# Cours nationaux du DES d'hématologie

- 3 Cours en présentiel, salle sur le site Villemin (Lariboisière), de 10h à 17h le vendredi, 3 séances
  - Le 26 Nov : Myélome, X Leleu
  - Le 25 février 2022 : LF, F Morschhauser
  - Le 13 mai 2022 : Dysimmunité, T Lamy
- 5 sessions qui auront lieu en visio selon un format resserré de 3h environ en deuxième partie d'AM (16h-19h)
  - Octobre 21 ; E Raffoux, urgences en hématologie à destination des phases socles, 2 sessions
  - 28 Janvier 22 ; Ph Rousselot, LMC et LAL Ph+
  - Vendredi 18 mars 2022 à 16h à 18 h, Stéphane Moreau,
    - Soins palliatifs : spécificités en hématologie et législation (C. Prodhomme, S. Moreau)
    - Place de l'information et éducation en hématologie (D. Bordessoule)
    - Dépendance et dignité (J. Ceccaldi)
    - Recherche en hématologie et éthique (C. Bommier, L. Simon)
  - Avril 22 : date à caler, V Asnafi, LALT
  - Juin 22 ; date à caler, JP Marolleau, Economie de la Santé

# Cours DES hématologie LMC et LAL B Ph+

- Jean-Michel Cayuela : biologie des hémopathies à chromosome philadelphie et BCR-ABL
- Philippe Rousselot : LMC
- Emmanuelle Clappier : MRD des LAL Ph+ et Ph-like
- Yves Chalandon : LAL Ph+ aspects cliniques et thérapeutiques

# Merci de remplir la liste des présents

- https://docs.google.com/forms/d/e/1FAIpQLSdqiKZhUjK_P7tb2xQO__p4FhZJL5TGLw2hlEVEbhpxUrI1gQ/viewform?vc=0&c=0&w=1&flr=0&usp=mail_form_link

# Leucémie Myéloïde Chronique

Philippe Rousselot

Service d'Hématologie et d'Oncologie, Centre Hospitalier de Versailles

Inserm U1173, Université de Versailles Saint-Quentin-en-Yvelines, Paris-Saclay

# Aspects diagnostiques

# Phase chronique

- Ce n’est pas une accélération car :
  - Blastes <15% dans le sang ou la moelle
  - Blastes + promyélocytes <30%
  - Basophiles dans le sang <20%
  - Plaquettes > 100 G/L
- Absence d’anomalie cytogénétiques additionnelles (ACA) au diagnostic
  - Discuté
  - Soit LMC PC avec ACA
  - Soit accélération cytogénétique d’emblée

# Ce n’est pas une phase blastique

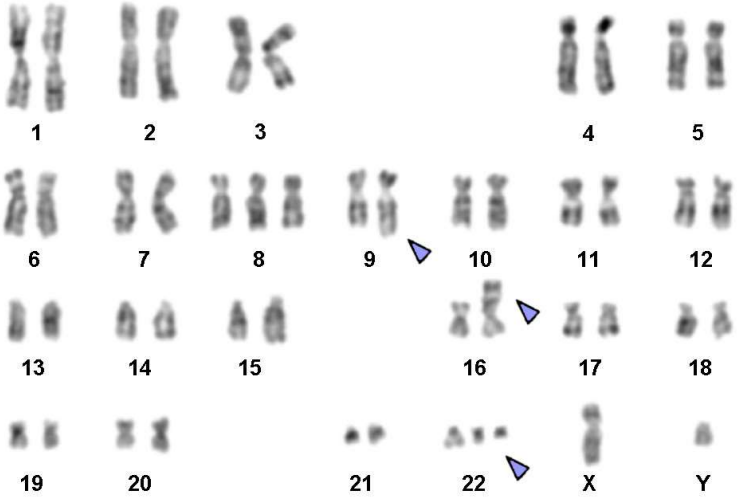
| | |
|---|---|
| **ELN criteria** | - **Blasts in blood or marrow ≥ 30%**<br>- **Extramedullary blast proliferation, apart from spleen** |
| **WHO criteria** | - **Blasts in blood or marrow ≥ 20%**<br>- **Extramedullary blast proliferation, apart from spleen**<br>- **Large foci or clusters of blasts in the bone marrow biopsy** |

- Phenotype
  - Myeloid blast crisis
  - Lymphoid blast crisis
- Cytogenetic analysis
  - Additional cytogenetic aberrations (ACAs)
- Molecular biology
  - Mutated genes
  - Mutations in the TK domain of BCR-ABL
- Medical history
  - BC at onset
  - BC after CP-CML

# Les ACA et autres anomalies

**Major route of karyotypic evolution**

trisomy 8
der(22)t(9;22)(q34;q11),
ider(22)(q10) t(9;22)(q34,q11)
isochromosome(17)(q10)
Monosomie 7




48,XY,+8,t(9;22)(q34;q11),der(16),t(16;17),+der(22).

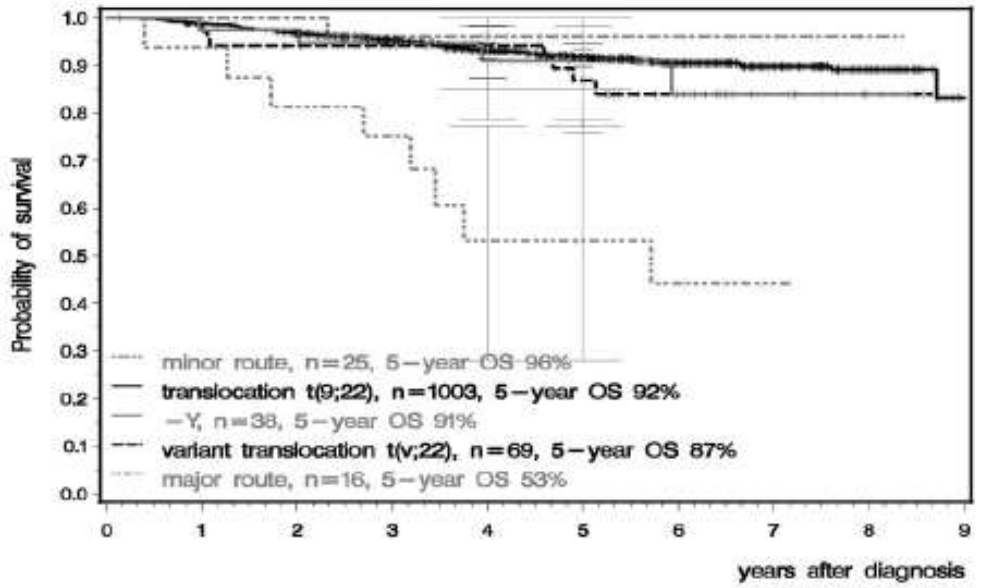
**Minor route of karyotypic evolution**

-Y
t(3;12)
t(4;6)
t(2;16)
t(1;21)

**Karyotype with variant t(v;22)**

| |
|---|
| 46,XY,t(9;14;22)(q34;p13:q11),inv(9)(p11q13)c[11] |
| 46,XY,t(3;9;22)(q25;q34;q11)[20] |
| 46,XY,t(6;9;22;9)(p23;q34;q11;q22)[17] |
| 46,XX,t(7;9;22)(q36;q34;q11)[25] |
| 46,XY,t(5;9;22)(q11.2;q34;q11)[25] |
| 46,XX,t(4;9;22)(q28;q34;q11)[16] |

# Prognostic of ACAs at diagnosis

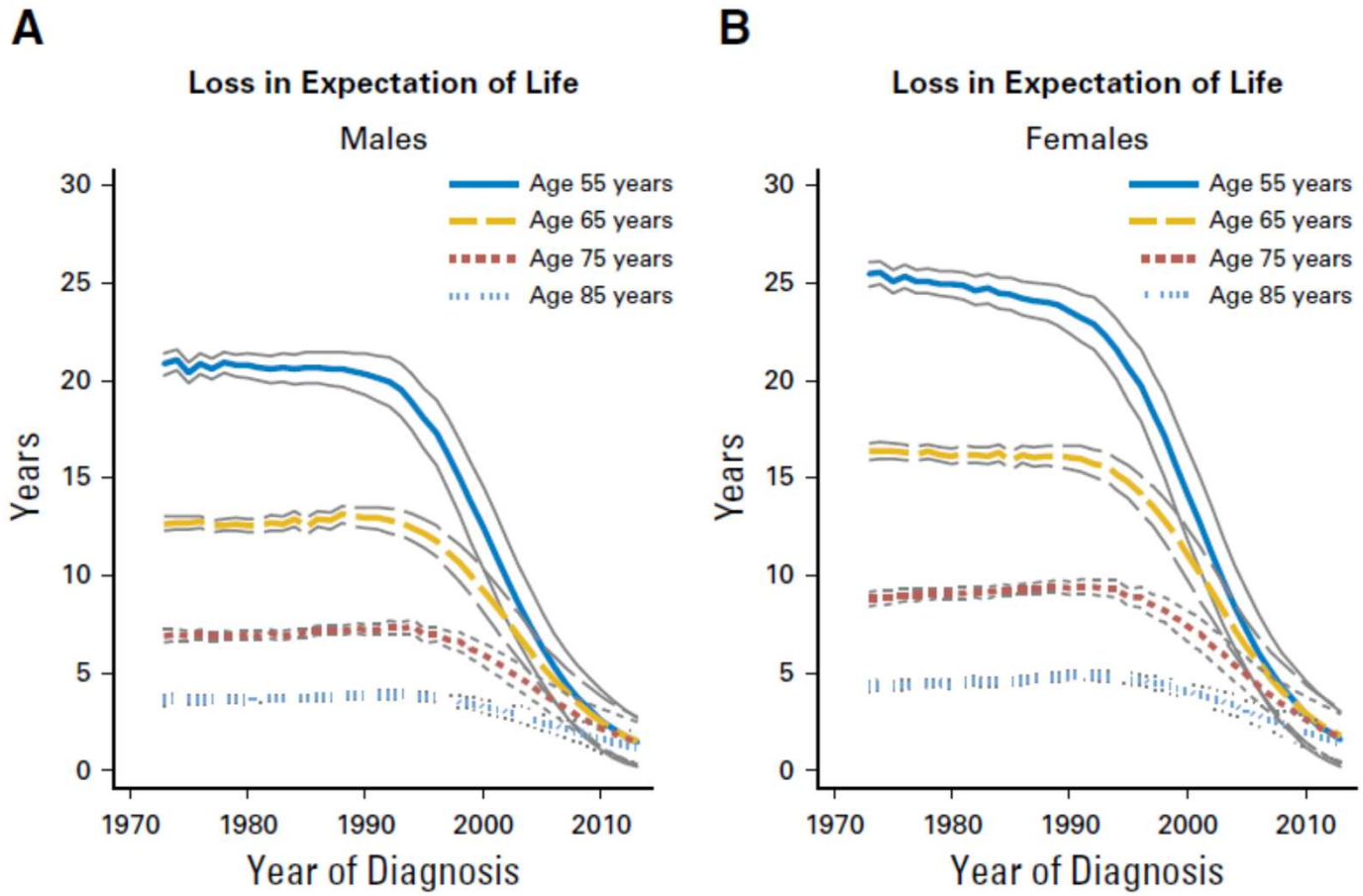



| Patients at risk | at diagnosis | 1 Year | 2 Years | 3 Years | 4 Years | 5 Years |
|---|---|---|---|---|---|---|
| translocation t(9;22) | 1003 | 988 | 942 | 816 | 663 | 518 |
| variant translocation t(v;22) | 69 | 67 | 61 | 51 | 47 | 32 |
| minor route | 25 | 25 | 25 | 23 | 18 | 12 |
| major route | 16 | 15 | 13 | 12 | 7 | 6 |
| -Y | 38 | 37 | 36 | 32 | 24 | 17 |

**Figure 5. OS in the t(9;22), t(v;22), and minor- and major-route ACA groups calculated by the Kaplan-Meier method and compared by the log-rank test.** Patients were censored at the last follow-up. The difference between the standard and the major-route groups was significant at $P < .001$.

# Aspects pronostics

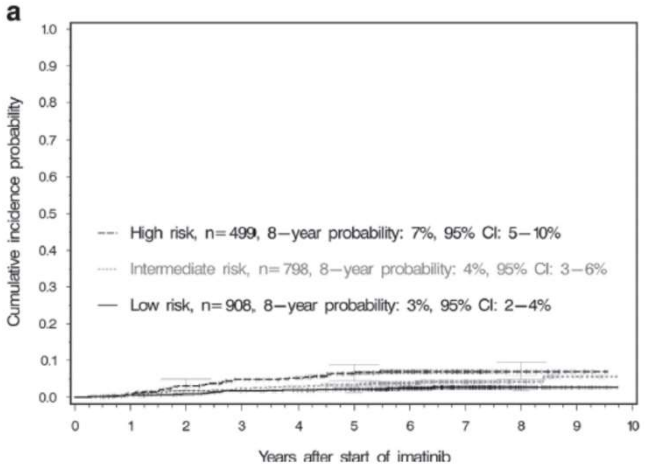
# Survie à long terme …




Bower H et al., J Clin Oncol 2016;34:2851-2857

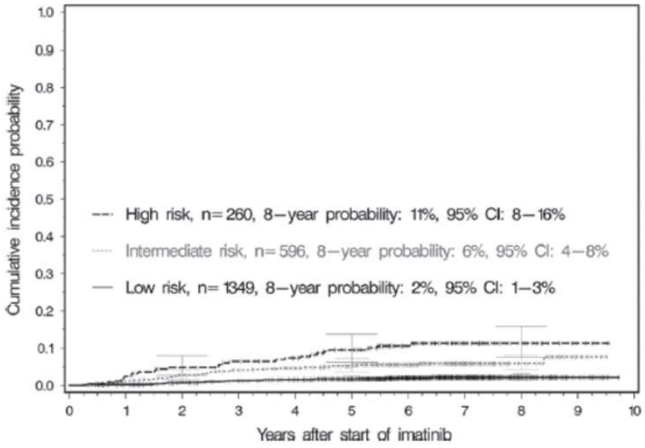
# Scores pronostiques et survie à l'ère des ITKs

- Score de SOKAL
  - Au diagnostic
    - Taille de la rate
    - Age
    - Plaquettes
    - % de blastes dans le sang
- Score de survie à long terme (score ELTS)




**Number of patients still at risk (n) at different years of observation**

| *Year* | *0* | *2* | *5* | *8* |
|---|---|---|---|---|
| *High risk, n* | 499 | 453 | 355 | 47 |
| *Intermediate risk, n* | 798 | 758 | 639 | 87 |
| *Low risk, n* | 908 | 855 | 749 | 86 |




**Number of patients still at risk (n) at different years of observation**

| *Year* | *0* | *2* | *5* | *8* |
|---|---|---|---|---|
| *High risk, n* | 260 | 226 | 179 | 28 |
| *Intermediate risk, n* | 596 | 557 | 451 | 60 |
| *Low risk, n* | 1349 | 1283 | 1113 | 132 |

Pfirrmann et al. Leukemia 2016

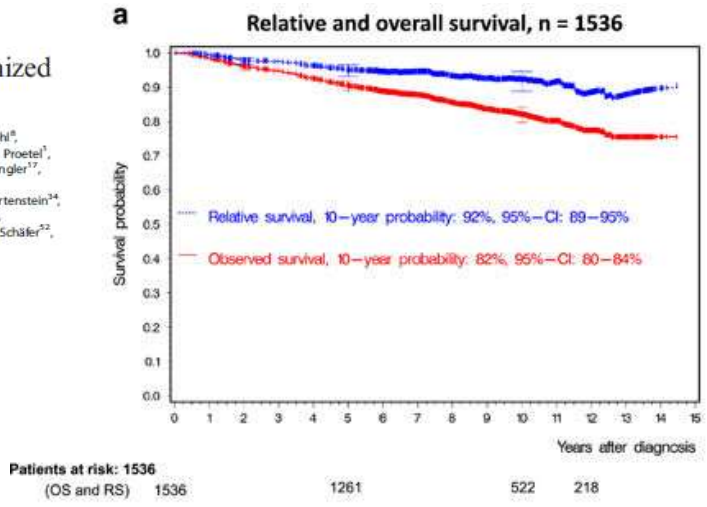
Leukemia (2017) 31, 2398–2406
www.nature.com/leu

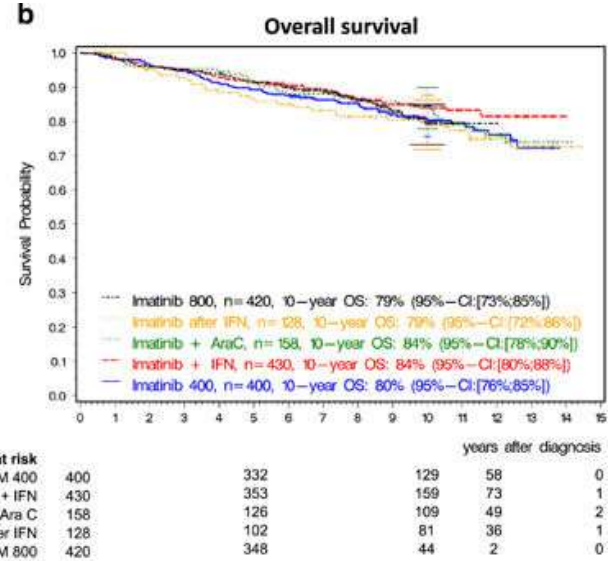
OPEN

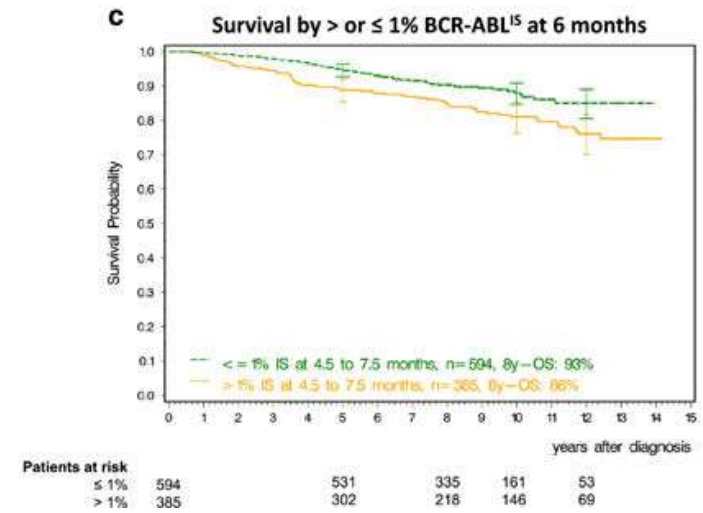
ORIGINAL ARTICLE

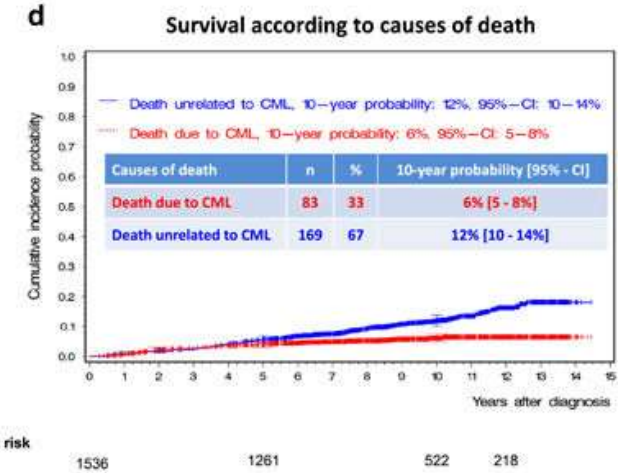
# Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants

R Hehlmann[1], M Lauseker[2], S Saußele[1], M Pfirrmann[2], S Krause[3], HJ Kolb[4], A Neubauer[5], DK Hossfeld[6], C Neri[7], A Gratwohl[8], GM Baerlocher[9], D Heim[8], TH Brümmendorf[10], A Fabarius[1], C Haferlach[11], B Schlegelberger[12], MC Müller[1], S Jeromin[11], U Proetel[1], K Kohlbrenner[1], A Voskanyan[1], S Rinaldetti[1], W Seifarth[1], B Spieß[1], L Balleisen[13], MC Goebeler[14], M Hänel[15], A Ho[16], J Dengler[17], C Falge[18], L Kanz[19], S Kremers[20], A Burchert[21], M Kneba[21], F Stegelmann[22], CA Köhne[23], HW Lindemann[24], CF Waller[25], M Pfreundschuh[26], K Spiekermann[4], WE Berdel[27], L Müller[28], M Edinger[29], J Mayer[30], DW Beelen[31], M Bentz[32], H Link[33], B Hertenstein[34], R Fuchs[10], M Wernli[35], F Schlegel[36], R Schlag[37], M de Wit[38], L Trümper[39], H Hebart[40], M Hahn[41], J Thomalla[42], C Scheid[43], P Schafhausen[6], W Verbeek[44], MJ Eckart[45], W Gassmann[46], A Pezzutto[47], M Schenk[48], P Brossart[49], T Geer[50], S Bildat[51], E Schäfer[52], A Hochhaus[53] and J Hasford[2] for the SAKK and the German CML Study Group

