TKI Resistance in Chronic Myeloid Leukemia

Updates and Challenges in the Management of Chronic Myeloid Leukemia
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Disclosures

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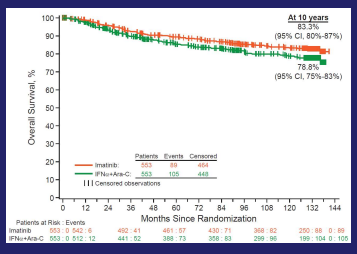
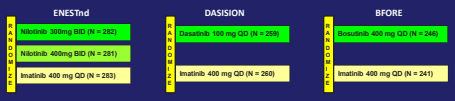
Ariad	yes	no	no
Blueprint	yes	no	no
Galena Biopharma	yes	no	no
Incyte	yes	yes	no
Novartis Pharma	yes	yes	yes
Pfizer, Inc.	yes	yes	yes

IRIS Study: 10-year Follow-up



Hochhaus et al, NEJM 2017

2G TKIs vs Imatinib in Treatment-Naïve CP-CML



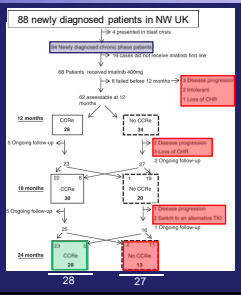
Saglio et al. NEJM 2017; Kantarjian et al. NEJM 2010; Cortes et al. JCO 2017

No Difference in Overall Survival – ENESTns as an Example

Approved frontline dose

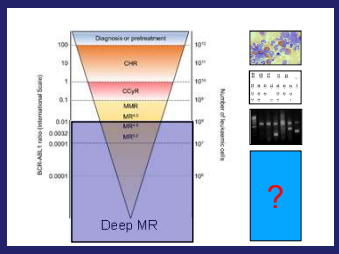
	Imatinib 400 mg QD (n = 283)	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)
Estimated 5-year PFS, %	**91.1**	**92.0**	**95.3**
Progressions and deaths, n	23	22	11
Hazard ratio (95% CI)	—	0.92 (0.51-1.65)	0.46 (0.23-0.95)
P value	—	.77	.03
Estimated 5-year OS, %	**91.6**	**93.6**	**96.0**
Total deaths, n	21	18	10
Deaths in patients with advanced CML, n[b]	15	6	4
Hazard ratio (95% CI)	—	0.84 (0.45-1.58)	0.46 (0.22-0.98)
P value	—	.58	.04

The Community Experience: High Rate of Imatinib Failure

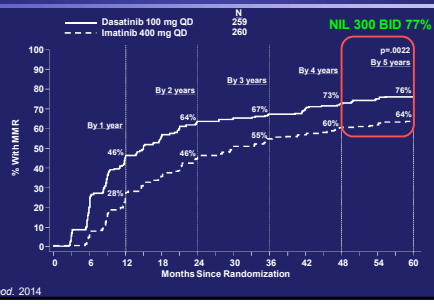


Lucas et al, BJH 2008

Disease Burden & Monitoring on the International Scale (IS)

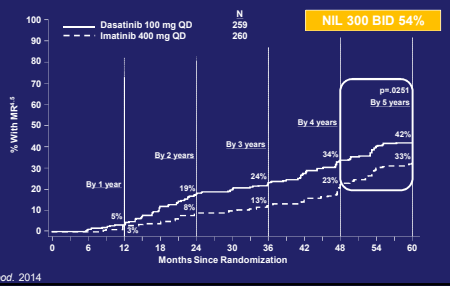


DASISION: Cumulative Incidence of MMR



Cortes JC, et al. *Blood*. 2014

DASISION: Cumulative Incidence of $MR^{4.5}$



Cortes JC, et al. *Blood*. 2014

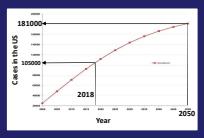
Therapeutic Milestones NCCN vs. ELN

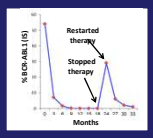
Month		Optimal	Warning	Failure
3	ELN	Ph⁺≤35% or BCR-ABL1<10%	Ph⁺ 65-95% or BCR-ABL1>10%	No CHR or Ph+>95%
	NCCN	Ph⁺≤35% or BCR-ABL1≤10%	NA	Ph⁺>35% or BCR-ABL1>10%
6	ELN	Ph⁺0% and/or BCR-ABL1<1%	Ph⁺1-35% and/or BCR-ABL1 1-10%	Ph⁺>35% and/or BCR-ABL1 >10%
	NCCN	Ph⁺≤35% or BCR-ABL1≤10%	NA	Ph⁺>35% or BCR-ABL1>10%
12	ELN	BCR-ABL1 <0.1%	BCR-ABL1 0.1-1%	Ph⁺ >0% BCR-ABL1 >1%
	NCCN	Ph⁺ 0%	NA	Ph⁺ >0%

Baccarani et al. Blood. 2013;122(6):872-84. Radich et al. J Natl Compr Canc Netw. 2014;12(11):1590-610

Challenges Remain

- Failure with 1st line TKI imatinib ~10% on studies
- Failure with 1st line dasatinib/Nilotinib/bosutinib* ~5% on studies
- 2G TKIs have long-term toxicities
- Treatment free remission limited to minority





* Limited follow-up with the new initial dose of 400mg daily

Recognizing TKI Failure

- Failure to reach milestones
- Loss of CHR
- Loss of CCyR
- Confirmed loss of MMR
- CCA/Ph⁺

Do not rush to conclusions!

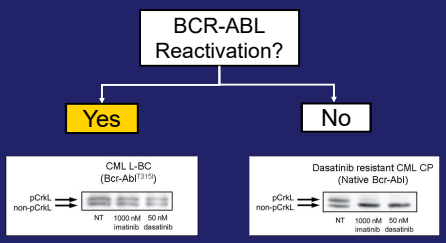
Non-compliance or drug interaction?

Laboratory error or imprecision?

No

Complete diagnostic workup
- Physical exam
- Bone marrow aspirate/biopsy
- Karyotyping
- BCR-ABL1 mutation screen

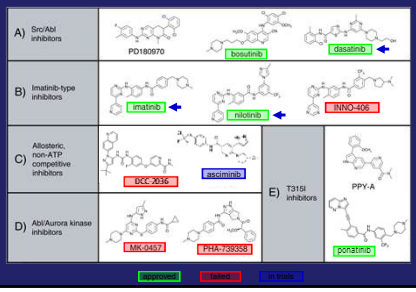
Mechanisms of TKI Resistance



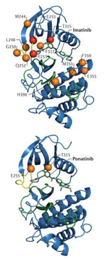
Factors Influencing Selection of Salvage Therapy

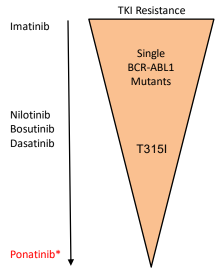
- Disease phase
- BCR-ABL1 mutation analysis
- Previous TKI exposure and response(s)
- Past medical history

ABL1 Kinase Inhibitors



Resistance Due to BCR-ABL1 Point Mutations





Relatively resistant
Completely resistant

O' Hare et al. Cancer Cell 2009.

