La LMC oltre i TKIs

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Background

- Thanks to TKIs, in our days the OS of most CML patients is expected to be similar to that of a control population without leukemia

- The majority of them however is bound to a life-long therapy with TKIs

The Goal of CML therapy is moving (?)

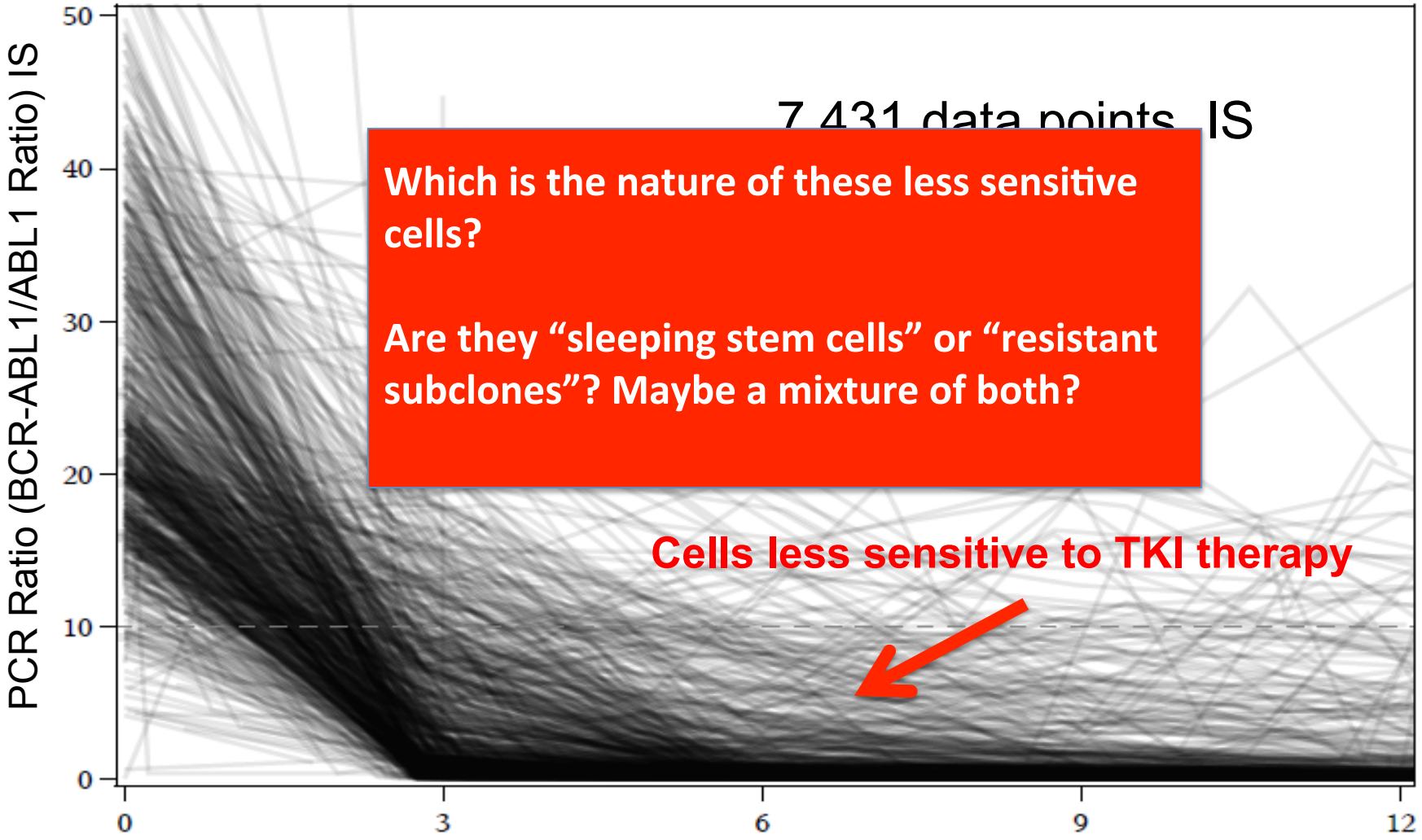
Disease control- Best OS

- A return to your normal life expectancy in the presence of on-going treatment?

Operational cure

- No evidence of disease in the absence of treatment – treatment free remission (TFR)

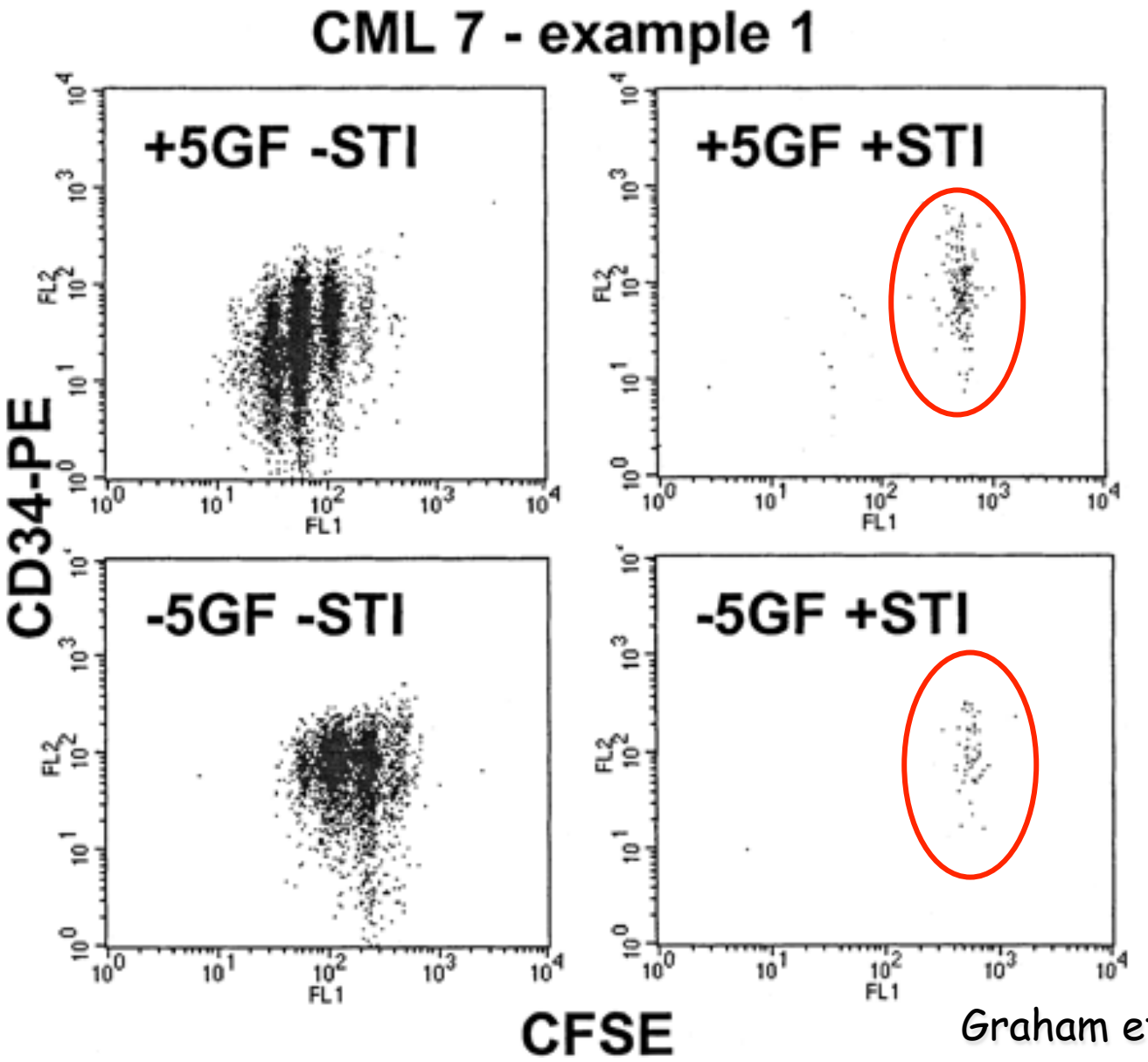
PCR data: all patients, both arms



SPIRIT 2
STI571 Prospective International Randomised Trial

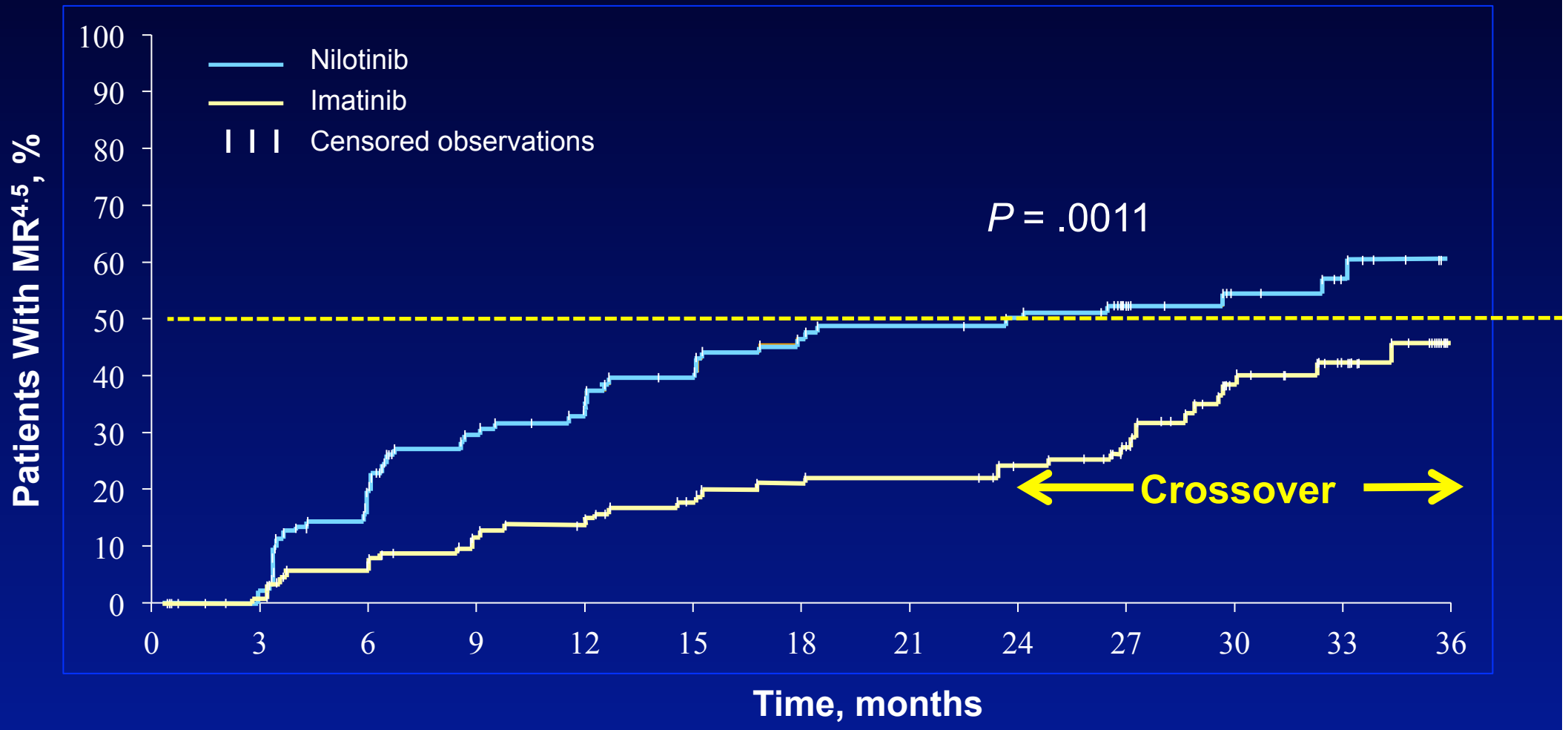
Courtesy of Stephen O’Brian

Primitive quiescent BCR-ABL+ leukemic stem cells are less sensitive to imatinib



Graham et al. Blood 2002

ENESTcmr - Time to Achievement of First $MR^{4.5}$



- Median time to $MR^{4.5}$ was accelerated by more than 1 year in the nilotinib arm (24 months versus not reached in the imatinib arm; $P = .0011$)

Leber B, et al. *Blood*. 2013:[abstract 94].