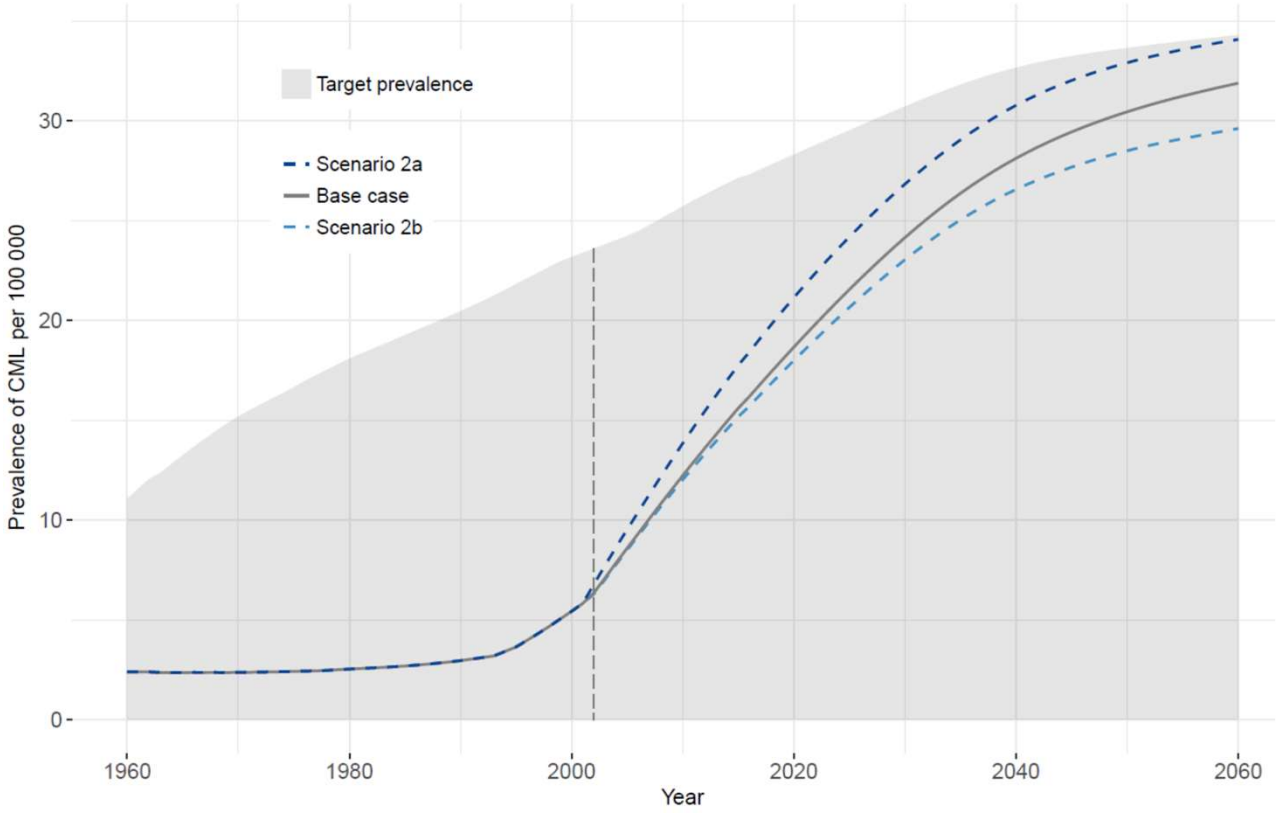


# Un modèle de prise en charge bientôt dépassé ?

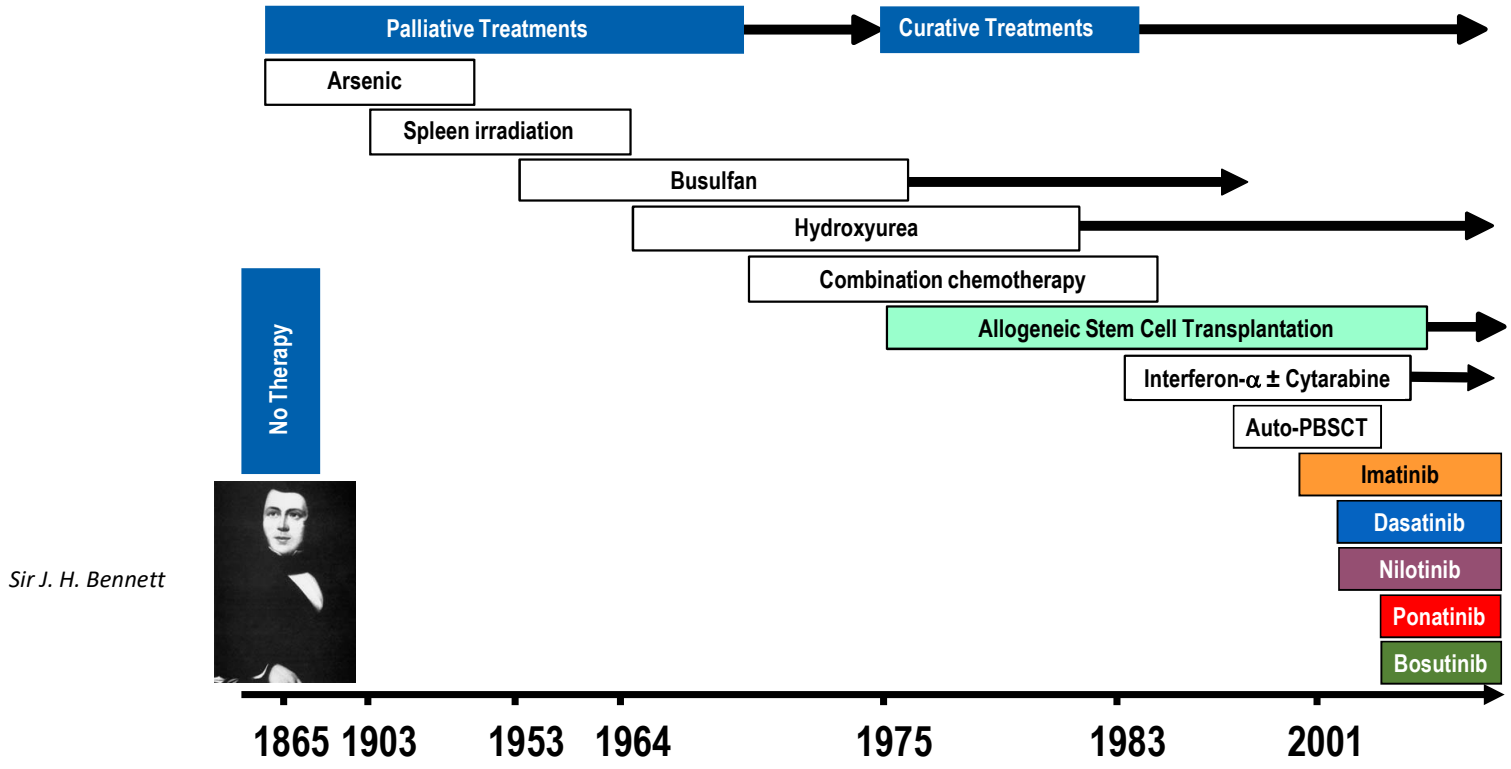



**Plus de 20000 patients**

Delord M. Leuk Res. 2018 Jun;69:94-99

# Historique des traitements

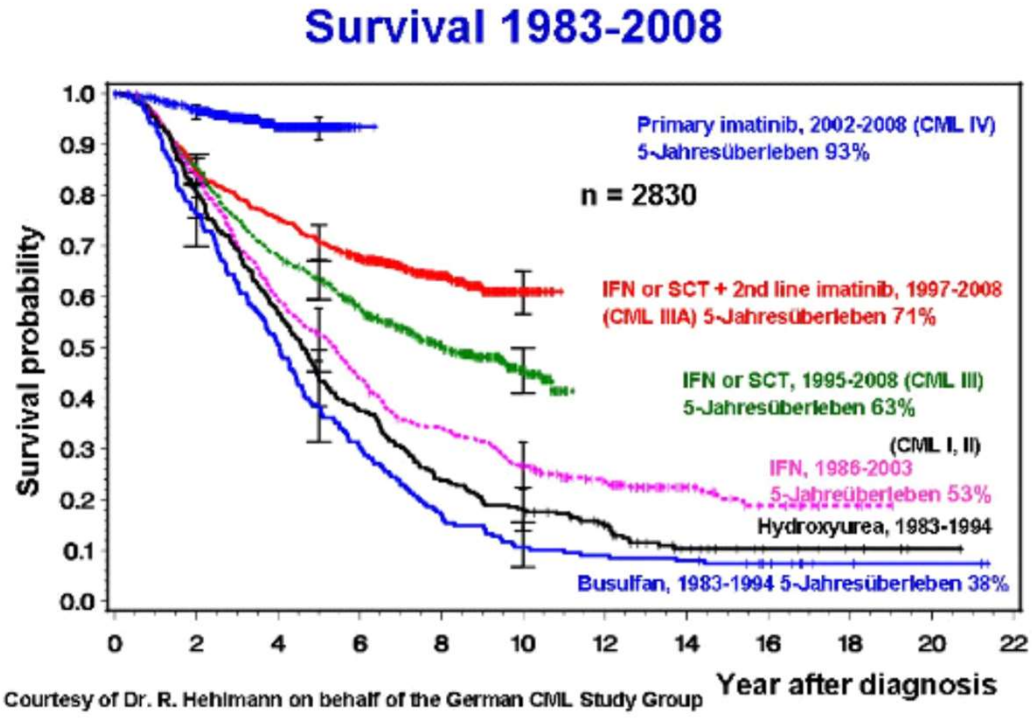
# Therapeutic history of CML



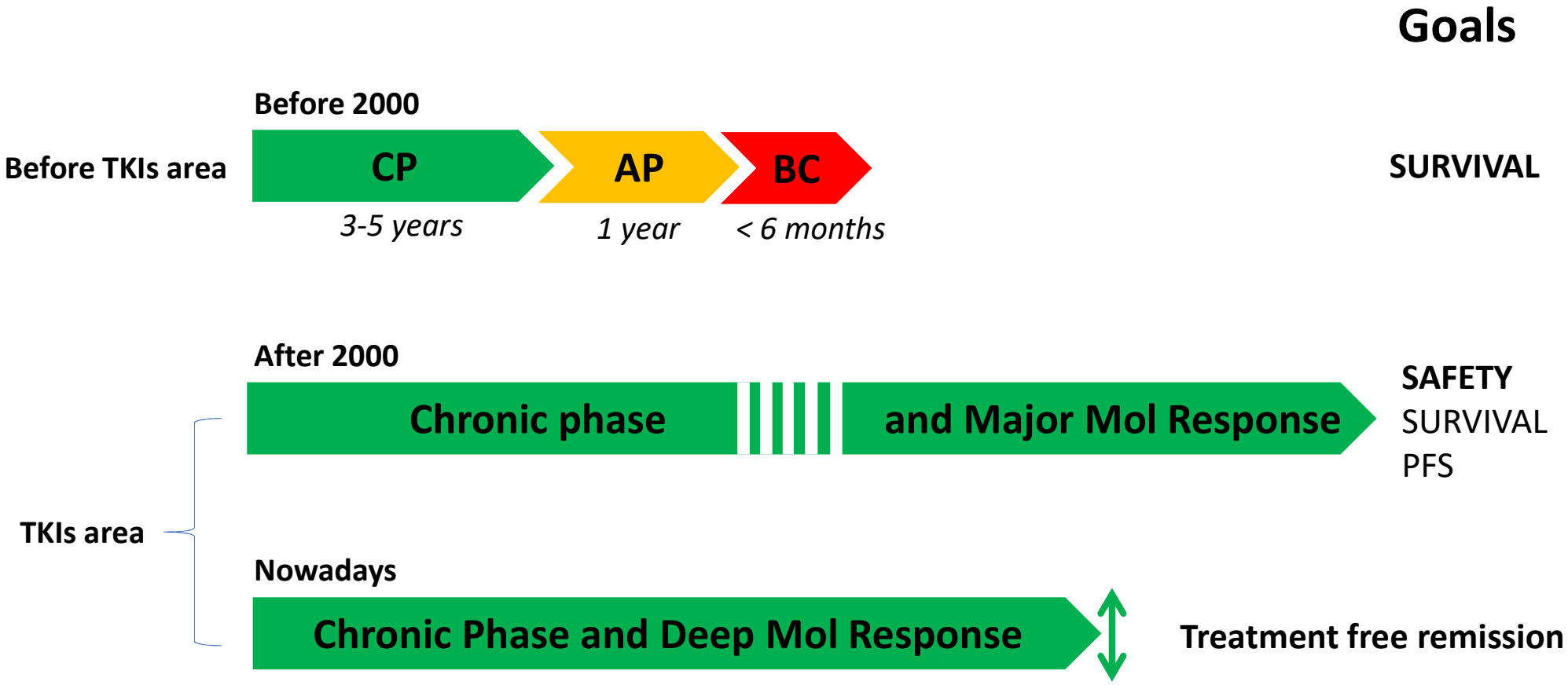

Adapted from J. Pavlu et al Blood 2011

# L'imatinib : inhibiteur de tyrosine kinase
# Application : la leucémie myéloïde chronique

- Modèle de traitement ciblé
- Révolution thérapeutique

# Evolving paradigms in CML




Adapted from J Goldman

# Les recommandations ELN 2020

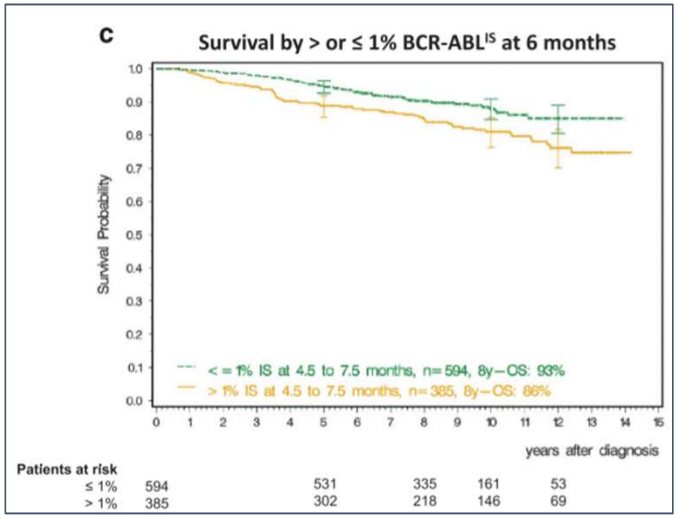
Leukemia (2020) 34:966–984
https://doi.org/10.1038/s41375-020-0776-2

REVIEW ARTICLE

Chronic myelogenous leukemia

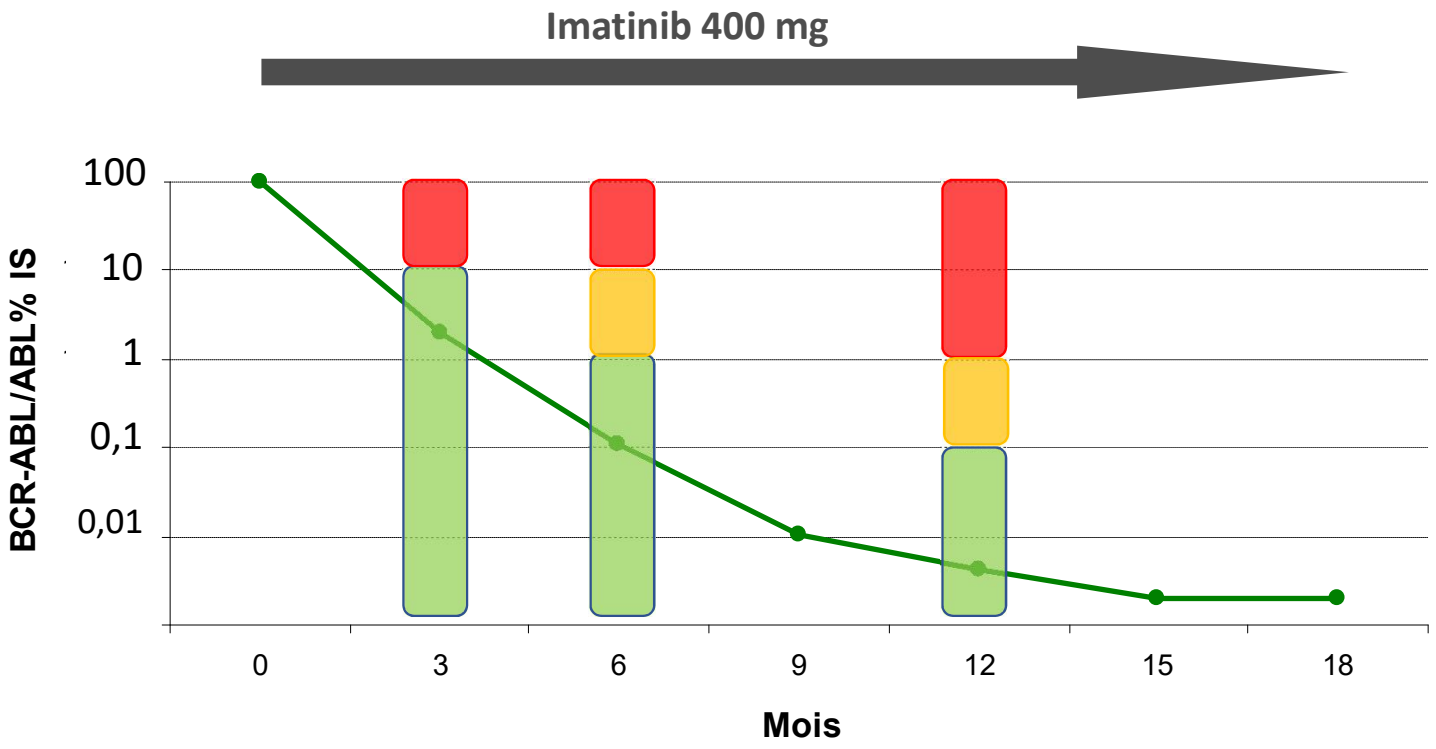
# European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

A. Hochhaus[1] · M. Baccarani[2] · R. T. Silver[3] · C. Schiffer[4] · J. F. Apperley[5] · F. Cervantes[6] · R. E. Clark[7] · J. E. Cortes[8] · M. W. Deininger[9] · F. Guilhot[10] · H. Hjorth-Hansen[11] · T. P. Hughes[12] · J. J. W. M. Janssen[13] · H. M. Kantarjian[14] · D. W. Kim[15] · R. A. Larson[16] · J. H. Lipton[17] · F. X. Mahon[18] · J. Mayer[19] · F. Nicolini[20] · D. Niederwieser[21] · F. Pane[22] · J. P. Radich[23] · D. Rea[24] · J. Richter[25] · G. Rosti[2] · P. Rousselot[26] · G. Saglio[27] · S. Saußele[28] · S. Soverini[2] · J. L. Steegmann[29] · A. Turkina[30] · A. Zaritskey[31] · R. Hehlmann[28,32]




| | Reponse optimale | Réponse non optimale<br>Situation d'alerte | Echec |
|---|---|---|---|
| **3 mois** | **BCR-ABL ≤ 10 %** | BCR-ABL > 10 % | **BCR-ABL > 10 %**<br>**si confirmé dans les 3 mois** |
| **6 mois** | **BCR-ABL ≤ 1 %** | *BCR-ABL > 1-10 % | **BCR-ABL > 10 %** |
| **12 mois** | **BCR-ABL ≤ 0,1 % (RMM)** | BCR-ABL > 0,1-1 % | **BCR-ABL > 1 %** |
| **Ensuite** | **BCR-ABL ≤ 0,1 % (RMM)**<br>**Si objectif TFR : BCR-ABL ≤ 0,01 % (RM4)** | BCR-ABL > 0,1-1 %<br>*Perte de RMM* | **BCR-ABL > 1 %**<br>**Mutations de résistance**<br>**Haut risque cytogénétique** |