* FDA-approved 12/2012

Past Medical History Impacts Therapy Selection

	IM	NIL	DAS	BOS	PON
Diabetes					
POAD					
CHF					
Prolonged QT					
PHT					
GI Bleeding					
IBS					
Pancreatitis					
Impaired LF					
Thrombembolism					

Problems Potential
- Low
- Somewhat elevated
- Elevated
- Typically contraindicated

- Few absolute contraindications
- Many better or worse picks
- Clinical judgment crucial

Relative Activity Profile of Various TKIs in Imatinib-Resistant Mutants

Mutation	IC_{50}-fold increase relative to WT (W=1)				
	Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
M244V	0.9	0.9	2.0	1.2	3.2
L248R	[illegible]	[illegible]	[illegible]	[illegible]	6.2
L248V	3.5	3.5	5.1	2.8	3.4
G250E	6.9	4.3	4.4	4.6	6.0
Q252H	1.4	0.8	3.1	2.6	6.1
Y253F	3.6	1.0	1.6	3.2	3.7
Y253H	8.7	0.6	2.6	[illegible]	2.6
E255K	6.0	9.5	5.6	6.7	8.7
E255V	[illegible]	5.5	3.4	[illegible]	[illegible]
D276G	2.2	0.6	1.4	2.0	2.1
E279K	3.6	1.0	1.6	2.0	3.0
E292L	0.7	1.1	1.3	1.8	2.0
V299L	1.5	[illegible]	8.7	1.3	0.6
T315A	1.7	6.0	[illegible]	2.7	0.4
T315I	[illegible]	[illegible]	[illegible]	[illegible]	3.0
T315V	[illegible]	[illegible]	[illegible]	[illegible]	2.1
F317L	2.6	2.4	4.5	2.2	0.7
F317R	2.3	[illegible]	[illegible]	2.3	4.9
F317V	0.4	[illegible]	[illegible]	0.5	2.3
M343T	1.2	1.1	0.9	0.8	0.9
M351T	1.8	0.7	0.9	0.4	1.2
F359I	6.0	2.9	3.0	[illegible]	2.9
F359V	2.9	0.9	1.5	5.2	4.4
L384M	1.3	0.5	2.2	2.3	2.2
H396P	2.4	0.4	1.1	2.4	1.4
H396R	3.9	0.8	1.6	3.1	5.9
F486S	8.1	2.3	3.0	1.9	2.1
L248R + F359I	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

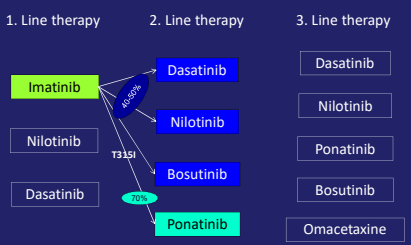
Sensitive	<2-fold difference
Moderately sensitive	2.1- to 4-fold difference
Resistant	4.1- to 10-fold difference
Highly resistant	>10-fold difference

Adapted from Redaelli S et al. *Am J Hematol.* 2012;87:E125-E128.

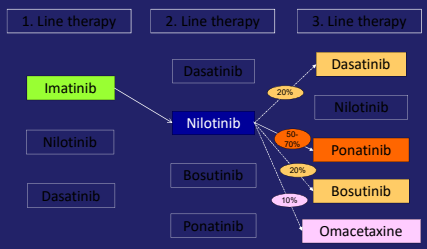
But: In vitro sensitivity is imperfect correlate of in vivo efficacy.

Eiring et al. Genome Biol. 2014;15(9):461

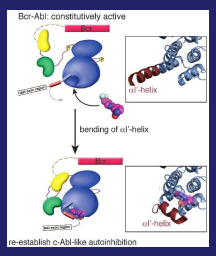
Treatment History and Salvage Therapy – Likelihood of CCyR



Treatment History and Salvage Therapy – Likelihood of CCyR



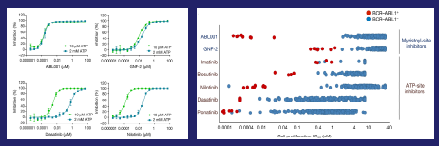
Binders at the Myristoylation Site Allosterically Enforce Autoinhibition



Hantschel O. Haematologica. 2012;97:195-97

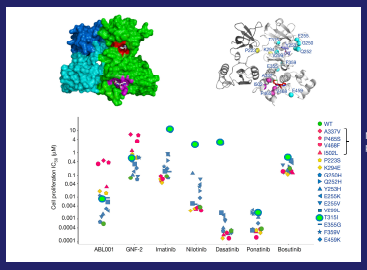
Asciminib: Allosteric BCR-ABL1 Inhibition

- Binds with high affinity to the myristoyl pocket of ABL1 kinase to mimic the native myristate ligand
- Ba/F3 BCR-ABL1 IC_{50}: ~3 nM
- Demonstrates an extremely selective kinase profile
- Currently in Phase 1/2



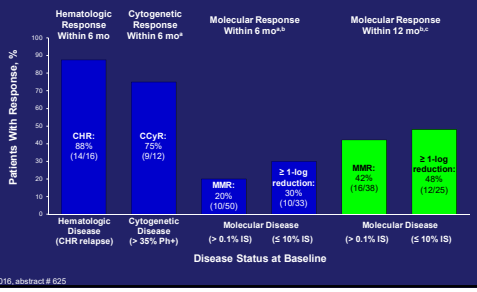
Wylie et al. Nature. 2017;543(7647):733-737

Activity of Asciminib in Comparison with Catalytic Site TKIs



Wylie et al. Nature. 2017;543(7647):733-737

Responses in Patients With CML Treated With Single-Agent BID ABL001 With ≥ 3 Months Exposure on Study

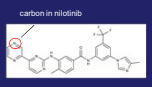


Hughes et al. ASH 2016, abstract # 625

Other BCR-ABL1 Inhibitors of Potential Interest

Radotinib

- Chemically almost identical to nilotinib
- Similar activity
- Approved in South Korea

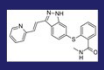


K0706

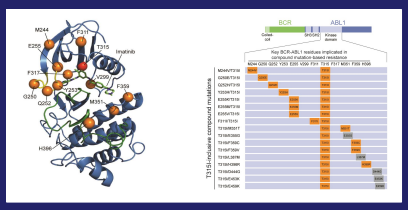
- Structure unpublished
- Active against BCR-ABL1^{T315I}
- Phase 1/2 study in refractory CML is ongoing (Sponsor: Sun Pharmaceuticals)

Axitinib

- Main targets VEGFR1-3; KIT; PDGFR
- Approved for RCC
- Selective activity against BCR-ABL1^{T315I} vs. native BCR-ABL1 (Pemovska et al. Nature 2015; Zabriskie et al. Leukemia 2015)

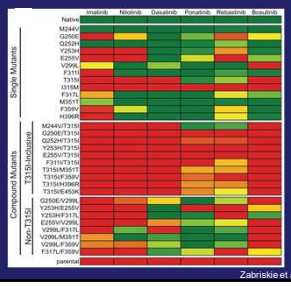


T315I-Inclusive Compound Mutations Confer Universal TKI Resistance



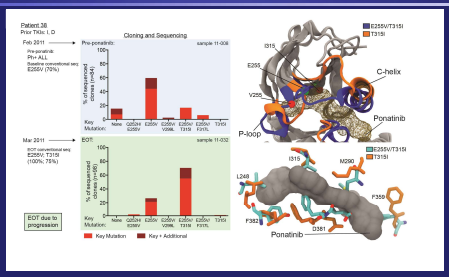
Zabriskie et al. Cancer Cell 2014

Cellular BCR-ABL1 TKI Sensitivity



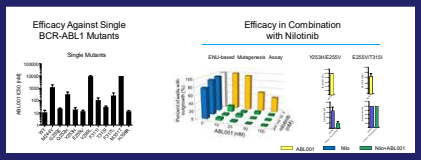
Zabriskie et al. Cancer Cell 2014

Rationalizing Resistance due to E255V/T315I



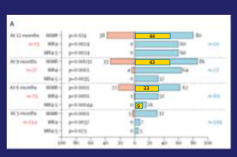
Zabriskie et al. Cancer Cell 2014

Efficacy of Ascminib alone and in Combination with Nilotinib



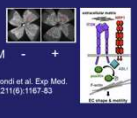
O'Hare T, Zabriskie M, Deininger M, unpublished

How far can we get with BCR-ABL1 Inhibition? Responses to Ponatinib 45mg vs. Imatinib 400mg Daily (EPIC Trial)



Cave: Low numbers at 9, 12 months due to study closure

Ponatinib:
- Potent
- Very long on-target time
- Long half-life
- Vascular toxicity



Raimondi et al. Exp Med. 2014;211(6):1167-83

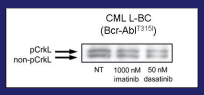
Lipton et al. Lancet Oncol. 2016. 17(5):612-21

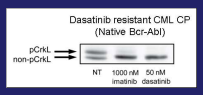
Mechanisms of TKI Resistance

BCR-ABL Reactivation?