Methods to Overcome the Resistance of Ph+ Progenitors

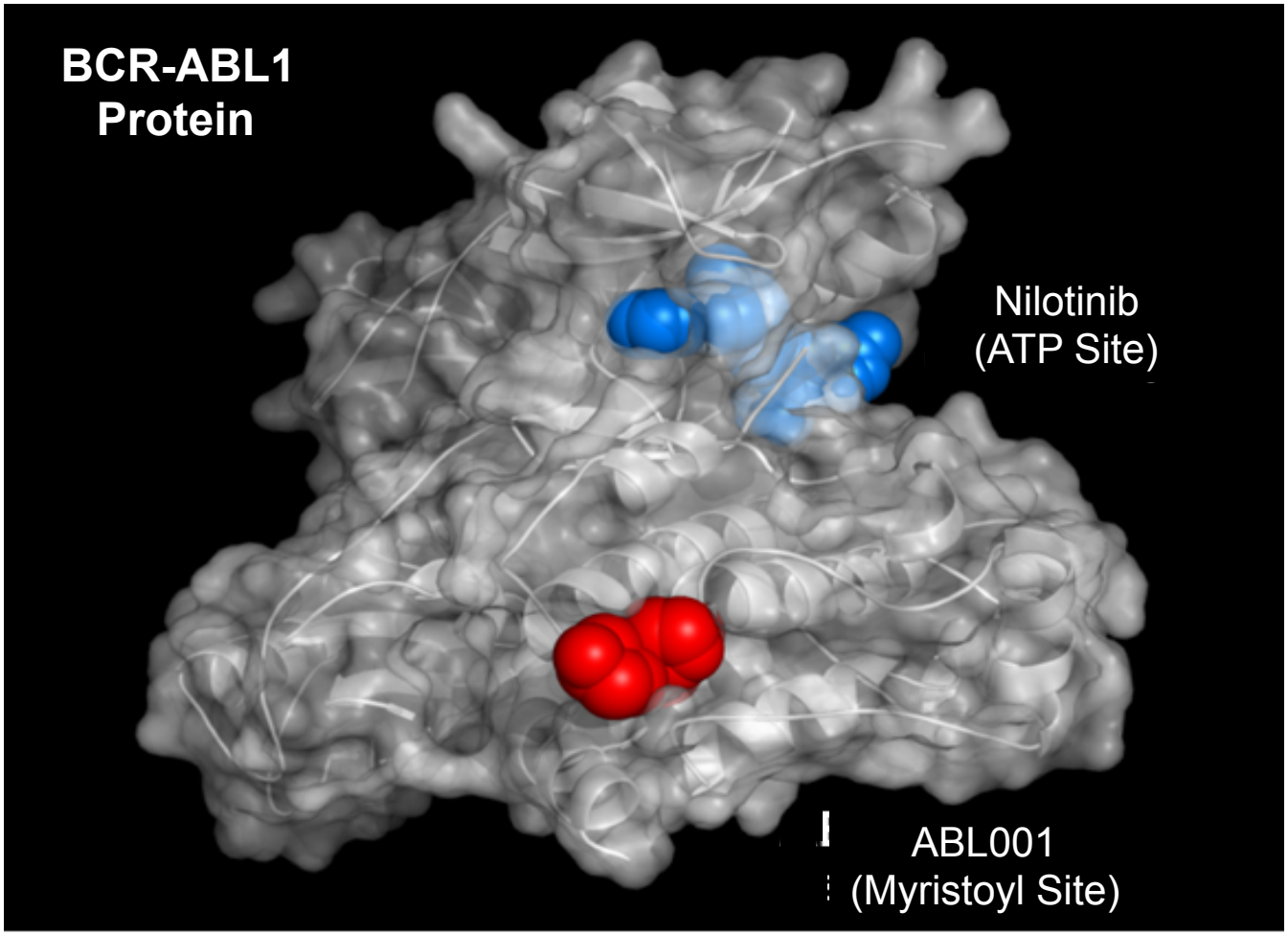
- To hit the molecular pathways implicated in their resistance
- To change the natural environment in which they can survive
- To exploit some phenotype differences with respect to their normal counterpart

Combination therapy

- TKIs of BCR-ABL with different mechanisms of action
- Drugs affecting molecular pathways other than BCR-ABL

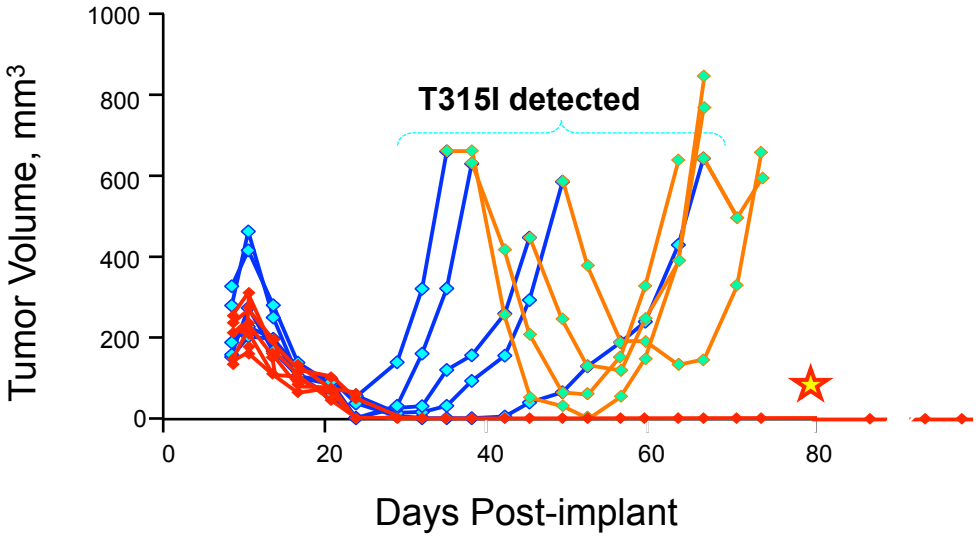
ABL001 Is a Potent, Specific Inhibitor of BCR-ABL1 With a Distinct Allosteric Mechanism of Action

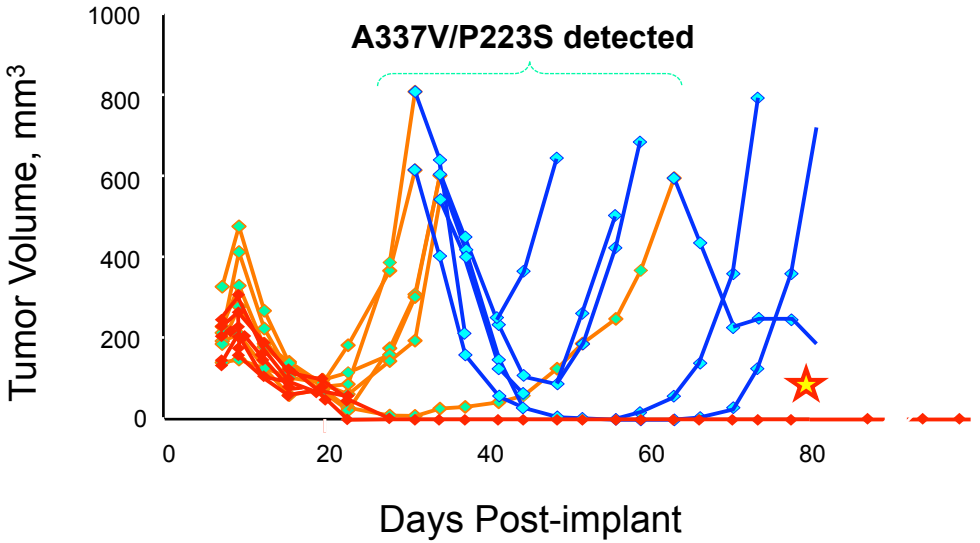
- Developed to gain greater BCR-ABL1 inhibition, with activity against BCR-ABL1 mutations conferring resistance to TKIs
- Potential to combine with TKIs for greater pharmacological control of BCR-ABL1



Ottmann O, et al. *Blood*. 2015:[abstract 138].

Combination of ABL001 and Nilotinib Prevents the Emergence of Resistance (KCL-22 CML Xenograft)[a]





Nilotinib (75 mg/kg) BID

ABL001 (30 mg/kg) BID

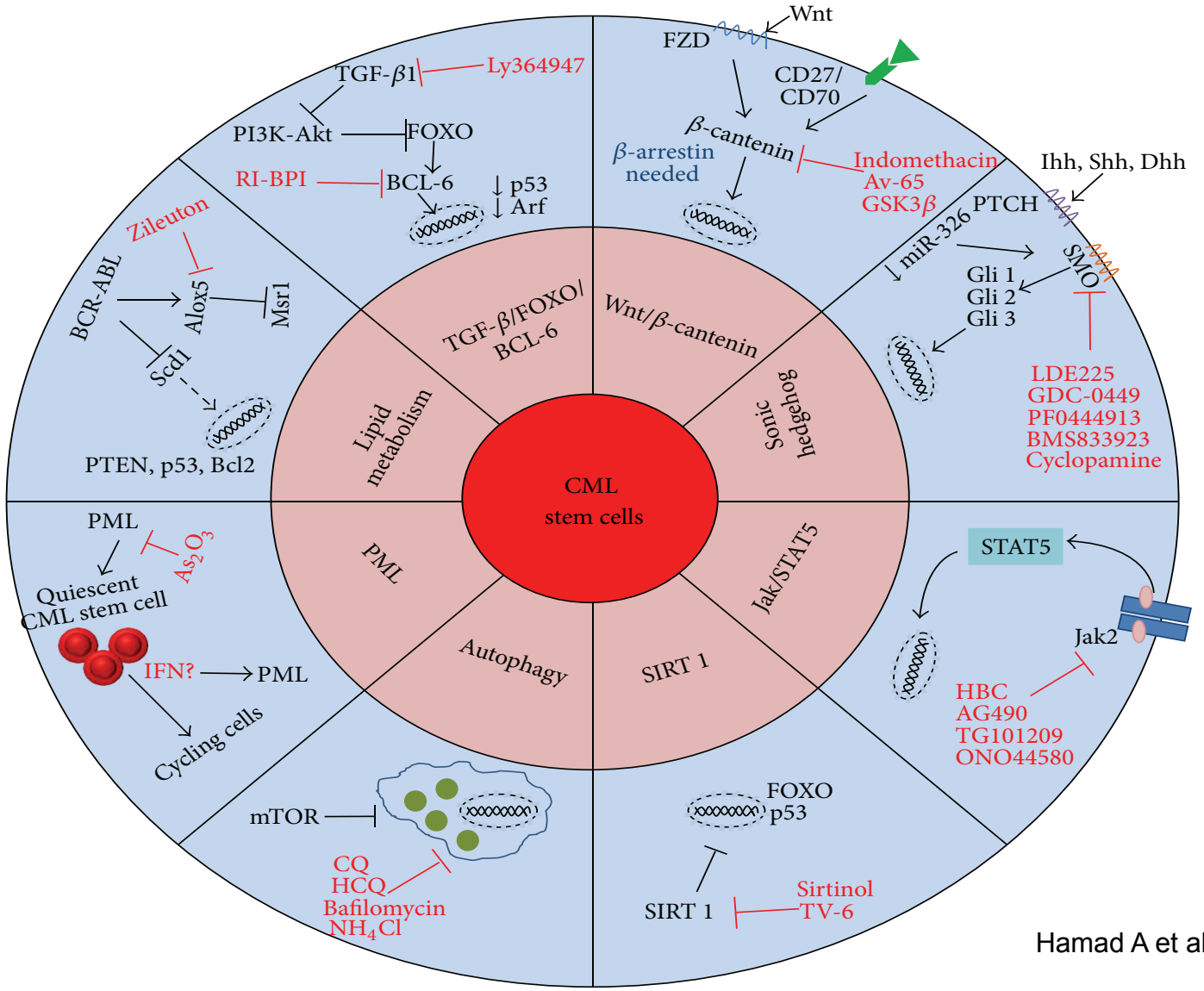
Nilotinib (75 mg/kg) BID + ABL001 (30 mg/kg) BID

Dosing stopped on day 77, all mice remain disease free > 176 days

[a] Each line represents individual animals.

