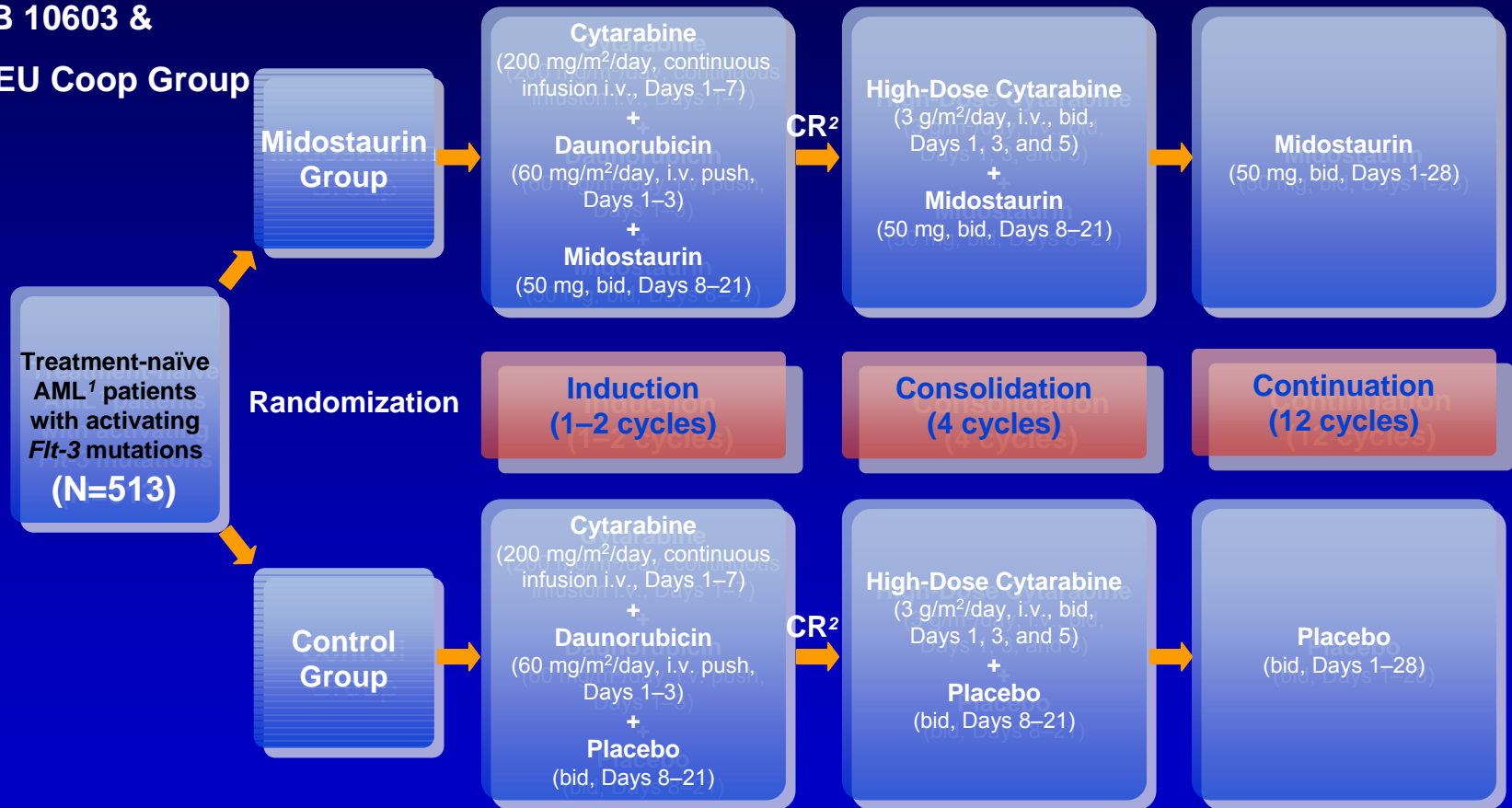


Stone RM, et al. *Blood*. 2006;108:Abstract 157.

RATIFY Trial: Exploring New Treatment Option for High Unmet Need Flt-3 Mutated AML Patients