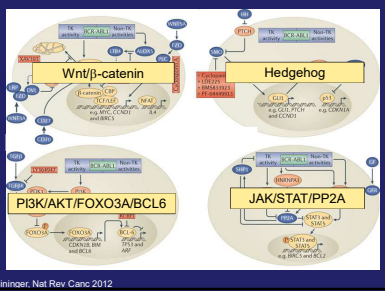
Yes

No



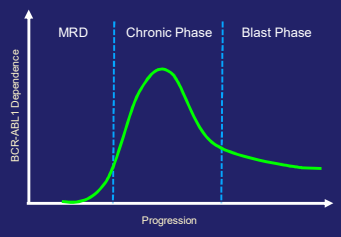


Alternative Survival Pathways in CML LSC



O'Hare, Zabriskie, Eiring, Deininger, Nat Rev Canc 2012

Instead of a Summary: How CML Works



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NIH/NCI
Aspire Mechanism
V Foundation

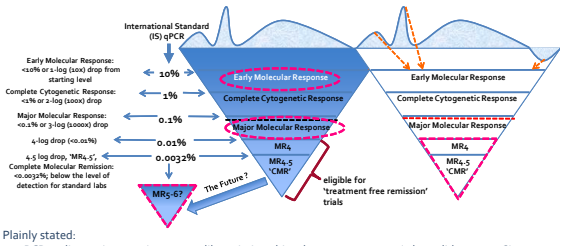
Multi-drug Resistant and Intolerant CML: *What to do?*

Michael J. Mauro, MD
Leader, Myeloproliferative Neoplasms Program
Memorial Sloan Kettering Cancer Center, New York, NY

Five Things

- What are we aiming for and what trips us up
- Approaching the 'failing patient': why? mutations, adherence, other?
- ABL001
- PF-114
- Ko706

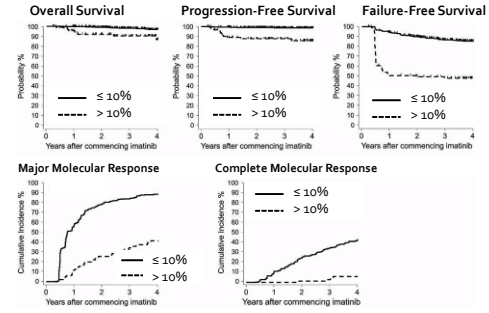
'Shrinking the iceberg': response expectations



Plainly stated:

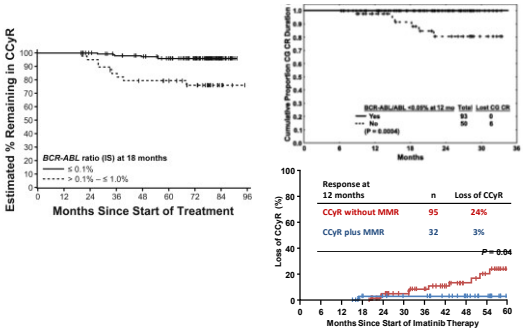
1. PCR at diagnosis = very important, like a timing chip when you run a race (where did you start?)
2. Early response at 3mo should be 'on track', 10x lower than start, ~10% (if you start ~100%)
3. Complete cytogenetic response (~1% on the PCR scale; 100x lower) is very important and protective
4. Major molecular response (MMR, ~0.1% on the PCR scale; 1000x lower) adds further protection
5. Deep Molecular remission: aiming for 0.01% or lower (10,000x lower than start) and staying that way

Impact of BCR-ABL values ≤10% @ 3 months



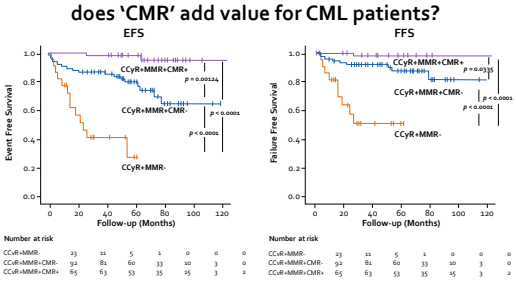
Branford S et al. Blood 2014;124:511-518

Value of MMR in prolonging remission



Hughes T, et al. *Blood* 2010; 116(19):3758-65; Cortes J et al. Clin Cancer Res 2005;11:3425-3432; Marin D, et al. *Blood 2008;* 112(12):4437-44

Aside from being a launching point for 'TFR' trials, does 'CMR' add value for CML patients?



EFS = event-free survival; FFS = failure-free survival.
CMR Defined as undetectable BCR-ABL with a sensitivity of at least 4.7 logs on 2 consecutive analyses at least 2 months apart.

Etienne G et al. Haematologica 2014;99:458-464

Choosing your tools: comparing TKI toxicity in CML

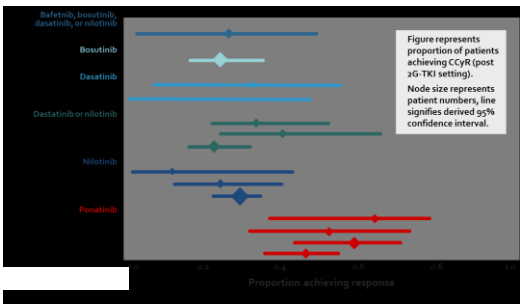
Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Dosing	QD/BID, with food	BID, without food (2h)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing; Emerging toxicity
Heme toxicity	intermediate	least	Most severe; ASA-like effect; lymphocytosis	~dasatinb in 2nd, 3rd line; ~nilotinib in 1st line	↑thrombocytopenia ASA-like effect
Non-Heme toxicity	Edema, GI effects, ↓Phos	↑lipase, ↑bili, ↑chol, ↑glu Black box: QT prolongation; screening req'd	Pleural / pericardial effusions	Diarrhea; transaminitis	↑lipase, pancreatitis; rash; hypertension; Black box: vascular occlusion, heart failure, and hepatotoxicity
Emerging toxicities	early question re: CHF; ?late renal effects	Vascular events (ICVE, IHD, PAD)	PAH (pulmonary arterial hypertension)	? Mild renal effects	Vascular events (ICVE, IHD, PAD, VTE)

Post-Imatinib: 2nd Generation TKIs offer similar benefits

	Dasatinib	Bosutinib	Nilotinib
Months follow-up	>24	Median of 24	>24
Complete Hematologic Response	89%	86%	77%
Major Cytogenetic Response	59%	54%	56%
Complete Cytogenetic Response	44%	41%	41%
2-year Progression Free Survival	80%	79%	64%
2-year Overall Survival	91%	92%	87%

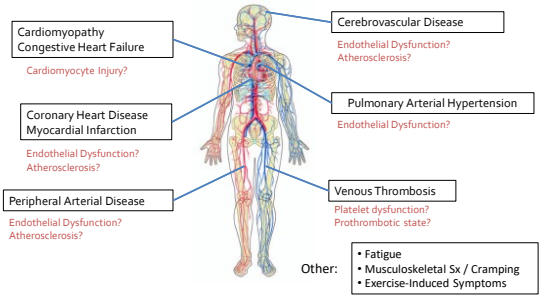
Shah et al. Haematologica 2010; 95: 232-40, Kantarjian et al. Blood 2011; 117: 1141-45; Cortes et al. Blood 2011; 118, 4567-76

3rd line therapy: Switch to alternate 2nd gen agent versus ponatinib?



Lipton J, et al. ASH 2013. Abstract 4010.

