Post-ASH 2015: Actualités dans la LMC

ASH | 57th Annual Meeting & Exposition
Orlando, FL • December 5-8, 2015

Mauricette Michallet
Service d'Hématologie
Centre Hospitalo-Universitaire Lyon Sud - France

3 catégories

- Actualités biologiques
- Actualités cliniques
- Qualité de vie des patients

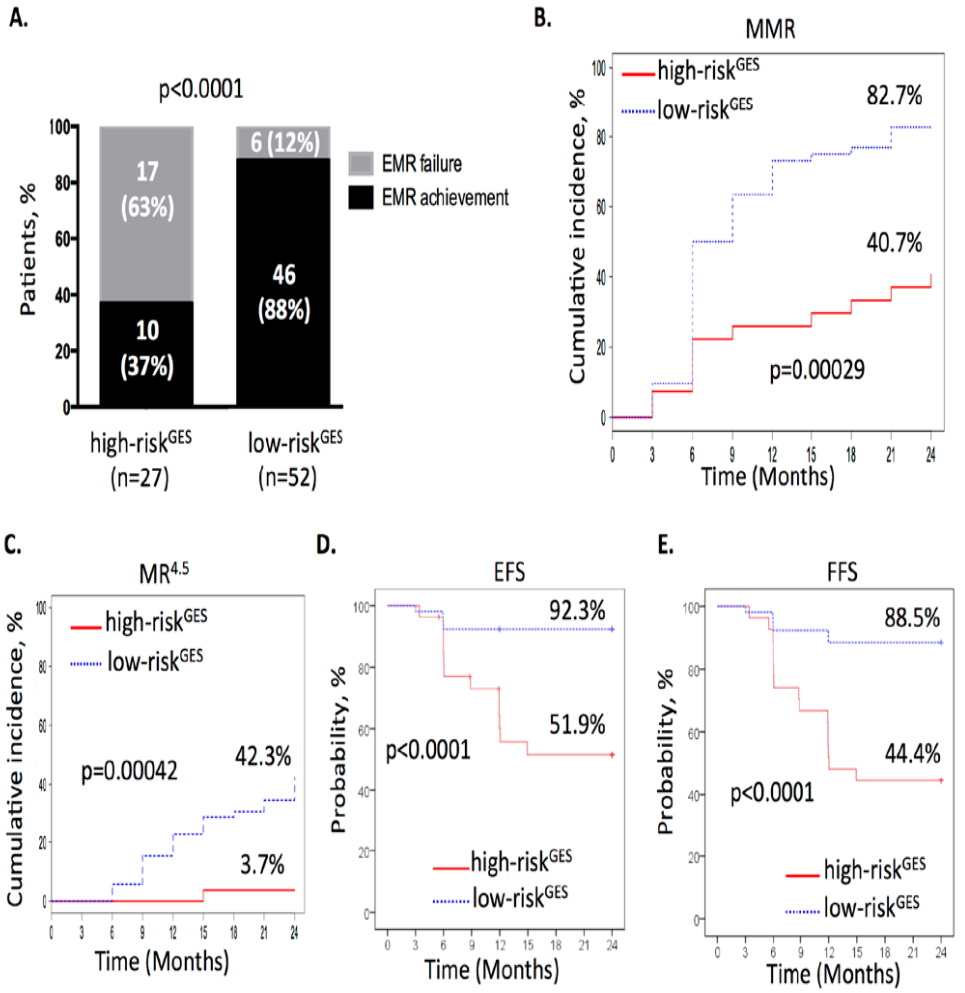
Actualités biologiques

Actualités biologiques: Signatures génétiques pronostiques

A 20 Gene Expression Signature That Predicts Early Molecular Response Failure in Chronic Phase CML Patients Treated with Frontline Imatinib. Kok et al. Abstract 596

- Recherche dans les CSP de 119 patients
- Early molecular response (EMR) failure: BCR-ABL1 >10% à 3 mois
- 20 gènes détectés au diagnostic: IGFBP2, CD3E, RASGRP1, BNIP3L, ETS1, PDK1, METTL7A, HECA, COL8A2, PRSS57, TMEM167A, SPAST, FZD7, VPS41, CDKN1B, CPXM1, SEPT7, RPS28, SLX4IP, et SRSF11

Faut-il changer les stratégies thérapeutiques dès le diagnostic ?



Actualités biologiques: Présence d'un nouveau marqueur CD93

CD93 Is a Novel Biomarker of Leukemia Stem Cells in Chronic Myeloid Leukemia. Kinstrie et al. Abstract 49

- **Le CD93 est un marqueur dérégulé dans les pathologies myéloïdes malignes (LAM)**
- **Il s'agit d'un marqueur des cellules souches trouvées dans la LMC**
- **Il persiste malgré le traitement par les ITK**
- **Pourra faire l'objet du suivi de la maladie résiduelle dans la LMC en + du BCR-ABL**
- **Des études sont en cours dans un contexte thérapeutique pour inhiber les CS CD93+**

Actualités biologiques: Cellules souches leucémiques (CSL) quiescentes

- **Les CSL sont la cible de plusieurs recherches**
- **Clé pour pouvoir éradiquer la maladie**
- **Intérêt évident de la santé publique (arrêt des traitements)**

- **Inhibition des voies de réparations de l'ADN spécifiques des CSL par des inhibiteurs spécifiques (PARP1 et RAD52) [1]**
- **Inhibition de la voie Wnt par un inhibiteur de la Porcupine acyltransferase (WNT974) associé au Nilotinib[2]**
- **Implication des cellules NK dans le maintien de la réponse moléculaire pendant et après TT par ITK (IM, Nilo, Dasa) [3,4]**

[1] *Sullivan K et al. Abstract 50* [2] *Agarwal P et al. Abstract 54*

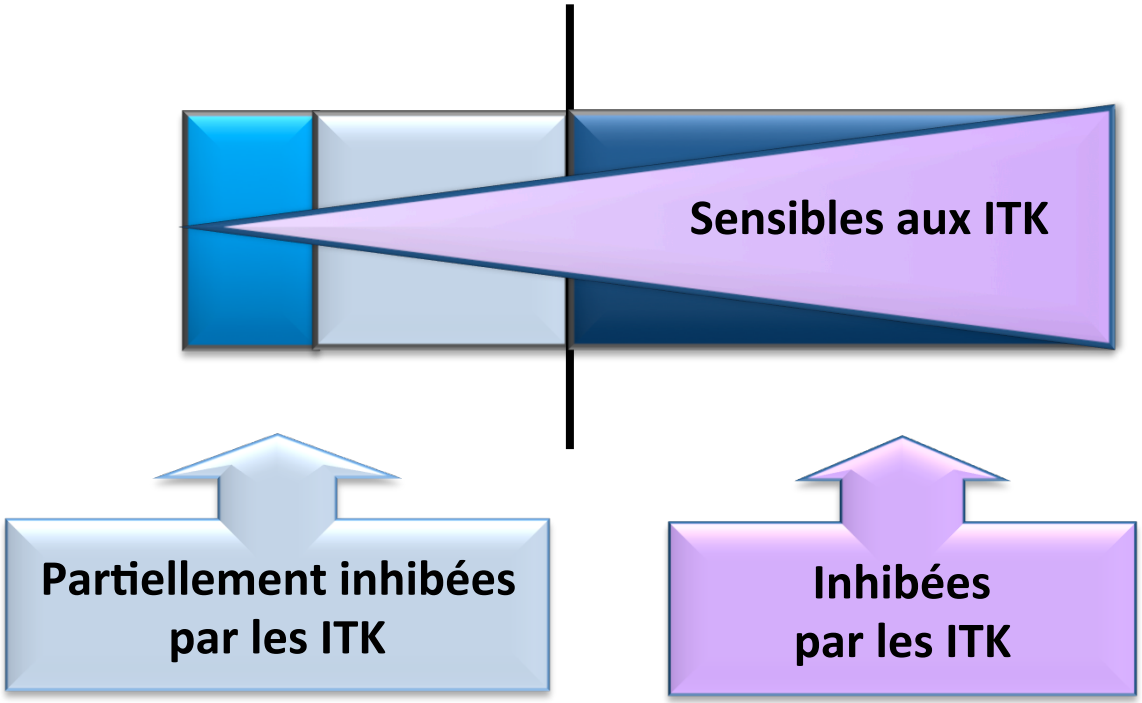
[3] *Hughes A et al. Abstract 18* [4] *Ilander M et al. Abstract 343*

Actualités cliniques

Thérapies combinées: Rationnel

Cellules souches Ph1⁺ (Partiellement en G_0)

