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Innovative phase III trials through Industry/Academic Collaboration: example of the RATIFY/CALGB 10603 study

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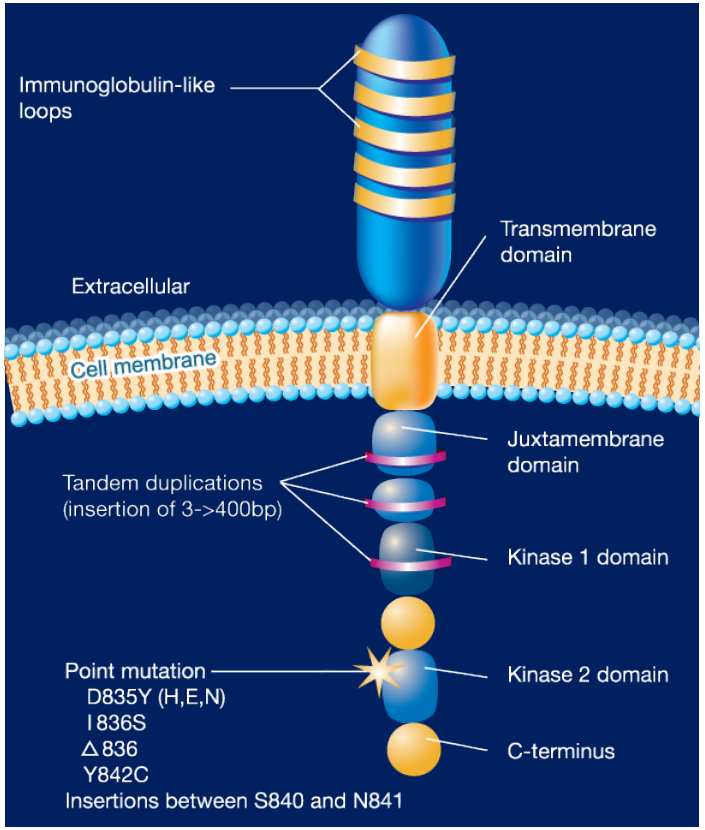
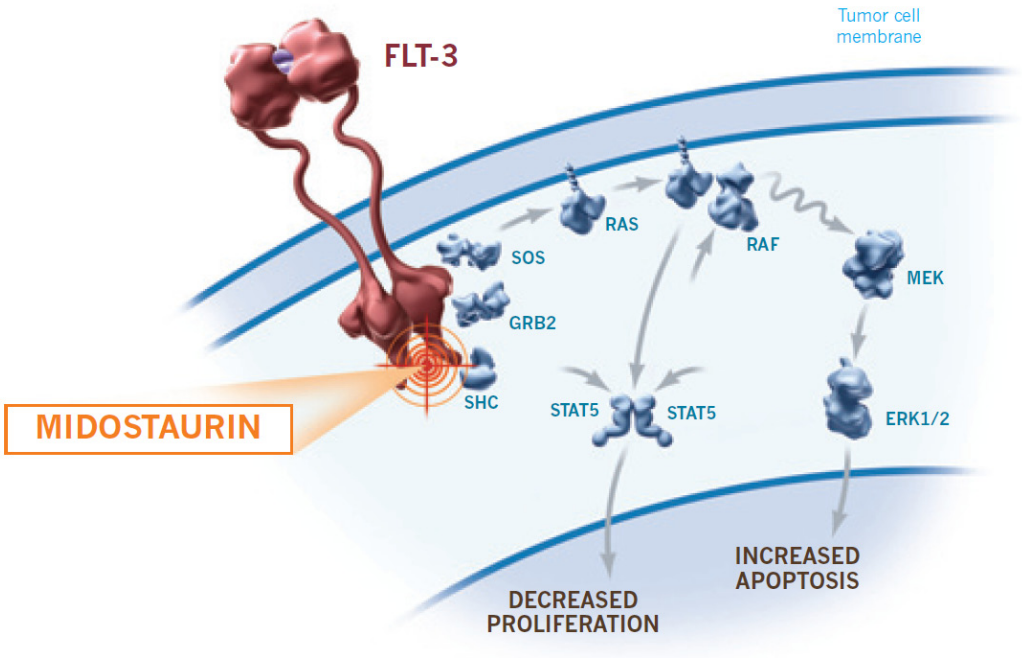
FLT3 Mutations in Acute Myeloid Leukemia