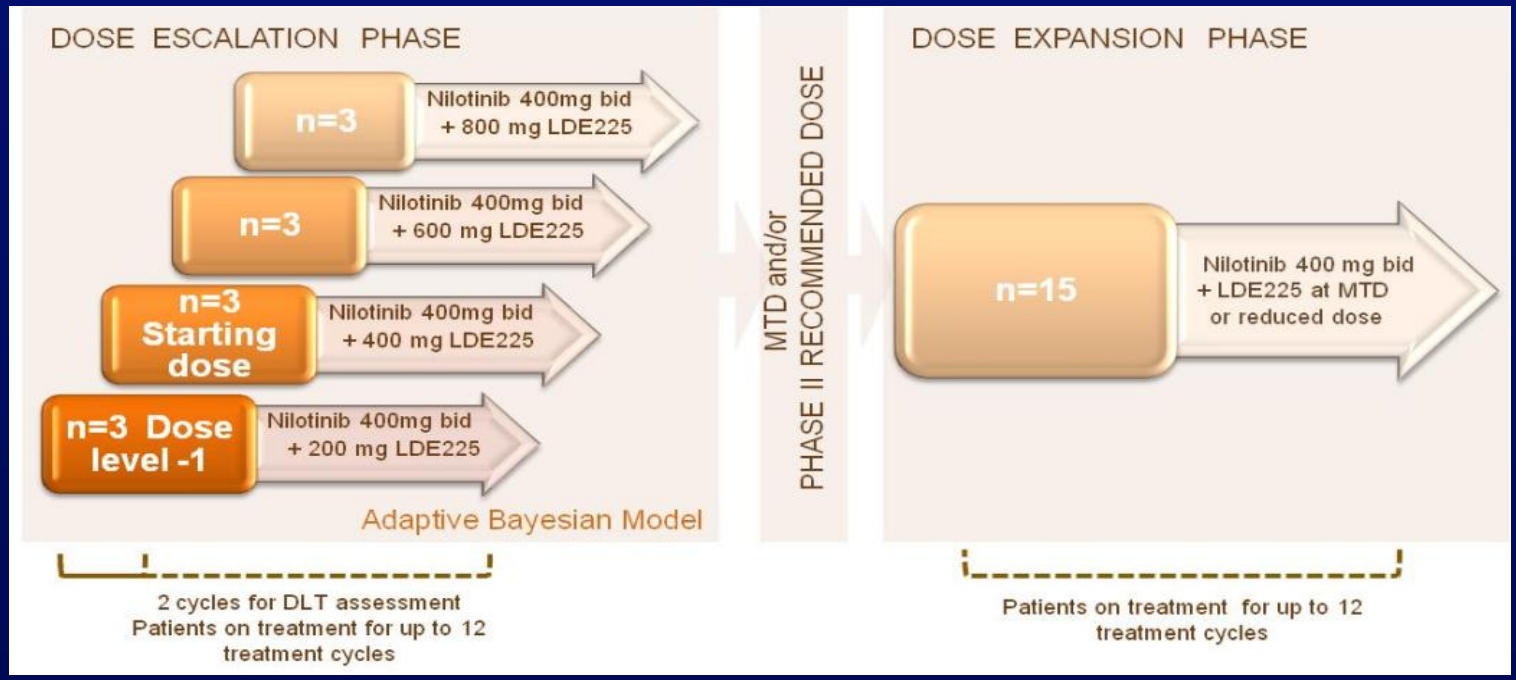
Wylie A, et al. *Blood*. 2014:[abstract 398].

Several strategies to hit pathways preferentially activated in LSCs with respect to NSCs



Hamad A et al. Stem cell int 2013

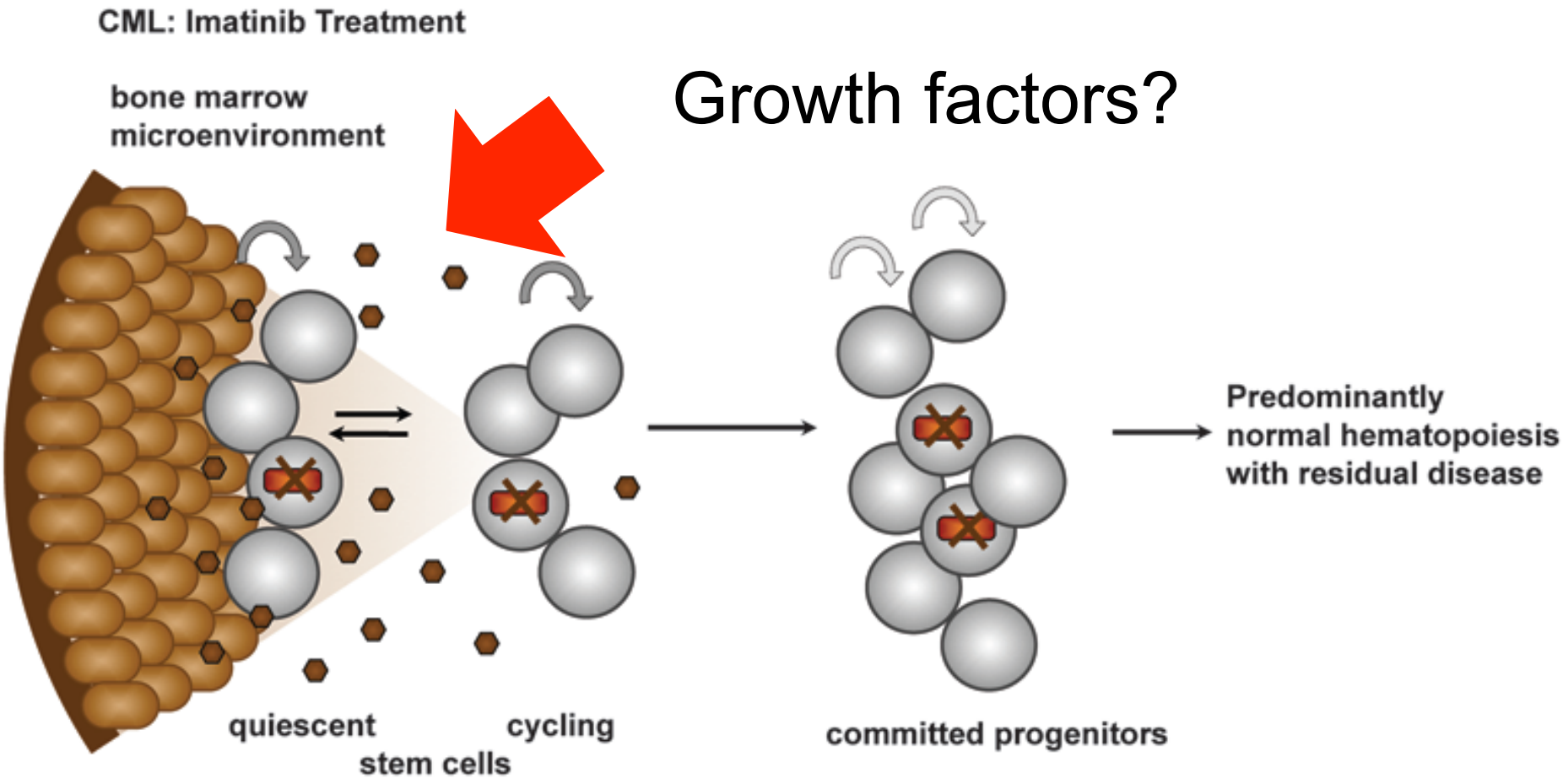
Single-arm Dose-finding Phase Ib Multicenter Study of the Oral Smoothened Antagonist LDE225 in Combination With Nilotinib in CML-CP Patients Who Have Failed Other TKIs (CAMN107Y2101)



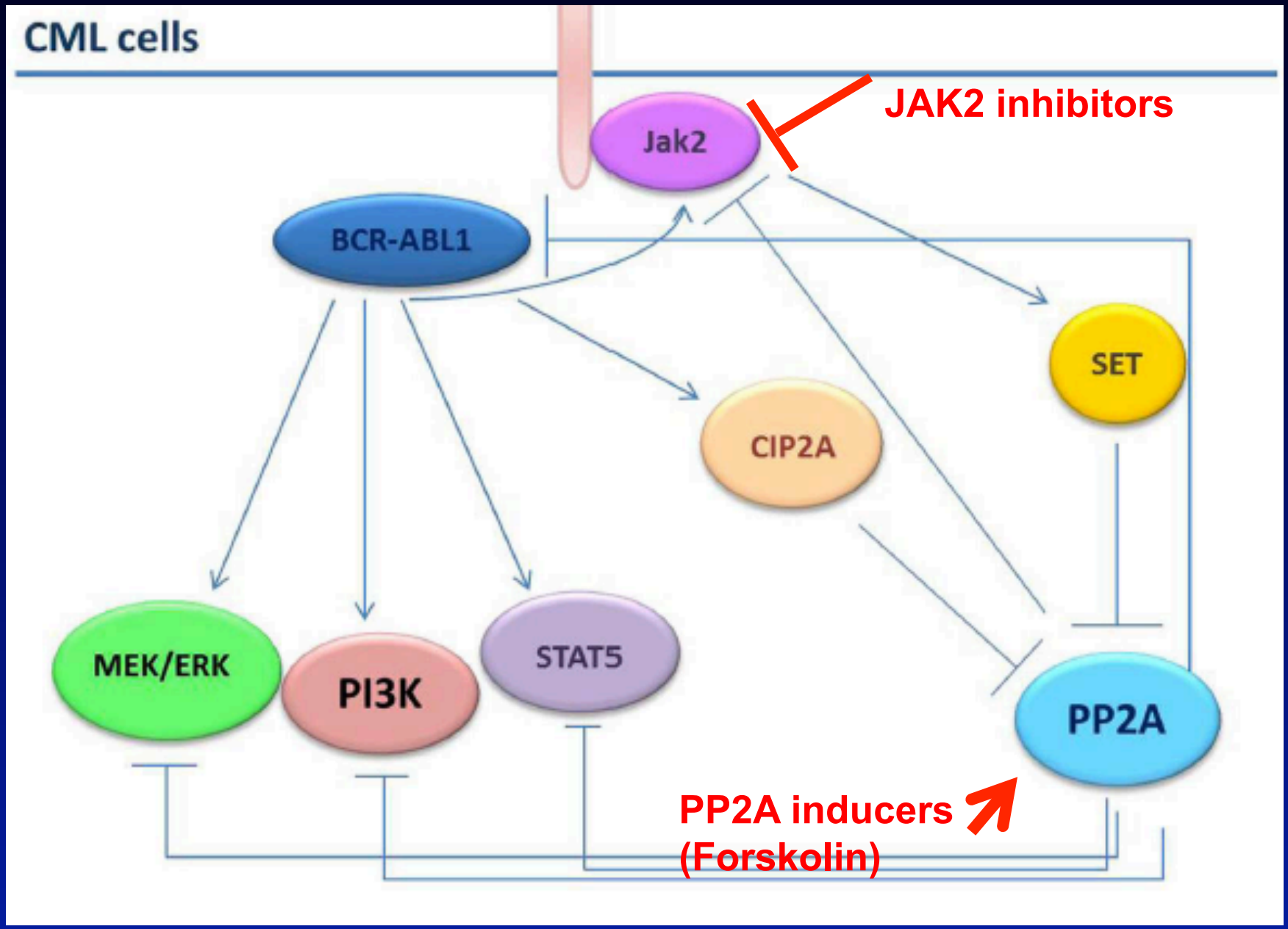
- CML-CP patients who failed prior therapy with other BCR-ABL inhibitors
- Primary outcomes:
  - Incidence rate and category of DLTs
  - Determination of MTD and/or recommended Phase II dose combinations of nilotinib with LDE225
- Secondary outcomes:
  - Rate of MMR, CMR, MCyR, CCyR
  - PK

http://clinicaltrials.gov/show/NCT01456676.