Populations Ph1⁺ sans auto-renouvèlement

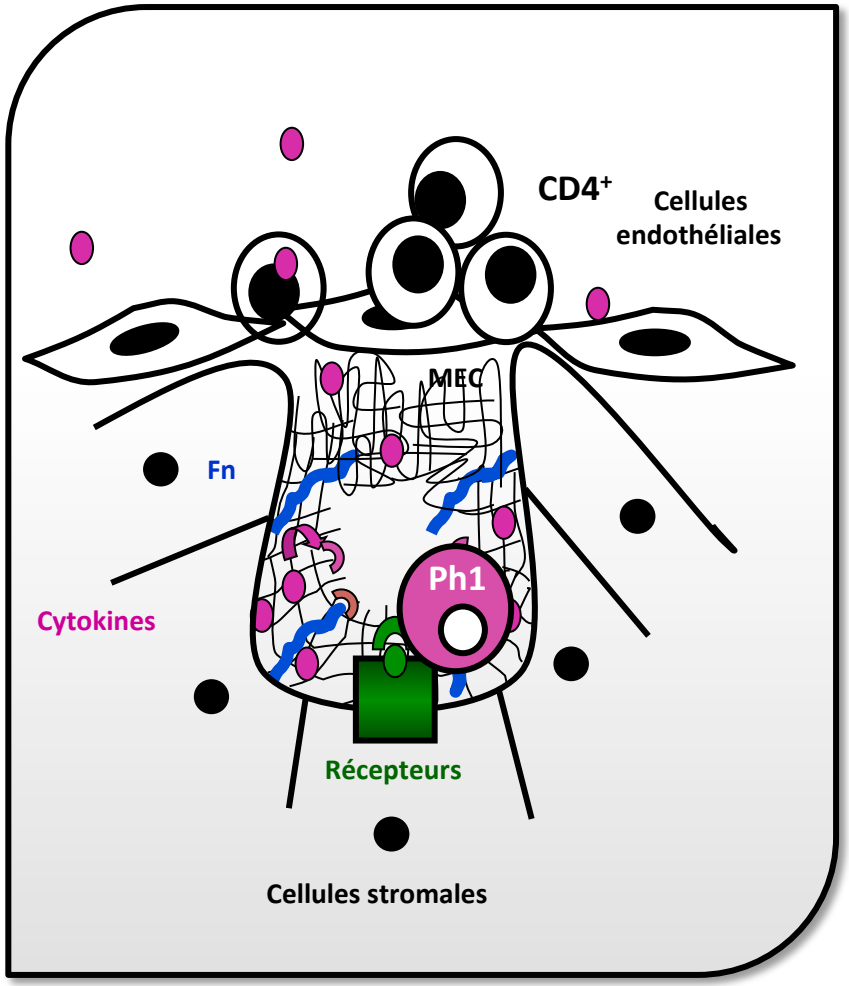


Rationnel biologique pour des Thérapies Combinées

- ITK 1, 2, 3
- IFN-a
- ~~Ara-C~~
- HU, Bus, OMA…
- Hydroxychloroquine
- Glitazones
- Autres

- Allogreffe/DLI
- IFN-a
- Vaccination

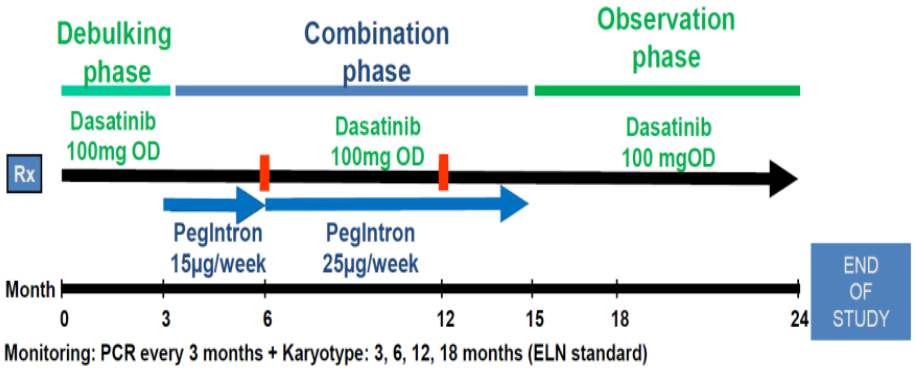
- G-CSF
- ~~IFN-a~~
- Plerixafor
- Ac anti-VLA-4
- Inhibiteurs Smo



Actualités cliniques: Dasatinib+ IFN-α peg (Groupe Nordique)

NordCML007

NordCML007- Outline
CP-CML at debut



Monitoring: PCR every 3 months + Karyotype: 3, 6, 12, 18 months (ELN standard)

Primary endpoint
Rate of MMR at M12
Study stops if excessive tox in run-in phase M6
(Phase IB)

Secondary endpoints:
CCyR, MMR, MR4 MR4.5
at standard time points.
Safety

Included from : Feb2013 - May 2014

Historical reference population: DASISION

ncml STUDY GROUP

Patient characteristics

		High risk
Included patients (n)	40	
Male/female (n)	31/9	
Mean and median age (range)	48 yrs (19-71)	
Sokal score mean (range)	0,82 (0,52-2,78)	25 %
Hasford score mean (range)	834 (0-2269)	15 %
EUTOS score mean (range)	39,5 (0-134)	15 %

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

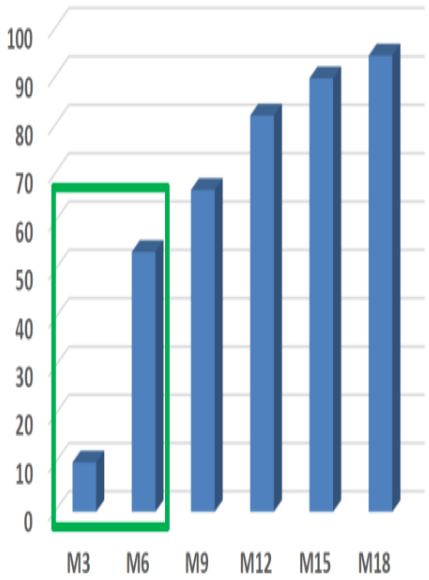
Hjörth-Hansen H. et al. Abstract 477

Actualités cliniques: Dasatinib+ IFN-α peg (Groupe Nordique)