The most significant 'late effects': CML TKI Associated Cardiovascular Adverse Effects



➔ Morbidity and mortality; ? Effect on survival observations in front-line studies?
➔ ? Delay/deferral of advantageous therapy both in front-line and salvage

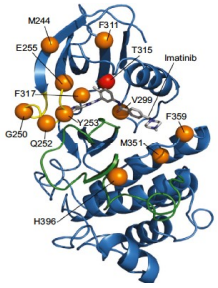
Omacetaxine for CML After Failure of ≥2 TKIs

Response, %	CP N=81	AP N=41
Primary endpoint(s)	Major Cytogenetic Response: 20%	Major Hematologic Response: 27%
	Complete Cytogenetic Response: 10%	Complete Hematologic Response: 24%
Median duration, months	17.7	9
Median Progression Free Survival, months	9.6	4.7
Median Overall Survival, months	33.9	16

- 11 patients (9 chronic phase, 2 accelerated phase) ongoing response
- Median 35 cycles over median 39 months
- Median response duration:
  - 14 months for chronic phase, 24 months for accelerated phase

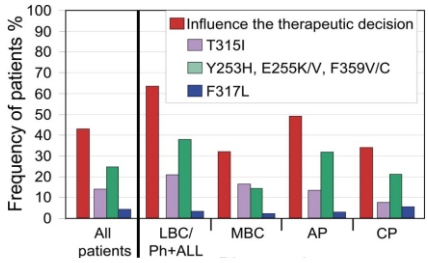
Kantarjian. Blood 120: abst 2767; 2012

Resistance to TKIs: point mutations



- >100 mutations described in imatinib and subsequent generation TKI treated patients; only a handful (~10) account for the vast majority (~85%) of clinically observed mutations
- Single and compound mutations are found in the same subset of 12 key positions

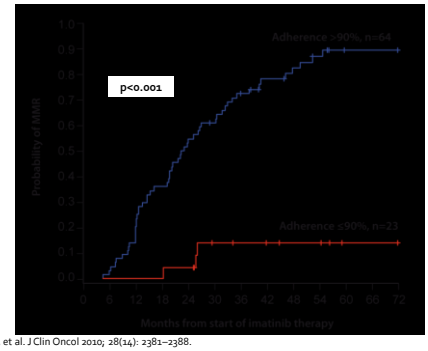
Likelihood mutation testing will influence TKI choice



Branford S et al, *Blood* 2009

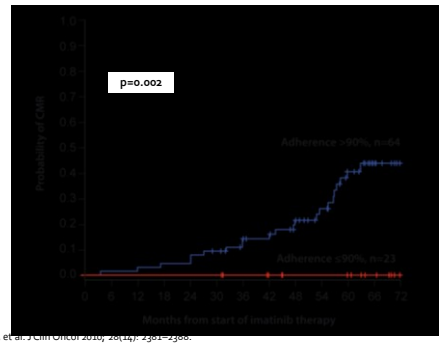
Adherence

6-year probability of MMR according to the measured adherence rate



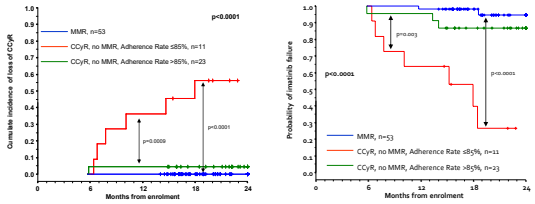
Marin D, et al. J Clin Oncol 2010; 28(14): 2381–2388.

6-year probability of CMR according to the measured adherence rate



Marin D, et al. J Clin Oncol 2010; 28(14): 2381–2388.

Adherence and the achievement of MMR are the only independent predictors for outcome



Marin D, et al. J Clin Oncol 2010; 28(14): 2381–2388.

Practical approach to a patient with resistance (or intolerance +/- resistance)

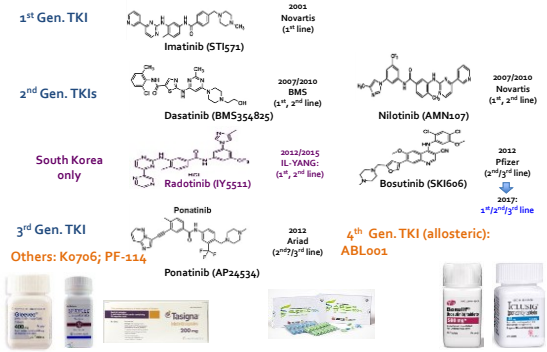
- First, determine what the disease state *requires*
  - disease phase
  - prior TKI exposure
  - mutational status
    - T315I unique
    - Select mutations may support role of specific 2nd generation TKIs
    - Predictive potential imprecise
    - 'iceberg' phenomenon
    - More detailed assays not routinely incorporated (deep sequencing, etc)
- Next, balance therapy risk and toxicity potential with known comorbidities
  - are there true 'contraindications'?
  - does risk outweigh benefit expected from therapy?
  - can risk be mitigated or anticipated?
  - enlist the patient's insight, trust, and awareness

What *is* the role of allografting in CML?

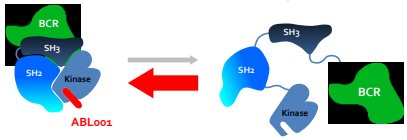
Status	*TKIs*	*Transplant*
Accelerated or Blast transformation has occurred	Interim treatment to best response/minimal residual disease	ASAP
Imatinib failure in chronic phase, T315I (+)	Ponatinib with caution, ABL001 (experimental)	If no response to Ponatinib/ABL001
Imatinib failure in chronic phase without clonal evolution, mutations, good response	Long-term second line TKIs	Third line post second TKI failure or beyond
IM failure in chronic phase with clonal evolution, mutations, poor response	Interim treatment to best response	Second line, taken case by case
Older age (≥65 – 70) post imatinib failure	Long-term second line TKIs	May forgo allo SCT for many yrs of QOL

New Agents: ABL001, PF-114, K0706

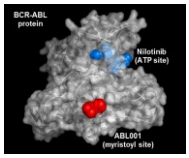
At present, *five* oral, small molecular kinase inhibitors approved in the US for Ph+ Leukemia: a 'spoil of riches'; more on the way?



4th generation TKI ABL001 Allosterically Inhibits BCR-ABL1 Kinase Activity



INACTIVE ACTIVE



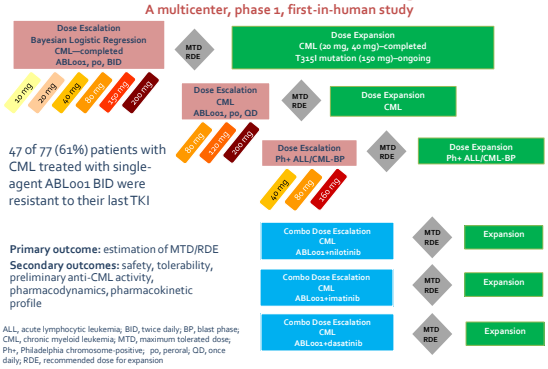
- Developed to gain greater BCR-ABL1 inhibition, with activity against BCR-ABL1 mutations conferring resistance to TKIs
- Potential to combine with TKIs for greater pharmacological control of BCR-ABL1

ABL001

Ottmann et al, ASH 2015 Abstract #138

ABL001X2101: Study Design

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



47 of 77 (61%) patients with CML treated with single-agent ABL001 BID were resistant to their last TKI

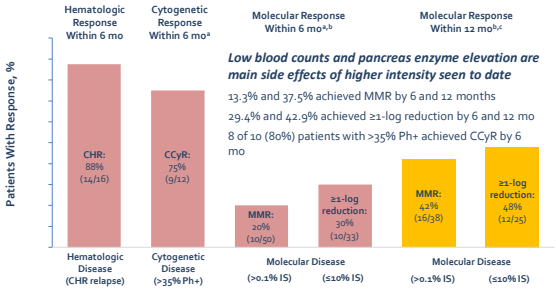
Primary outcome: estimation of MTD/RDE

Secondary outcomes: safety, tolerability, preliminary anti-CML activity, pharmacodynamics, pharmacokinetic profile

ALL, acute lymphocytic leukemia; BID, twice daily; BP, blast phase; CML, chronic myeloid leukemia; MTD, maximum tolerated dose; Ph+, Philadelphia chromosome-positive; po, peroral; QD, once daily; RDE, recommended dose for expansion

Hughes TP, et al. *Blood*. 2016; 128 (22). [abstract 625].