# La réponse moléculaire



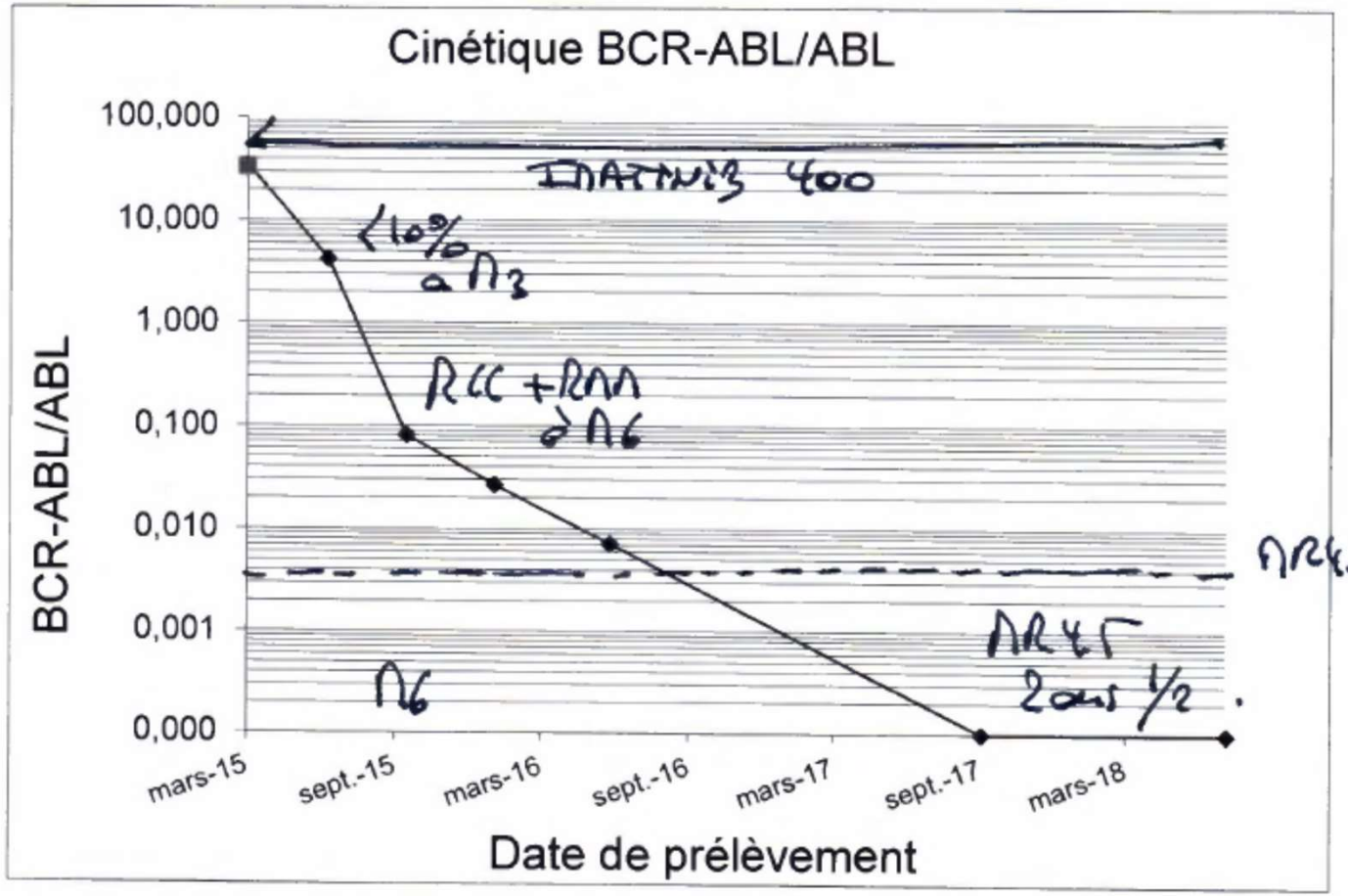

**BCR-ABLIS ≤ 1% = RCyC**

**BCR-ABLIS ≤ 0,1% = RMM**

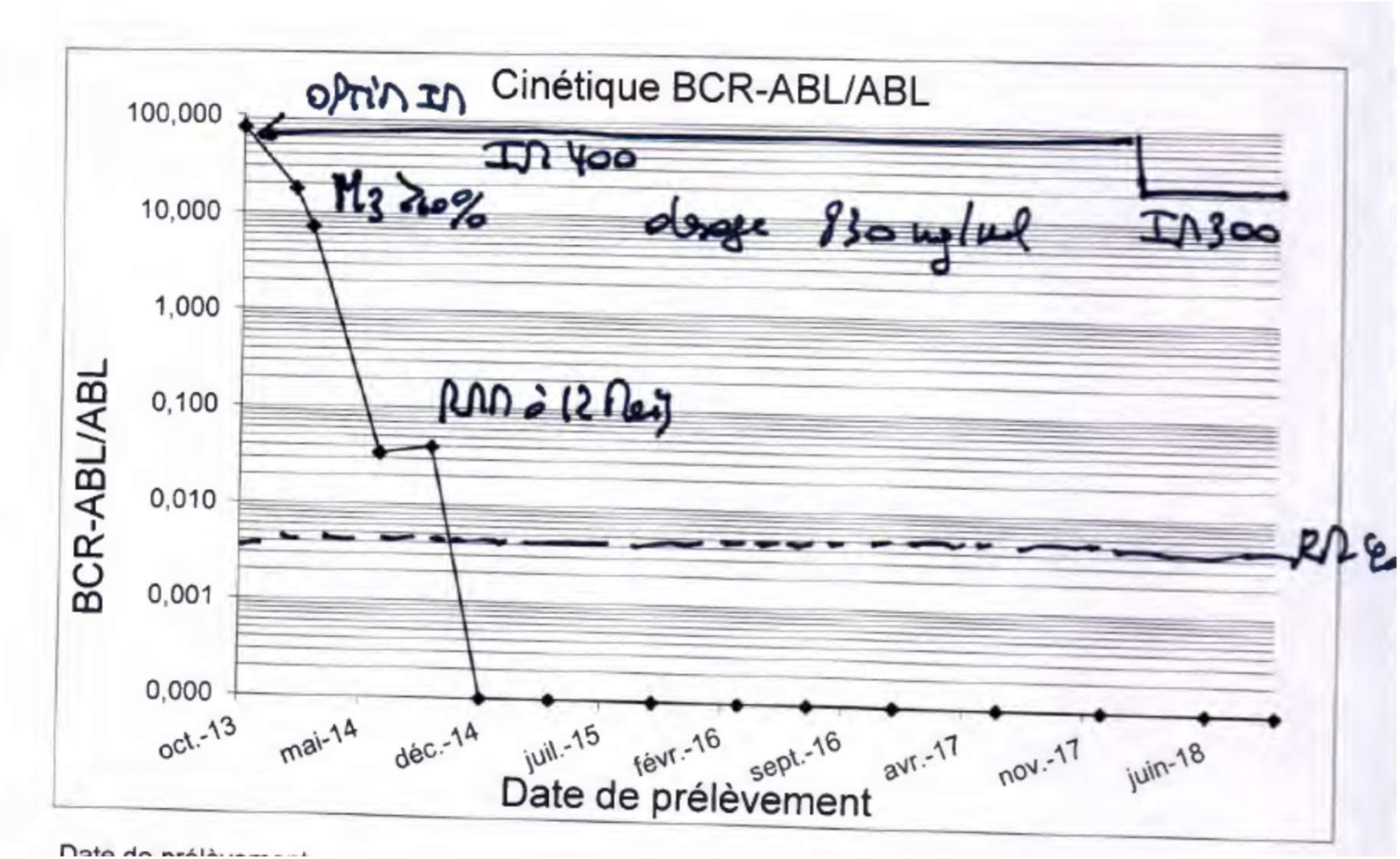
**BCR-ABLIS ≤ 0,01% = RM4**

**BCR-ABLIS ≤ 0,0032% = RM4.5**

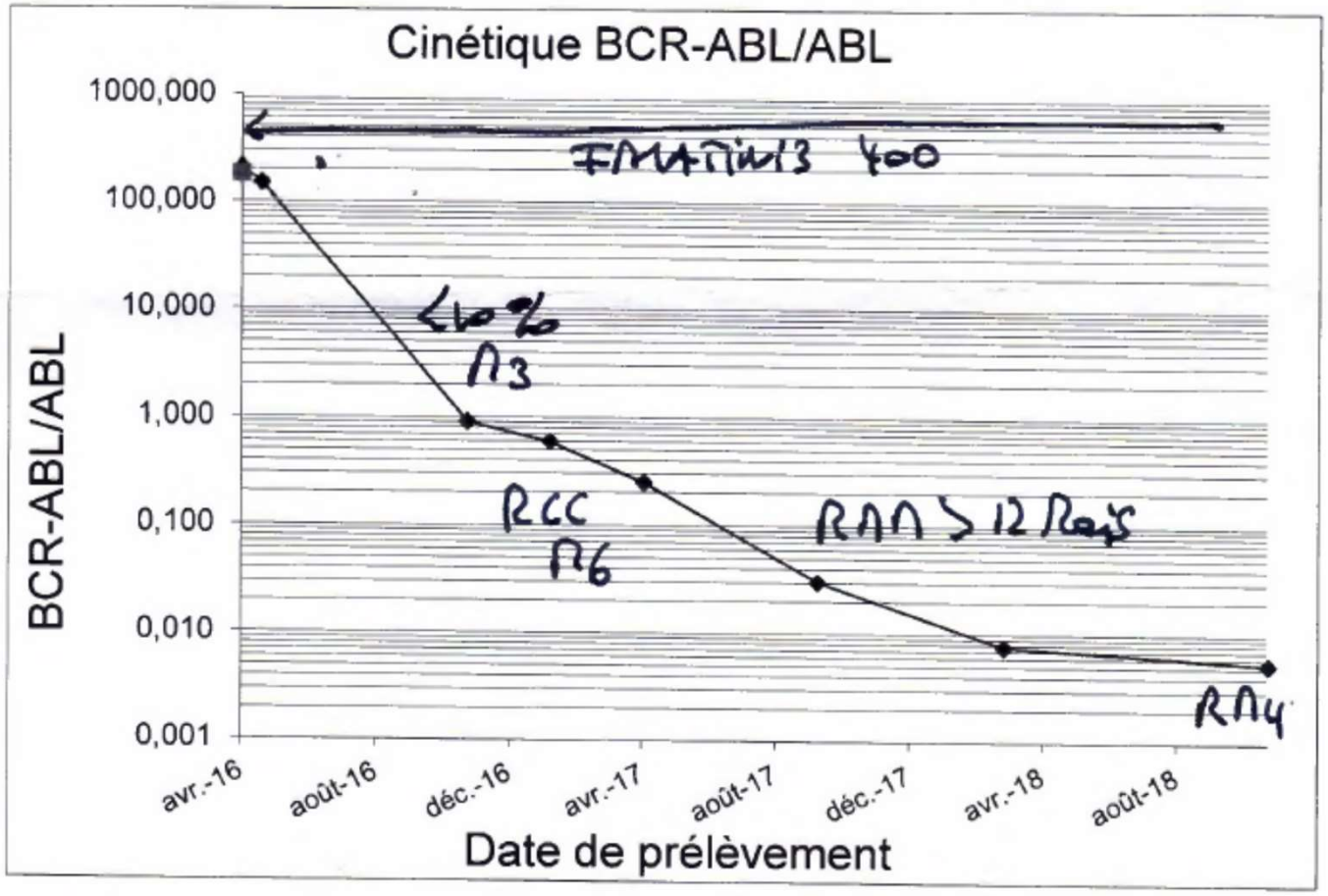
# Pt1. DDN 25/01/1987. Homme. Sokal Bas.



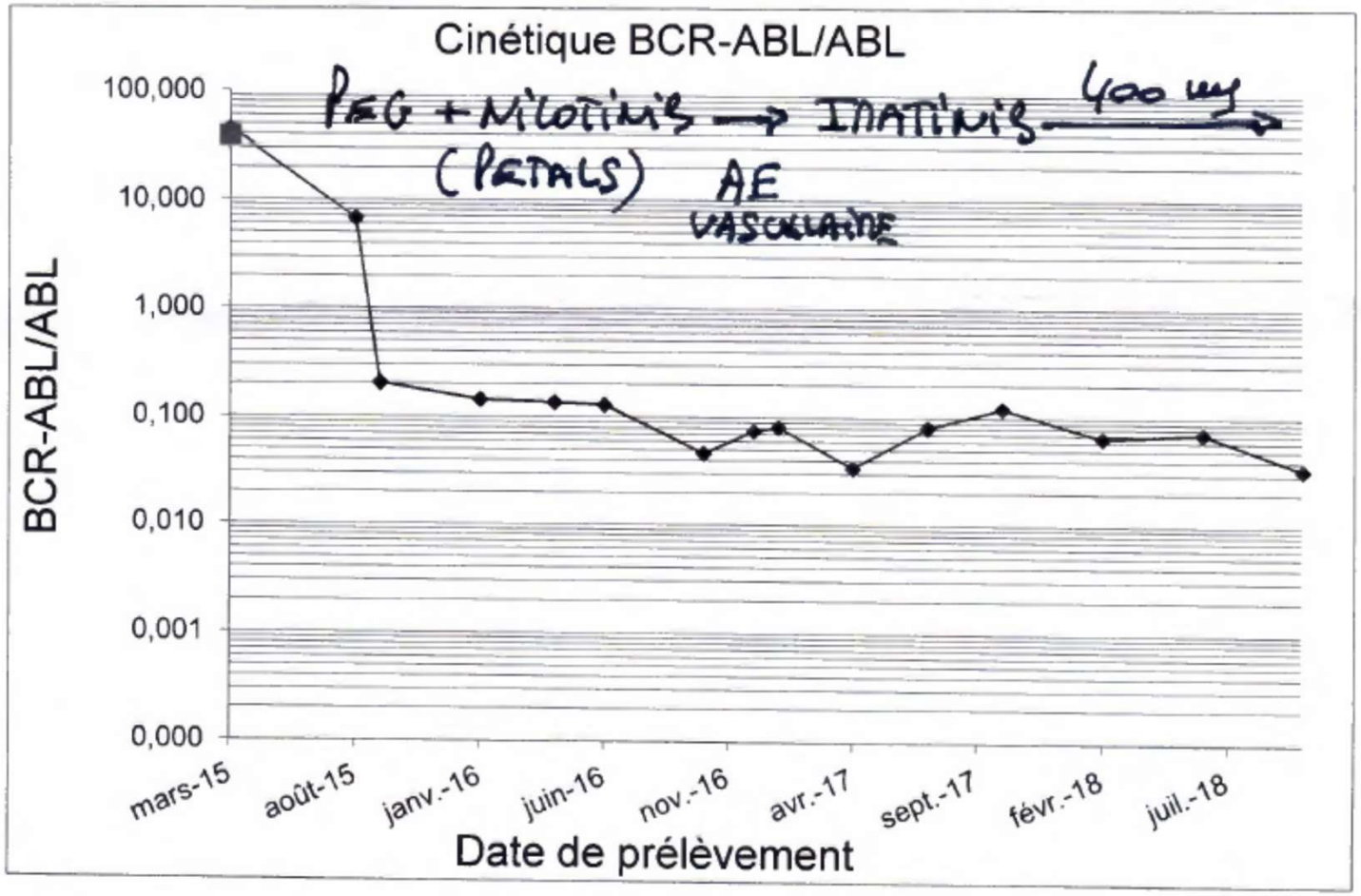
# Pt2. DDN 31/12/1948. Femme. Sokal Bas.



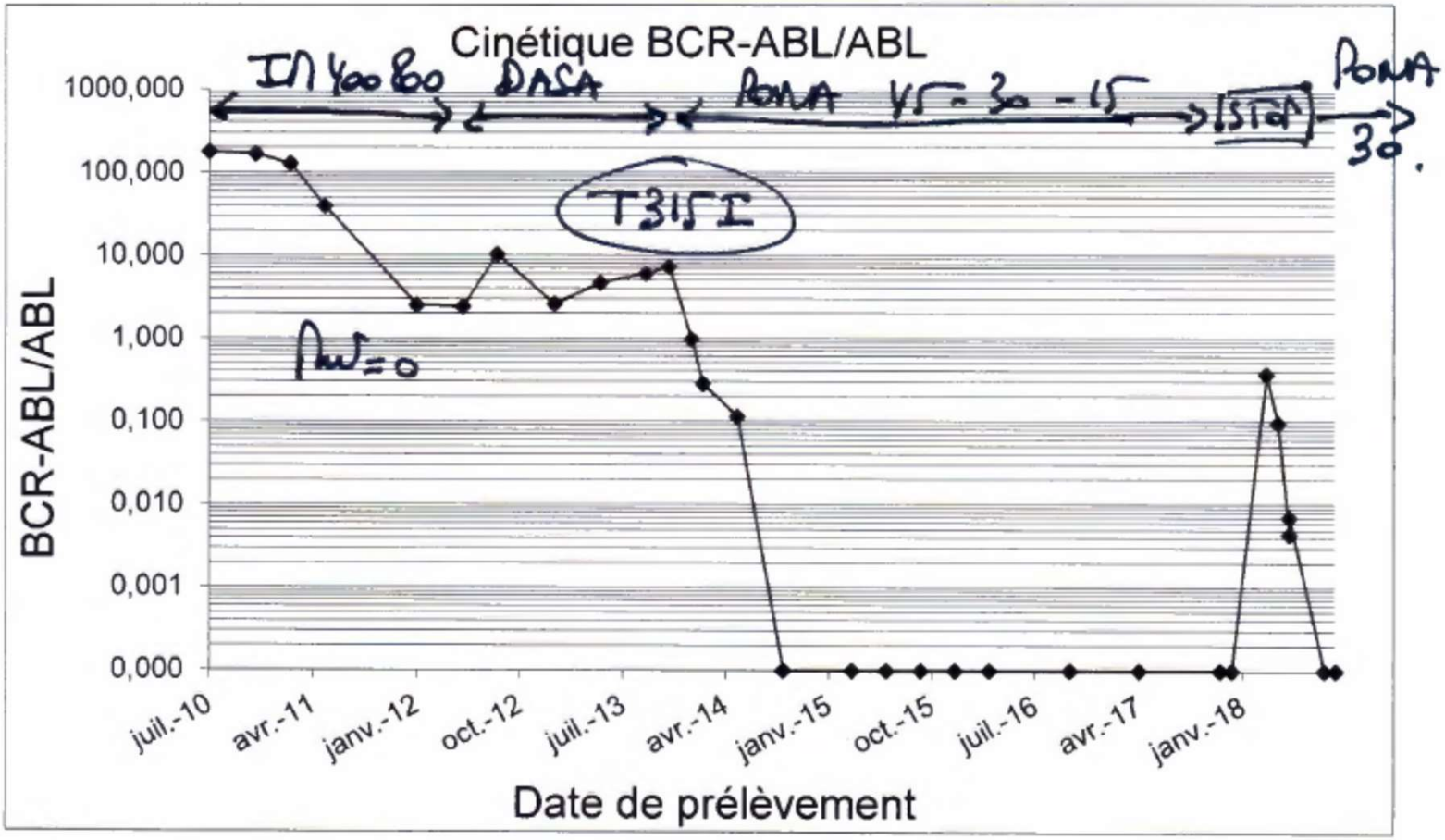
# Pt3. DDN 7/10/1948. Homme. Sokal Bas.



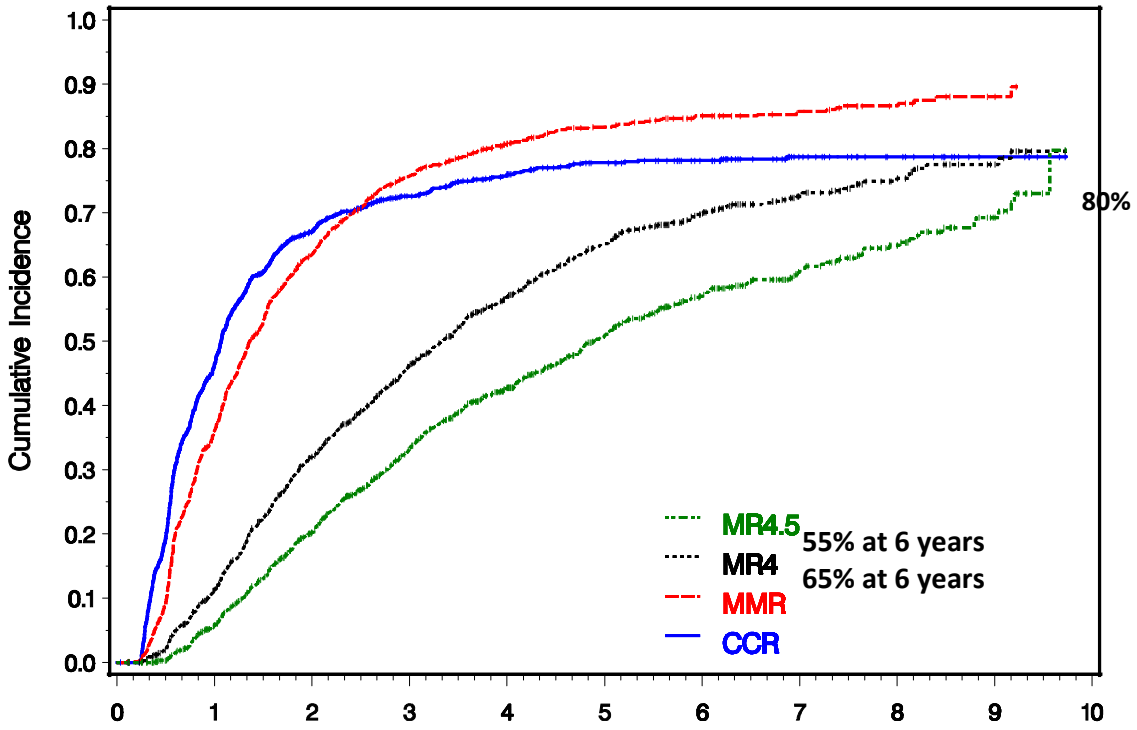
# Pt5. DDN 7/09/1958. Homme. Sokal Bas.