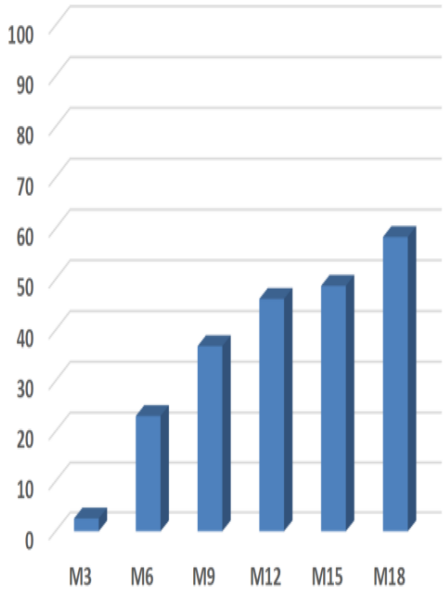
NordCML007

Réponses Moléculaires

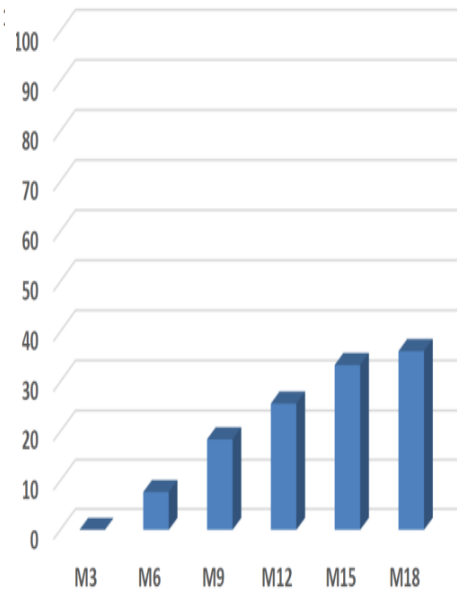
MMR



MR4



MR4.5



No progressions

5 pts failures (ELN): No mutations

3 patients switched to NIL

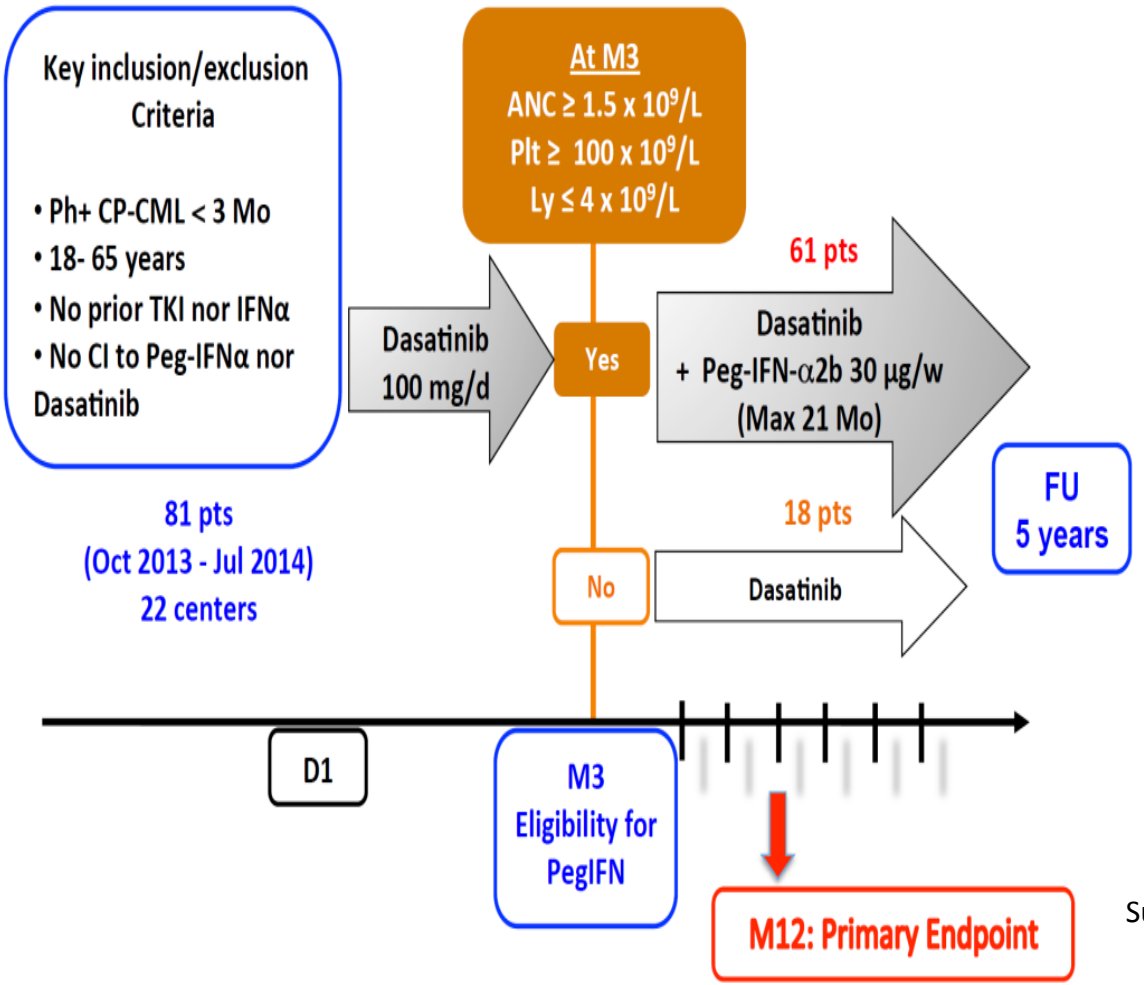
1 SCT

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Hjörth-Hansen H. et al. Abstract 477

Actualités cliniques: Dasatinib+ IFN-α peg (Groupe Fi-LMC)

DASA-PegIFN



Suivi médian : 12 mois

Primary endpoint: Cumulative rate of MR4.5 by 12 months.
Secondary endpoints: Safety, doses, discontinuation, efficacy

fiolmc
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

ASH 57th Annual Meeting & Exposition
Orlando, FL • December 5-8, 2015

Roy L et al. Abstract 137

DASA-PegIFN

Caractéristiques des patients

- N=81 pts
- 2 pts excluded from the statistical analysis : 1 CML related death before therapy , 1 screening failure

	All N=79	Peg-IFN at M3 N=61	Not eligible to Peg-IFN at M3 N=18
Median Age, (range) *(Inclusion criteria ≤ 65y)*	**48** (20-65)	45 (20-65)	51 (24-63)
Gender, Male, n (%)	44 (**56**)	34(56)	10 (56)
Spleen, n (%)	34 (**44**)	22 (37)	12 (67)
Sokal, n (%)			
Low	34 (**44**)	30 (51)	4 (22)
Int	30 (**39**)	21 (36)	9 (50)
High	13 (**17**)	8 (14)	5 (28)
EUTOS, n (%)			
High	7 (**9**)	5 (8)	2 (11)

At M3, 1 criteria
ANC < 1.5 x 10^9/L
Plt < 100 x 10^9/L
Ly ≥ 4 x 10^9/L

fiolmc
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

Roy L et al. Abstract 137

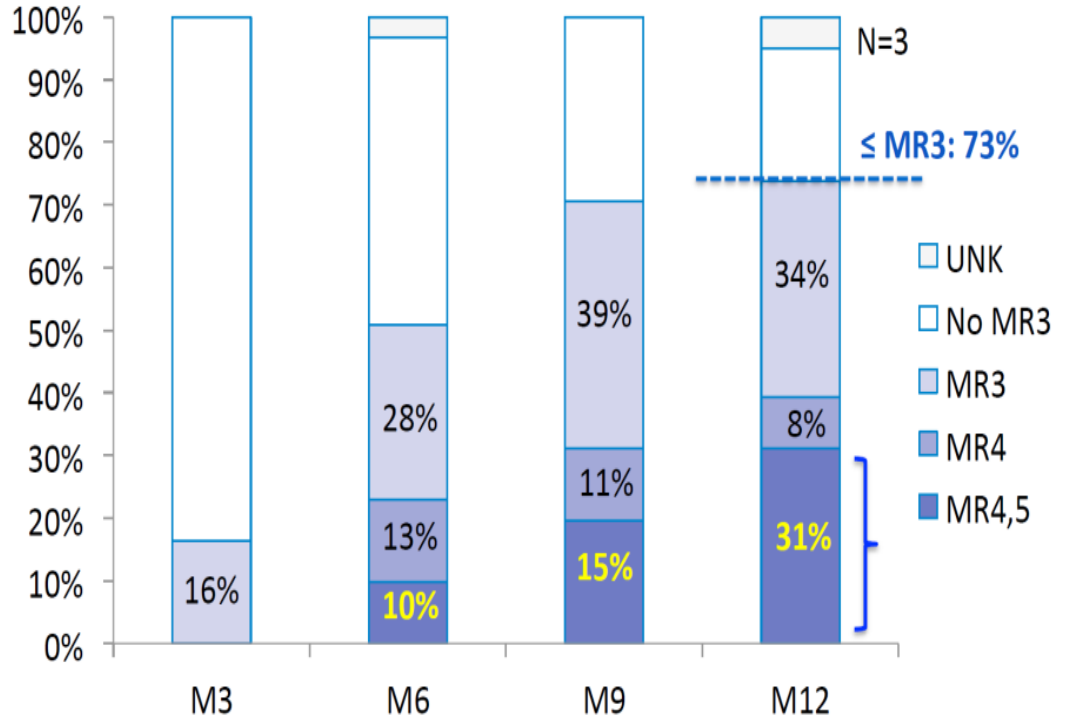
Actualités cliniques: Dasatinib+ IFN-α peg (Groupe Fi-LMC)

DASA-PegIFN

Peg-IFN eligible patients, n=61

Molecular Response Rates (IS) (At)

- ITT Analysis *And « maximal bias » method (unknown = failure)*



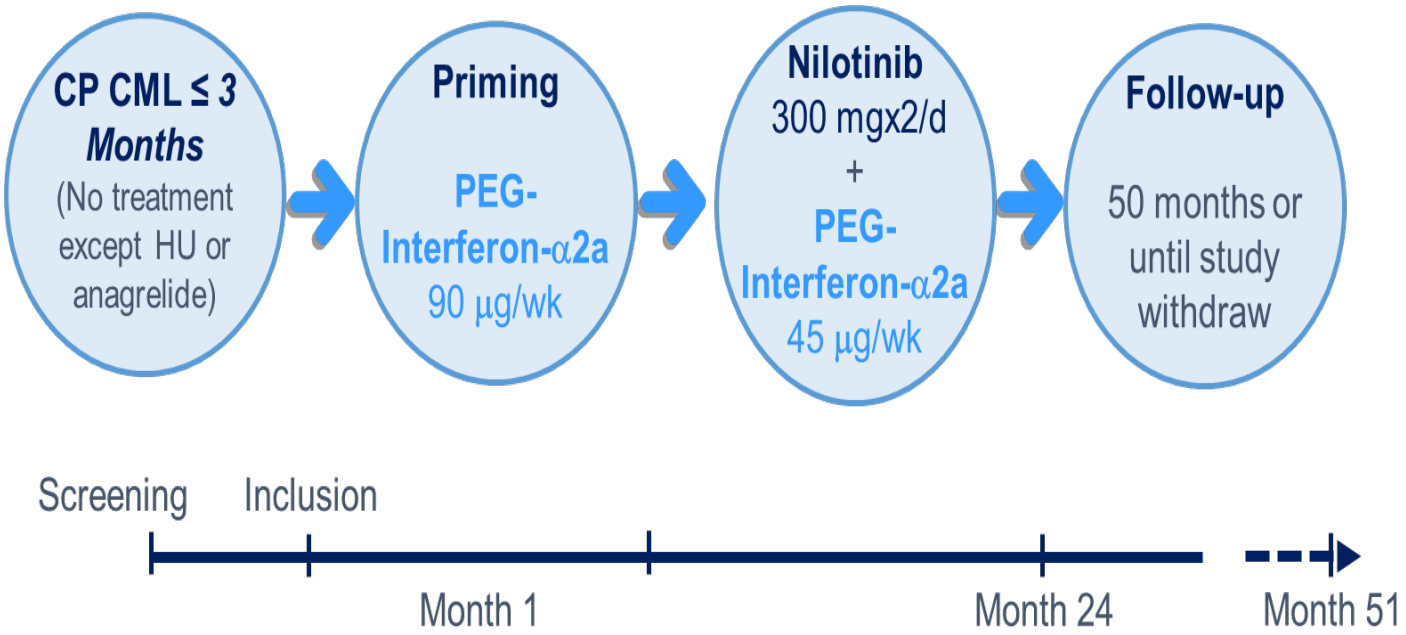
- All pts (n=79), **MR 4.5: 25% at M12,**

fiolmc
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

Roy L et al. Abstract 137

Actualités cliniques: Nilotinib + IFN-α peg (Groupe Fi-LMC)