The Hematopoietic Niche Can Provide Support to CML Progenitor Cells Survival

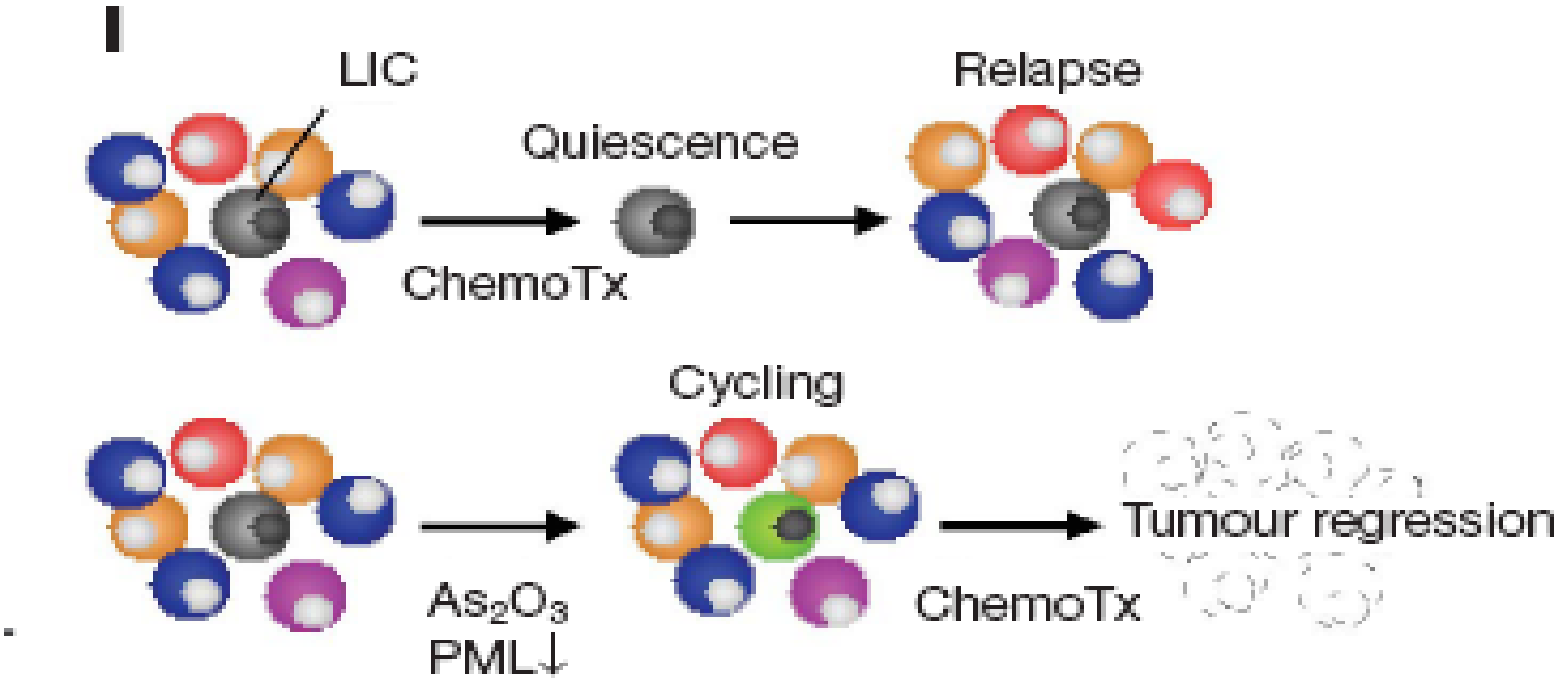


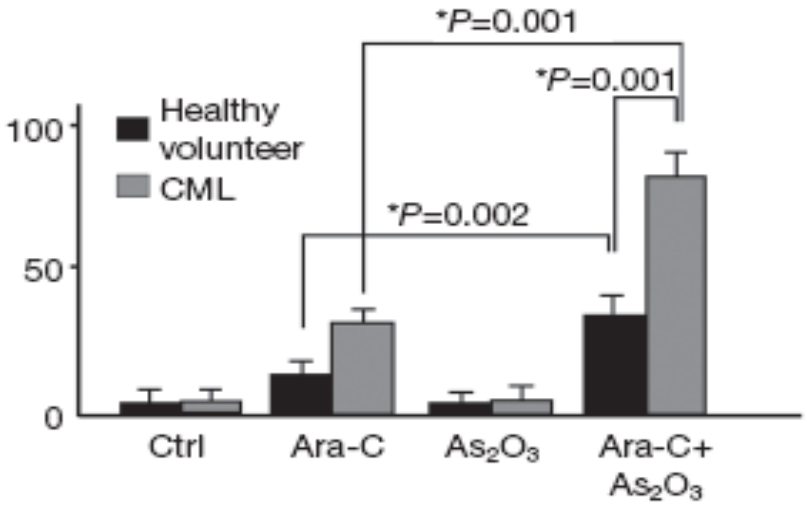
Corbin AS et al., 2011



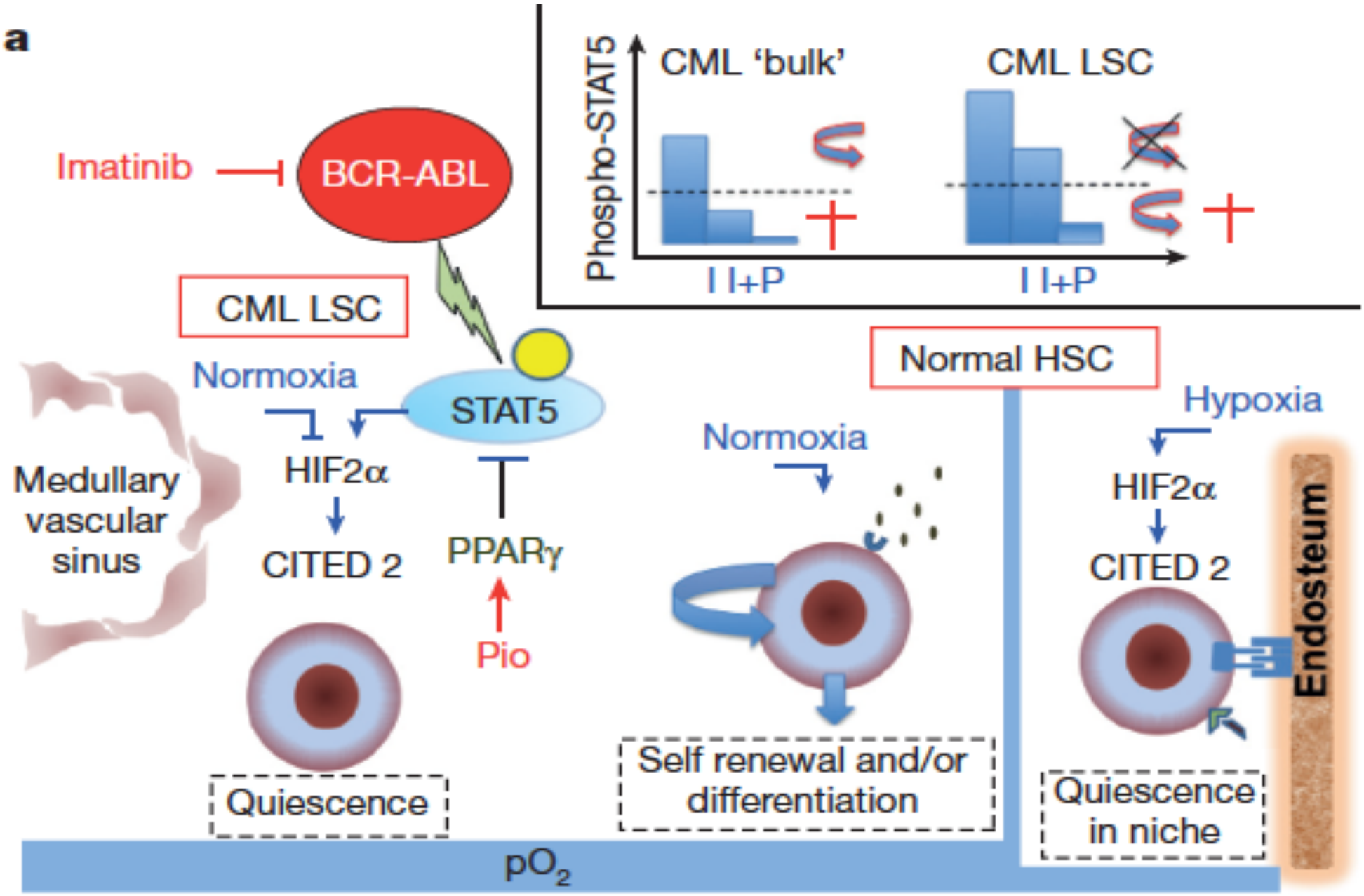
Courtesy of Danilo Perrotti

ATO decreases PML expression

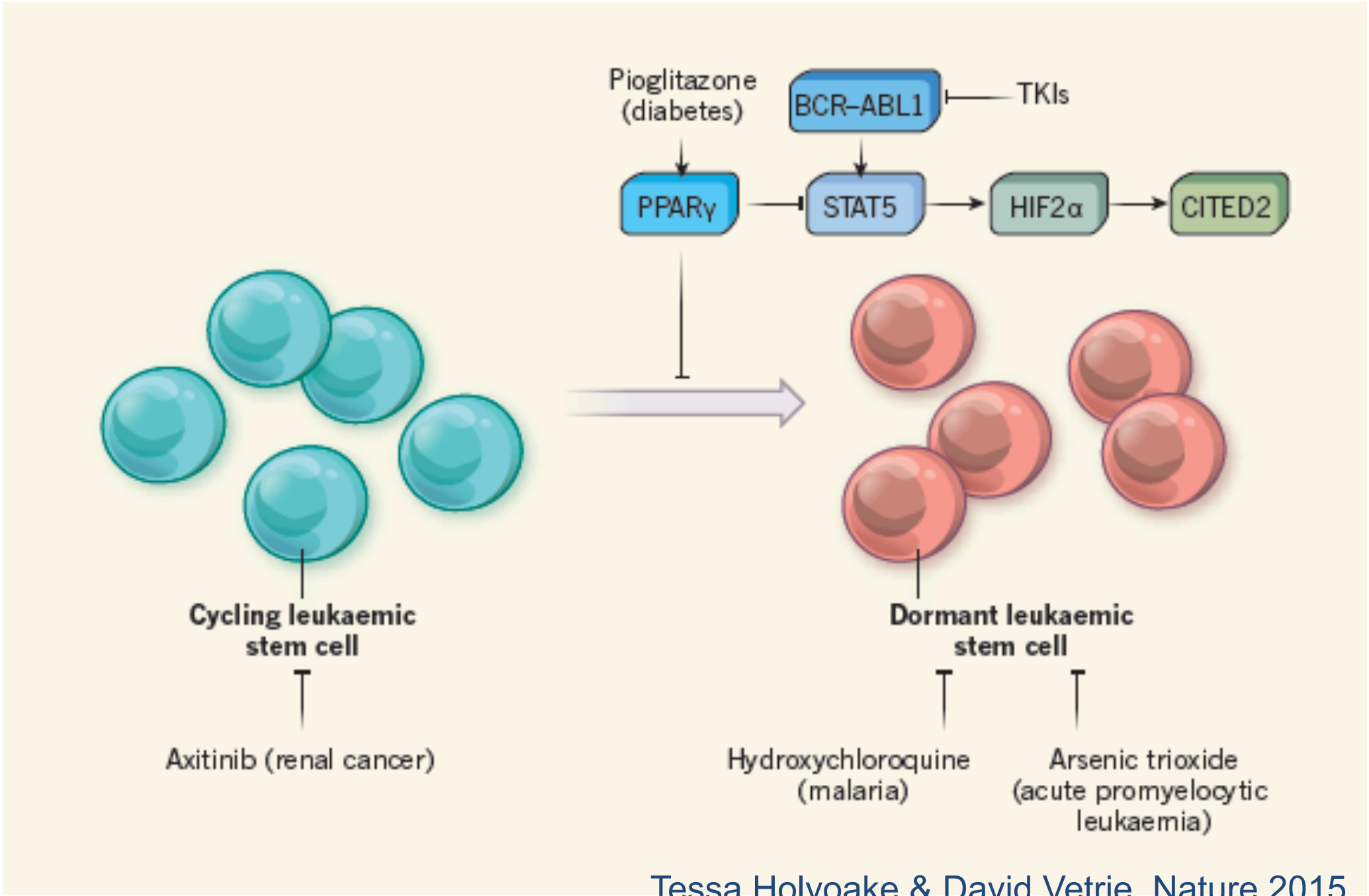




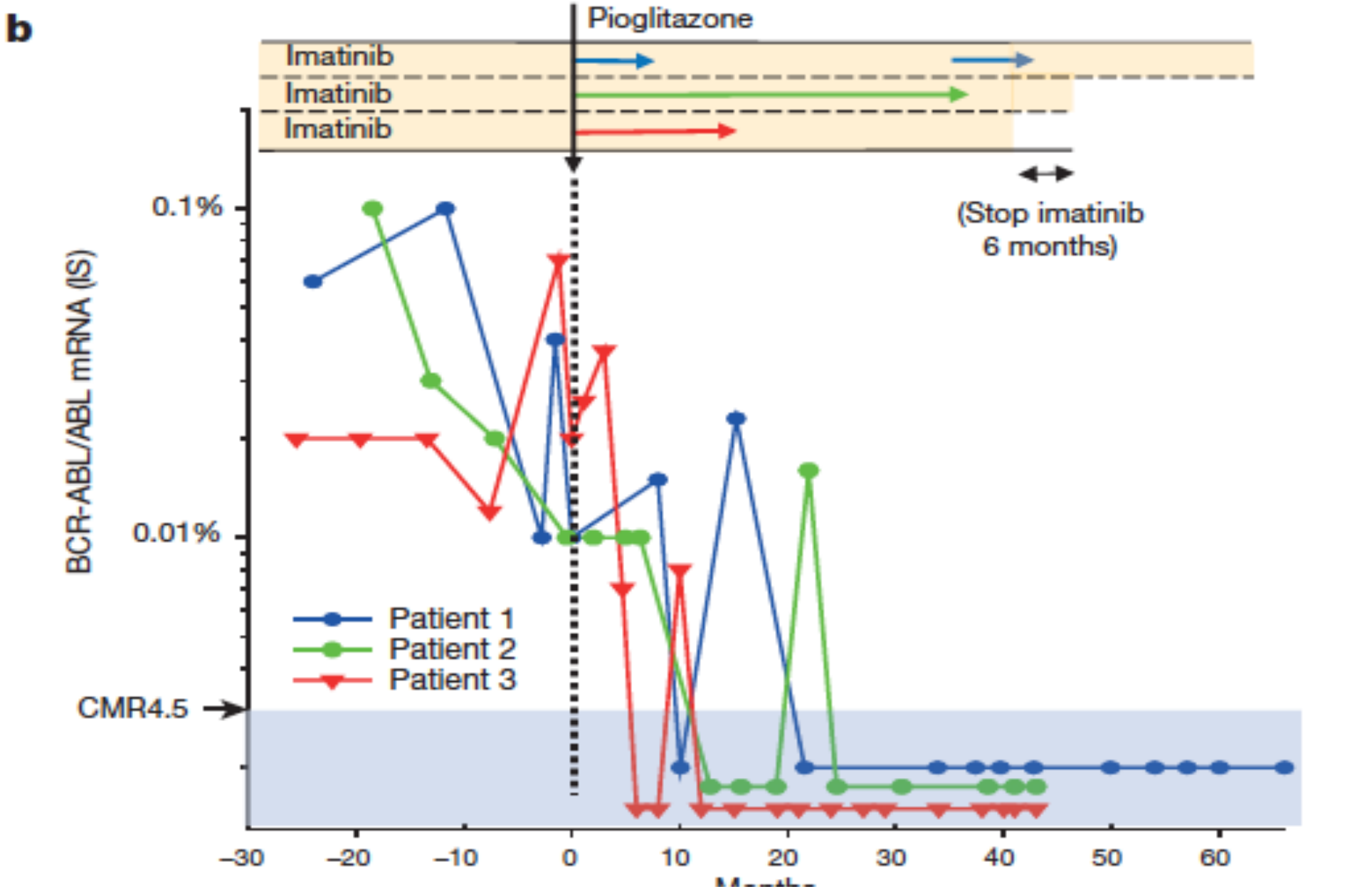
Ito et al: Nature 2008



Prost S et al., Nature 2015



Tessa Holyoake & David Vetrie, Nature 2015



Stephane Prost et al., Nature Medicine 2015

Ph-positive cells are very sensitive to immuno-mediated suppression

BMT and SCT data

- clear GVL effect (less GVL in “twins” transplant)
- efficacy of DLI therapy in patients who relapsed
- long-term relapses in patients who became apparently PCR-negative