# Pt13. DDN 14/08/1966. Homme. Sokal Int.



# Improvement of the MR with time




**Patients at risk:** years after diagnosis

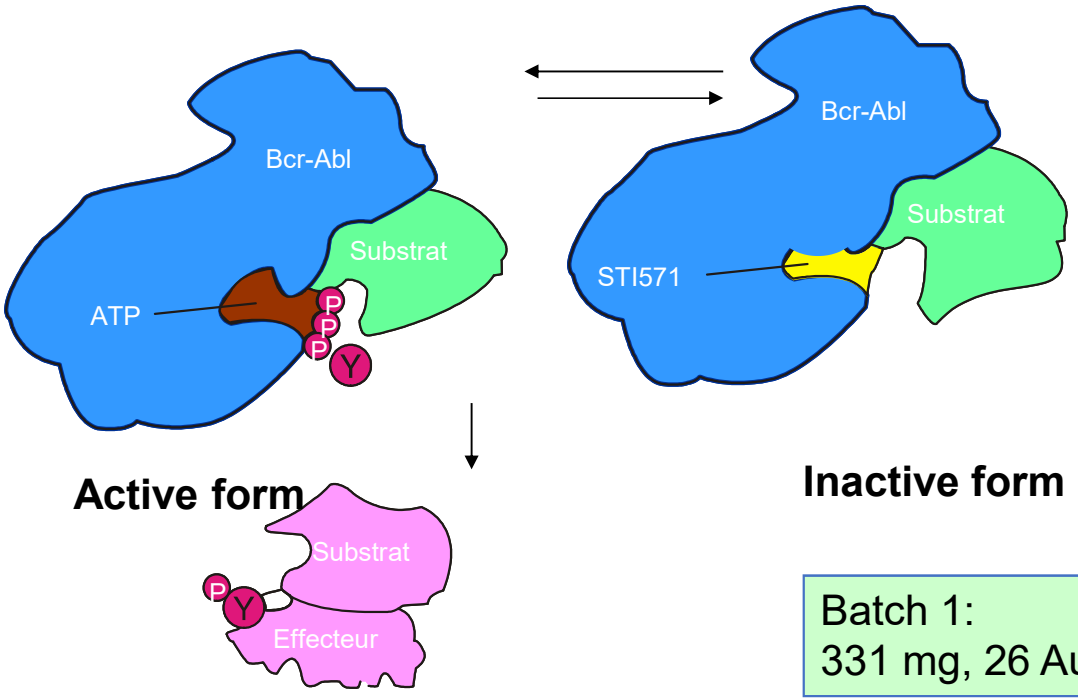
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| CCR | 1445 | 673 | 308 | 187 | 125 | 87 | 64 | 33 | 18 | 6 |
| MMR | 1409 | 793 | 356 | 172 | 98 | 61 | 34 | 22 | 11 | 3 |
| CMR4 | 1409 | 1125 | 739 | 479 | 305 | 191 | 110 | 60 | 29 | 12 |
| $CMR^{4.5}$ | 1347 | 1143 | 831 | 579 | 398 | 267 | 162 | 90 | 48 | 18 |

Hehlmann et al., JCO 2013, accepted

# Les traitements de première ligne en France en 2021

# Tyrosine Kinase inhibitor:

## Imatinib mesylate (STI571, CGP57148, Glivec®)




Batch 1:
331 mg, 26 August 1992

# Les AMM et les posologies des AMM

| Molécule | LMC- PC 1ère ligne | Posologie journalière | LMC- PC Ligne ≥ 2 | Posologie journalière | LMC-PB | Posologie journalière |
|---|---|---|---|---|---|---|
| Imatinib | X | 400 mg | | - | X | 400 mg x 2 |
| Dasatinib | *(X)* | 100 mg | X | 100 mg | X | 140 mg |
| Nilotinib | X | 300 mg x 2 | X | 400 mg x 2 | | |
| Bosutinib | X | 400 mg | X | 500 mg | X | 500 mg |
| Ponatinib | | 45 mg | X (T315I) | 45 mg | X | 45 mg |

# Toxicités des ITKs

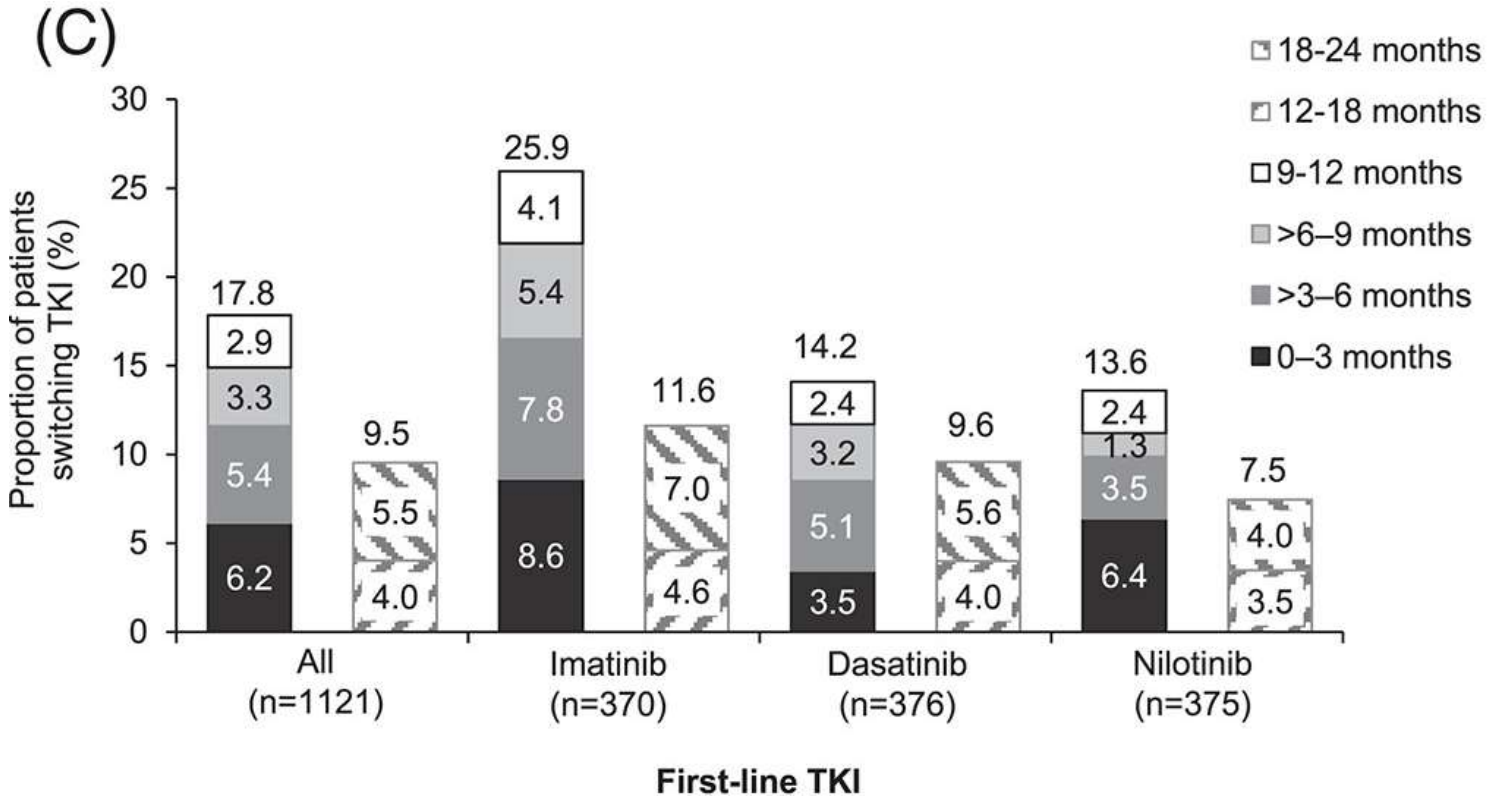
REVIEW

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

JL Steegmann[1], M Baccarani[2], M Breccia[3], LF Casado[4], V García-Gutiérrez[5], A Hochhaus[6], D-W Kim[7], TD Kim[8], HJ Khoury[9], P Le Coutre[8], J Mayer[10], D Milojkovic[11], K Porkka[12,13], D Rea[14], G Rosti[2], S Saussele[15], R Hehlmann[16] and RE Clark[17]

| Effets Indésirables | Imatinib | Nilotinib | Dasatinib | Bosutinib | Ponatinib |
|---|---|---|---|---|---|
| Œdème Facial | ++ | +/– | +/– | +/– | – |
| Œdème Périphérique | + | +/– | + | +/– | – |
| Epanchement pleural | – | – | ++ | – | – |
| Epanchement péricardique | – | – | +/– | – | – |
| Constipation | + | + | – | – | + |
| Diarrhée | ++ | + | + | ++ | – |
| Réactivation Virale | – | – | +/– | – | – |
| Saignements majeurs | +/– | – | +/– | – | – |
| Maladie Oblitérante Artérielle Périphérique | –* | ++ | +/–* | +/–* | ++ |
| Thrombose Veineuse | – | – | – | – | +/– |
| Hypertension Pulmonaire | – | – | +/– | – | –– |
| Rash | + | ++ | + | + | ++ |
| Crampes musculaires ou myalgie | ++ | + | + | +/– | + |
| ↑ glycémie à jeun | + | ++ | – | – | – |
| ↑ lipase ou amylase | + | + | – | – | + |

# Tyrosine kinase inhibitor interruptions, discontinuations and switching in patients with chronic-phase chronic myeloid leukemia in routine clinical practice: SIMPLICITY




Tyrosine kinase inhibitor interruptions, discontinuations and switching in patients with chronic-phase chronic myeloid leukemia in routine clinical practice: SIMPLICITY, First published: 05 October 2018, DOI: (10.1002/ajh.25306)

# Gestion des posologies

**Evaluation du bénéfice/risque à l'échelon individuel aidé par…**

- **Prise en compte de facteurs prédictifs d'EIs (graves) :**
  - Age : épanchement pleural et dasatinib
  - Facteurs de risque et historique vasculaire : nilotinib et ponatinib
  - Hépatopathies chroniques : bosutinib
- **Intérêt d'une prophylaxie primaire active :**
  - Troubles du transit et bosutinib
  - Traitements adaptés au risque cardiovasculaire : étude PALERMO
- **Gestion de la dose :**
  - Escalade/désescalade de dose : BOSUSTEP, Bosutinib 100 – 200 – 300 – 400 mg
  - Rationalisée : outil pharmacocinétique : OPTIM-DASA, dasatinib selon résiduelle < 3 nM
  - Selon la réponse au traitement : OPTIC, si RCC réduction ponatinib à 15 mg
    DESTINY, tout ITK, si RMM, demi-dose

# Quel ITK choisir ?

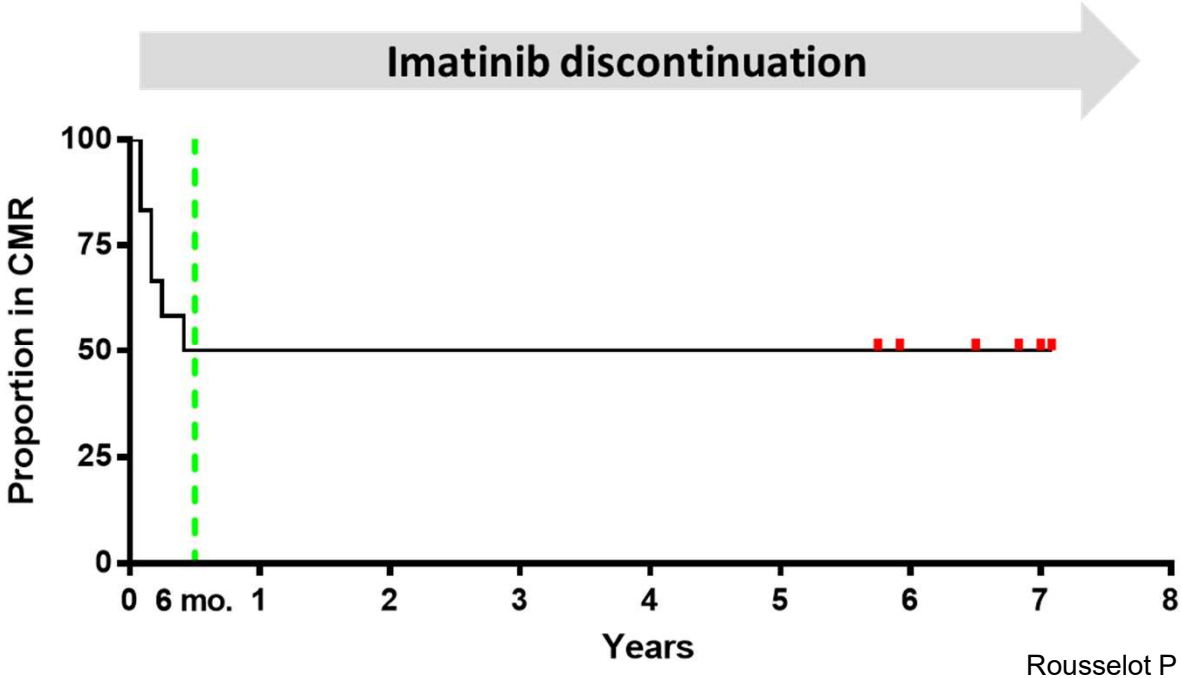
# Objectif : survie à long terme

| ITK2G *vs* IM 400 mg/j | ENESTnd (nilotinib 300 mg x 2)<br>Saglio, *NEJM* 2010<br>Kantarjian, *Leukemia 2021* | DASISION (dasatinib 100 mg/j)<br>Kantarjian, *NEJM* 2010<br>Cortes, *J Clin Oncol 2016* | BFORE (bosutinib 400 mg/j)<br>Cortes, *JCO* 2017<br>Brümmendorf, *ASH 2020* |
|---|---|---|---|
| < 10 % à M3 | - | - | 75 % *vs* 57 % |
| RCC dans les 12 mois | 80% *vs* 65%, p < 0,001<br>HR Sokal 74% *vs* 49% | *77% *vs* 66%, p = 0,007<br>HR Hasford 78% *vs* 64% | 77% *vs* 66%, p = 0,0075 |
| RMM à M12 | *40% *vs* 22%, p < 0,001<br>HR Sokal 17% *vs* 41% | 46% *vs* 28%, p = 0,0001 | *47% *vs* 37%, p = 0,02<br>HR Sokal 34% *vs* 17% |
| RMM cumulative | 83% *vs* 70% à 10 ans | 76% *vs* 64% à 5 ans | 74% *vs* 65% à 5 ans |
| RM4.5 cumulative | 64% *vs* 45% à 10 ans | 42% *vs* 33% à 5 ans | 48% *vs* 37% à 5 ans |
| PFS/EFS/OS | **EFS 92% *vs* 90% à 10 ans**<br>**OS 88% *vs* 88% à 10 ans** | **PFS 85% *vs* 86% à 5 ans**<br>**OS 91% *vs* 90% à 5 ans** | **EFS 91% *vs* 93% à 5 ans**<br>**OS 95 *vs* 95% à 5 ans** |
| Arrêt de l'ITK randomisé | 40% *vs* 50% à 10 ans | 39% *vs* 37% à 5 ans | 40% *vs* 43% à 5 ans |

# Les arrêts de traitement

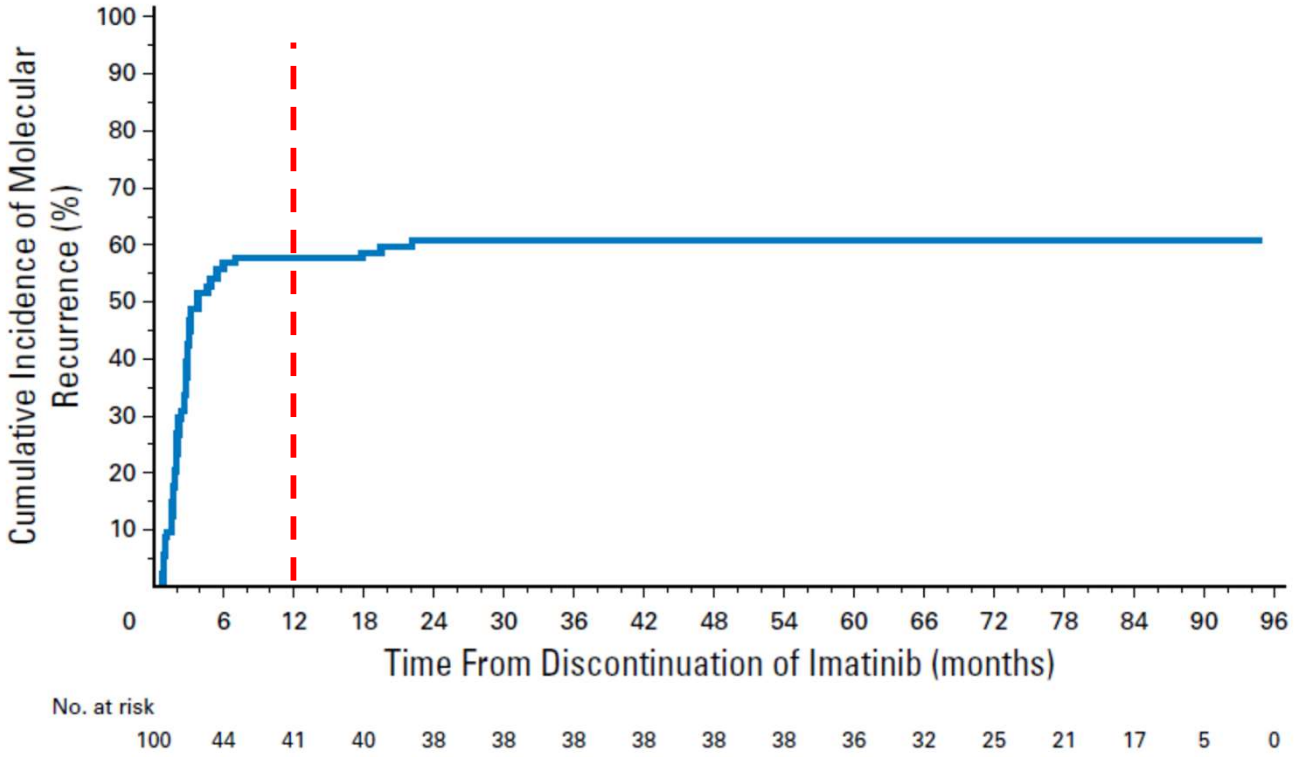
# The Pilot Stop IMatinib (pilot STIM) Study more than 10 Years ago…

- 12 patients in long term CMR with imatinib : STOP imatinib
- **Definition of CMR : CMR 4.5 during 2 years (BCR-ABL$^{IS}$ < 0.0032%)**
- **Definition of relapse : Two consecutive positive RTQ-PCR**
- 6 patients relapsed early and 6 remained treatment free on the very long term




Rousselot P et al., *Blood*. 2007;109:58–60; and personal data.

# The multicentric STIM1 study (n=100)

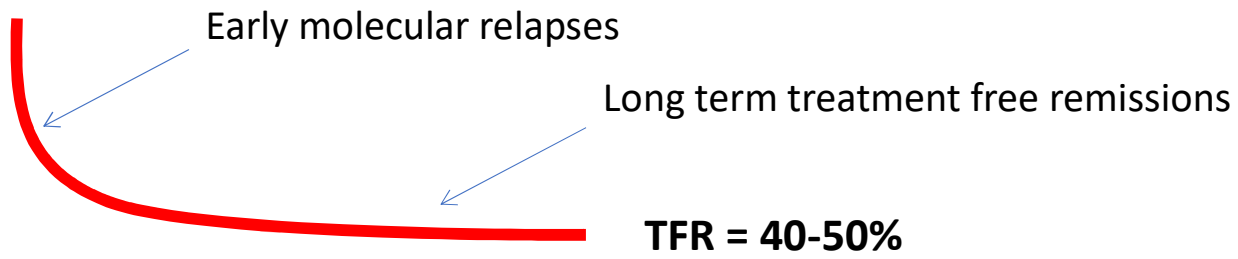



**Cumulative incidence of molecular recurrence 60%**

STIM1. Etienne G, et al. J Clin Oncol 2016.

# Results are reproducible

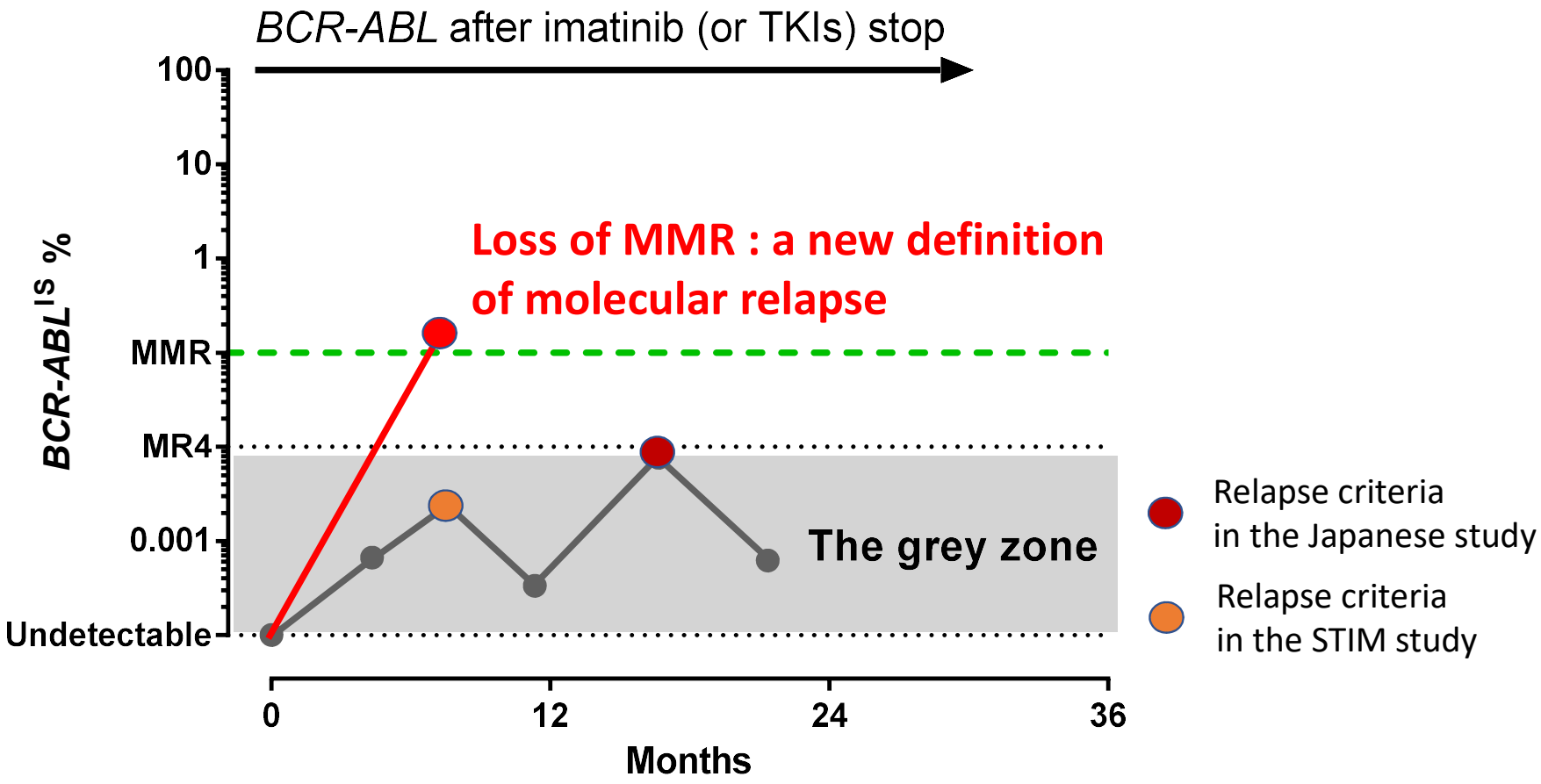
- > 1000 patients in clinical trials over the world
- All curves have a very similar shape




  - Across
    - Different studies
    - Different countries
  - Despite
    - Differences in eligibility criteria
    - Differences in molecular relapse criteria

Rousselot P et al., Blood. 2007;109:58–60.
Mahon FX, et al, Lancet Oncol. 2010; 11:1029-35.
Ross D, et al. *Blood*. 2013;122:515-522.
Yhim HY, et al. Leuk Res. 2012;36(6):689-693.
Takahashi N, et al. *Haematologica.* 2012;97:903-906.