NiloPeg : 48 mois de suivi médian

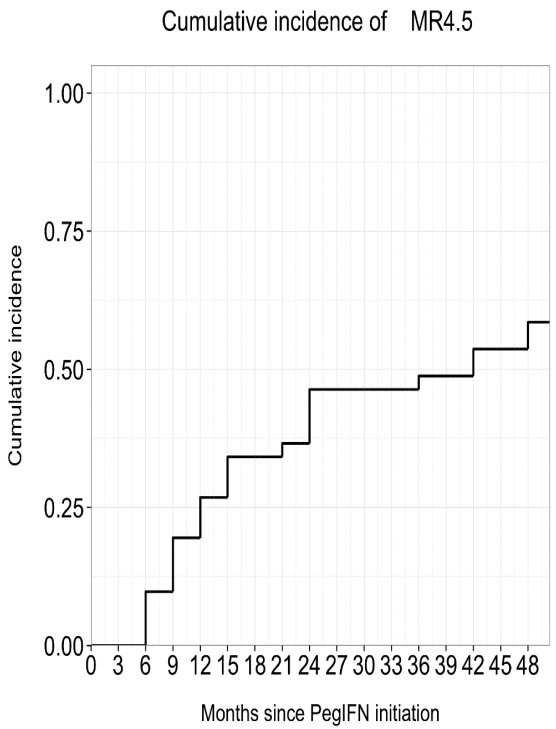


Primary endpoint: Rate of confirmed molecular response 4.5 (MR4.5) at 12 months.

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Nicolini FE et al. Abstract 1578

NiloPeg : 48 mois de suivi médian



A LA DATE DE DERNIER SUIVI :

- 8 patients (19.5%) were in TFR for a median of 6.8 (0.5-9.5) months after 2-year consecutive MR4.5, and none lost MMR.
- One lymphoid blast crisis (died after allogeneic SCT).
- No additional grade 3-4 hematologic or biochemical toxicities occurring after 24 months
- 10 patients (24%) switched for another TKI for insufficient cytogenetic or molecular response (2 patients) or for toxicity (8 patients)
- 5 patients presented cardio-vascular events (3 coronary stenosis, 1 brain stroke 1 PAOD)

Nicolini FE et al. Abstract 1578

ITK2 + Interferon pégylé : En résumé

«At » Mois 12	Nord CML007* Phase Ib	DasaPeg* Phase II	NiloPeg** Phase II
Traitements à l'essai	Dasatinib + Peg-IFNα2b	Dasatinib + Peg-IFNα2b	Nilotinib+ Peg-IFNα2a
Patients éligibles	39	79	41
CCyR (%)	97%	NA	100%
MMR (%)	85%	59%	76%
MR4 (%)	46%	32%	51%
MR4.5 (%)	22%	25%	17.5%

*12 mois d'ITK
** 11 mois d'ITK

Hjörth-Hansen H. et coll, ASH 2015, abstract #477

Roy L. et coll, ASH 2015, abstract #134

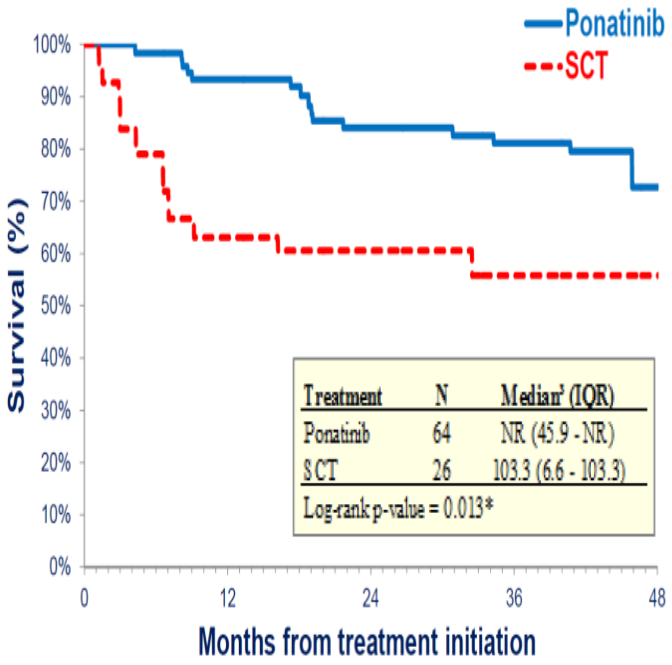
Nicolini F. E. et coll, Lancet Haematol 2015 & ASH 2015, abstract #1578

Il ne s'agit pas d'études comparatives et ne peuvent être comparées une à une

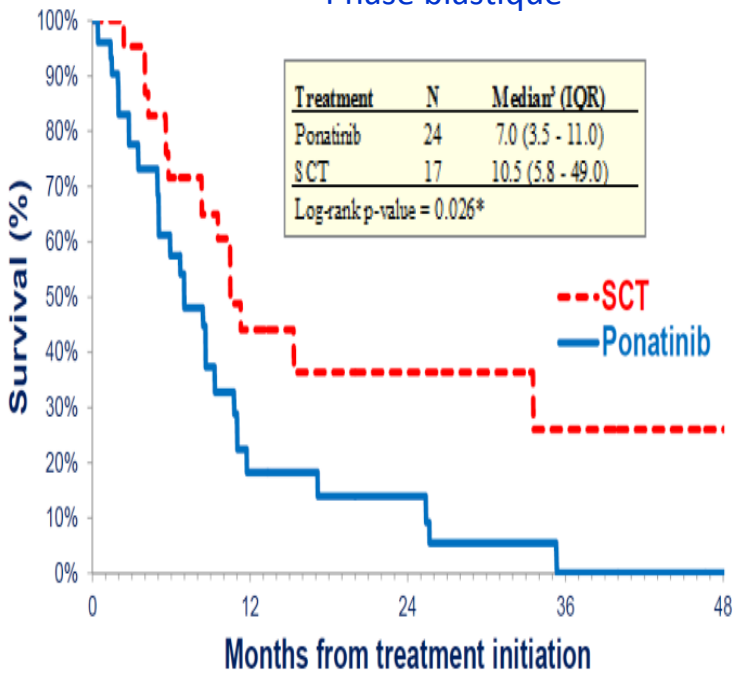
LMC T315I : Allogreffe ou Ponatinib ?

Matching patients T315I PACE versus registre EBMT

Phase chronique



Phase blastique



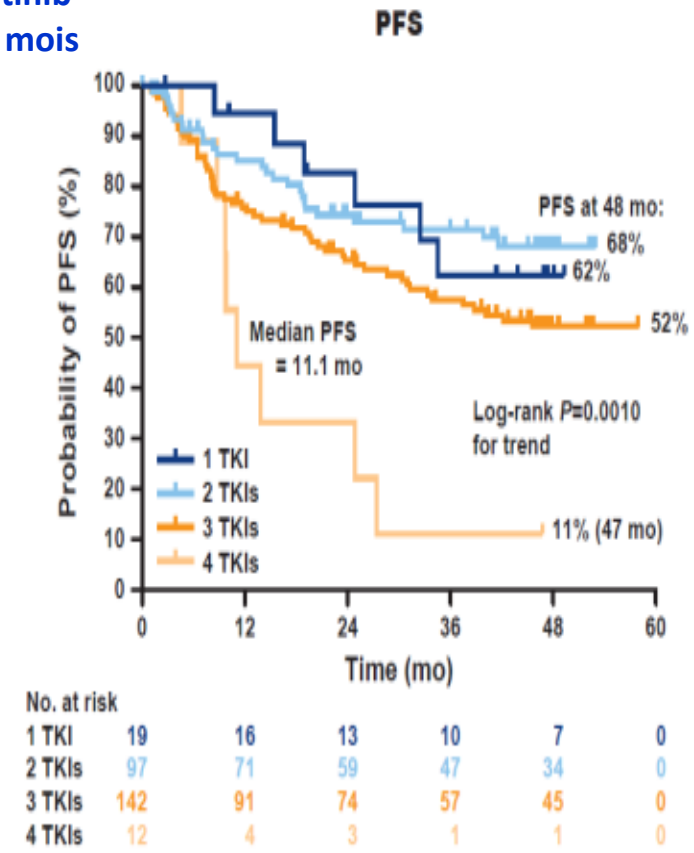
[p=0.88 pour les phases accélérées]

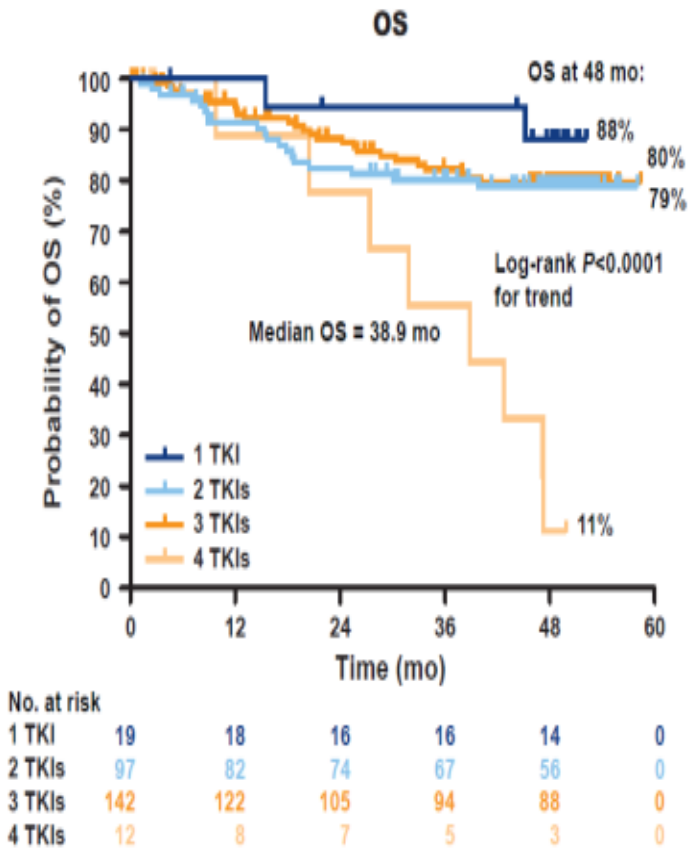
ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Nicolini FE et al. Abstract 480