- Constitutive activation of the receptor can be caused by:
  - Internal tandem duplication (ITD)
    - 3 to > 400 base pairs inserted into the receptor in-frame
    - Most often in the JMD but also in the JMD hinge region and the TKD
    - Observed in 17%-25% of adult patients with AML
    - Observed in 11%-22% of pediatric patients with AML
  - Missense mutations in the interkinase domain-activating loop
    - Observed in 8%-12% of adult patients with AML
    - Observed in 3%-7% of pediatric patients with AML
- Presence of the FLT3-ITD mutation has a negative impact on DFS and OS



Midostaurin (PKC412): Multi-target Kinase Inhibitor



- Oral, Multi-target kinase inhibitor
- Potent inhibitor of a spectrum of FLT-3 mutants
- Also inhibits other molecular targets important for AML (VEGFR-2, PDGFR, c-KIT, Pgp-mediated MDR)
- Current development efforts are focusing on FLT3-AML and Agressive Systemic Mastocytosis

Barry EV, et al. Blood. 2007;110(13):4476–4479.
Stone R, et al. J Clin Oncol. 2010 Aug 23. [Epub ahead of print].
Kottaridis PD, et al. Blood. 2001;98:1752–1759.
Stone RM, et al. *Blood*. 2005;105:54-60.

The History of RATIFY/CALGB 10603

- Midostaurin (PKC412)
  - First clinical trial, in healthy volunteers began in 1995
  - Given its broad specificity across many kinases, midostaurin has been investigated in several solid tumors and hematologic malignancies
  - Demonstrated clinical activity in wild-type and FLT3-mutated AML in ph1-2 trials

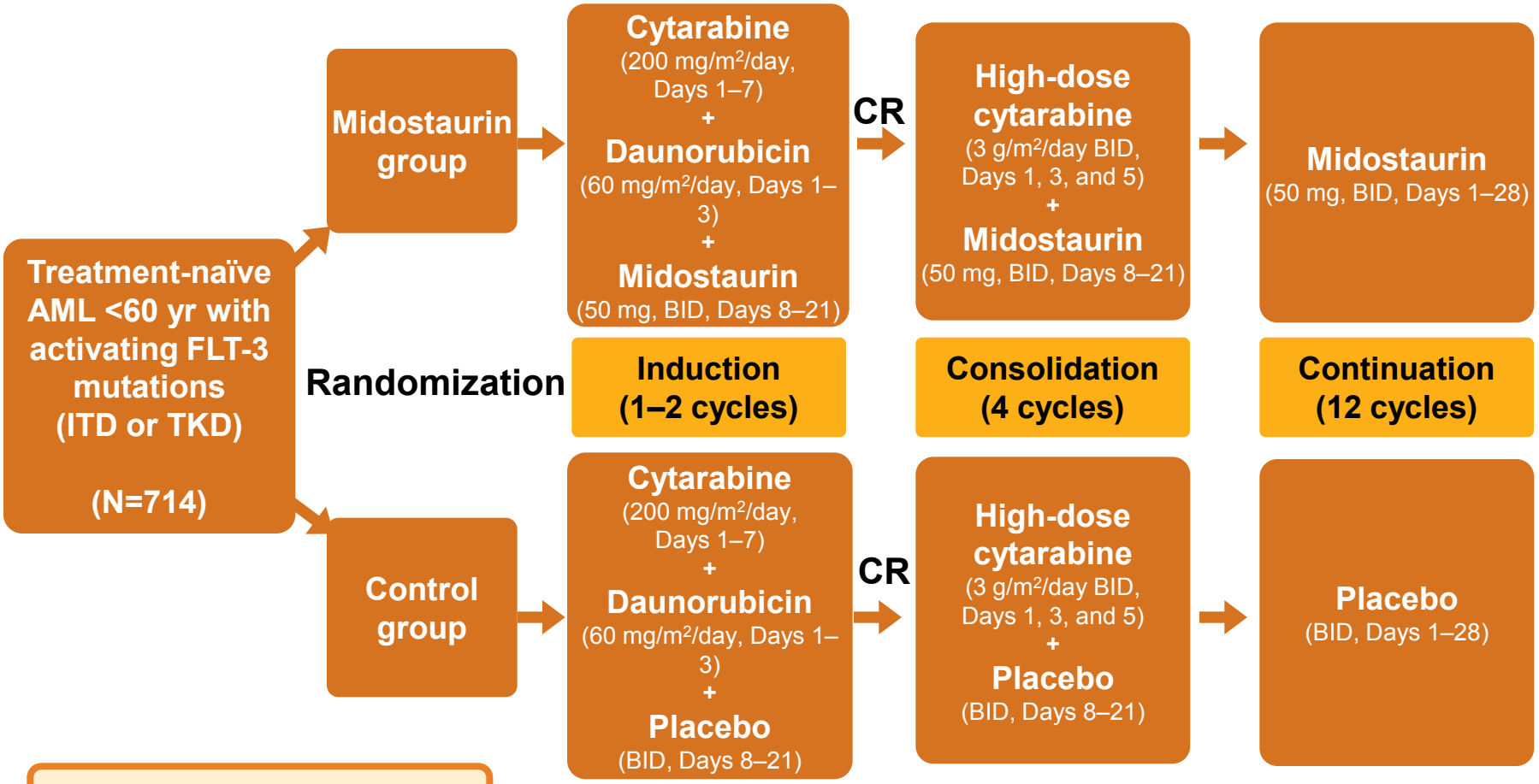
- CALGB and Novartis had mutual interest and complementary resources
  - Midostaurin had demonstrated activity in FLT3-mutated AML
  - Novartis was exploring opportunities for a pivotal phase III trial
  - CALGB had a history of correlative focus on FLT3
  - CALGB had the idea, the trial slot, and the scientific expertise
  - Novartis had the global operational infrastructure to bring together multiple coop groups and centers