IFN-α therapy

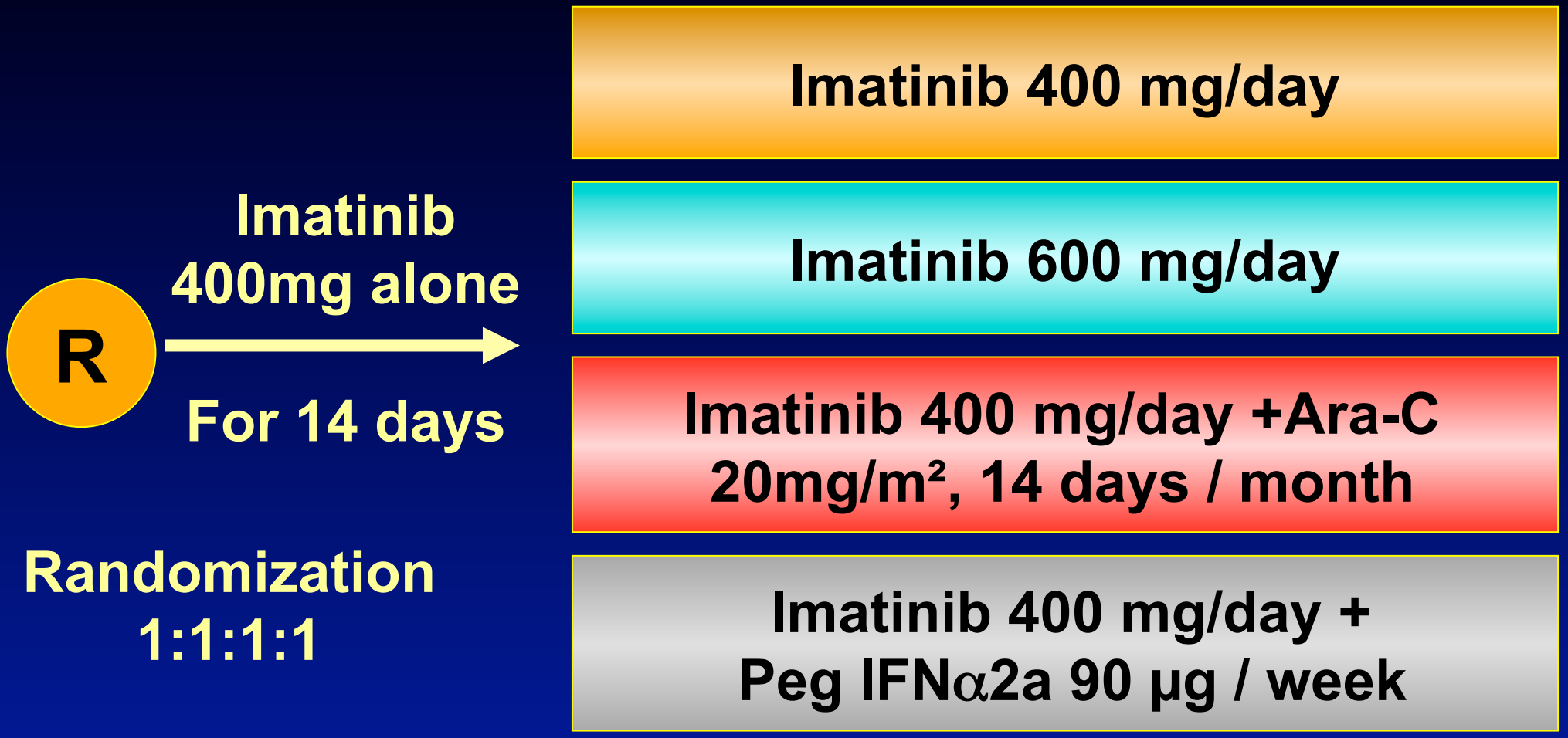
- Anti-proliferative effect?
- Immuno-mediated suppression?
- Combination of the two mechanisms?

Interferon + Imatinib combination studies

	FRENCH SPIRIT[1]	NORDIC[3]	Ger-CML Study IV[2]	MDAnderson[4]
IFN type	PEG	PEG	No PEG	PEG + G-CSF (IMA 800)
MMR	Yes	Yes	No	No
CCyR	No	No	No	No
Survival	No	NA	No	No
Toxicity	Yes	Yes	No	Yes

1. *Preudhomme C et al., N Engl J Med. 2010;363(26):2511-21.*
2. *Hehlmann R et al., JCO 2011;29:1634-1642.*
3. *Simonsson B, et al. Blood 2011;118(12):3228-3235*
4. *Cortes J et al. Cancer. 2011;117(3):572-80.*

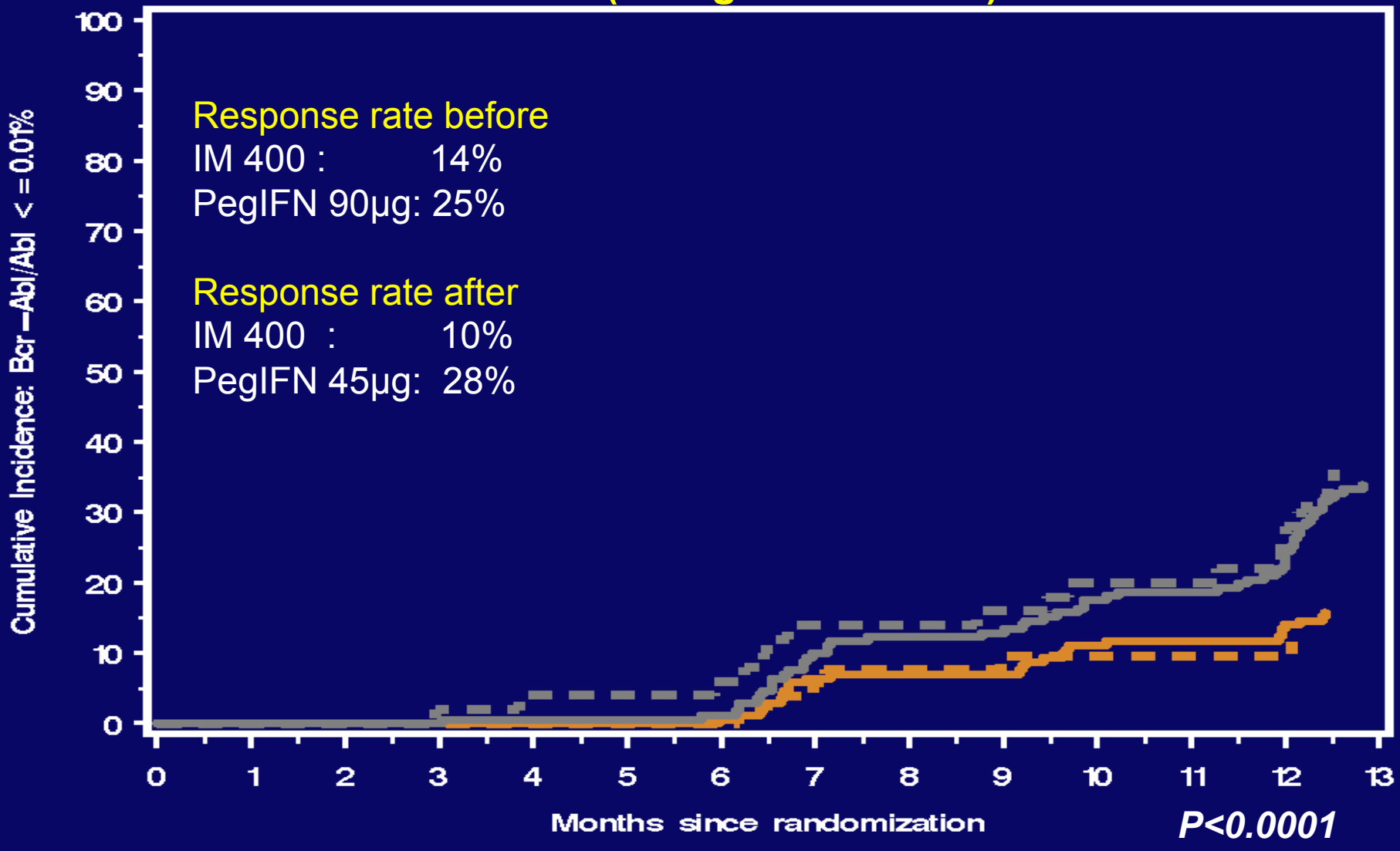
SPIRIT trial: Study design



Guilhot F et al. ASH Annual Meeting 2009; Preudhomme C et al., N Engl J Med. 2010 Dec 23;363(26):2511-21.