Etude PACE: Mise à jour à 4 ans

Phases chroniques:
110 (41%) encore sous Ponatinib
Durée médiane de Pona: 32 mois
~29% EI artériels occlusifs





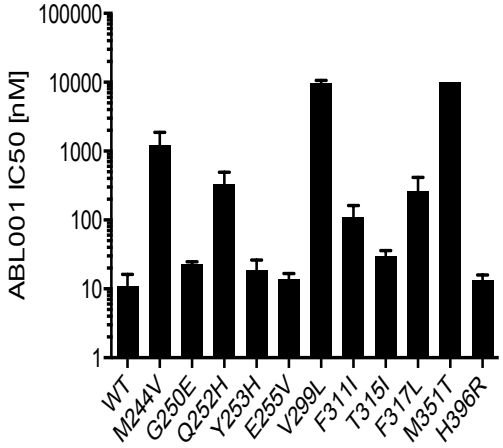
ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

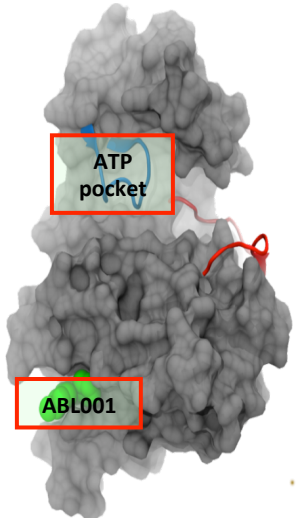
Hochhaus A et al. Abstract 4025

Actualités cliniques: ABL001 inhibiteur allostérique du BCR-ABL

ABL001

- Potent and selective allosteric inhibitor of BCR-ABL1 and ABL1/2
- Active against cell lines with ATP binding site BCR-ABL1 mutants and in murine BCR-ABL1+ tumor model
- Phase I trial ongoing
- Rapid absorption in humans
- Short half life: median 5-6h

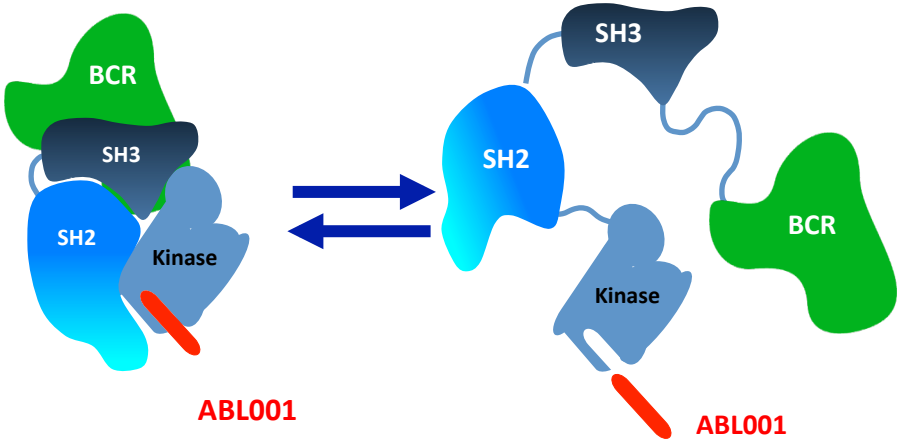




BCR-ABL1 kinase domain

BCR-ABL1 INACTIVE CONFORMATION

BCR-ABL1 ACTIVE CONFORMATION



ABL001

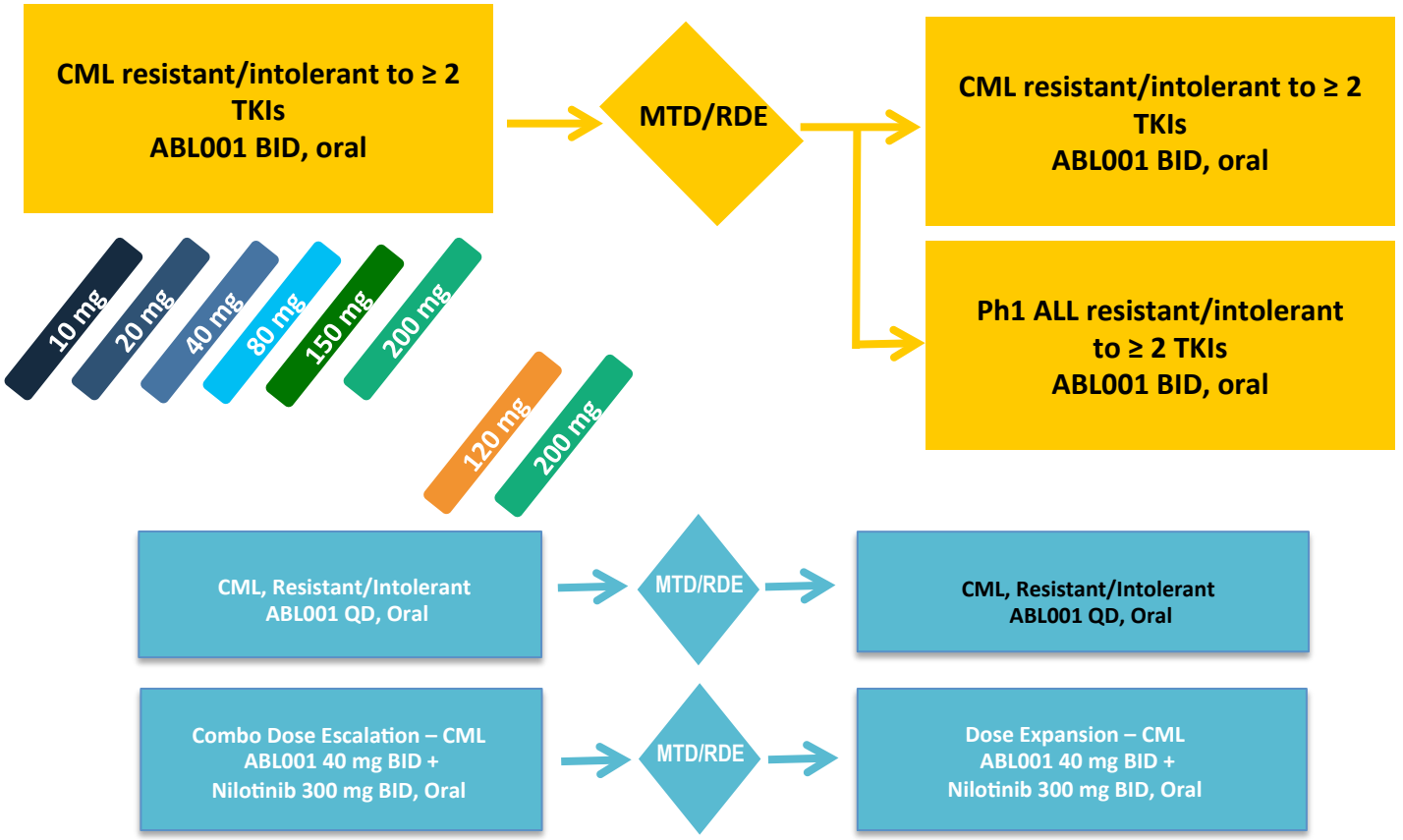
ABL001

O'Hare T. et al. ASH Annual Meeting 2015. Abstract #1565.

Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

ABL001X2101: Study design

A multicenter, phase 1, first-in-human study



Primary outcome: Estimation of MTD (maximum tolerated dose) /RDE (recommended doses for expansion)
Secondary outcomes: Safety, tolerability, preliminary anti-CML activity, pharmacodynamics, pharmacokinetics

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

Demographics and baseline characteristics

	n = 59
Median age (range), years	**56** (23 - 78)
Male / female, n (%)	**36** (61) / **23** (39)
ECOG 0 / 1 or 2, n (%)	**58** (98) / **1** (2)
Prior lines of therapy, median (range)	**3.5** (2-5)
2 prior TKIs, n (%)	**24** (41)
≥ 3 prior TKIs, n (%)	**35 (59)**
Resistant to prior TKI, n (%)	**45 (76)**
Intolerant to prior TKI, n (%)	**14** (24)
CML-CP / -AP, n (%)	**58 (98) / 1 (2)**
TKD non-mutated / mutant / not evaluable, n (%)	**18 (31) / 14 (24) / 27 (46)**

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

Dose limiting Toxicities

Definitions

Table 6-5 Criteria for defining dose-limiting toxicities

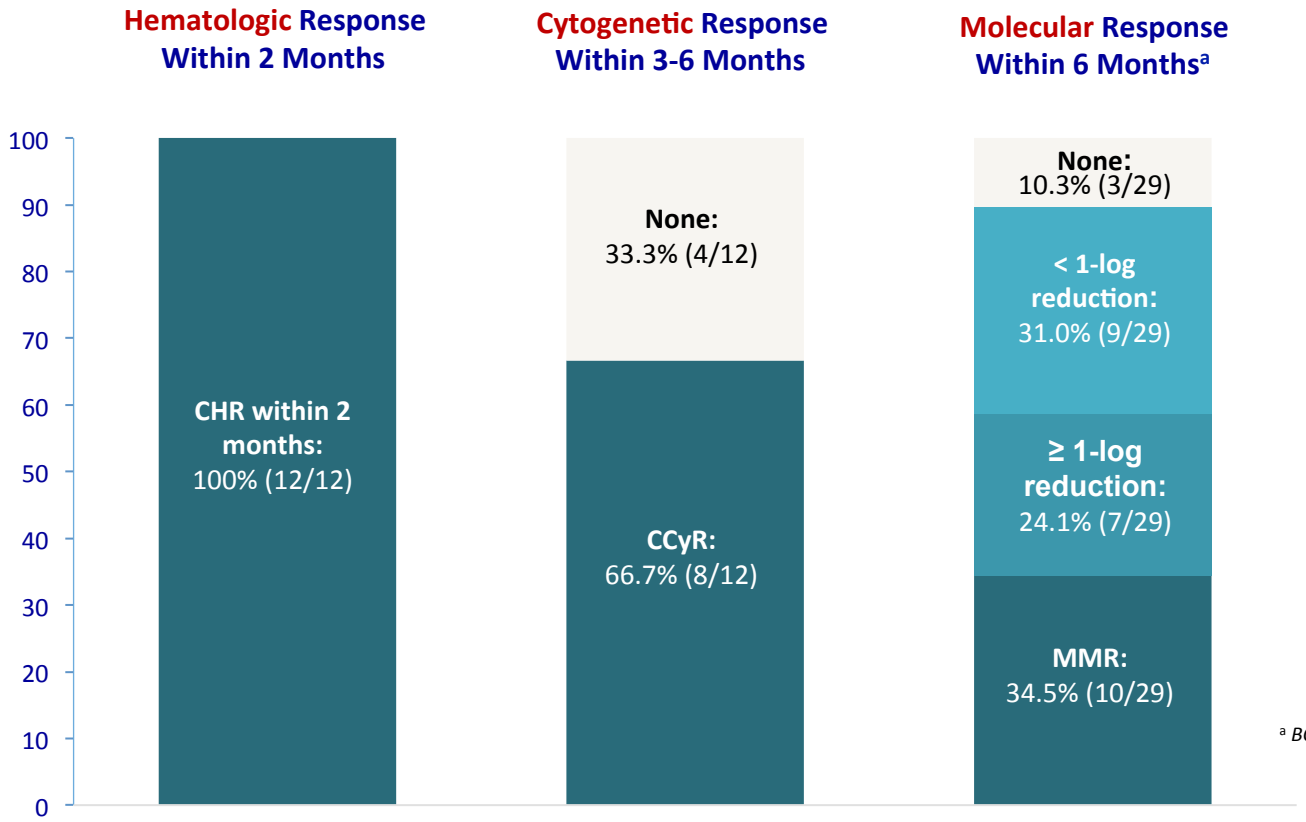
Toxicity	Any of the following criteria for which relationship to study treatment cannot be ruled out:
Hematology (CML)	CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting more than 5 days
	CTCAE grade 4 thrombocytopenia (platelets < 25 x 10^9/L) or grade 3 thrombocytopenia with bleeding
	CTCAE grade 4 febrile neutropenia (fever > 38.3°C)
	CTCAE grade 4 anemia unexplained by underlying disease
	CTCAE grade 3 anemia will not be considered a DLT unless judged to be a hemolytic process secondary to study treatment.
Hematology (Ph+ ALL)	Since marrow aplasia is an expected consequence of Ph+-ALL therapy, only persistent pancytopenia that continues for ≥ 42 days and is not related to leukemic infiltration will be considered as a DLT. Bone marrow evaluation may be required to determine if marrow aplasia is due to leukemia.
Gastro-intestinal	≥ CTCAE grade 3 vomiting or nausea uncontrolled by medical management ≥ CTCAE grade 3 diarrhea despite optimal anti-diarrhea treatment
Pancreatic	Asymptomatic CTCAE Grade 3 or 4 elevation of amylase (of pancreatic origin) or lipase or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis) ≥ Grade 3 pancreatitis
Other adverse events	≥ CTCAE grade 3 AEs of any other type, except for the exclusions noted below
	Any other clinically significant toxicity that in view of the Investigator and Novartis is considered dose-limiting
Exceptions to DLT criteria	≤ 3 days of CTCAE grade 3 fatigue
	CTCAE grade 3 or 4 lymphopenia or alopecia of any grade
	Grade 3 electrolyte abnormalities that can be corrected in 7 days or less and are considered by the investigator to be not clinically important
CTCAE version 4.03 will be used for grading all AEs and laboratory abnormalities.	

Findings

- **All pts had >1 post-baseline safety assessmer**
- **No death occurred on study**
- **Dose escalation is ongoing**
- **5 dose-limiting toxicities:**
  - Grade 3 lipase increase n=2
  - Grade 2 myalgia/arthralgia n=1
  - Grade 3 acute coronary event n=1
  - Grade 3 bronchospasm n=1

Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

Responses in patients with ≥ 3 months of follow-up on study (n = 29)



[a] *BCR-ABL1*^{IS} reduction achieved.

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

Actualités cliniques: ABL001 inhibiteur allostérique du BCR-ABL

Conclusions

- ABL001 was generally well tolerated in heavily treated CML patients resistant to or intolerant of prior TKIs
- Preliminary pharmacokinetic exposures appear linear in the dose range tested
- Early evidence of single-agent efficacy at ≥ 10 mg BID

- Clinical activity across TKI-resistant mutations (eg, V299L, F317L, Y253H)
- Myristoyl binding pocket mutations (V468H, I502L) may lead to clinical resistance
- Allosteric inhibition of BCR-ABL1 is a promising therapeutic approach in patients with C

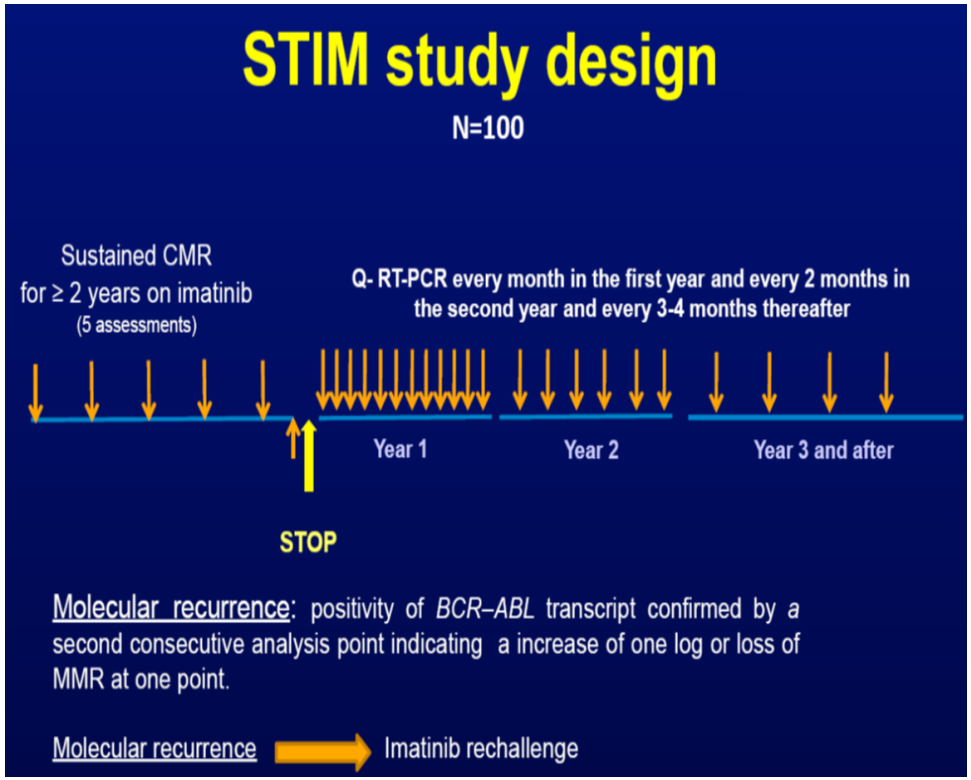
- Enrollment ongoing to determine a recommended dose and to assess safety and tolerability