Fischer T, et al. *J Clin Oncol*. 2010;28:4339-4345
Stone R, et al. *Leukemia*. 2012;26:2061-2068.

Midostaurin in FLT-3 mutated AML Phase III CALGB 10603 Study

RATIFY
Randomized AML Trial in FLT3 in <60 Year Olds

Stone, et al. ASCO 2011. Abstract #199



- **Primary endpoint: OS**

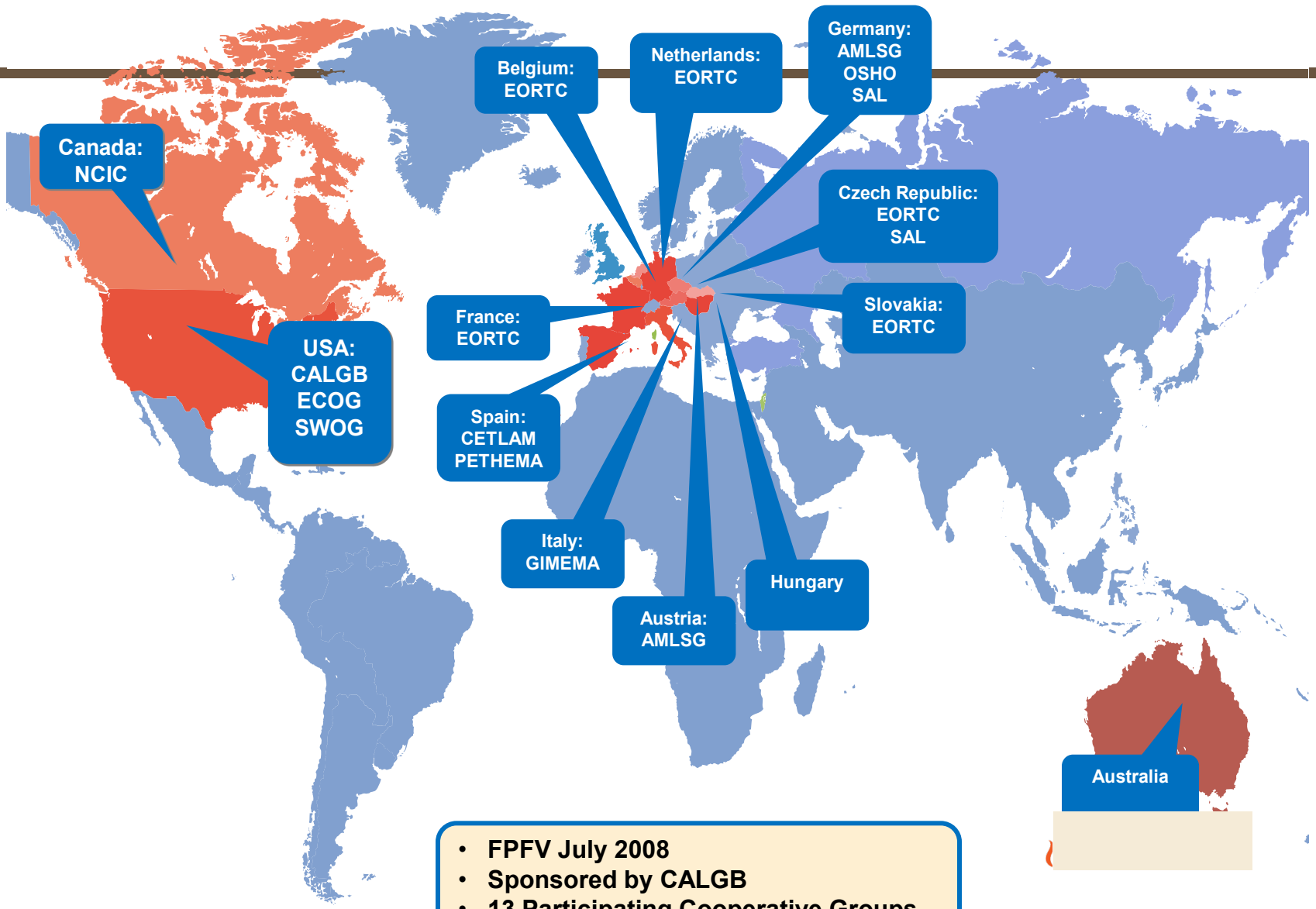
RATIFY primary responsibilities

	CALGB	Other groups	Novartis