Superior Molecular Responses by 12 months

(≤4 log reduction IS)

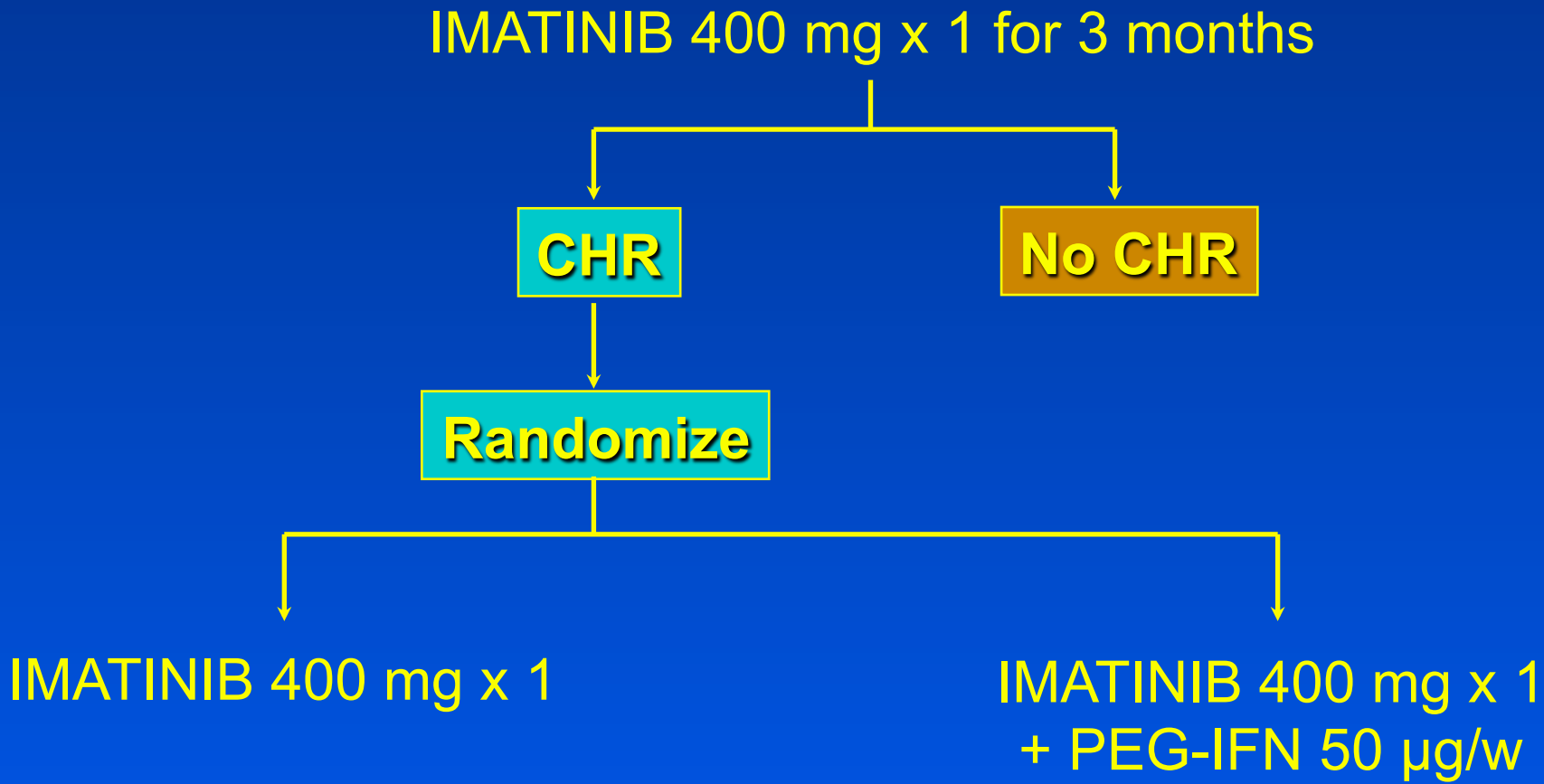


IM+ IFN Peg — Pre (171) — Post (50)

IM — Pre (171) — Post (52)

Johnson-Ansah H, et al. Blood 2011;118(21): [abstract 456] Oral Presentation

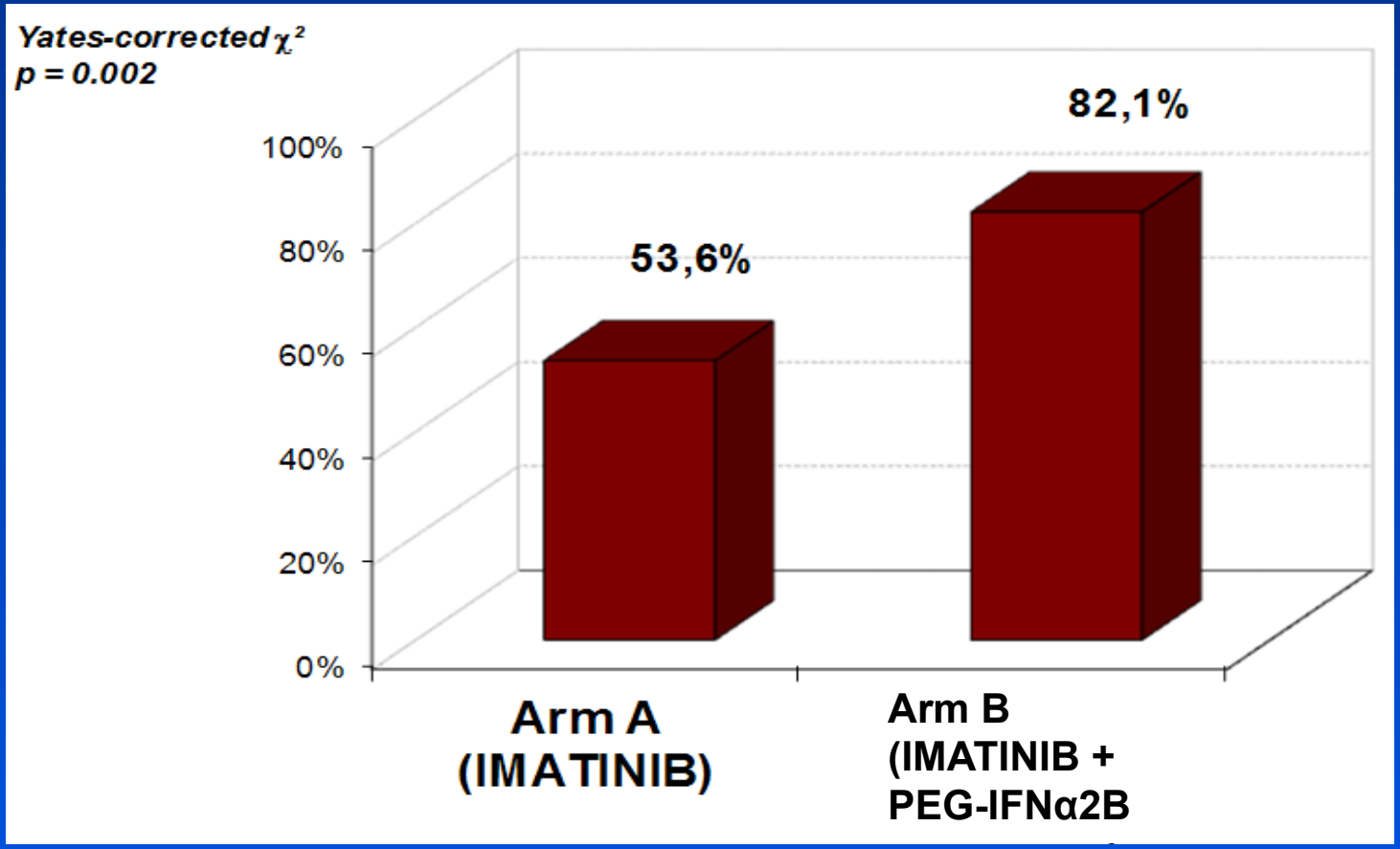
NordCML002 (Sokal IR/LR)



Primary endpoint: MMR at 12 months

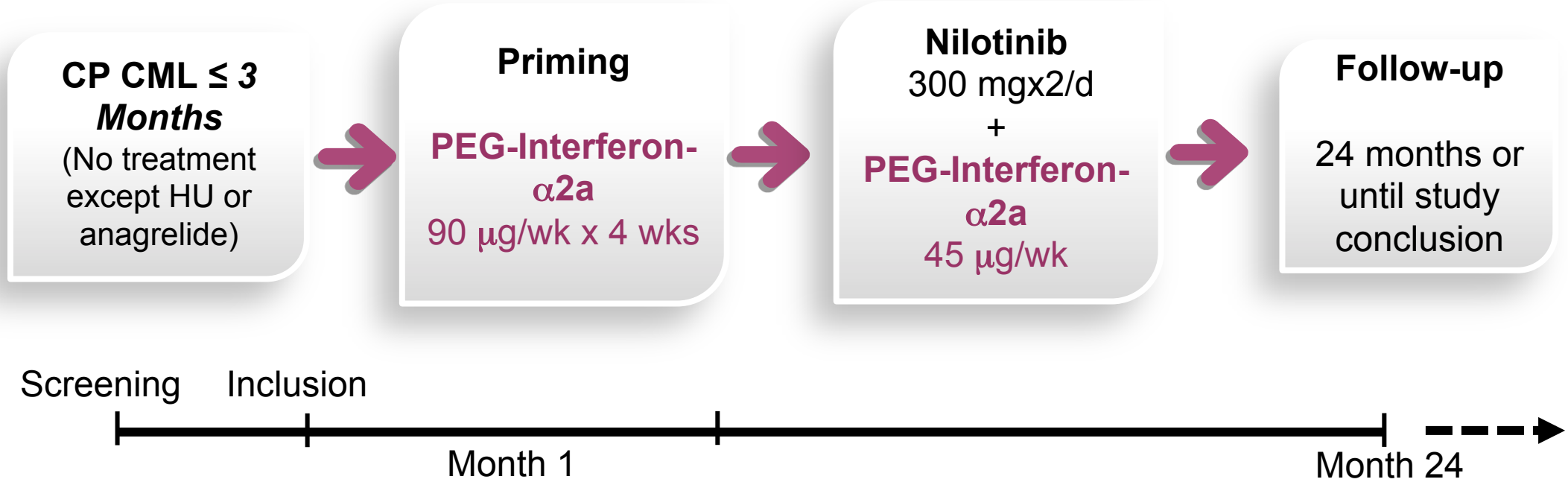
Simonsson B, et al. Haematologica 2010;95(12): [abstract 1110].
Simonsson B, et al. Blood 2011;118(12):3228-3235

MMR at week 52 per treatment arm (ITT)



Simonsson B, et al. Blood 2011;118(12):3228-3235

Nilotinib + (Peg)IFN-α2a: NiloPeg trial design



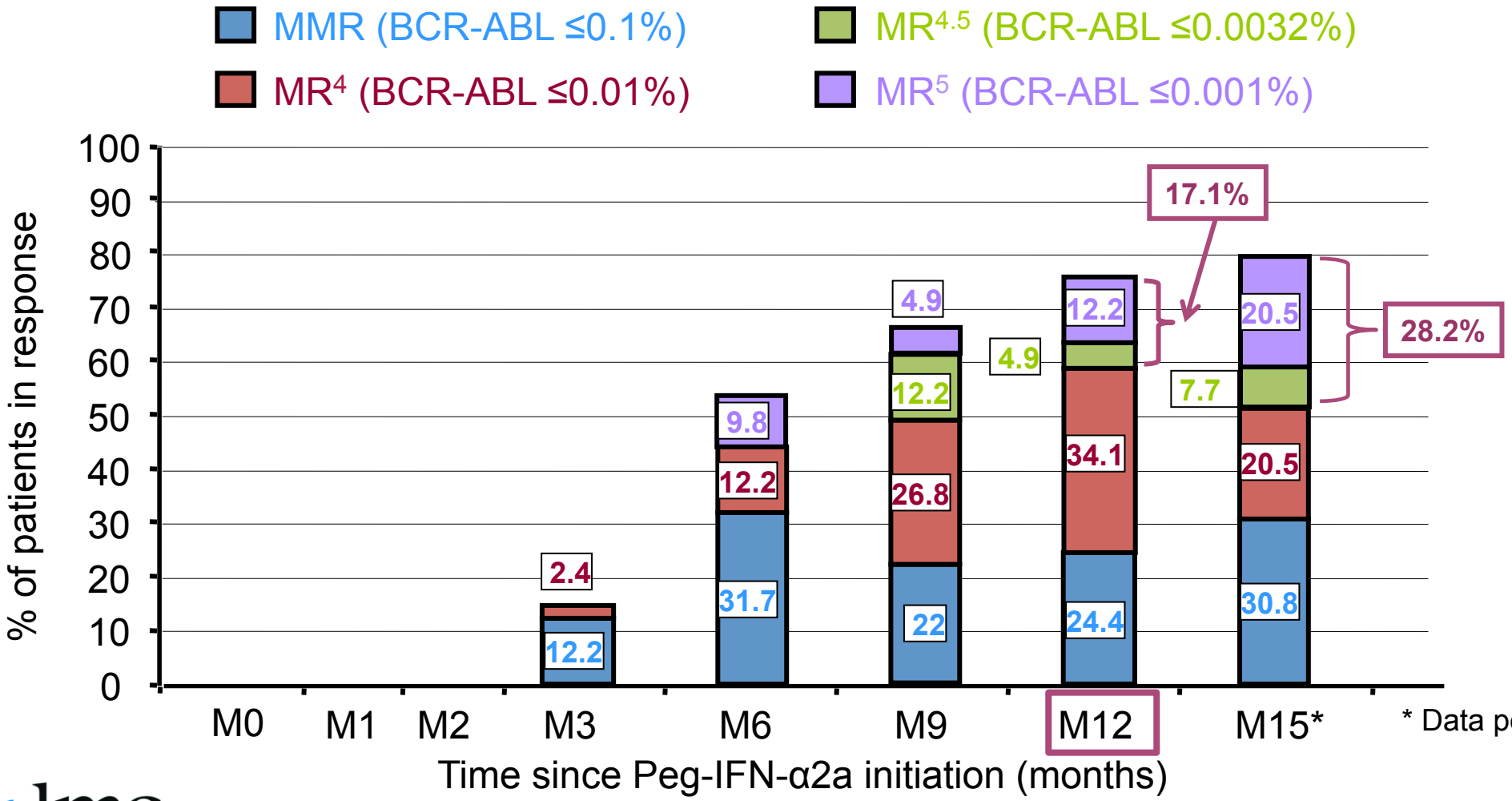
- 42 patients enrolled
- All Sokal risk scores