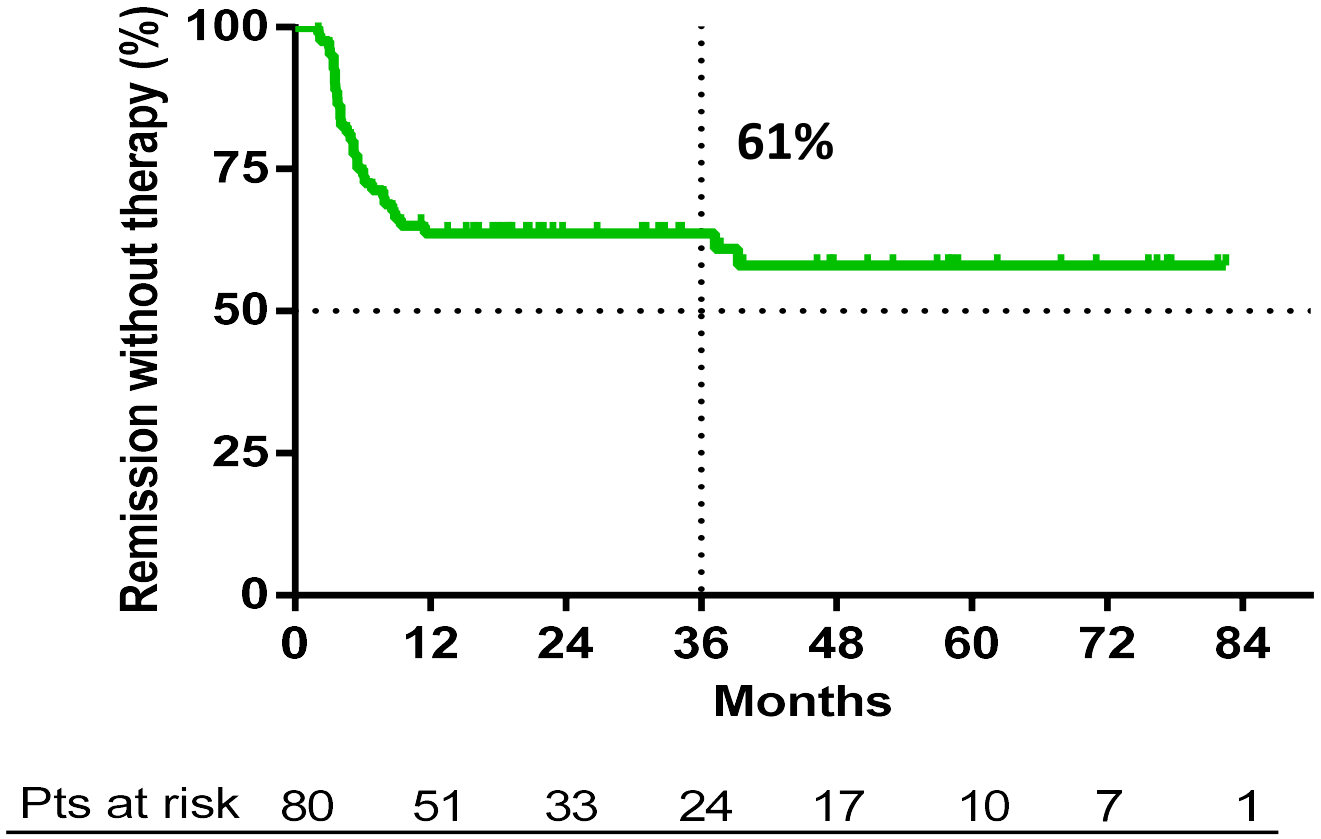
# How to define a molecular recurrence ?




Rousselot et al. J Clin Oncol. 2014 Feb 10;32(5):424-30.

# TFR using loss of MMR for molecular relapse

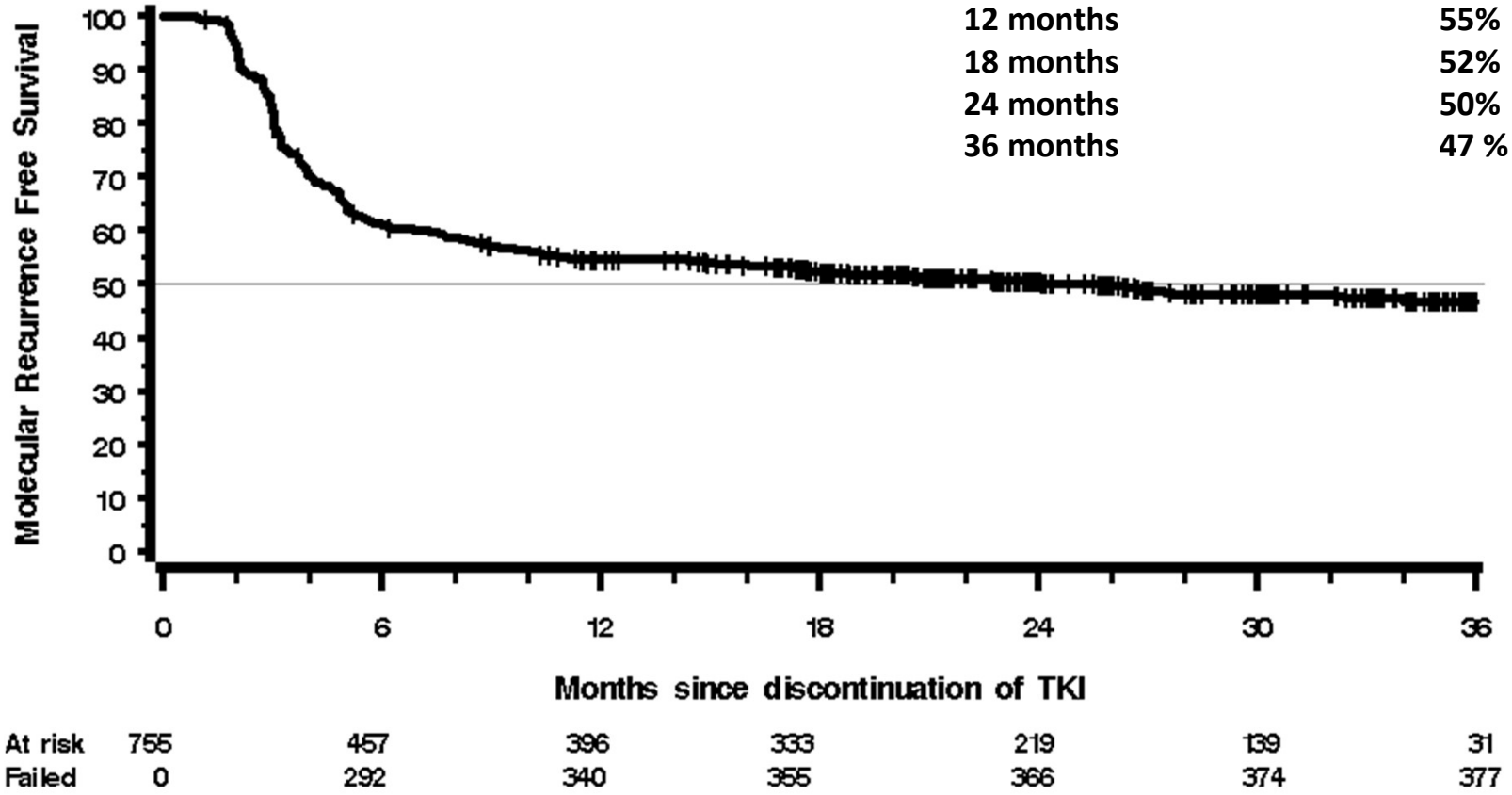
A-STIM study (80 pts)




Rousselot et al. J Clin Oncol. 2014 Feb 10;32(5):424-30.

# Molecular recurrence-free survival (n=755)

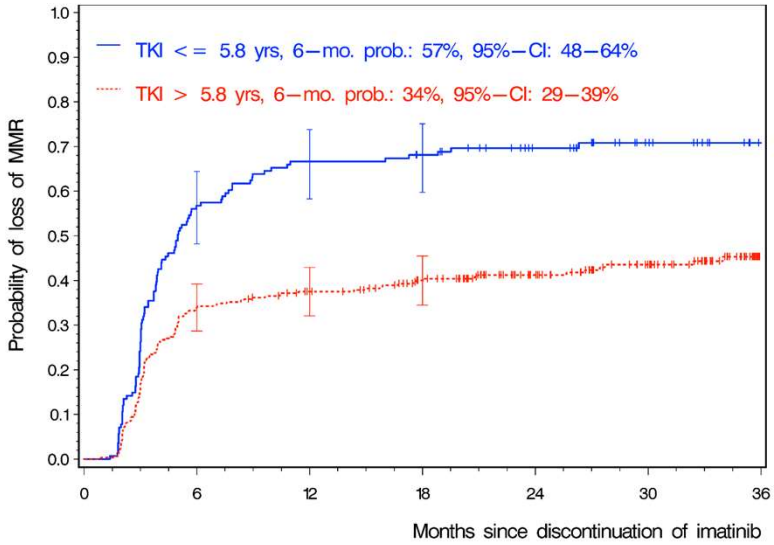
| Months | MRFS | (95% CI) |
|---|---|---|
| 6 months | 61% | (58% - 65%) |
| 12 months | 55% | (51% - 58%) |
| 18 months | 52% | (49% - 56%) |
| 24 months | 50% | (47% - 54%) |
| 36 months | 47 % | (43% - 51%) |




EURO-SKI presented by FX Mahon at ASH 2016

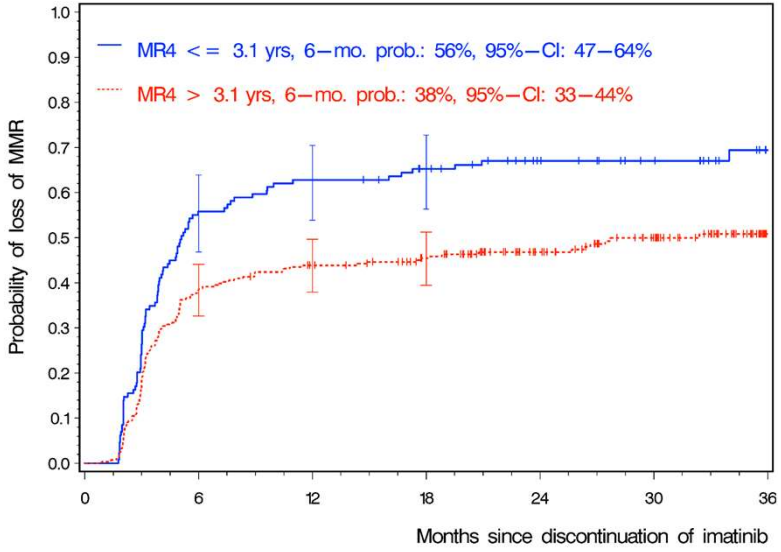
# EUROSKI: Factors associated with MRFS

**Duration of imatinib treatment**




N=448

**Duration of MR4 during imatinib**

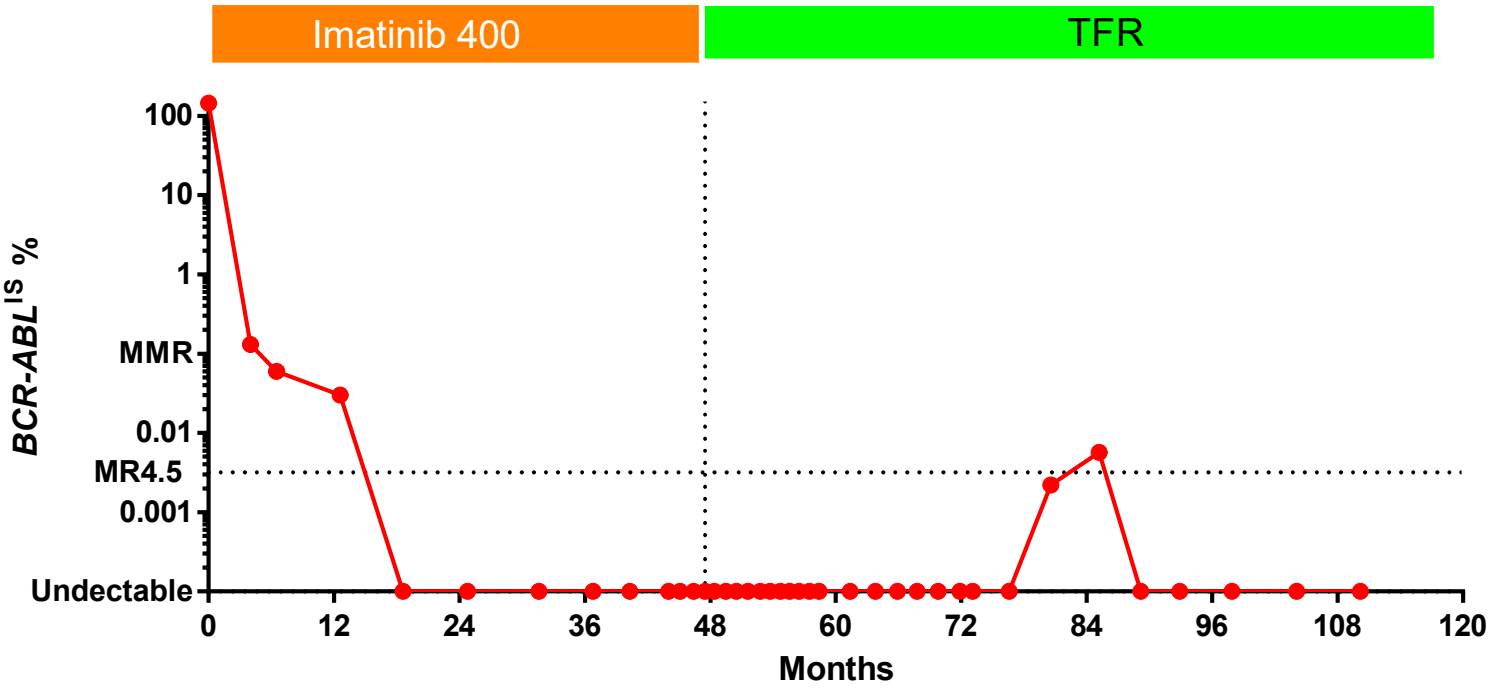



N=405

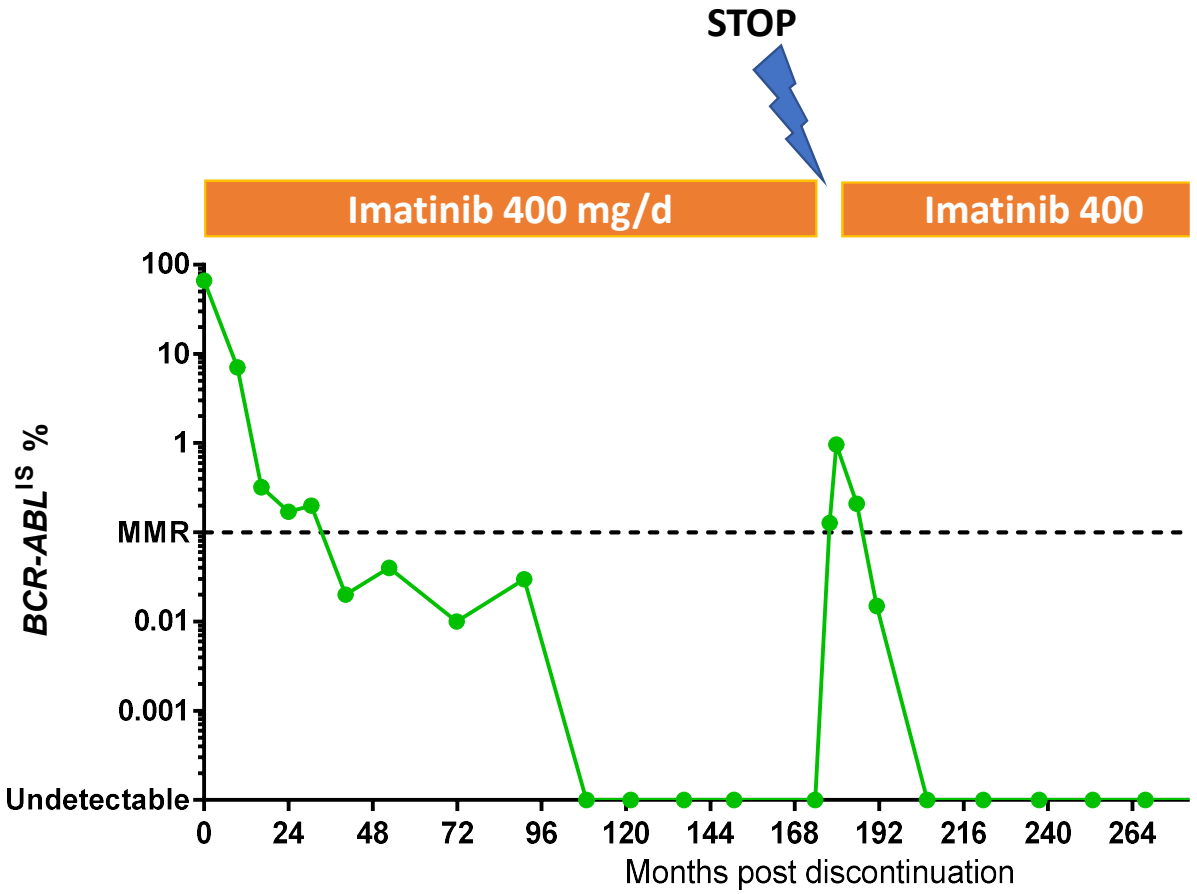
- **Positive impact of interferon therapy**
- **No impact of Sokal score, age, gender**

Mahon FX et al. *Blood*. 2016:[abstract 787].
Pfirrmann M et al. *Blood*. 2016:[abstract 789].

**Mrs L, 47 years, CML low risk, 2008**



# Molecular response after loss of MR




Personal data

# Critères pour l'arrêt du traitement

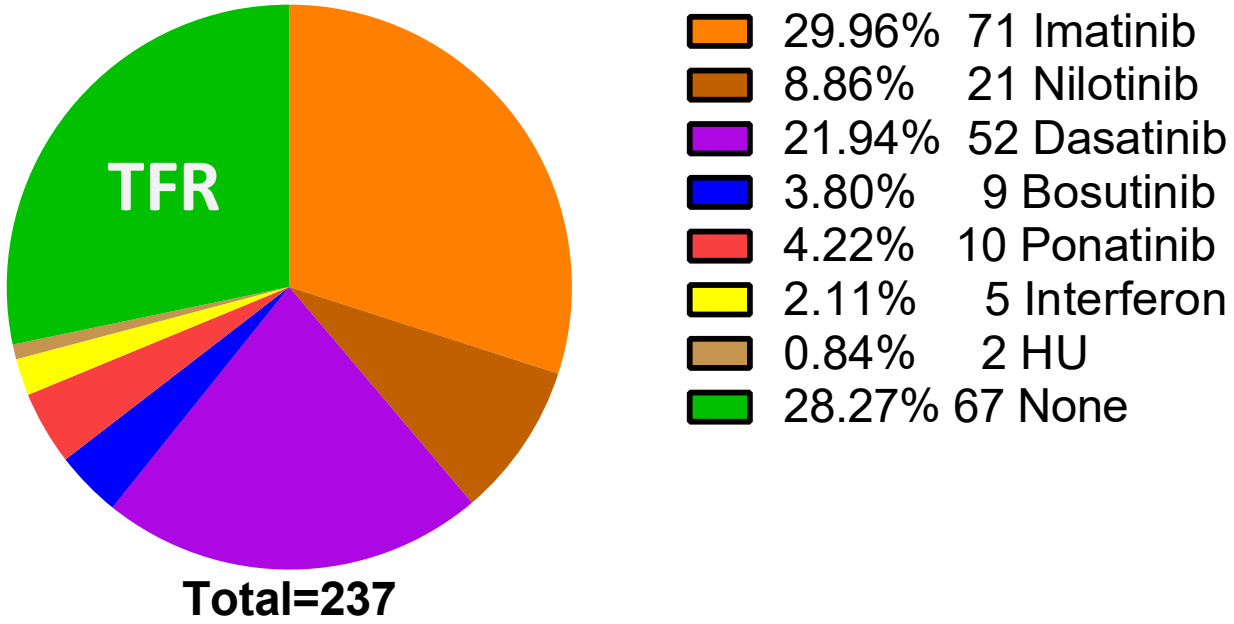
| Reference | Hughes *et al.* Blood 2016 | Rea *et al.* Cancer 2018 | Radich *et al.* J Natl Compr Canc Netw. 2018 | Hochhaus *et al.* Leukemia 2020 |
|---|---|---|---|---|
| Proposed selection criteria for optimal TKI discontinuation | CP only<br><br>*BCR-ABL1* transcript e13a2 or e14a2<br><br>MR4.5 sustained > 24 months<br><br>TKI duration > 8 years<br><br>Optimal response to first-line TKI<br><br>Sokal non high | CP only<br><br>*BCR-ABL1* transcript e13a2 or e14a2<br><br>MR4.5 sustained > 24 months<br><br>TKI duration > 5 years<br><br>No prior AHSCT, progression, resistance, suboptimal response or warning<br><br>≥ 18 years at TKI discontinuation | CP only<br><br>Prior evidence of quantifiable *BCR-ABL1* transcript<br><br>MR4 sustained ≥ 24 months<br><br>TKI duration ≥ 3 years<br><br>No prior history of accelerated or blast phase CML<br><br>Age ≥ 18 years | CP-CML in first CP<br><br>Typical *BCR-ABL1* transcript (e13a2, e14a2)<br><br>MR4 > 3 years or MR4.5 > 2 years<br><br>TKI duration > 5 years<br><br>First-line TKI or 2nd line if change related to intolerance<br><br>No prior treatment failure |