Trial sponsor	✔ (North America)		✔ (outside North America)
Site coordination	✔ (North America)	✔	✔ (outside North America)
FLT3 testing	✔	✔	
Protocol author	✔ (principal investigator)	✔	
Database	✔		
DSMB	✔		
Publications	✔	✔	
Regulatory Submission			✔

CALGB 10603

RATIFY

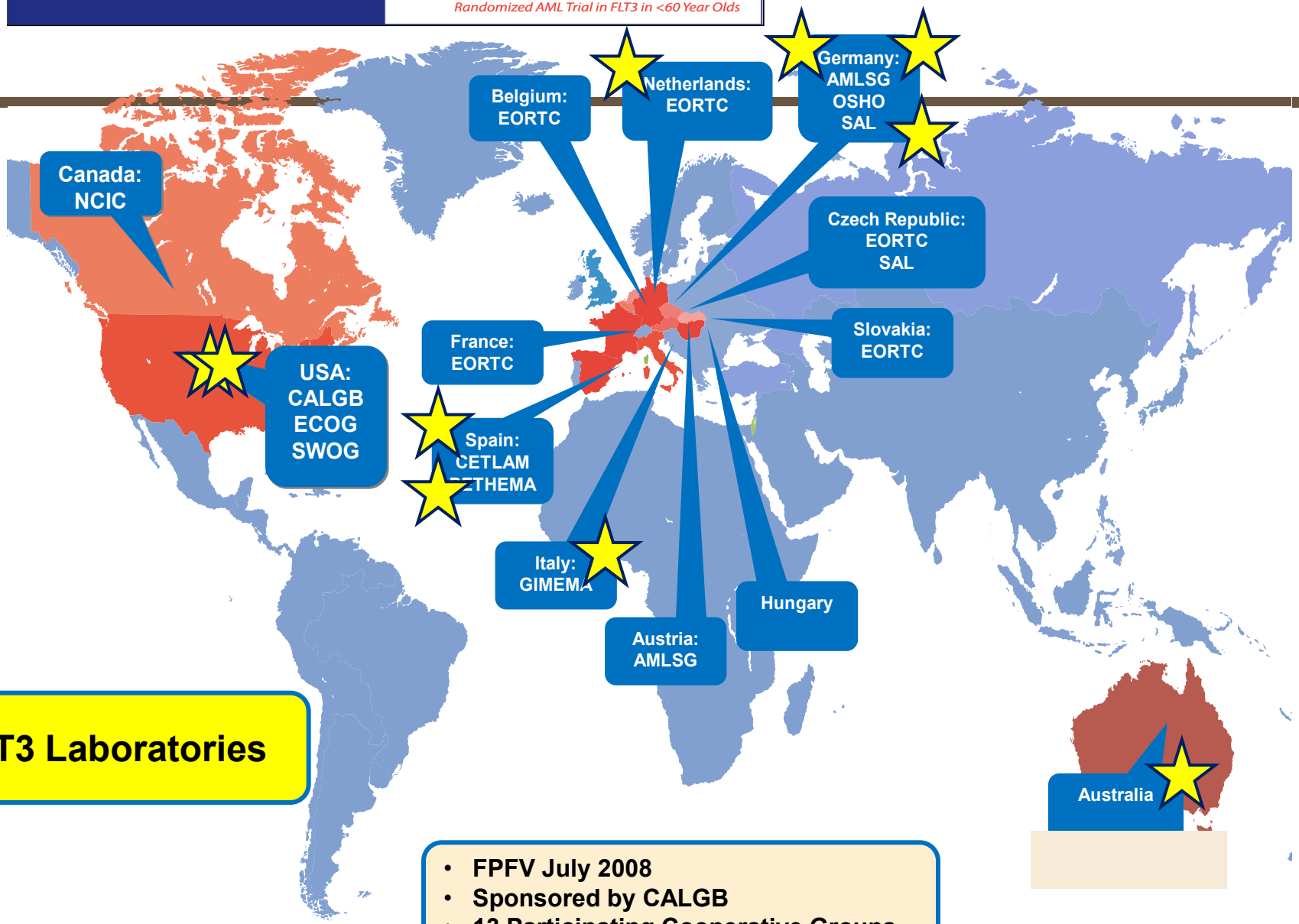
Randomized AML Trial in FLT3 in <60 Year Olds