Responses in Patients With CML Treated With Single-Agent BID ABL001 With ≥3 Months Exposure on Study



Low blood counts and pancreas enzyme elevation are main side effects of higher intensity seen to date

13.3% and 37.5% achieved MMR by 6 and 12 months

29.4% and 42.9% achieved ≥1-log reduction by 6 and 12 mo

8 of 10 (80%) patients with >35% Ph+ achieved CCyR by 6 mo

CCyR, complete cytogenetic response; CHR, complete hematologic response; IS, International Scale; MMR, major molecular response; mo, months

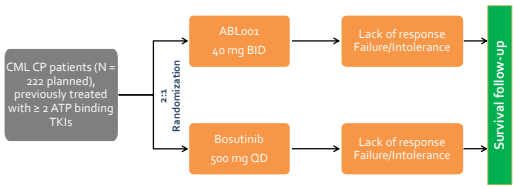
[a]Patients had ≥6 months of treatment exposure or achieved response within 6 months

[b]*BCR-ABL*[1]^{IS} reduction achieved

[c]Patients had ≥12 months of treatment exposure or achieved response within 12 months

Hughes TP, et al. *Blood*. 2016; 128 (22). [abstract 625].

CABL001A2301 (Planned): Study Design
A phase 3, Multicenter, Open-label, Randomized Study of ABL001 Versus Bosutinib



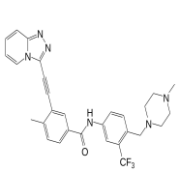
- **Primary endpoints:** Major Molecular Response (MMR) rate at 24 weeks
- **Key secondary endpoint:** MMR rate at 96 weeks

BID, twice daily; CML, chronic myeloid leukemia; CP, chronic phase; QD, once daily; TKI, tyrosine kinase inhibitor

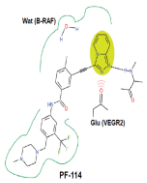
PF-114 phase 1 study

PF-114 – Novel 3rd Generation Inhibitor of Bcr-Abl

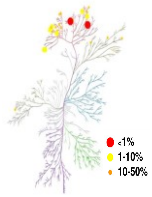
- PF-114: 3rd generation Abl inhibitor, close structural analog of ponatinib
- PF-114 rationally designed to avoid inhibition of numerous off-target kinases and potentially avoid life-threatening side effects



PF-114



Structure-inspired disruption of off-target interactions with kinases like VEGFR2 and B-Raf



PF-114 kinase inhibition profile (100 nM)

PF-114 phase 1 study

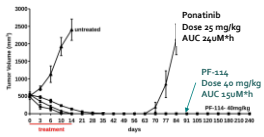
Pre-clinical Characterization of PF-114

- Cytotoxicity to Ph+ ALL PDLTC and BaF3 cells with native BCR/ABL and mutant variants

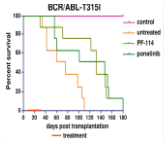
Cell line	Bcr-Abl variant	IC50, nM*
PDLTC, VB	p210	15
PDLTC, PH	P185	3
PDLTC, CM	p210	7
PDLTC, KW	p185	5
PDLTC, DW	p185	7
PDLTC, BV	p185	3
PDLTC, KO	p185, T315I	75
BaF3	p185, Y253F	25
BaF3	p185, E255K	25
BaF3	p185, F317L	100

*Medical Clinic of Ghoethe University, Frankfurt, Germany

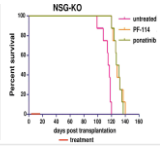
- Xenograft K562 CML cell line model



Orthotopic murine BaF3 cell model of T315I+ CML



NSG Mice iv xenograft of human T315I Ph+ALL



PF-114 phase 1 study

Phase 1 Study Design and Outcome Measures

- **Design**
  - 3+3 dose escalation till MTD (DLT during 1-st 28-day cycle)
  - Expanded cohorts (10-15 pts each) at ≤MTD; total enrollment ~44 pts
- **Eligibility**
  - CML CP or CML AP patients who failed ≥2 TKIs, or intolerant of TKIs, or with T315I
- **Primary endpoints**
  - DLT(s) during 1-st 28-day cycle
  - MTD
- **Secondary endpoints**
  - Incidence of AEs
  - PK
  - Rates of hematologic, cytogenetic, molecular responses
- **Exploratory endpoints**
  - Pharmacodynamic response (p-CrkL/CrkL)
  - Pharmacogenetic relations (response across BCR/ABL mutant forms)

PF-114 phase 1 study

Preliminary Analysis of Safety: Hematologic Adverse Drug Reactions

	n of patients with adverse drug reactions			
	Gr 1	Gr 2	Gr 3	Gr 4
Blood and lymphatic system disorders	**4/24**	**1/24**	**3/24**	
neutropenia	2	1	2	
thrombocytopenia	2		2	
anemia	1			

PF-114 phase 1 study

Non-Heme AEs

	n of patients with adverse drug reactions			
	Gr 1	Gr 2	Gr 3	Gr 4
Skin and subcutaneous tissue disorders	**18/24**	**13/24**	**4/24**	
psoriasiform skin lesions	13	10	3	
dry skin	5	1		
itching	2	1		
rash	1	1	1	
hyperemia	1	1		
Gastrointestinal disorders	**7/24**	**1/24**		
diarrhea	6	1		
abdominal pain	2			
nausea	1			
stomatitis	1			
pain in the right hypochondrium	1			
General disorders and administration site conditions	**1/24**			
fever	1			
Nervous system disorders	**2/24**			
dizziness	1			
headache	1			

PF-114 phase 1 study

Biochemical AEs

	n of patients with adverse drug reactions			
	Gr 1	Gr 2	Gr 3	Gr 4
Investigations	**4/24**	**2/24**		
hypophosphatemia		1		
increase of cholesterol	1	1		
increase of LDL	1			
decrease of HDL	1			
increase of ALT	1			
increase of AST	1			
increased level of creatinine	1			

PF-114 phase 1 study

Preliminary Analysis of Efficacy of PF-114

Phase of CML	BCR/ABL mutation status	Total number of patients	Rate of CHR		Rate of MCyR	
			%	n*/N**	%	n*/N***
Chronic	T315I	9	40	2/5	80	4/5
	All	21	36	4/11	40	4/10
Acceleration	T315I	1	0	0/1	0	0/1
	All	2	50	1/2	0	0/2
Blast	T315I	1	100	1/1	0	0/1

n* - number of patients who achieved response during treatment
N** - number of patients evaluable for hematologic response assessment: were not in CHR at enrollment
N*** - number of patients evaluable for cytogenetic response assessment: were not in MCyR at enrollment and completed at least 3 cycles

PF-114 phase 1 study

Conclusions

- PF-114 mesylate exhibits anti-leukemia activity in a heavily pretreated CML patients including those with T315I mutation
- MTD has not been reached
  - 50, 100, 200, 400, 500 mg dose cohorts have been studied
  - 600 mg cohort is currently being studied
- A single DLT of grade 3 erythematous rash observed
- No cardiovascular events have been observed
- A Phase 2 multicenter international study is planned for 2018

K0706: Program

K0706: Novel BCR-ABL tyrosine kinase inhibitors for treatment of Chronic Myeloid Leukemia (CML)

K0706: equipotent to Ponatinib in CML cellular & in vivo efficacy assays with limited potential for off-target effects based on the long term toxicity studies*

K0706: as an efficacious, tolerable and safer treatment alternative for Chronic Myeloid Leukemia or Ph+ Acute Lymphoid Leukemia patients who have failed ≥ 2 lines of therapies and/or ineligible due to comorbidities which limit the administration of other TKIs

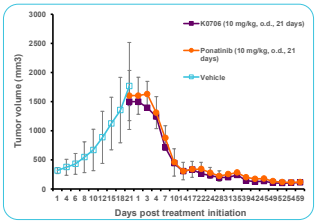
Courtesy of Sun Pharma / personal communication

SUN-K0706: Preclinical Data Summary

In vitro

Kinases	IC_{50} (nM) SUN-K706	IC_{50} Ponatinib
Abl	0.9	0.7
Abl(T315I)	8	2
Abl (M351T)	0.8	0.3
Abl (Q252H)	0.8	0.4
Abl(Y253F)	1	0.3

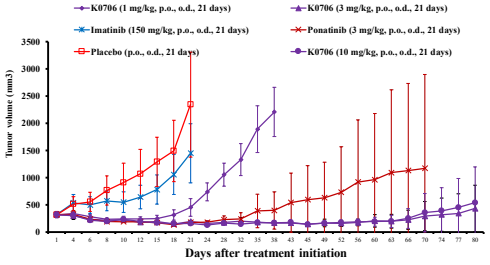
In vivo



- Effective against the wild type and mutation bearing CML cell lines
- Caused tumor regression in an imatinib-resistant xenograft model