Etienne G et al. Cancer Medicine 2021

# How many CML-CP patients in TFR in my institution ?

Versailles CML cohort

237 patients, ≥ 5 years from Dg

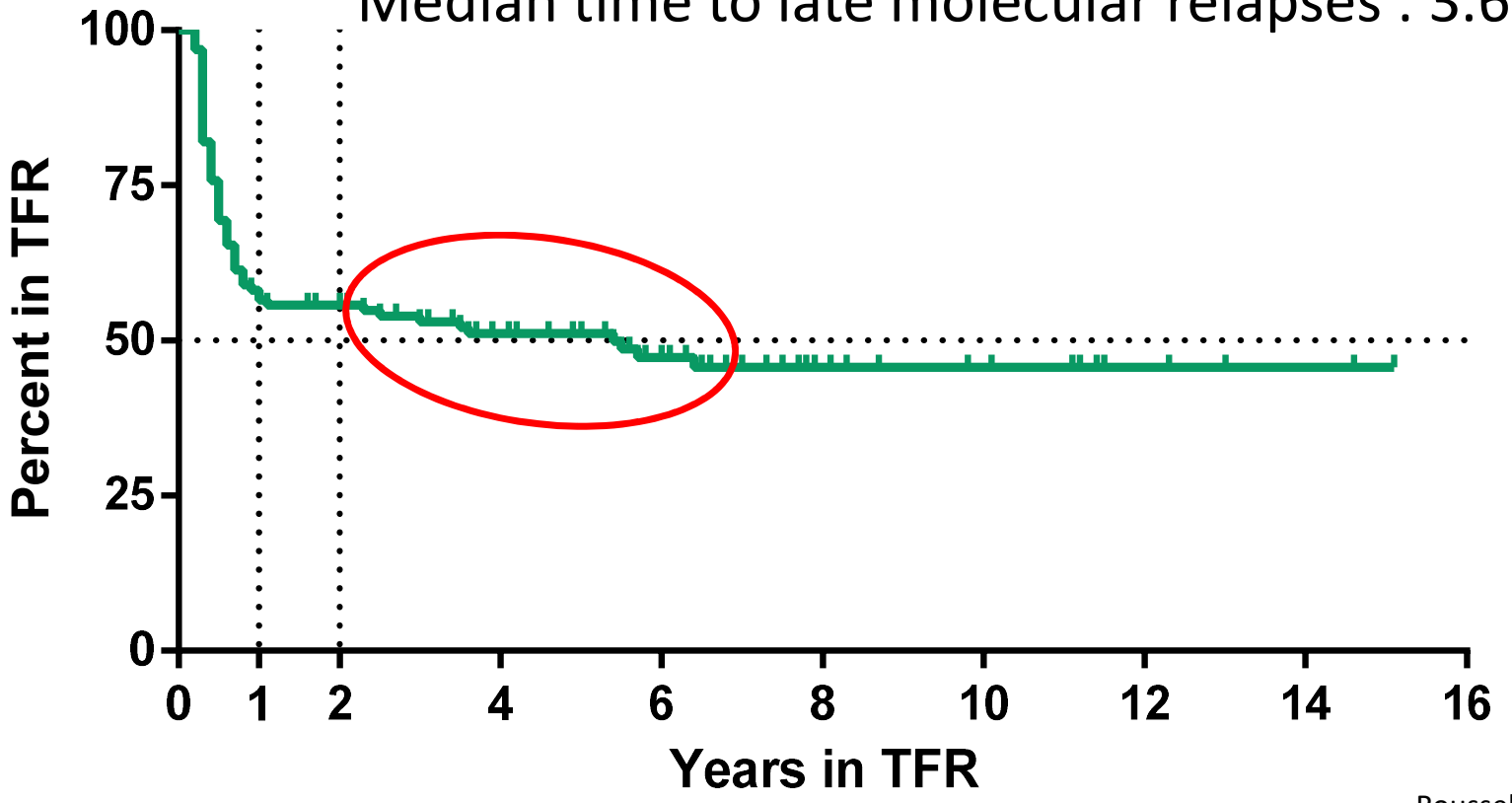



Rousselot : Personal data.

# Late relapses (> 2 years in TFR1)

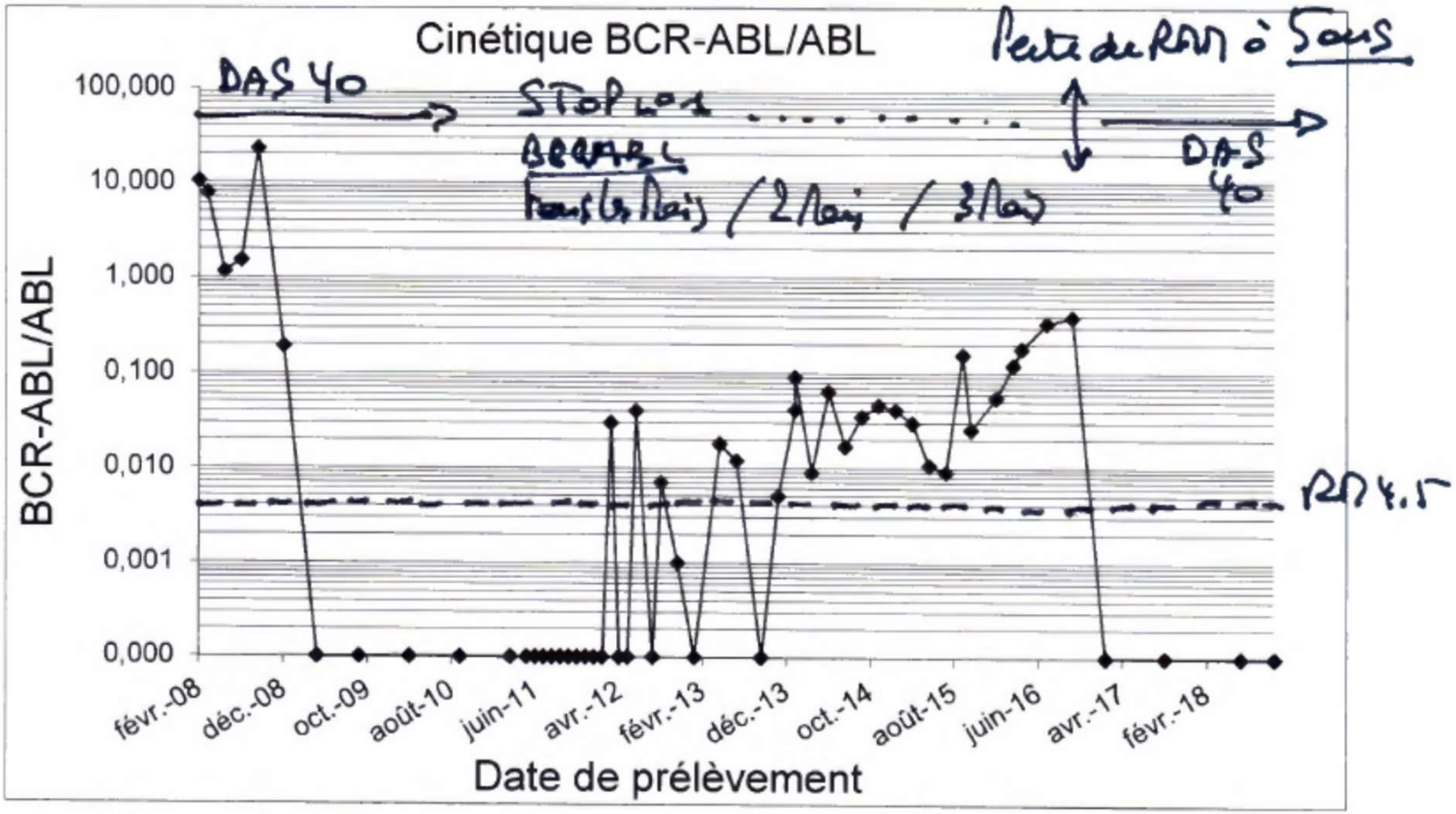
**n=9** out 65 molecular relapses (**13.8%**)

Median time to late molecular relapses : 3.6 years (2.3-6.3)

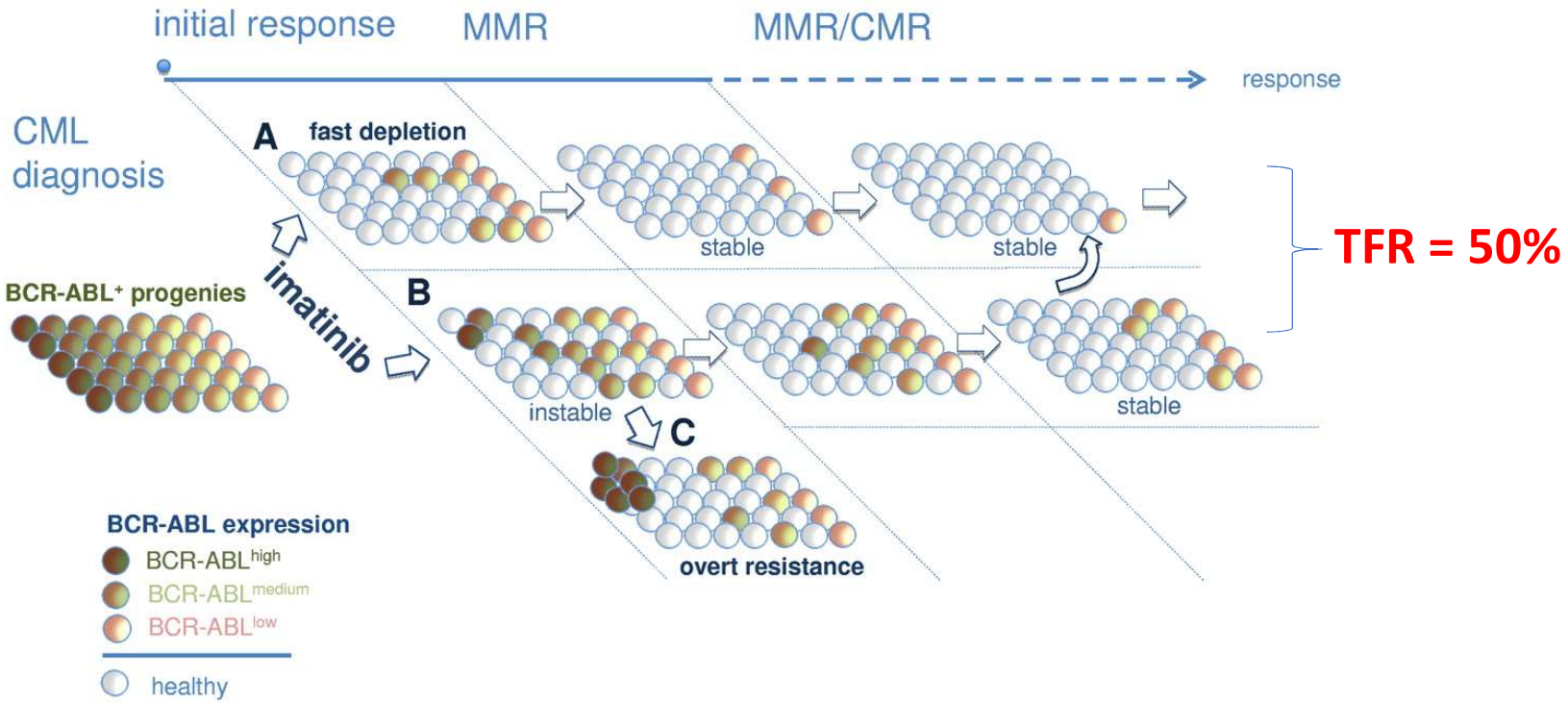



Rousselot et al. Blood Advance 2020

# Pt12. DDN 22/01/1958. Femme. Sokal Bas.



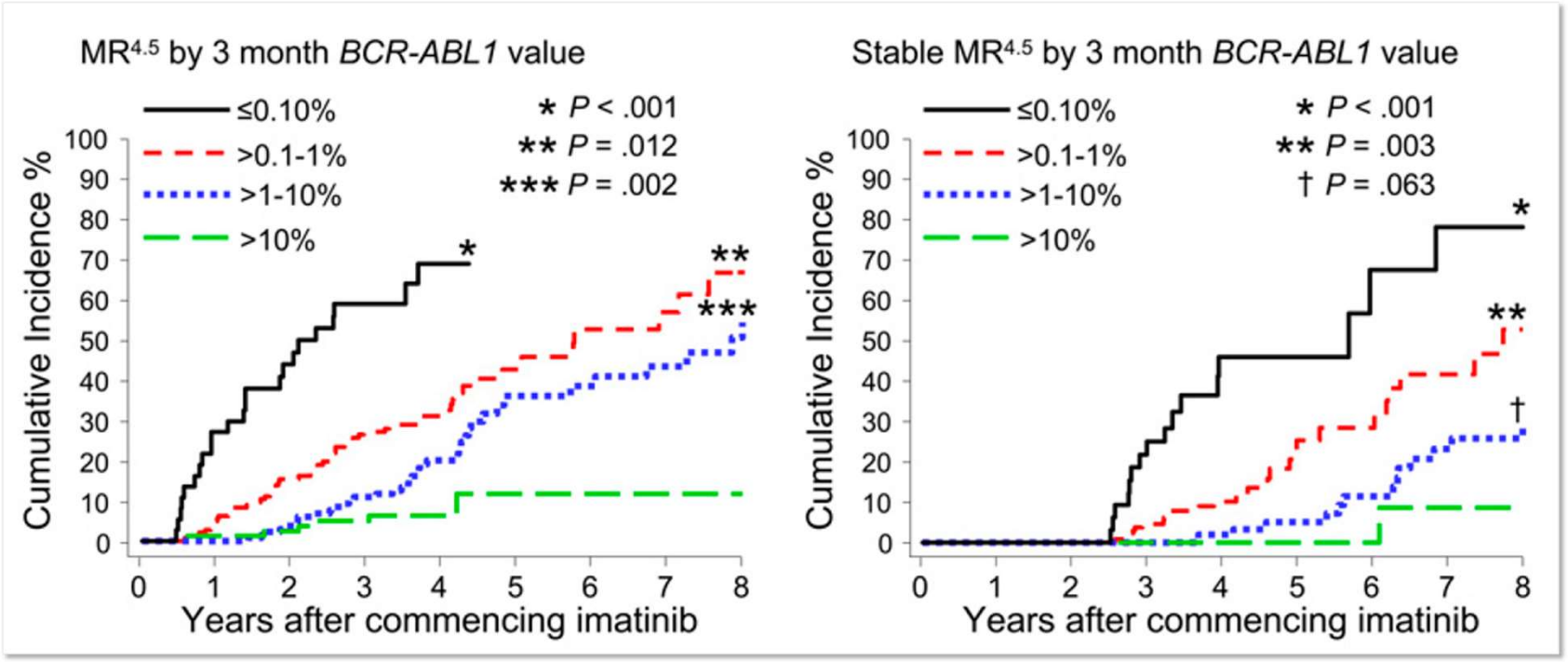
# Limitations of TKI monotherapy




adapted from Kumari A et al. Blood.2012;119(2):530-539.