- FPFV July 2008
- Sponsored by CALGB
- 13 Participating Cooperative Groups

CALGB 10603

RATIFY
Randomized AML Trial in FLT3 in <60 Year Olds

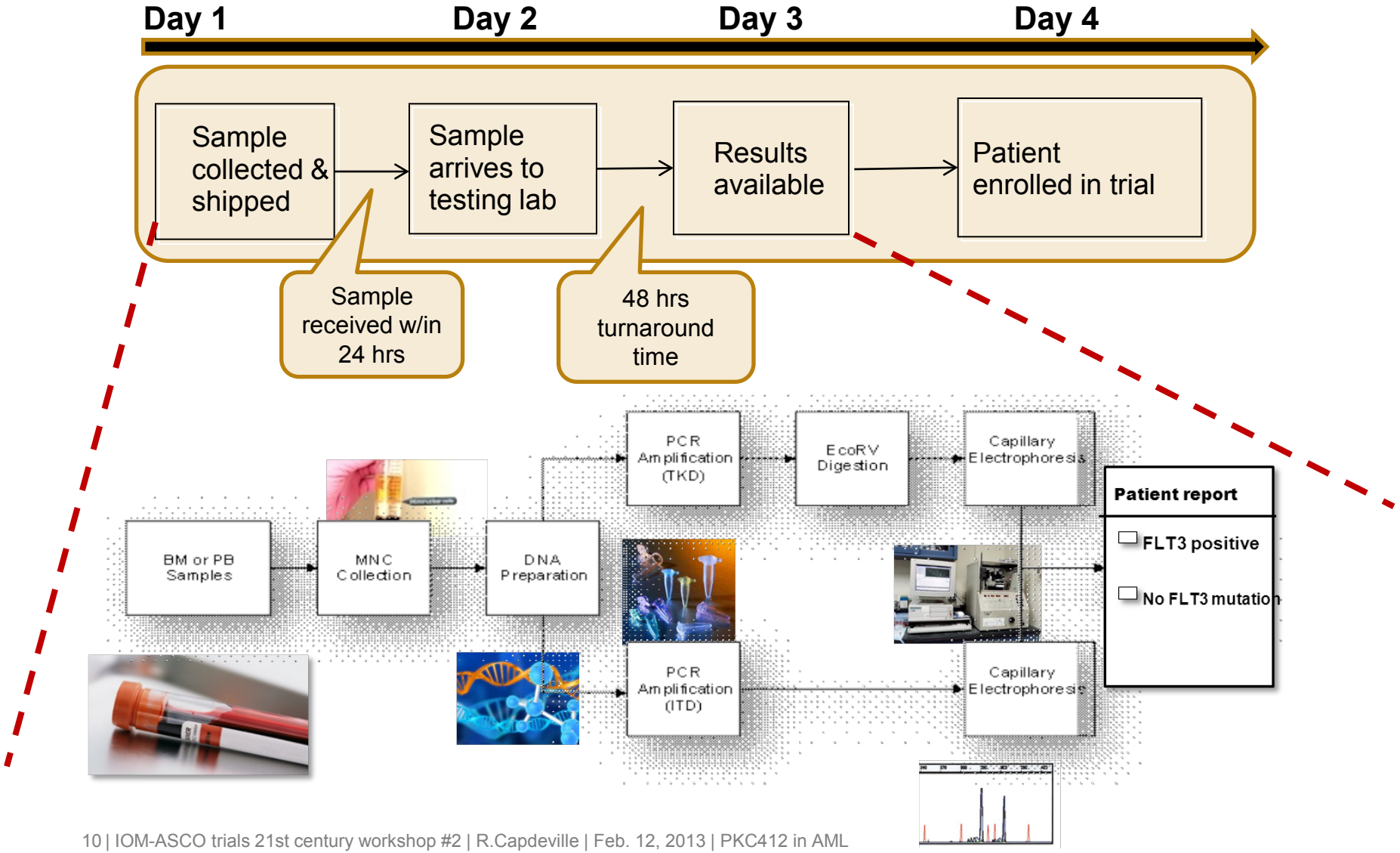


FLT3 Laboratories

- FPFV July 2008
- Sponsored by CALGB
- 13 Participating Cooperative Groups

RATIFY patient FLT3 screening within 3 days

Use of a common protocol across testing laboratories



Clinical Trial Assay (CTA) versus Companion Diagnostic (CDx)

- Clinical trial assays (CTA) and companion diagnostics (CDx), have to meet different technical and regulatory requirements even if the same methods are used.
- The commitment to develop a CDx assay at a later stage in drug development results in the need to bridge the CTA assay to the CDx version of the assay
  - Need to ensure sample collection/consent for CDx testing
  - Conduct of a rigorous bridging study to assess the concordance in the CTA/CDx results

Accomplishments – What Worked Well

RATIFY
Randomized AML Trial in FLT3 in <60 Year Olds

- Common goal – novel lifesaving therapy for patients
- 3277 AML patients screened (July 08 – March 11)
  - 719 patients (22%) randomized globally
  - Efficiency of FLT3 screening: main CALGB lab (OSU) average turn around time 26.3 hours upon receipt of sample
- Areas of specialized research focus were allowed
  - Cytogenetic research samples set aside
- Joint clinical trial team overseeing day-to-day operations

Challenges

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Randomized AML Trial in FLT3 in <60 Year Olds

- Need to integrate different perspectives: academic interest in improving standard of care versus regulatory submission