Courtesy of Sun Pharma / personal communication

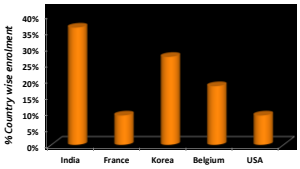
K0706:Long-term monitoring of K562 xenograft growth

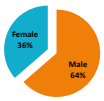


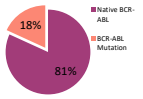
Courtesy of Sun Pharma / personal communication

Part B: Subject Profile & Disposition

Toxicity: ICH in BP patient, tenosynovitis with successful rechallenge







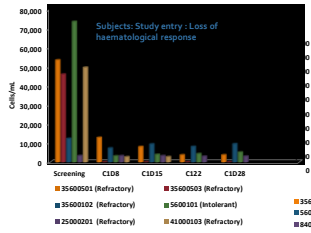
1 Subject: T315I mutation
1 Subject: F359V mutation
1 Subject: T315I mutation status under investigation

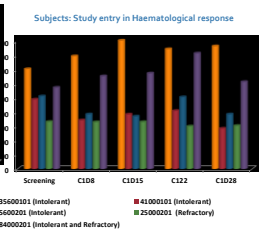
	Cohort/Dose level				
Disposition of Subject	12 mg	24 mg	48mg	66mg	All Subjects
Subjects enrolled (N)	1	1	6	3	11
Received study medication (N)	1	1	6	3	11
Subjects completing Cycle 1 (N)	1	1	5	2	10
No of Cycles completed	Cycle 9	Cycle 5	Cycle 3	Cycle 1	NA
Subjects discontinued (N)	Nil	Nil	1 (SAE)		1 (SAE)

Courtesy of Sun Pharma / personal communication

Efficacy

Hematological response



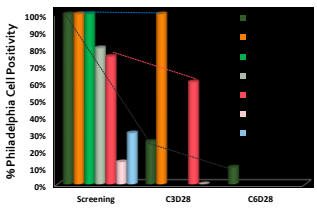


- 9/11 Subjects demonstrated complete hematological response by end of Cycle 1
  - *3/11 Achieved; 6/11 Maintained*
- Transient self-limiting grade 1 /2 neutropenia associated with study drug was observed in 2/11 subjects
- This was self-limiting and recovered by end of Cycle 1 without intervention

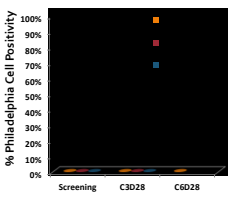
Courtesy of Sun Pharma / personal communication

Efficacy

Cytogenetic response



Subjects: Study entry :Loss of cytogenetic response



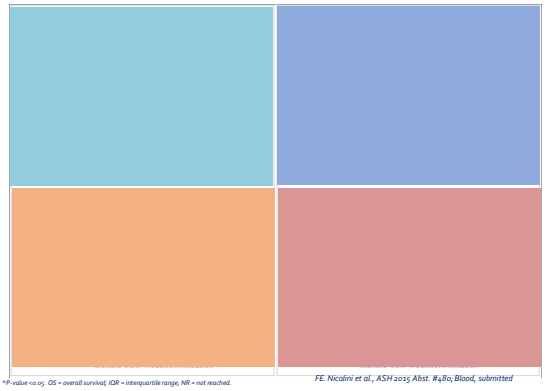
Subjects: Study entry: Complete cytogenetic response

- Cytogenetic response data in maturing process
- Subject with loss of cytogenetic response transition: Partial cytogenetic response & evolving cytogenetic response
- Subjects with complete cytogenetic response: Maintained cytogenetic response

**: Not applicable; Subject discontinued from study*

Courtesy of Sun Pharma / personal communication

In CP and AP CML, No Early Gain in Overall Survival with SCT *vs* Ponatinib

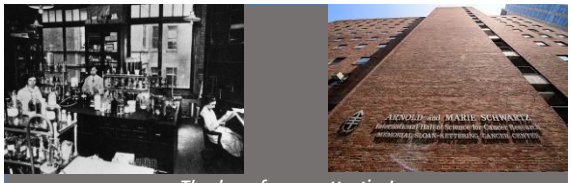


*P-value <0.05. OS = overall survival; IQR = interquartile range; NR = not reached.

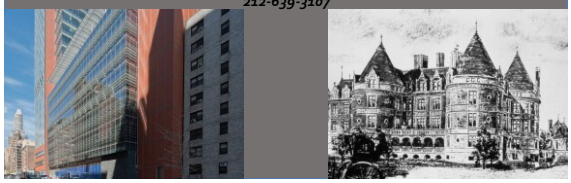
FE. Nicolini et al., ASH 2015 Abst. #480; Blood, submitted

Conclusions

- CML is highly treatable; 'functional cure' appears feasible
- Generic imatinib is here; more TKIs still in development
- Early response increasingly predictive of long term success
- Resistance based in mutations *can* drive treatment choice but is likely quite complex; Novel agents in study (ABL001)
- Second /third line therapy effective, needs to be carefully chosen (risk/benefit of ponatinib *vs* other alternatives)
- SCT still needed as an option
- New options/new drugs on the horizon



Thank you for your attention!
Questions?
maurom@mskcc.org
212-639-3107



DANA-FARBER CANCER INSTITUTE

Upfront Treatment Strategies for Patients with CML

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2017 Master Class Course

Presenter Disclosure Information

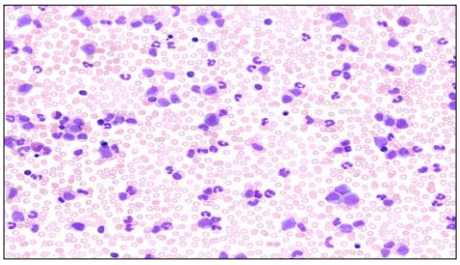
The following relationships exist related to this presentation:

- Dr. Daniel DeAngelo has served as a consultant for Amgen, Celgene, Incyte, Novartis, Pfizer, Shire and Takeda Pharmaceuticals
- I have also received research funding from Glycomimetics and Blueprint Pharmaceuticals

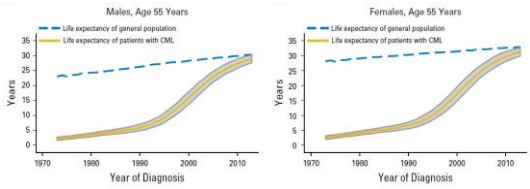
Off-Label/Investigational Discussion

In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

CML: Management in the Era of Multiple Tyrosine Kinase Inhibitors

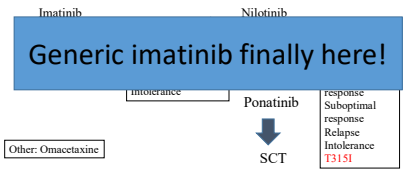


Life Expectancy of Patients with CML Approaches the General Population



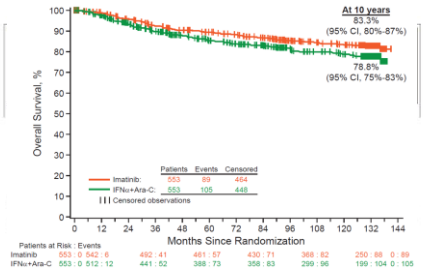
Bower et al., *J Clin Oncol* 2016 34: 2851-7.

CML Current Status: 2018



What Can We Expect From Front-line Imatinib in CP CML?

IRIS Trial Data

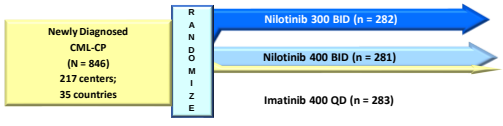


A Hochhaus, RA Larson, F Guilhot, et al. *New Engl J Med* 2017 376: 917-27.