# Objectif : arrêt du traitement

- La réponse moléculaire précoce prédit la réponse moléculaire tardive

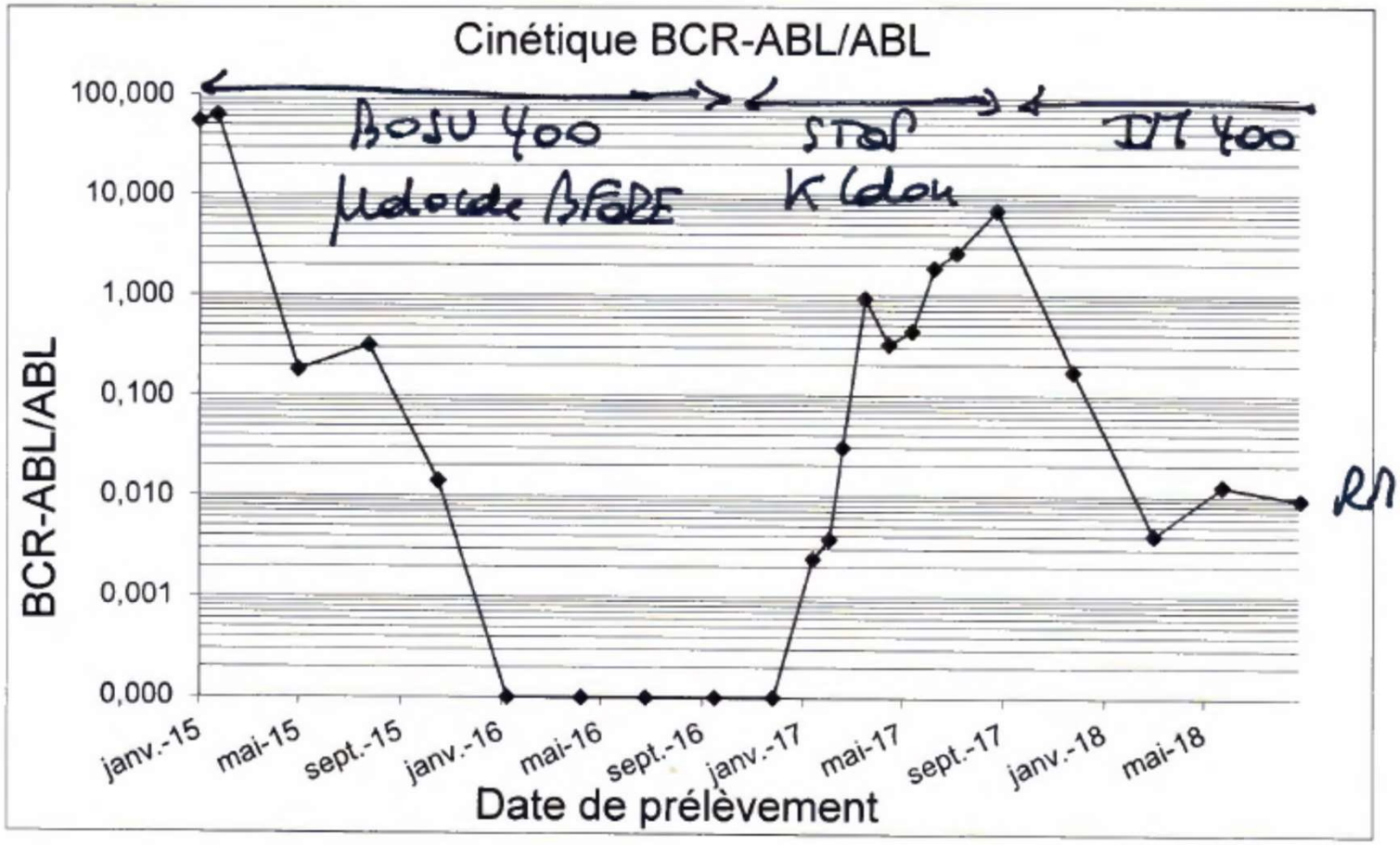



Branford S et al. Blood 2013;121:3818-3824

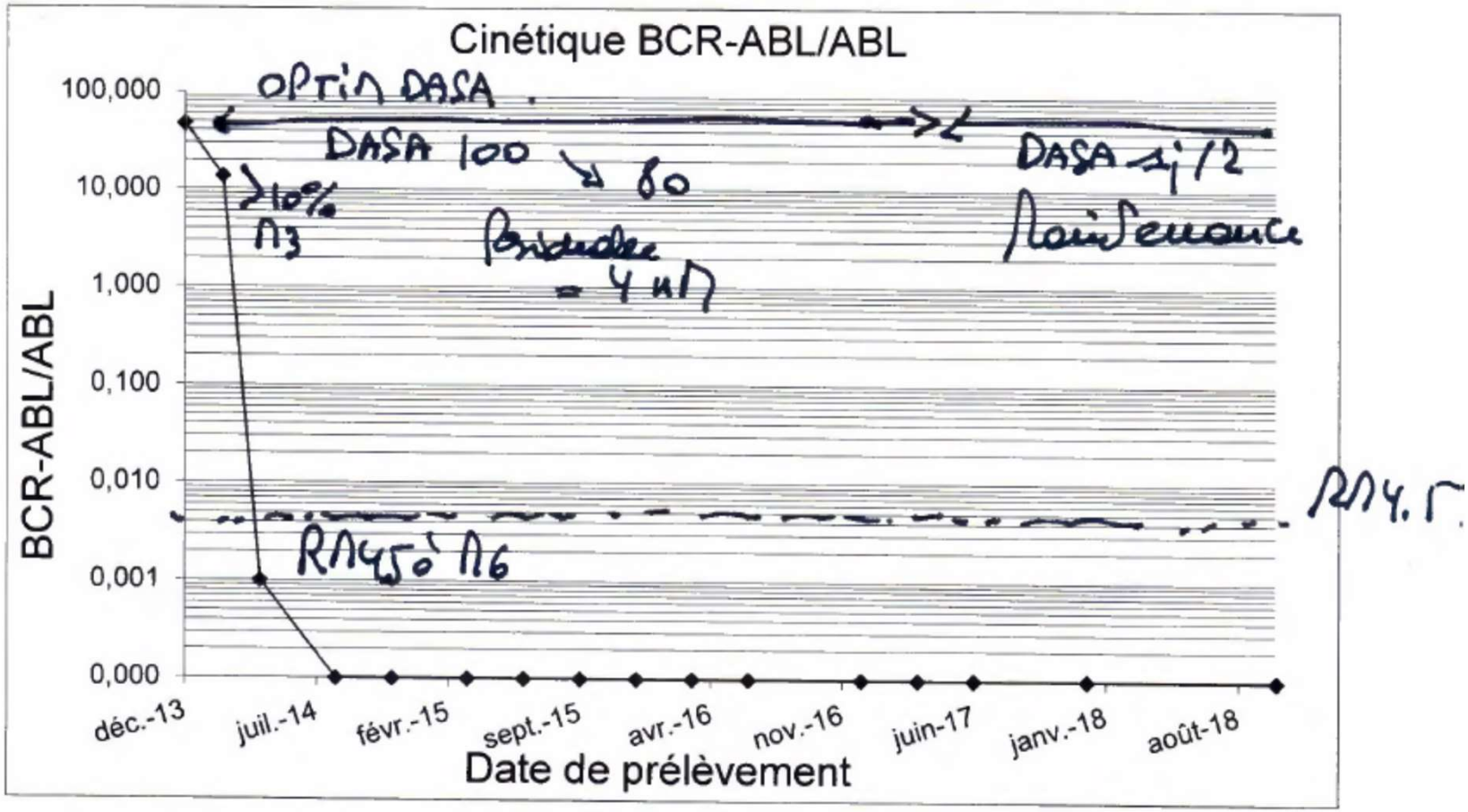
# Objectif : arrêt du traitement

| ITK2G *vs* IM 400 mg/j | ENESTnd (nilotinib 300 mg x 2)<br>Saglio, *NEJM* 2010<br>Kantarjian, *Leukemia 2021* | DASISION (dasatinib 100 mg/j)<br>Kantarjian, *NEJM* 2010<br>Cortes, *J Clin Oncol 2016* | BFORE (bosutinib 400 mg/j)<br>Cortes, *JCO* 2017<br>Brümmendorf, *ASH 2020* |
|---|---|---|---|
| **< 10 % à M3** | - | - | 75 % *vs* 57 % |
| **RCC dans les 12 mois** | 80% *vs* 65%, p < 0,001<br>HR Sokal 74% *vs* 49% | *77% *vs* 66%, p = 0,007<br>HR Hasford 78% *vs* 64% | 77% *vs* 66%, p = 0,0075 |
| **RMM à M12** | ***40% *vs* 22%, p < 0,001**<br>**HR Sokal 17% *vs* 41%** | **46% *vs* 28%, p = 0,0001** | ***47% *vs* 37%, p = 0,02**<br>**HR Sokal 34% *vs* 17%** |
| **RMM cumulative** | 83% *vs* 70% à 10 ans | 76% *vs* 64% à 5 ans | 74% *vs* 65% à 5 ans |
| **RM4.5 cumulative** | **64% *vs* 45% à 10 ans** | **42% *vs* 33% à 5 ans** | **48% *vs* 37% à 5 ans** |
| **PFS/EFS/OS** | EFS 92% *vs* 90% à 10 ans<br>OS 88% *vs* 88% à 10 ans | PFS 85% *vs* 86% à 5 ans<br>OS 91% *vs* 90% à 5 ans | EFS 91% *vs* 93% à 5 ans<br>OS 95 *vs* 95% à 5 ans |
| **Arrêt de l'ITK randomisé** | 40% *vs* 50% à 10 ans | 39% *vs* 37% à 5 ans | 40% *vs* 43% à 5 ans |

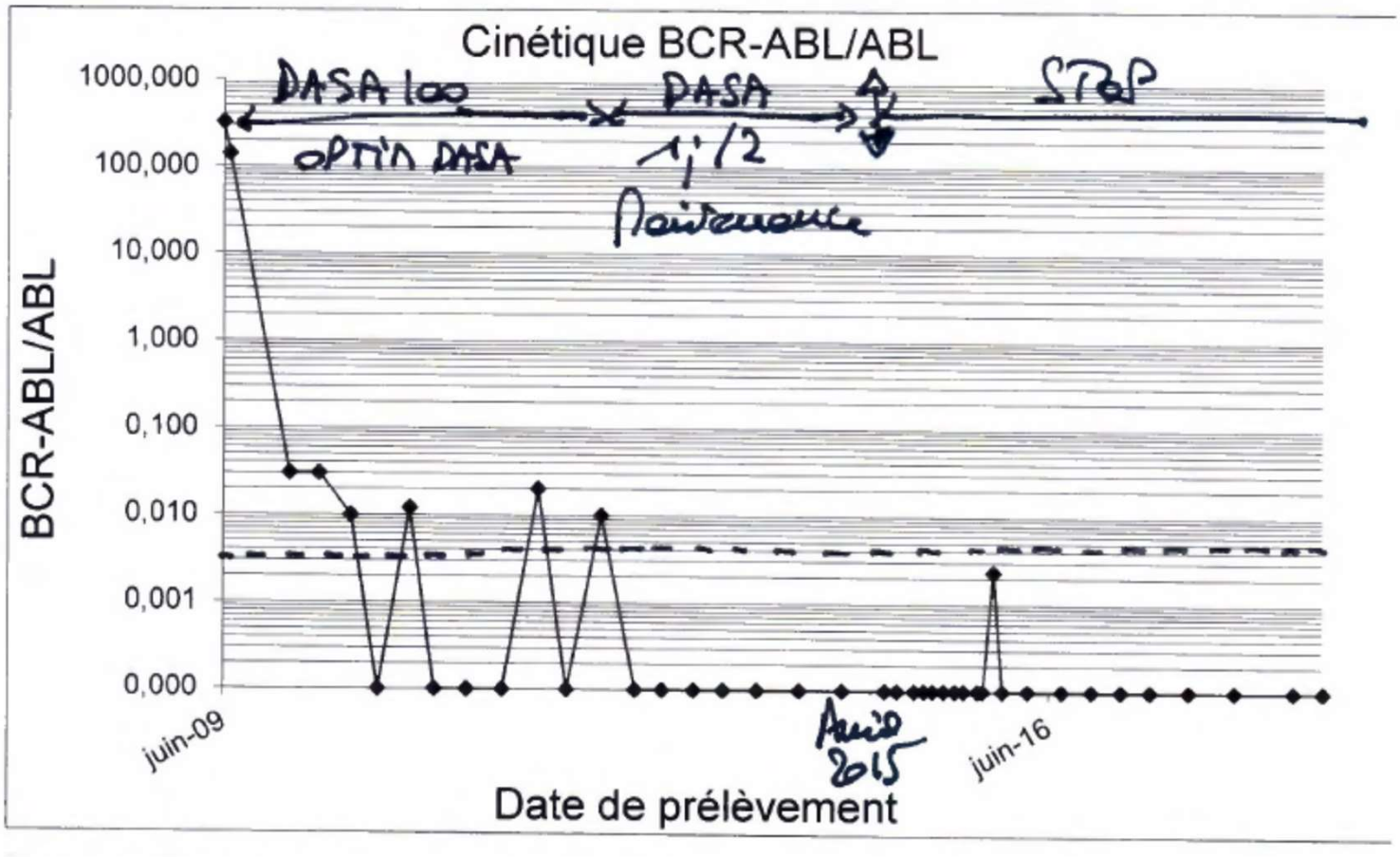
# Pt15. DDN 24/09/1945. Homme. Sokal Low.



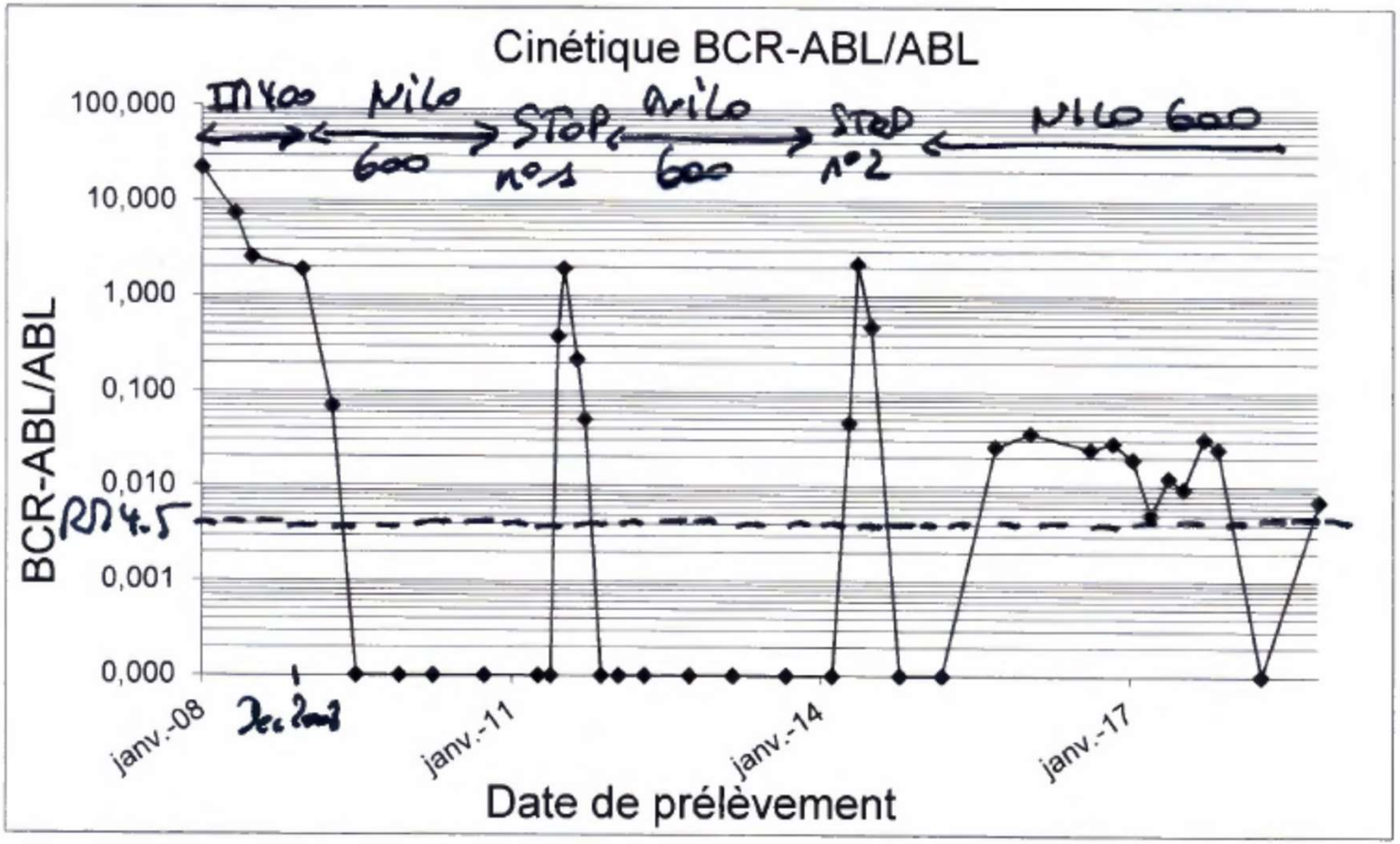
# Pt4. DDN 10/06/1982. Homme. Sokal Elevé.



# Pt10. DDN 08/08/1968. Homme. Sokal Bas.



# Pt11. DDN 25/04/1954. Femme. Sokal Int.



# Pregancy

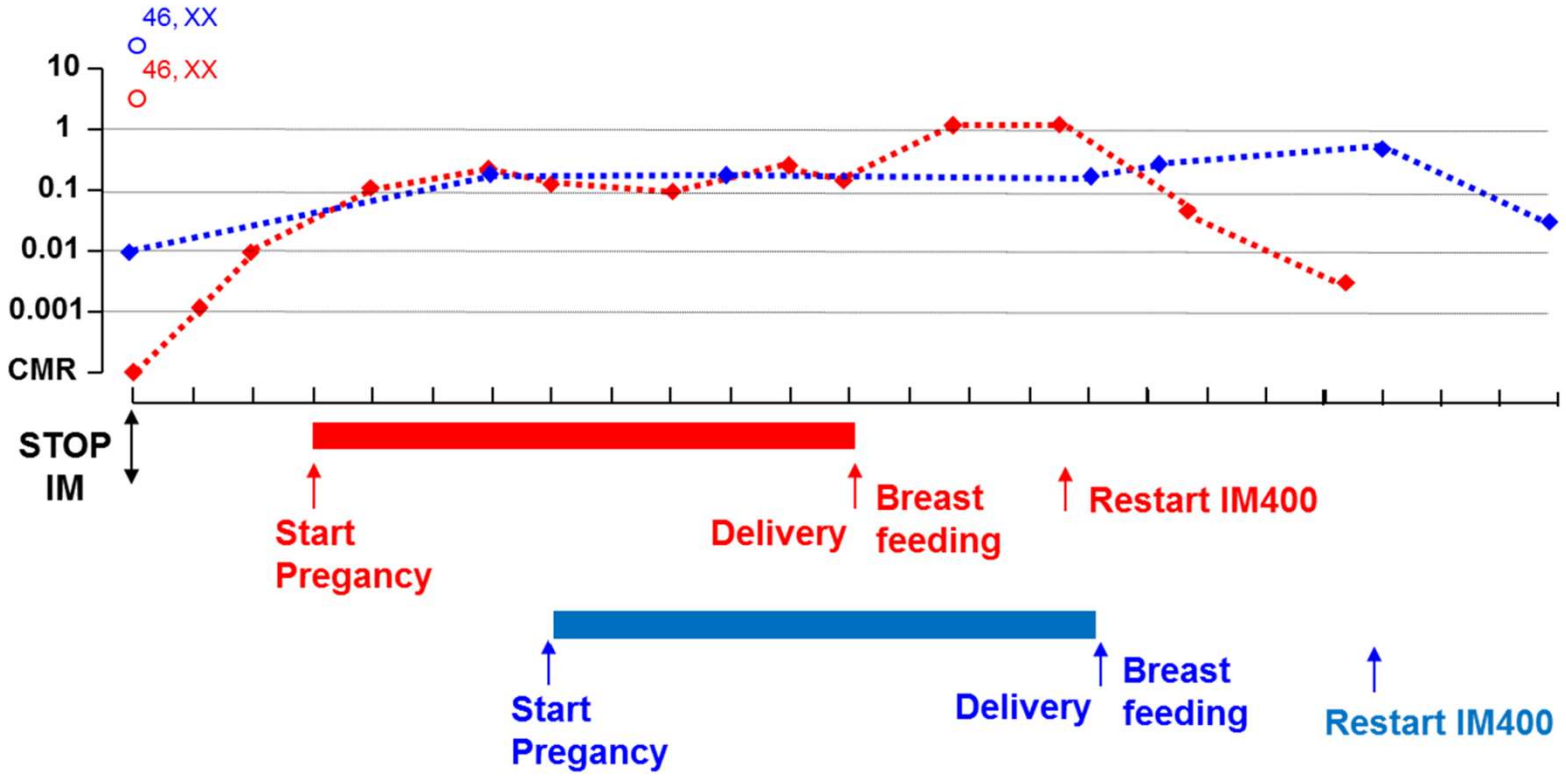
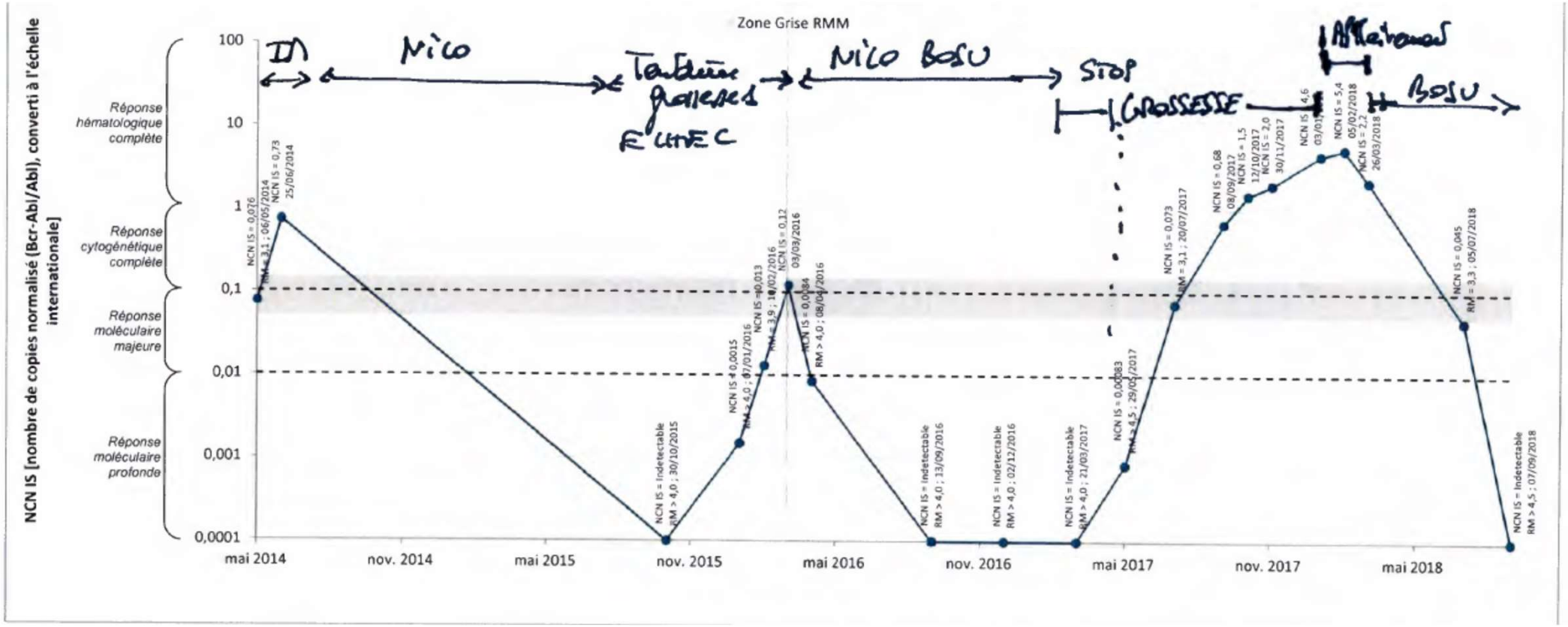


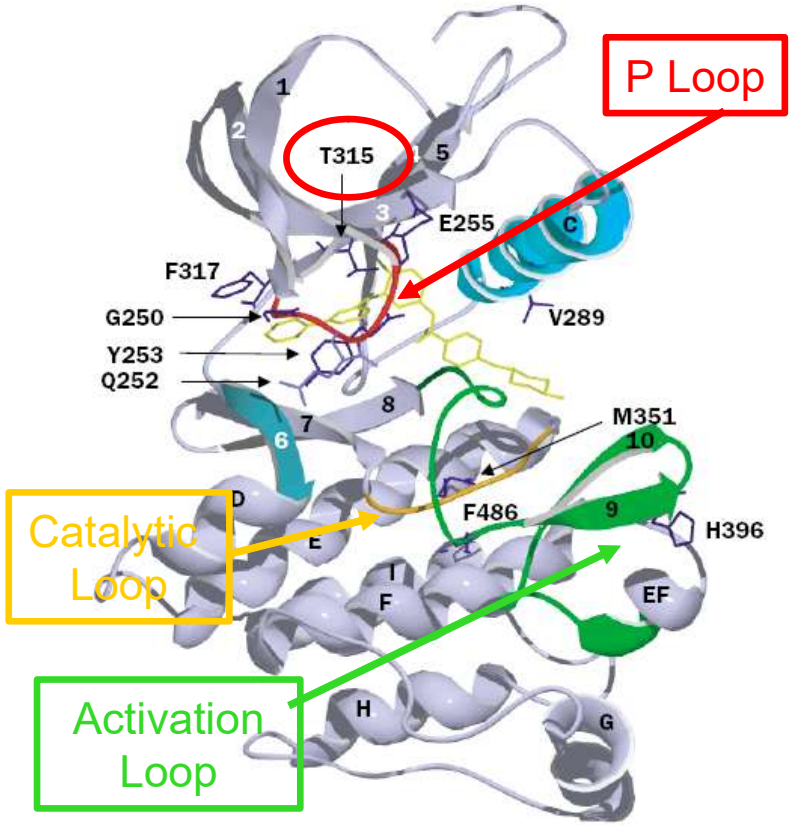

Figure 1. Example of two pregnancies with normal delivery. The two patients loose MMR but not CCyR. Imatinib was restarted after breastfeeding and patients regained MMR.