CALGB 10603 &

Major EU Coop Group



Primary endpoint: overall survival

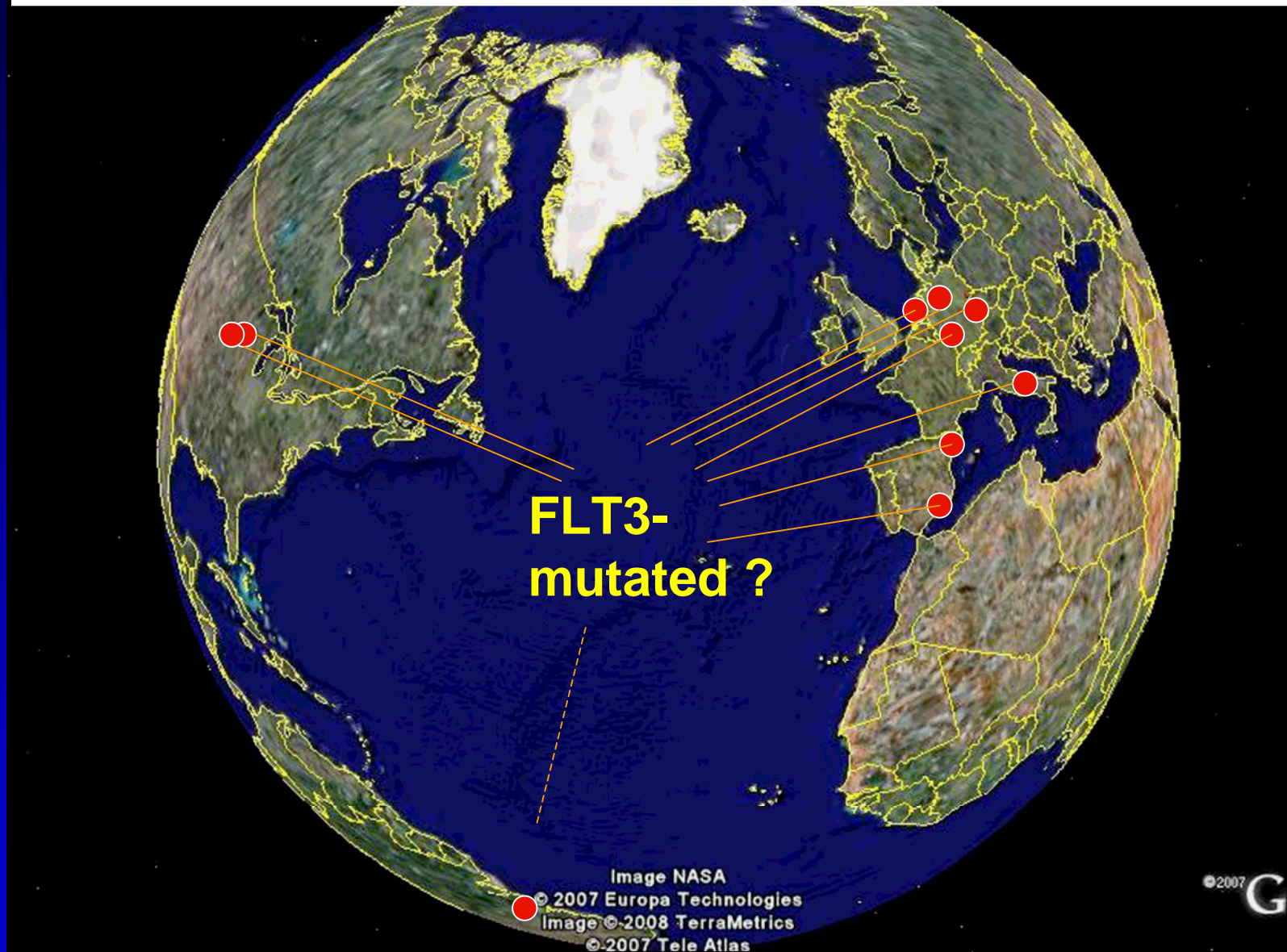
RATIFY: CALGB Intergroup Study (CALGB 10603)



RATIFY: FLT3 Mutation Analysis

- Lab results will specify:
 - FLT3^{WT} or FLT3^{mut}
 - FLT3^{mut} TKD FLT3^{mut} ITD
 - If ITD, allelic ratio (mut to WT) <0.7 or ≥0.7 for stratification