- There are consistent data from multiple studies demonstrating that patients who have very rapid responses with any TKI have excellent long term outcomes and that some patients with slower responses fare more poorly.
- Responses are faster with "second" generation TKIs

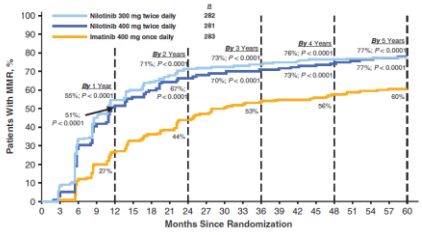
ENESTnd: Nilotinib vs Imatinib in Newly Diagnosed Chronic Phase CML

- Primary endpoint: MMR at 12 mos, defined as ≤ 0.1% BCR-ABL(/ABL ratio) on International Scale
- Secondary endpoint: CCyR by 12 mos
- Other endpoints: time/duration of MMR and CCyR; EFS, PFS, time to AP/BP, OS
- Stratification by Sokal risk



Saglio G, et al. *N Engl J Med*. 2010;362(24):2251-2259.

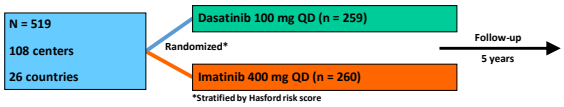
ENESTnd: Cumulative Incidence of MMR



* *P* values are nominal.
† For each arm, the curve stops at the latest time point at which a patient first achieved MMR.

Hochhous A, et al. *Leukemia*. 2016: 1044-1054.

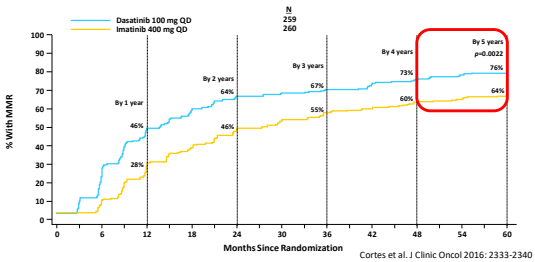
Dasatinib vs Imatinib in Treatment-naive CML: DASISION



- Primary endpoint: Confirmed CCyR *by* 12 months
- Secondary/other endpoints: Rates of CCyR and MMR; times to confirmed CCyR, CCyR and MMR; time in confirmed CCyR and CCyR; PFS; overall survival

Kantarjian H, et al. *N Engl J Med*. 2010;362(24):2260-2270.

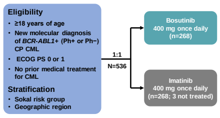
DASISION: Cumulative MMR Rates Over Time



Cortes et al. J Clinic Oncol 2016: 2333-2340

BFORE Study Design: First-line Bosutinib vs Imatinib in CML

- BFORE (NCT02130557) is an ongoing (expected duration 5 years), multinational, randomized, open-label, two-arm, phase 3 study
- Prespecified primary endpoint:
  - MMR at 12 months in the mITT population
- mITT population: Ph+ patients with e13a2/e14a2 transcripts, excluding Ph− patients and those with unknown Ph status and/or *BCR-ABL* transcript type*
  - Bosutinib: n=246
  - Imatinib: n=241
- Current analysis based on ≥18 months of follow-up†



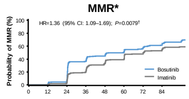
- * 12 Ph− patients (ie, 0 of ≥10–99 metaphases at baseline; n=6 in each arm), 8 patients with atypical transcripts (n=3 in bosutinib arm; n=5 in imatinib arm), and 31 patients with unknown Ph status (n=13 in bosutinib arm; n=18 in imatinib arm [includes 2 patients also listed as having atypical transcripts]).
- † All *P* values, except MMR at 12 months and CCyR by 12 months in the mITT population, are for descriptive purposes only; no adjustments for multiple comparisons.
- CCyR=complete cytogenetic response; CML=chronic myeloid leukemia; CP=chronic phase; ECOG PS=Eastern Cooperative Oncology Group performance status; mITT=modified intent-to-treat; MMR=major molecular response; Ph=Philadelphia chromosome

Gambacorti-Passerini et al., ASH 2017, abstract #896

Cumulative Incidence of Response (mITT Population)

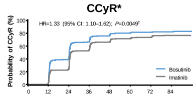
BFORE: First-line Bosutinib vs Imatinib in CML

Cumulative Incidence of MMR*



Patients at risk, n								
Bosutinib	246	232	206	119	94	75	58	39
Imatinib	241	235	204	151	116	87	62	38

Cumulative Incidence of CCyR*



Patients at risk, n								
Bosutinib	246	229	121	50	20	8	5	2
Imatinib	241	229	149	70	40	20	12	2

* 18-month data shown; data after 72 weeks subject to change to due to incomplete follow-up.
† Gray's test *P*-value.
CI=confidence interval; CML=chronic myeloid leukemia; CCyR=complete cytogenetic response; HR=hazard ratio; mITT=modified intent-to-treat; MMR=major molecular response

Gambacorti-Passerini et al., ASH 2017, abstract #896

BUT….

NO SURVIVAL ADVANTAGE with nilotinib, dasatinib or bosutinib in randomized trials

Only about 60-65% of patients remain on their initial drug

And then there are the toxicities…

LONGER TERM FOLLOW-UP OF SECOND and THIRD GENERATION TKIs

- Dasatinib - late pleural effusions, pulmonary hypertension; T/NK cells
- Nilotinib – hyperglycemia, peripheral arterial occlusive disease, other arterial thromboses
- Bosutinib – less information; diarrhea and transaminitis
- Ponatinib - MAJOR arterial thrombotic issues

CML Molecular Response Milestones

***BCR-ABL1* (IS)**	**3 months**	**6 months**	**12 months**	**> 12 months**
> 10%	YELLOW	RED		
1% - 10%	GREEN		YELLOW	RED
0.1% - 1%		GREEN		YELLOW
≤ 0.1%			GREEN	

	Clinical Considerations	**Treatment options**
RED	Evaluate compliance and drug interactions Mutation testing	Switch to alternate TKI Consider screen for HSCT
YELLOW	Same as above	Consider switch to alternate TKI or continue (may increase dose of imatinib to 800 mg)
GREEN	Monitor response and toxicity	Continue same TKI

NCCN 2017 Guidelines

CML Monitoring Frequency

The 3 month QRT-PCR may be uniquely important in defining long term outcome!

If these criteria aren't met (primary resistance, ~15% on imatinib): check for ABL TKD mutation and switch therapy

Repeat marrow exams are not necessary once CCyR achieved (check at 6 months and 6 months thereafter prn) (PB FISH also reasonable)

Check QPCR q 3 months x 3yrs, then q 3-6 months thereafter or if increase by 1 log after MMR achieved, then repeat in 1-3 months

When to check for ABL TKD mutation and switch therapy:

loss of response (heme or cytog relapse) or disease progression to AP/BP

confirmed 1 log increase in bcr-abl1 transcript and loss of MMR

NCCN Guidelines 2017; Mahon et al., *Lancet Oncol 2010; 11: 1029–35*

CML Response Definitions, Monitoring and Milestones

Response Type	Response Definition	When It Should be Achieved
Complete hematologic response (CHR)	Normalization of blood counts; resolution of disease signs and symptoms	**<1-3 months**
Initial Molecular response	Reduction in *BCR-ABL* transcript levels in peripheral blood by ≥ 1 log, or *BCR-ABL/ABL* **ratio reduced to ≤ 10 % IS**	**<3 months**
Major cytogenetic response (MCyR)	≤ 35% Ph+ cells	**<6 months**
Complete cytogenetic response (CCyR)	0% Ph+ cells	**<12 months**
Major molecular response (MMR)	Reduction in *BCR-ABL* transcript levels in peripheral blood by ≥ 3 log, or *BCR-ABL/ABL* ratio reduced to ≤ 0.1% IS	**<12 - 18 months**
Complete molecular response (CMR)	Reduction in *BCR-ABL* transcript levels in peripheral blood by ≥ 4.5 log, or undetectable *BCR-ABL/ABL* transcript	**??**

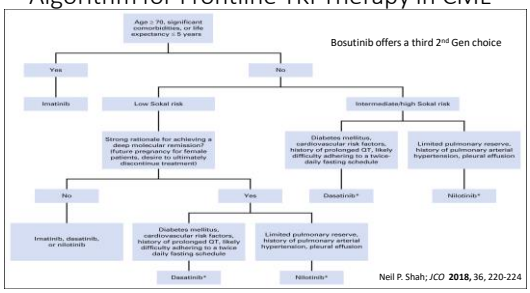
Jabbour E, et al. *Cancer*. 2007;109(11):2171-2181.
Marin D, et al (European LeukemiaNet) *Blood* 2008;112(12):4437-4444.
Marin D et al *J Clin Oncol* 2011; 30(3):232-8.