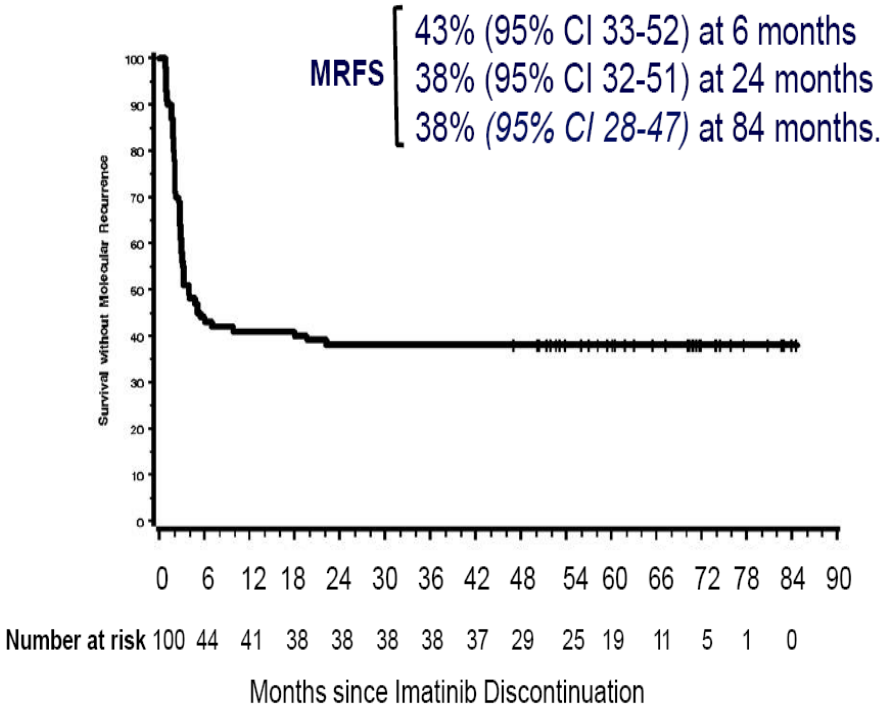
ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.

Actualités cliniques: Arrêt des ITK

Molecular Recurence-Free Survival (MRFS) after imatinib discontinuation
Median follow-up = 65 months accounting for competing events (death in complete molecular remission without any relapse, n





ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Etienne G. et al. ASH Annual Meeting 2015. Abstract #345.

ITK de 2ème génération d'origine Coréenne, étude phase III

Study Design

- ≤3 months after diagnosis of chronic-phase Ph+ CML (n=241)
- 24 sites
- 4 Asian countries (KR, TH, PH & IDN)
- Enrollment : 2011.08 – 2014.02

Randomized*

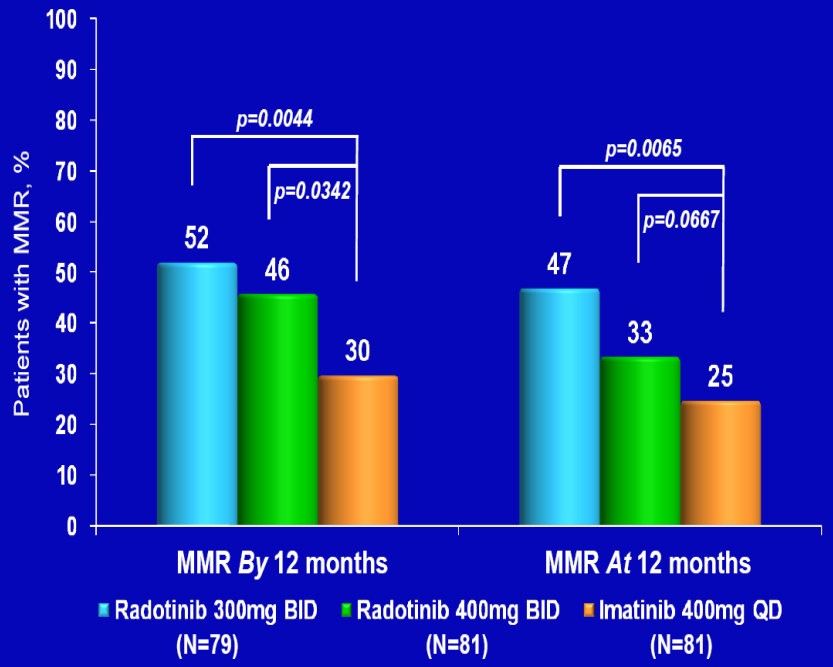
- Radotinib 300 mg BID (n = 79)
- Radotinib 400 mg BID (n = 81)
- Imatinib 400 mg QD (n = 81)

→ Extension follow-up 3 years after 1 year treatment

- Primary endpoint: MMR by 12 months
- Secondary endpoints: CCyR & CMR by 12 months, MMR at 12 months, Disease Progression
- Other endpoints: OS, PFS

*Stratified by Sokal risk score.

Major Molecular Response at Each Time



MMR: Major Molecular Response, BCR-ABL1 transcript level ≤ 0.1% ($MR^{3.0}$)

Data cut-off: 17Mar2015

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Kwak J. et al. ASH Annual Meeting 2015. Abstract #476.

Conclusions

- Radotinib demonstrated significantly higher molecular response rate at both 300mg BID and 400mg BID group compared with imatinib
- Radotinib 300mg BID, 400mg BID vs Imatinib 400mg QD: 52%, 46% vs 30%
- Treatment failure and suboptimal response in all radotinib groups were fewer than imatinib group and no progression in all groups was occurred
- The safety profiles of the radotinib and imatinib were different, and most AEs were manageable and well-controlled by dose reduction
- These phase 3 data suggest that radotinib can become a new promising 1st line therapy for patients with newly diagnosed chronic phase CML

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Kwak J. et al. ASH Annual Meeting 2015. Abstract #476.

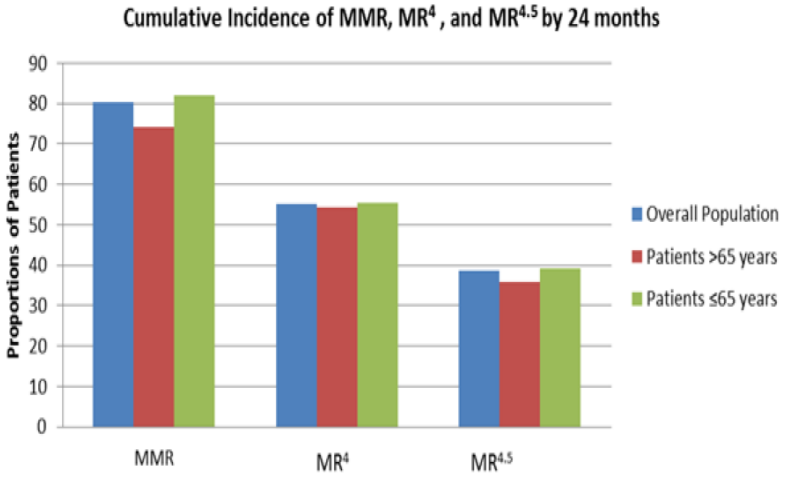
Actualités cliniques: Sujets âgés, étude ENEST1st, patients > 65 ans

- Sujets âgés de plus en plus nombreux
- Comment les manager: Nilo 300 mg x 2/j
- Résultats restent comparables aux sujets jeunes

- Attention toxicité spécifique:
  - Nausées, douleurs abdominales
  - Asthénie
  - Anémie

- Quid des évènements vasculaires ?

Adverse Event	*Patients ≤65 years (n = 851) %*	*Patients >65 years (n = 201) %*
Rash	*23.2*	*13.8*
Headache	*17.1*	*7.6*
Pruritus	*16.0*	*18.6*
Fatigue	*14.0*	*13.3*
Thrombocytopenia	*11.0*	*7.6*
Nasopharyngitis	*10.8*	*8.6*
Alopecia	*10.8*	*9.5*
Nausea	*9.8*	*17.6*
Diarrhea	*8.0*	*11.4*
Asthenia	*8.4*	*11.0*
Anemia	*5.1*	*10.5*
Abdominal pain	*6.9*	*10.5*
Dry skin	*8.2*	*10.0*



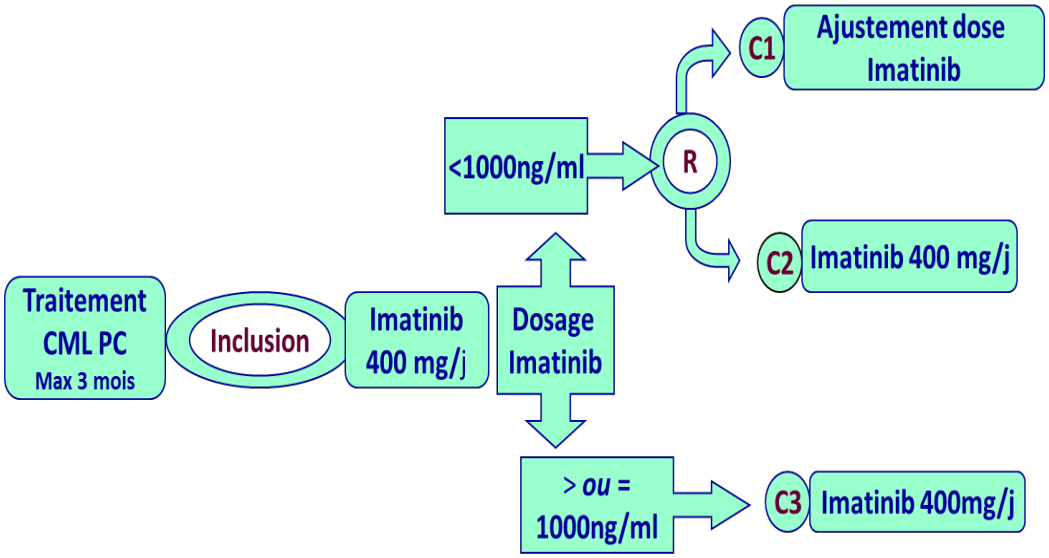
Giles FJ. et al. ASH Annual Meeting 2015. Abstract #479.