Nicolini FE, et al. Blood (ASH) 2012: Abstract 166

fiolmc
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

Nilotinib + (Peg)IFN-α2a: NiloPeg trial results

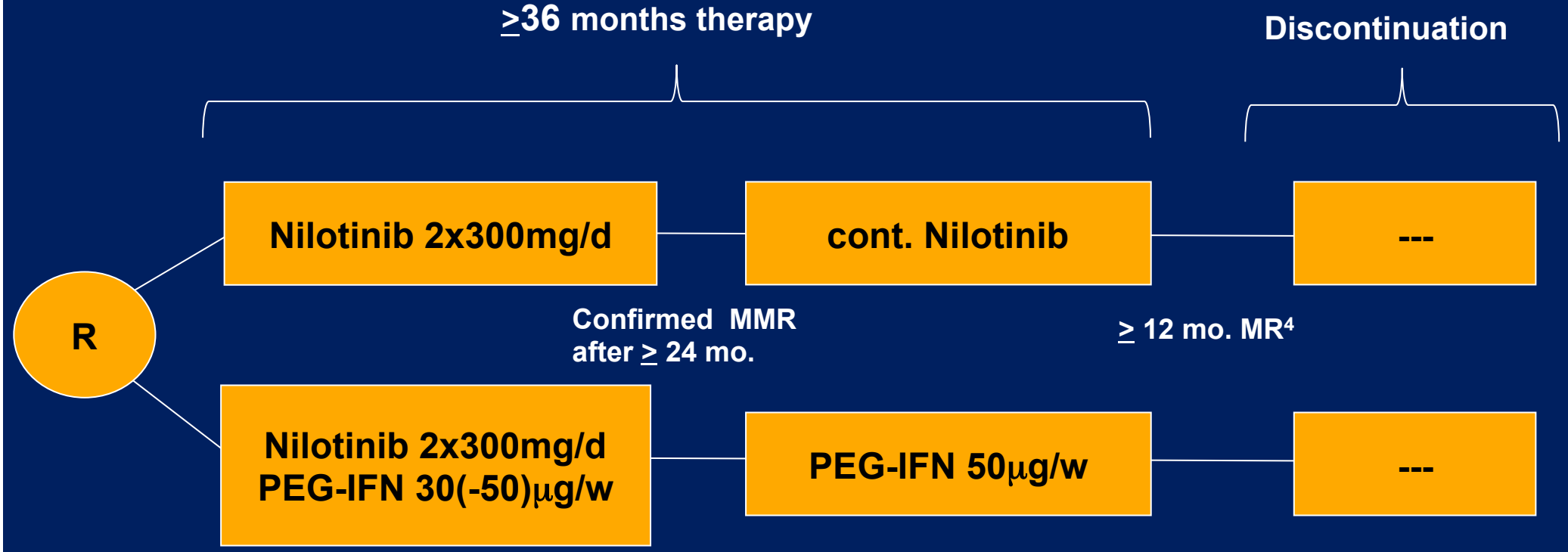
- Molecular responses *[Intention To Treat analysis]*



fiolmc
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

Nicolini FE, *et al., Blood* 2012;120:[abstract 166].

CML V (TIGER) study



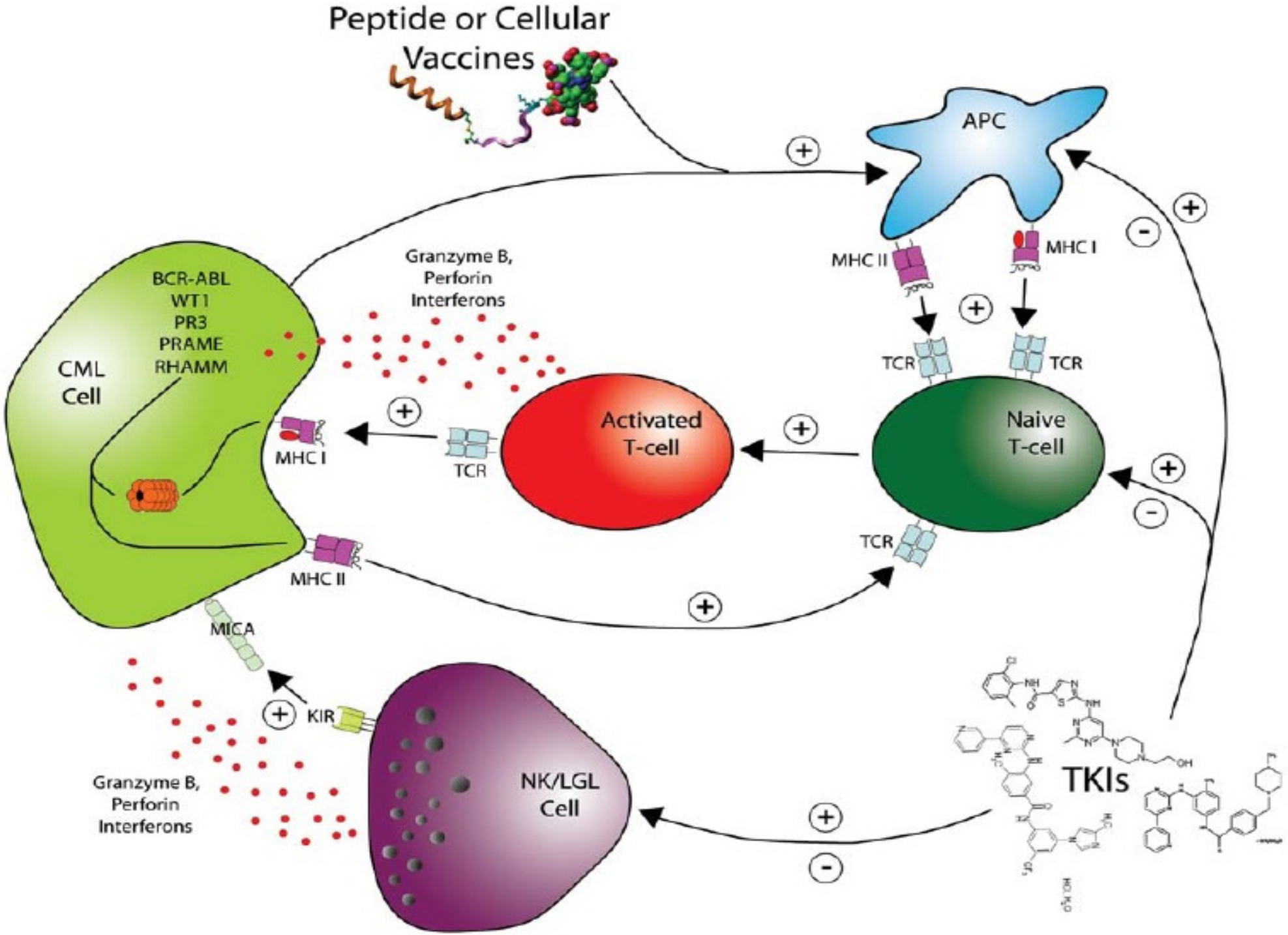
Nilotinib Intolerance → Imatinib
Nilotinib Resistance → Transplantation/Dasatinib
Suboptimal Response → Nilotinib 400 mg BID