ABCDE Steps to Reduce CV Risk in Patients with CML

- A
  - Awareness of CV risks and signs
  - Aspirin in appropriate patients
  - Ankle-brachial Index (ABI) at baseline and f/u
- B
  - Blood pressure control
- C
  - Cigarette/tobacco cessation
  - Cholesterol monitoring and treatment
- D
  - Diabetes mellitus monitoring and treatment
  - Diet and weight control
- E
  - Exercise

Moslehi and Deininger, *J Clin. Oncol* 2015 33: 4210-8

Algorithm for Frontline TKI Therapy in CML



Bosutinib offers a third 2nd Gen choice

Neil P. Shah; *JCO* **2018,** 36, 220-224

Chronic Myeloid Leukemia: Conclusions

- Chronic Myeloid Leukemia
  - Generic imatinib finally here
  - First line imatinib vs nilotinib vs dasatinib vs bosutinib?
    - How to choose? Imatinib a very reasonable choice for elderly and low-risk patients
    - Late side effects important (CV for nilotinib; pleural effusions for dasatinib)
    - Compliance still most important
  - Need to minimize CV risk factors
  - Need to better understand the "ultimate" goal of therapy
    - Cytogenetic remission vs. major molecular response vs complete molecular remission?

Questions & Answers

Are we ready for treatment discontinuation?

Javier Pinilla-Ibarz MD, PhD
Senior Member
Malignant Hematology Department
H. Lee Moffitt Cancer Center

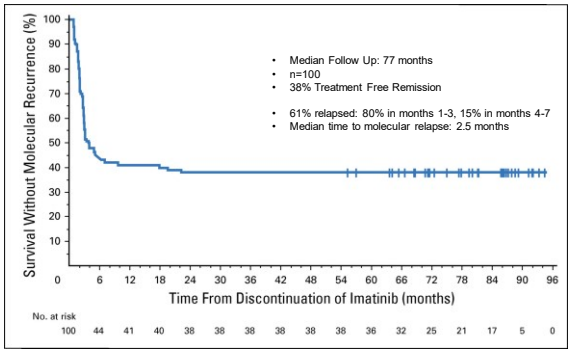
Disclosures

- Consulting: Novartis, Pfizer and Takeda.
- Speaker Bureau: Takeda.

Why consider stopping?

- TKI therapy is associated with reduced QOL
- High cost to patient and society
- Potential for long term toxicity
  - Cardiovascular
  - Pulmonary
  - Thyroid dysfunction
- Children and adolescents:
  - Substantial growth abnormalities
  - Effect on pregnancy/fertility

Long Term Follow Up From STIM



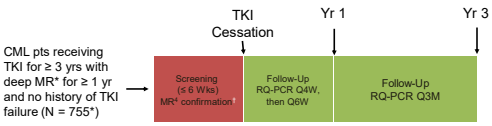
Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

Multivariate Analysis From STIM

- Two factors predictive of molecular relapse
  1. High-risk Sokal score at diagnosis
     - HR 2.22
     - 95% CI 1.11-4.42
     - P=0.024
  2. Imatinib duration < 58.8 months prior to discontinuation
     - HR 0.54
     - 95% CI 0.32-0.92
     - P=0.024

Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

EURO-SKI: Study Design



*In primary analysis of 868 preregistered pts.
†MR4, defined as detectable BCR-ABL ≤ 0.01%, or undetectable BCR-ABL in samples with ≥ 10,000 ABL or ≥ 24,000 GUS transcripts, respectively.

Primary endpoint: molecular recurrence (BCR-ABL > 0.1%, ie, loss of MMR)

- Largest TFR study to date
- Goal was to establish criteria for TKI discontinuation

Sauselle S, et al. ASH 2017. Abstract 313.

EURO-SKI: Molecular Recurrence-Free Survival

Month	Pts at Risk, n	MRFS, % (95% CI)
6	457	61 (58-65)
12	396	55 (51-58)
18	333	52 (49-56)
24	219	50 (47-54)
36	31	47 (43-51)

Sauselle S, et al. ASH 2017. Abstract 313.

EURO-SKI: Conclusions

- Study defined stopping criteria for TKI cessation in CML patients who achieve durable deep MR
- Preferred cutoffs for 6-mo probability of MMR loss
  - TKI duration: 5.8 yrs
  - MR^4 duration: 3.1 yrs
- Probability of TFR increased almost linearly per each additional year of first-line imatinib and duration of MR^4

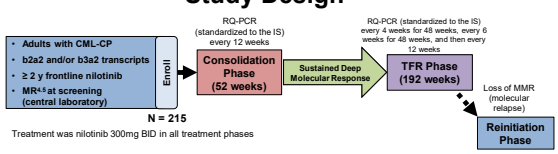
Sauselle S, et al. ASH 2017. Abstract 313.

ENESTfreedom

Enrollment and Inclusion Criteria	
Total enrollment	n=215
Minimum treatment duration required prior to discontinuation	≥3 years frontline nilotinib
Minimum response required prior to discontinuation	Sustained $MR^{4.5}$ for at least 1 year

- 37.9% of nilotinib 300mg BID treated patients on ENESTnd met the inclusion criteria for attempting TFR on ENESTfreedom

Study Design

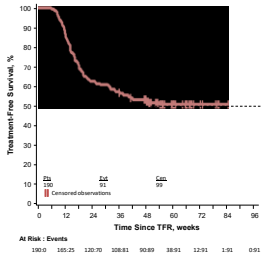


Treatment was nilotinib 300mg BID in all treatment phases

Hochhaus A. ASCO Annual Meeting 2016. Abstract #7001

Primary Endpoint and Treatment-Free Survival

Kaplan-Meier Estimated Treatment-Free Survival[a]



- 190 patients entered the TFR phase
- 51.6% of patients (95% CI, 44.1-58.9%) remained in TFR after 48 weeks

[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.

Hochhaus A. ASCO Annual Meeting 2016. Abstract #7001

TKI Withdrawal Syndrome

– Diffuse musculoskeletal pain and joint pain

– Occurs in approximately 30% of patients after stopping TKIs

– Median duration 6 months

Lee et al. Haematologica. 2016 Jun;101(6):717-23.
Richter et al. J Clin Oncol. 2014;**32**(25):2821–2823.

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Chronic Myeloid Leukemia
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

DISCONTINUATION OF TKI THERAPY[1]

- Discontinuation of TKI therapy appears to be safe in selected CML patients.
- [illegible] more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- [illegible]
- Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and [illegible]
- Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- [illegible]
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- [illegible]
- [illegible] *BCR-ABL1* transcript.
- [illegible] *BCR-ABL1* [illegible] ≤ 0.1% IS) after discontinuation of TKI therapy.
- Access to a reliable qPCR test with a sensitivity of detection [illegible] and provides results within 2 weeks.
- Monthly molecular monitoring for one year, then every 6 weeks for the second year, and every 12 weeks thereafter [illegible] is recommended [illegible]
- Prompt resumption of TKI within 4 weeks of a loss of MMR with molecular monitoring every 4 weeks until MMR is re-established, then every 12 weeks thereafter [illegible] who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after three months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.
- [illegible] discontinuation, including TKI withdrawal syndrome.
- Reporting of the following to a member of the NCCN CML panel is strongly encouraged:
  [illegible]
  Progression to accelerated or blast phase CML at any time.
  Failure to regain MMR after three months following treatment reinitiation.

Is Stopping TKI Realistic?

50% achieve MR4 or MR 4.5

50% restart TKI

70-80% of newly diagnosed patients with CML will need long term TKI therapy

Atallah et al EHA iCMLf 2017

Conclusions

- Most patients with chronic phase CML will do well with current therapy
- Stopping TKIs is ready for prime time
  - A select group of patients
  - With proper monitoring
- Multi-team approach is a key component to the success and safety of TFR