- RATIFY has high operational complexity due to:
  - The involvement of 13 cooperative groups at a global level
  - The need for a quick turnaround for the results of FLT3 screening prior to randomization
- A registration study adds many additional requirements to the usual regulatory obligations governing the conduct of clinical studies

  Examples:
  - Single phase III trial as a pivotal component of a complex NDA; safety reporting; monitoring and auditing
  - Clinical Trial Assay requiring bridging to a Companion Diagnostic to be co-submitted for approval along with RATIFY

Learnings

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Randomized AML Trial in FLT3 in <60 Year Olds

- Keep data flow simple where possible
- Importance of an open collaboration and defined joint study team
  - Clearly outline expectations and requirements of each partner
  - Be open for innovative approaches in managing operations
- Need to find the right balance between independence in the academic oversight of the trial and the need to have a well-functioning joint operational management of the trial on a day-to-day basis

Concluding Thoughts

RATIFY
Randomized AML Trial in FLT3 in <60 Year Olds

- Conduct of large phase III trials in a rare, & molecularly-defined patients population requires large and complex collaborations at a global level
- Such trials involve the integration of multiple scientific, clinical, statistical, technical, regulatory, and operational capabilities
- Cooperative groups and pharmaceutical industry organizations have complementary skills which can be leveraged to deliver this kind of innovative trials