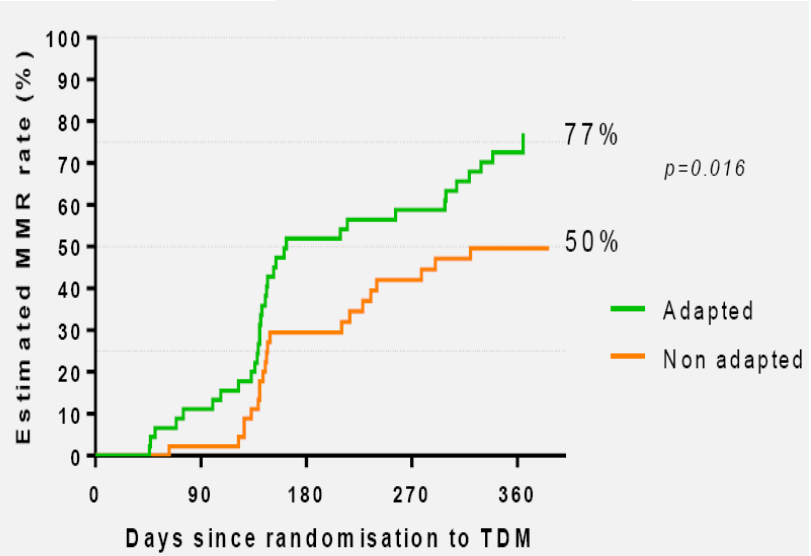
Actualités cliniques: étude OPTIM Imatinib

- **Monitoring pharmacologique de l'Imatinib**
- **A permis d'ajuster la posologie chez 2/3 de patients**
- **Améliore les taux de RMM à M12**
- **Intérêt pour la venue des génériques de l'Imatinib**

MMR by 12 months
(post randomization)

Improved MMR in a magnitude similar to 2nd gen TKI

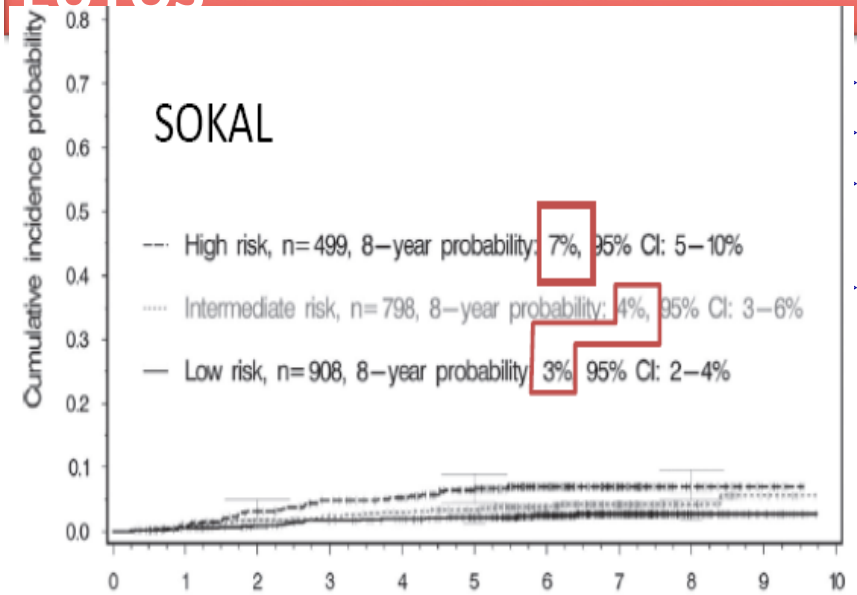


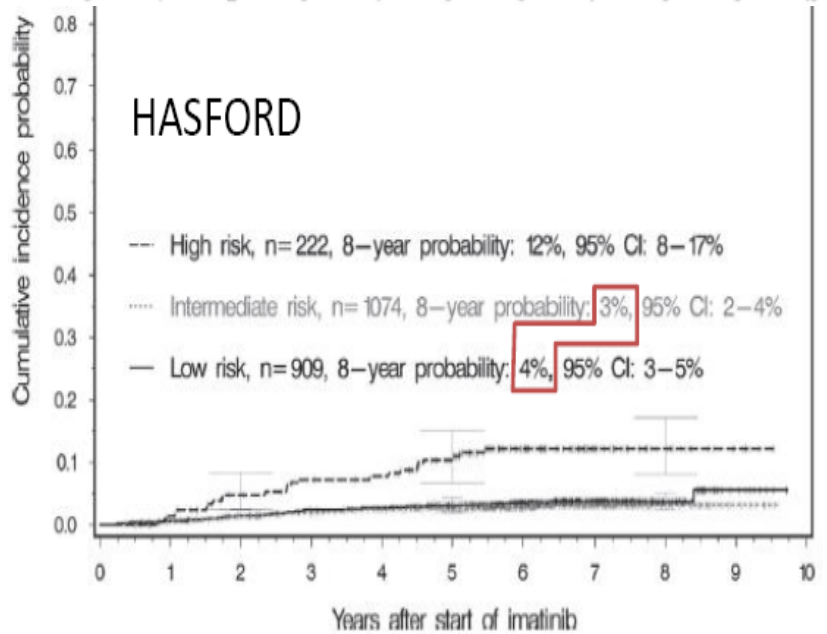


ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Rousselot P, et al. ASH Annual Meeting 2015. Abstract #133.

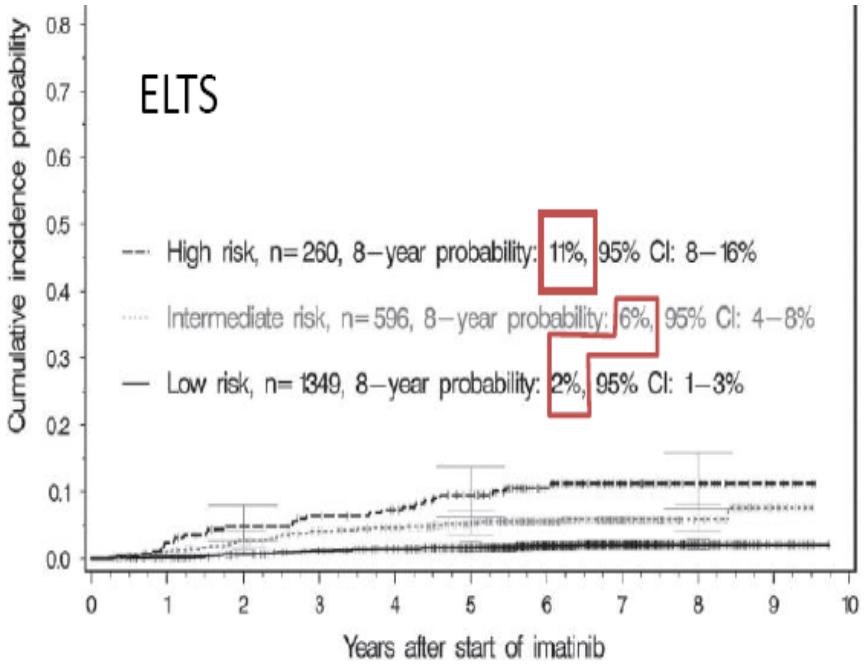
Actualités cliniques: meilleur score pronostique à long terme: EUTOS





- N= 2205 patients
- ELN/EUTOS registry
- Prospectively enrolled(2002-2006)
- Imatinib-based ttt

	Sokal (1984)	Euro/Hasford (1998)	EUTOS (2011)
	Chemo	IFN-a	Imatinib CCR 18 mo
Age	x	x	
Spleen size	x	x	x
Blasts %	x	x	
Platelet count		x	
Basophils %		x	x
Eosinophils %		x	



ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Pfirrmann M, et al. ASH Annual Meeting 2015. Abstract #595.

Qualité de vie des patients

Qualité de vie des patients: Etude Allemande

- Peu de données sur ce thème
- Enquête Allemande envoyée à 1634 patients
  - 858 réponses
  - Les femmes rapportent le plus une altération de la QDV
    - en comparant aux hommes
    - en comparant à la population générale
  - Altération de la QDV persiste pendant toute la durée du traitement

Cette enquête doit servir de base pour les études d'arrêt

Saussle S, et al. ASH Annual Meeting 2015. Abstract #2773.

Qualité de vie des patients: syndrome douloureux après arrêt ITK

- **Douleurs ostéo-articulaires post ITK: 24% des patients, durée 7 mois**
- **Physiologie ? Diagnostic exclusivement clinique**
- **Facteurs de risque: ATCD de douleurs articulaires, durée de TT par ITK**
- **Gérable avec AINS, corticoïdes, infiltration locale**

Study	Prevalence	Onset	TKI	Location	Duration
Euroski and STIM-2 (n= 428)	24%	21 days	Imatinib and nilotinib (n=2)	Shoulders Spine	A few weeks to several months

ASH 57th Annual Meeting & Exposition Orlando, FL • December 5-8, 2015

Berger M, et al. ASH Annual Meeting 2015. Abstract #137.