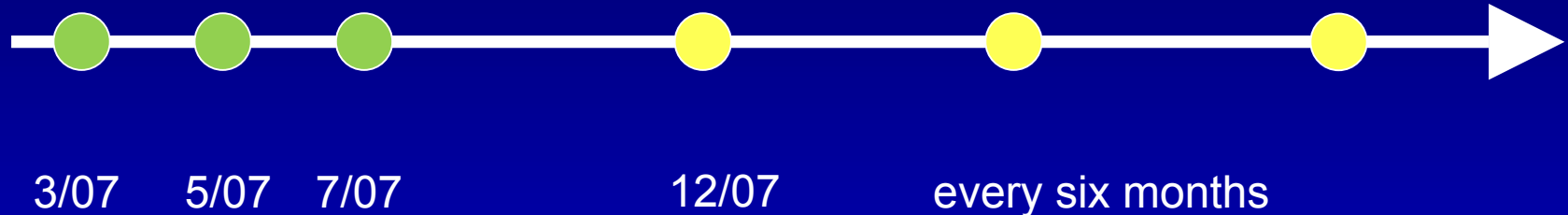
RATIFY: Participating Labs



FLT3-Diagnostics: International Validation

Prevalidation phase

Crossvalidation phase



3 x 11 samples
8 ITD
3 TKD

25 samples

15 ITD

- 5 wt samples
- 5 ITD ratio 0.7
- 5 ITD ratio 0.05

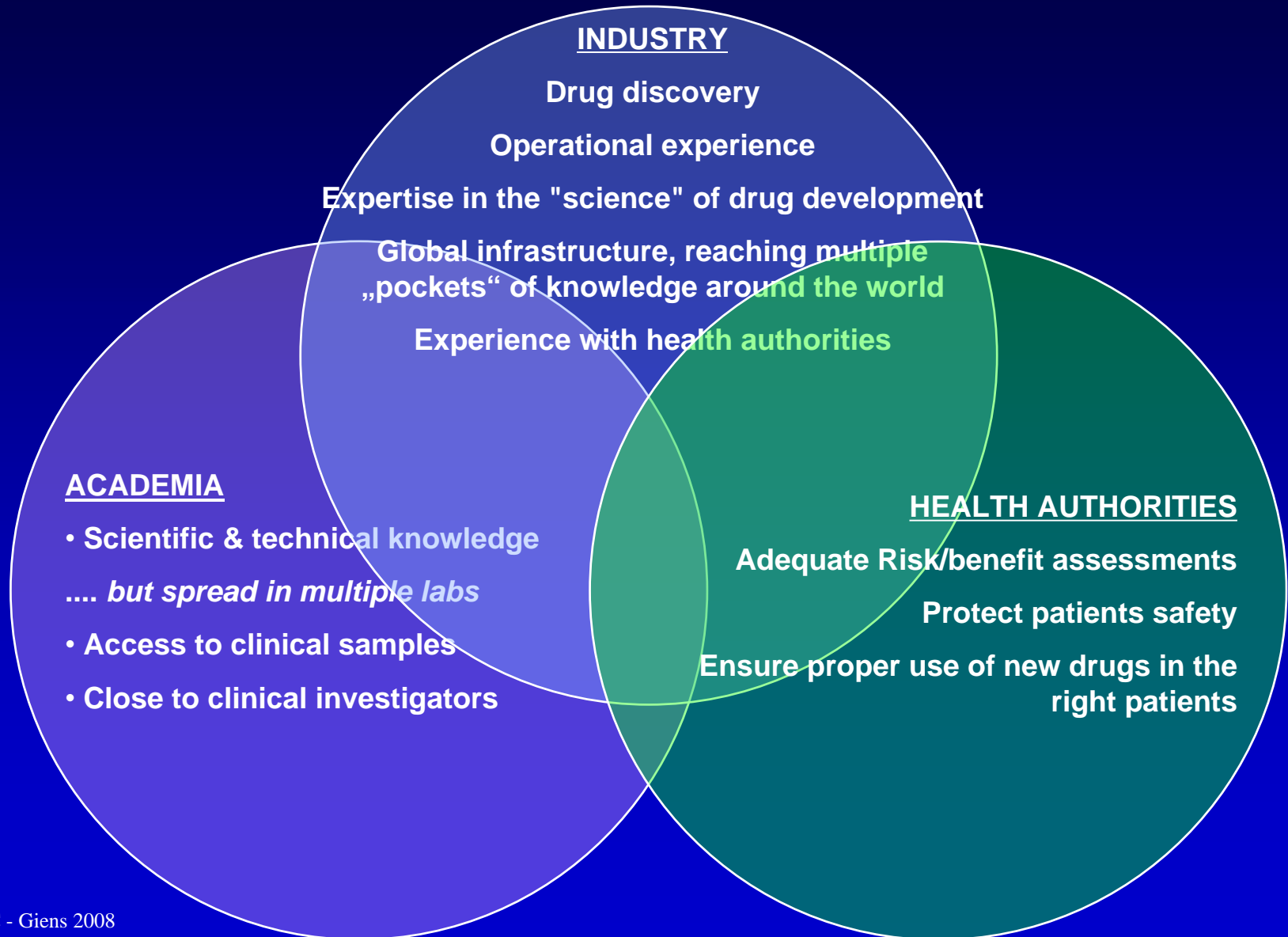
10 TKD

- 5 TKD ratio 0.05
- 5 TKD wt

Conclusion (1)

- Moving an assay from "*proof of the concept*" to large global registration phase III trials is a complex endeavor involving multiple hurdles
- This complexity cannot be underestimated
- Managing this complexity *proactively* is key to successfully develop important targeted anticancer therapies

Connecting knowledge and experience



Conclusion (2)

- The resolution of the challenges of developing and "scaling up" biomarkers provide an ideal platform to optimize industry-academic partnership, exploiting each other expertise

Acknowledgements

- The numerous investigators and scientists, with whom I worked closely on the programs presented here
- The patients, whom by their participation to these trials are contributing enormously to expand our knowledge on the use of anticancer therapies
- The numerous colleagues at Novartis, who helped me assembling the data needed for this presentation

Question

What are the hurdles in moving a "proof of the concept" biomarker research assay into a large scale registration clinical trial ...,

... and subsequently into a clinical management tool?

RAD001 in Breast Ca Ph 2 (NCI-Canada)

Better anti-tumor activity with daily than weekly