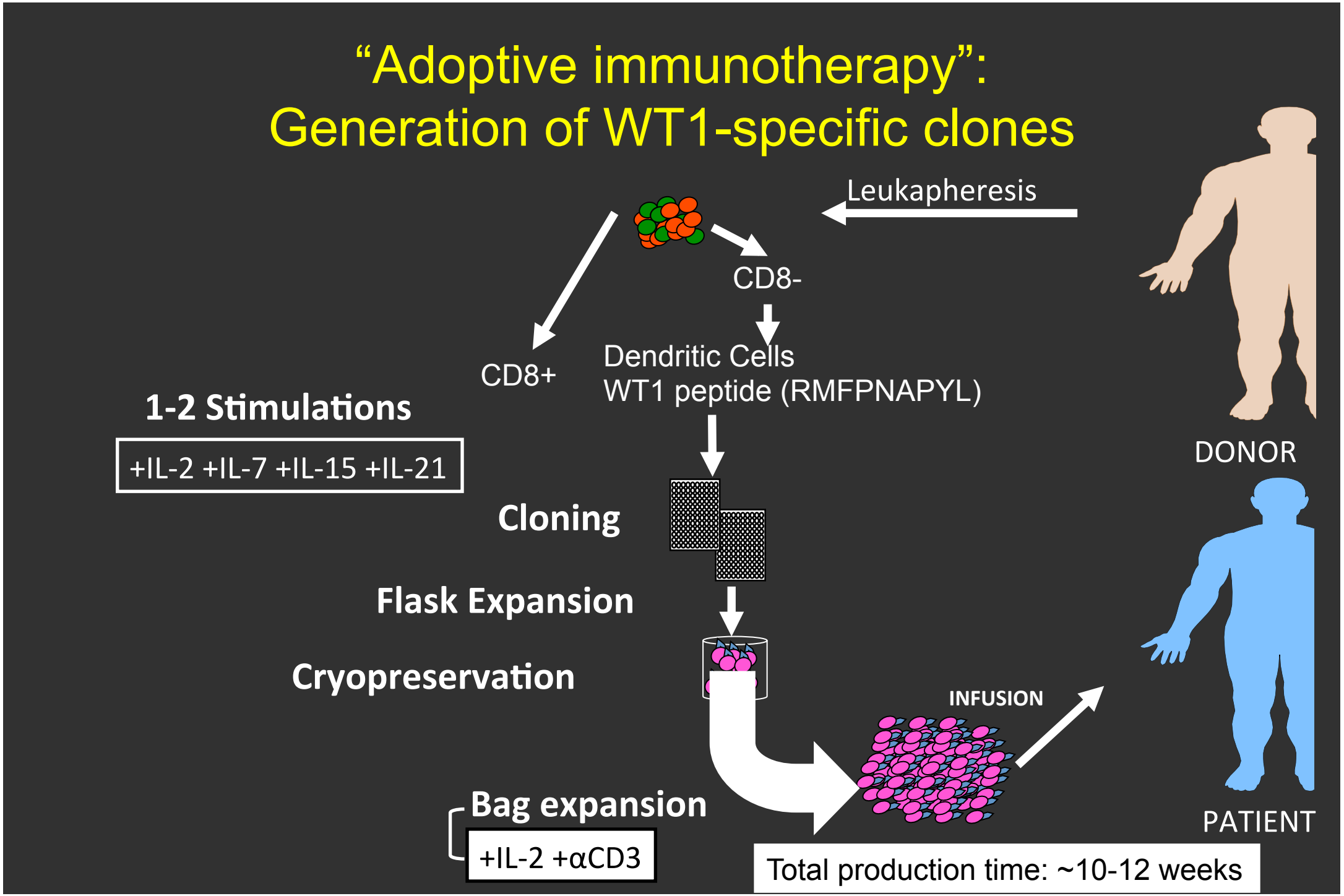
Induction **Maintenance** **Cure?**

A. Hochhaus, pers. comm.

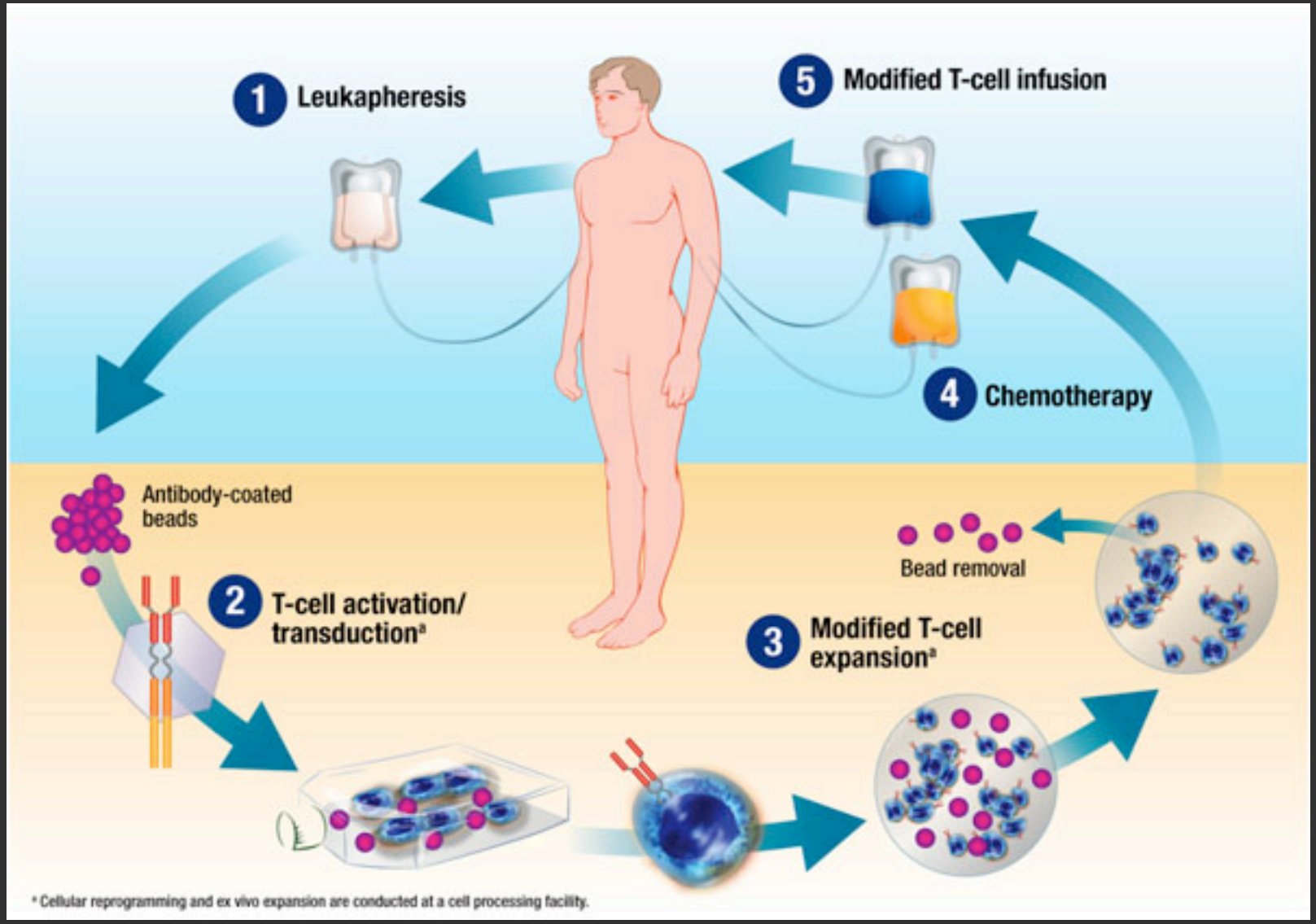
Immuno-adoptive therapy approaches to try to eradicate Ph+ stem cells

- Ph-pos cells specific antigens?
  - BCR-ABL junction peptides (Bocchia M et al.)
- Antigens preferentially expressed by Ph-positive cells:
  - IL1R1 (Järås M et al., PNAS 2010)
  - WT1(David Scheinberg, Baltimore 2012)
  - PR1 antigens (Kanodia S et al., PLoSOne 2010)

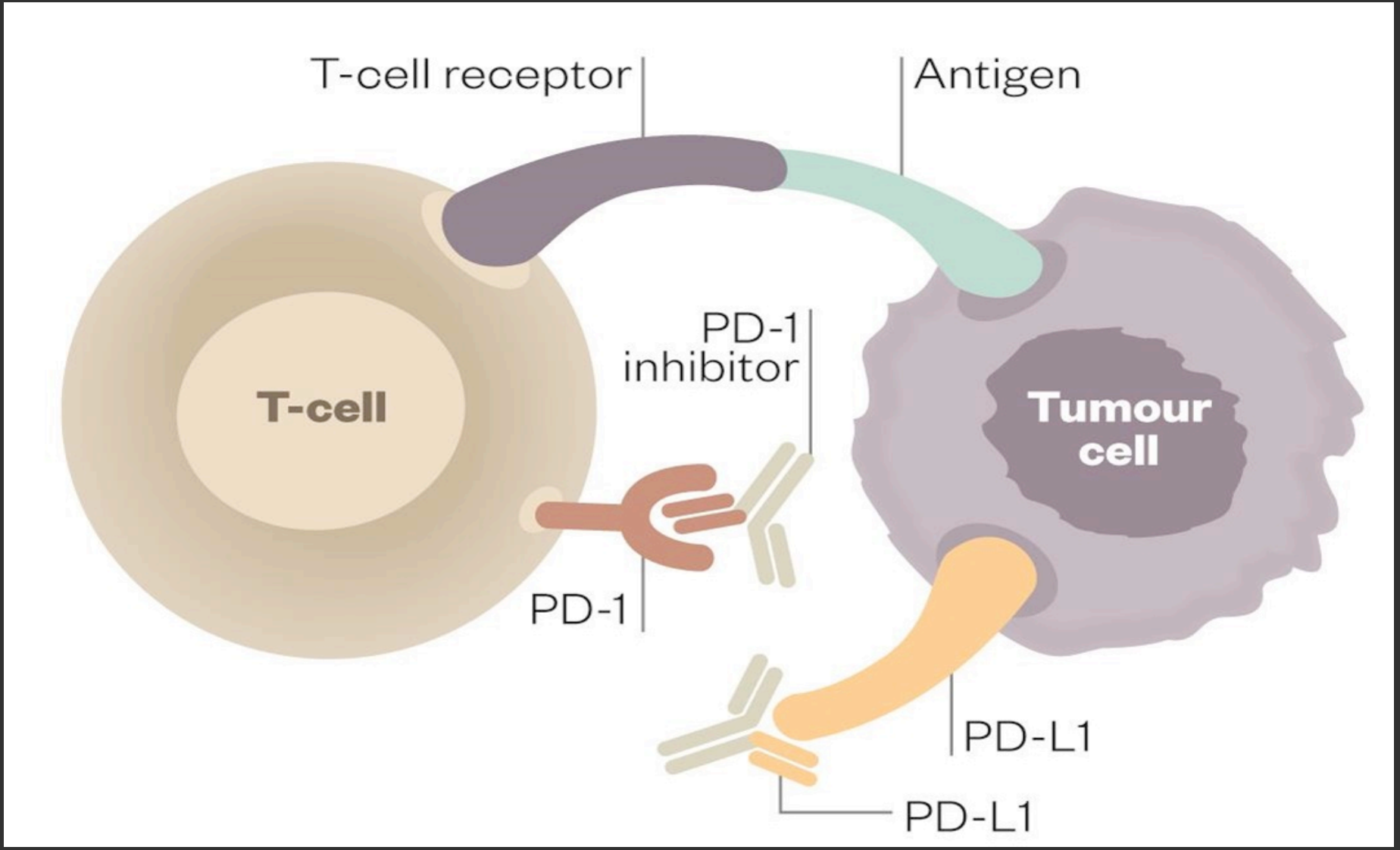

Peptide or Cellular Vaccines
APC
MHC II
MHC I
TCR
TCR
Granzyme B, Perforin Interferons
BCR-ABL
WT1
PR3
PRAME
RHAMM
CML Cell
MHC I
TCR
Activated T-cell
Naive T-cell
TCR
MHC II
MICA
KIR
Granzyme B, Perforin Interferons
NK/LGL Cell
TKIs


"Adoptive immunotherapy":
Generation of WT1-specific clones
Leukapheresis
CD8-
CD8+
Dendritic Cells
WT1 peptide (RMFPNAPYL)
1-2 Stimulations
+IL-2 +IL-7 +IL-15 +IL-21
DONOR
Cloning
Flask Expansion
Cryopreservation
INFUSION
Bag expansion
+IL-2 +αCD3
PATIENT
Total production time: ~10-12 weeks

CAR-T cell?


1 Leukapheresis
5 Modified T-cell infusion
4 Chemotherapy
Antibody-coated beads
2 T-cell activation/ transduction[a]
Bead removal
3 Modified T-cell expansion[a]
[a] Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

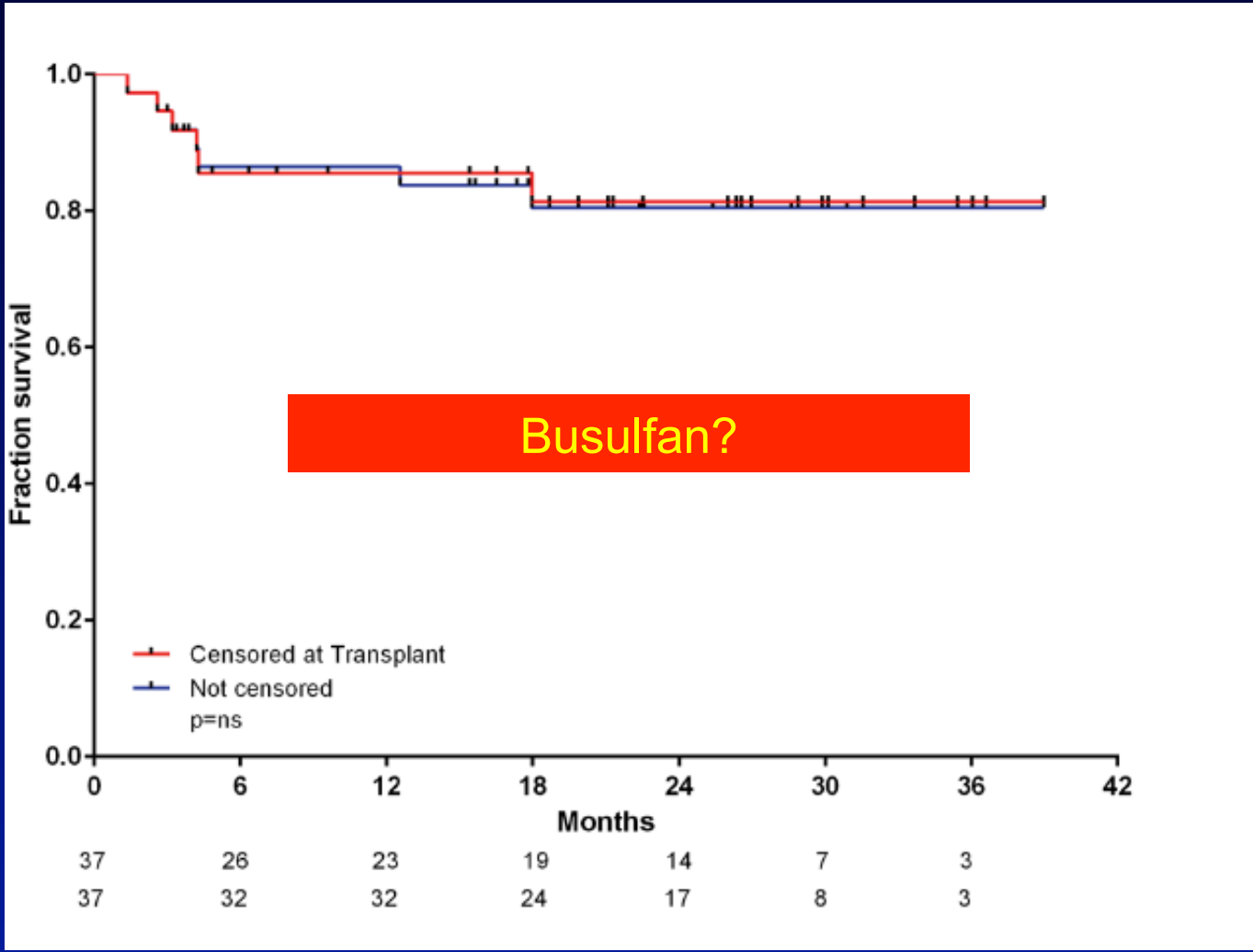
Check-point inhibitors?



Conclusion:
Major Questions Are Still Unanswered

- Does the immune system still play a role in CML in the TKI era?
- To which extent could we use drugs that will target not only the leukaemic stem cells but also other stem cells?

Chemotherapy?



Jabbour E et al., Lancet Oncology 2016

Thank you!

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Discussion