Personal data

# Pt14. DDN 16/04/1977. Femme. Sokal Low.

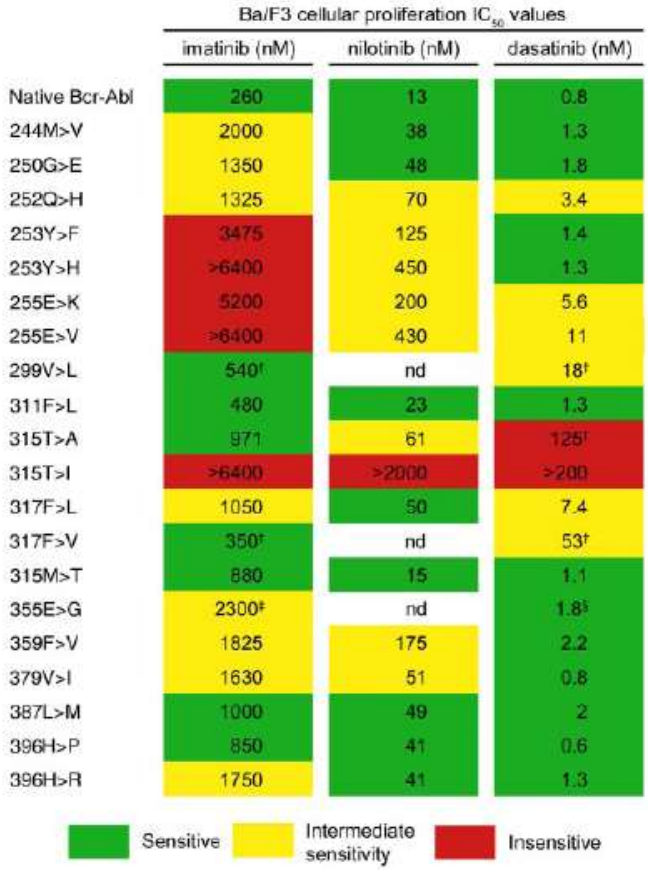


# BCR-ABL TK domain mutations




0'Hare, Blood 2007

# Dasatinib – Nilotinib
# IC50 for mutations in vitro

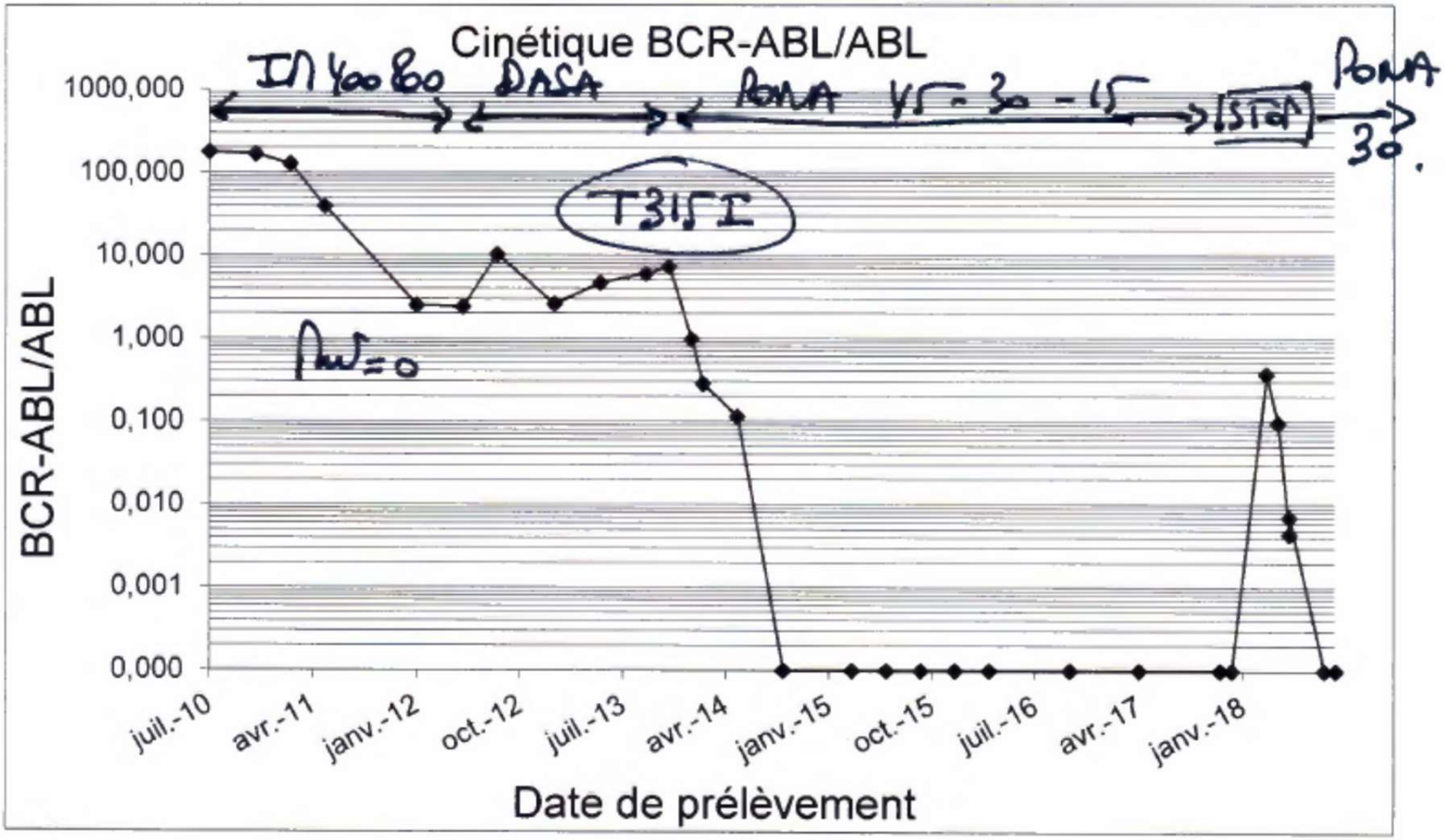


| | Ba/F3 cellular proliferation $IC_{50}$ values | | |
|---|---|---|---|
| | imatinib (nM) | nilotinib (nM) | dasatinib (nM) |
| Native Bcr-Abl | 260 | 13 | 0.8 |
| 244M>V | 2000 | 38 | 1.3 |
| 250G>E | 1350 | 48 | 1.8 |
| 252Q>H | 1325 | 70 | 3.4 |
| 253Y>F | 3475 | 125 | 1.4 |
| 253Y>H | >6400 | 450 | 1.3 |
| 255E>K | 5200 | 200 | 5.6 |
| 255E>V | >6400 | 430 | 11 |
| 299V>L | 540† | nd | 18† |
| 311F>L | 480 | 23 | 1.3 |
| 315T>A | 971 | 61 | 125† |
| 315T>I | >6400 | >2000 | >200 |
| 317F>L | 1050 | 50 | 7.4 |
| 317F>V | 350† | nd | 53† |
| 315M>T | 880 | 15 | 1.1 |
| 355E>G | 2300‡ | nd | 1.8§ |
| 359F>V | 1825 | 175 | 2.2 |
| 379V>I | 1630 | 51 | 0.8 |
| 387L>M | 1000 | 49 | 2 |
| 396H>P | 850 | 41 | 0.6 |
| 396H>R | 1750 | 41 | 1.3 |

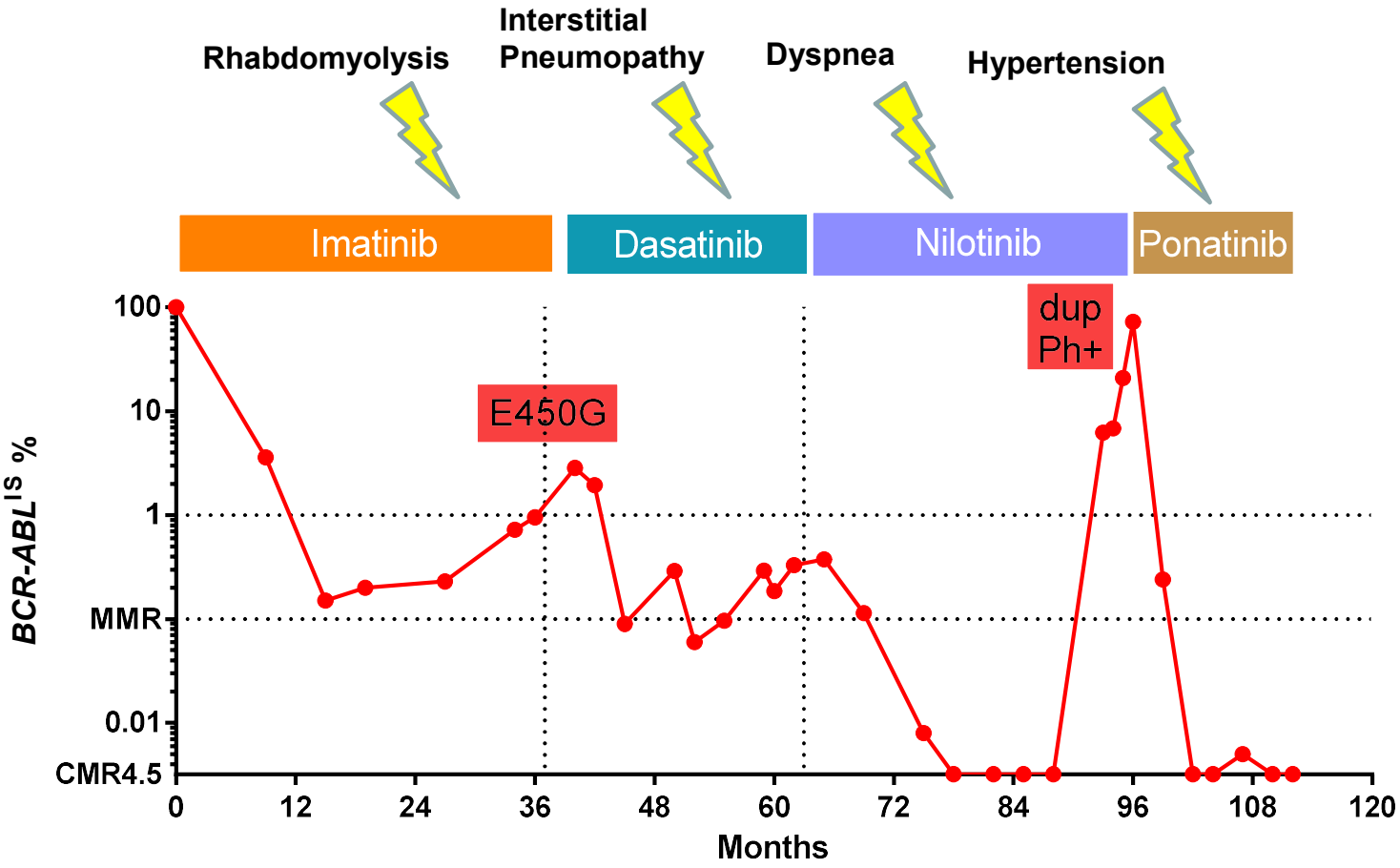
Sensitive | Intermediate sensitivity | Insensitive

O'Hare et al. Blood 2007;110:2242.

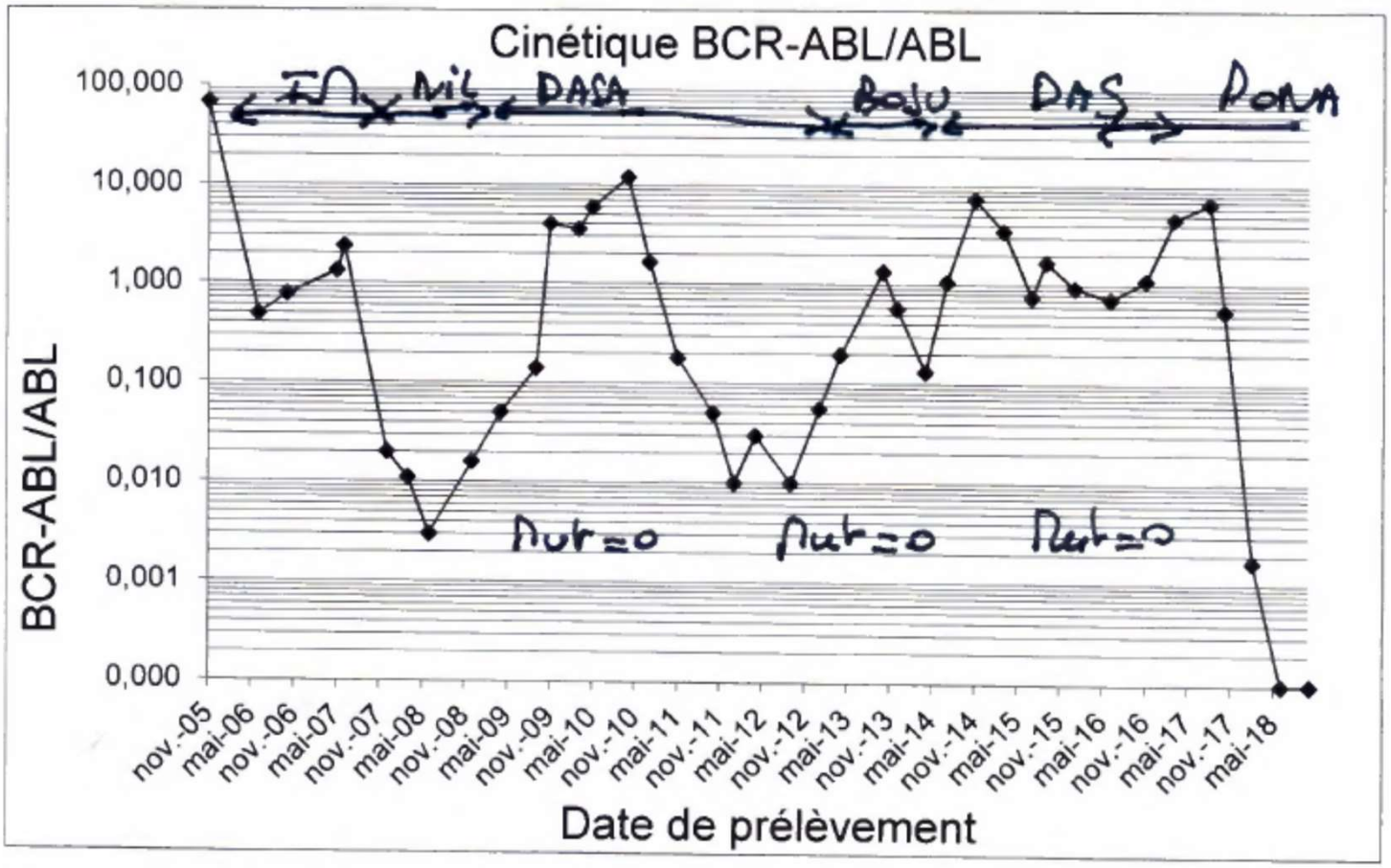
# Pt13. DDN 14/08/1966. Homme. Sokal Int.



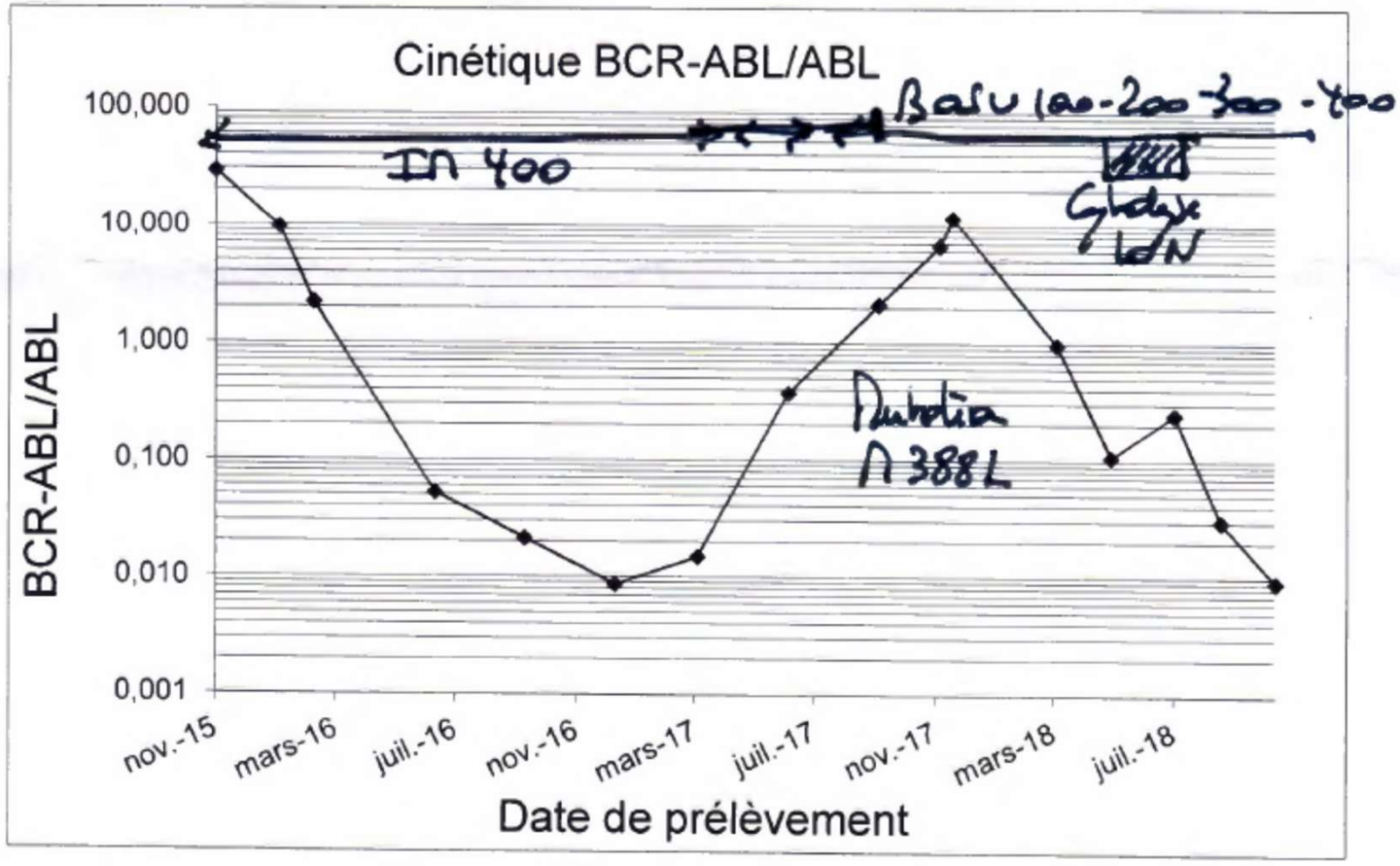
**Mr B, 53 years, CML low risk, 2005**



# Pt8. DDN 11/02/1954. Femme. Sokal Bas.

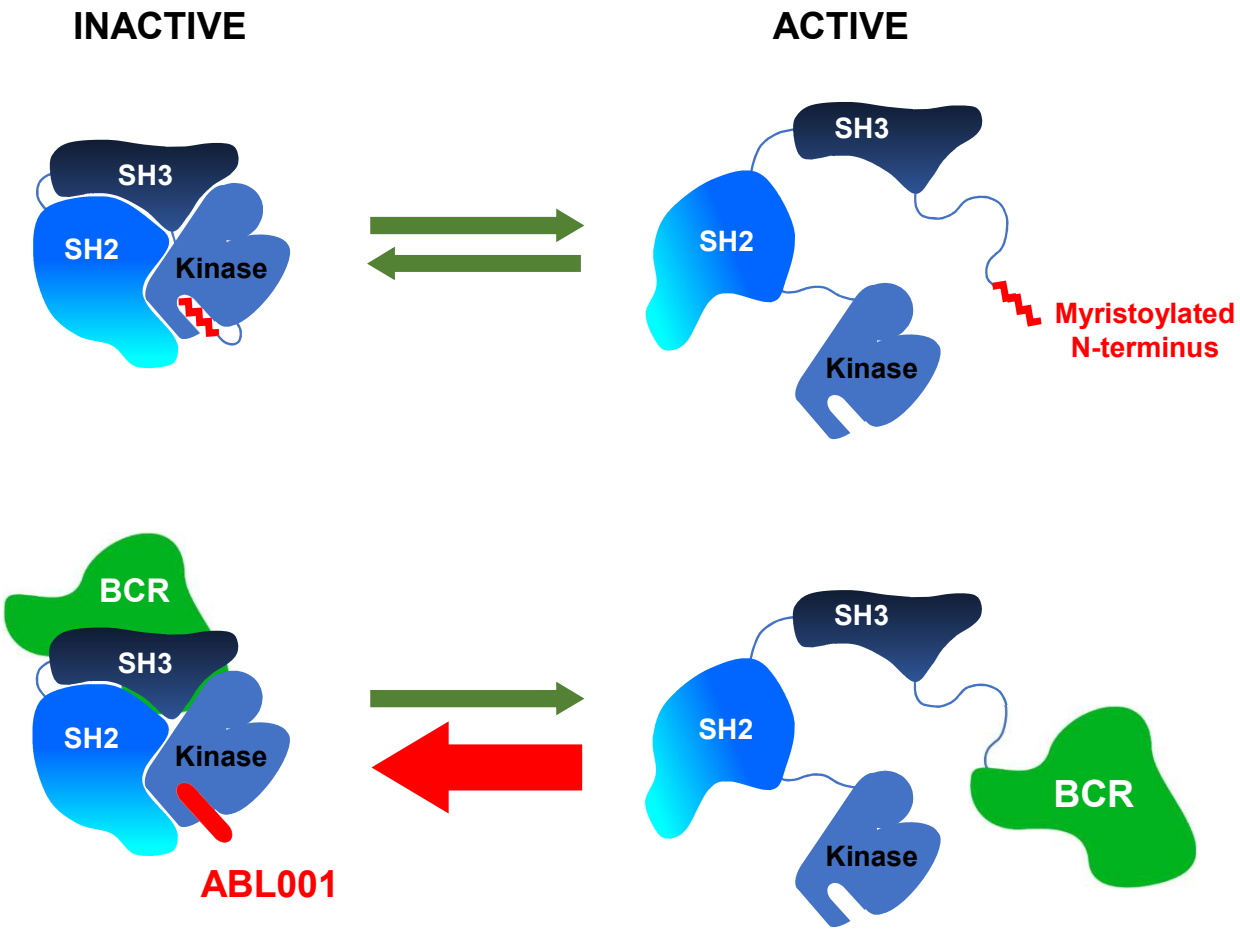


# Pt6. DDN 5/06/1956. Homme. Sokal Int.



# Myristoylated N-terminus Serves as a Negative Regulator of ABL1 Enzymatic Activity

## ABL001 : ASCIMINIB



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A Beulaygue
JP Beressi

Association Laurette Fugain
Information sur le don de plaquettes et aide à la recherche sur les maladies du sang

FONDATION ARC POUR LA RECHERCHE SUR LE CANCER
Reconnue d'utilité publique

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