Treating T315I-Positive Chronic Myeloid Leukemia (CML)

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Objectives

- Discuss significance of BCR-ABL mutations in CML
- Identify treatment options available for T315I positive CML
- Summarize the data related to each agent's approval
- Highlight key monitoring parameters and counseling points for these agents

CML

- Caused by expression of BCR-ABL oncoprotein
  - t(9;22)
  - Philadelphia chromosome (Ph+)
- 2014 estimates
  - 5,980 new cases
  - 810 deaths
- Median age at diagnosis: 50-55 years

Fausel C. JMCP. 2007;13(Suppl S-a):S8-S12.
ACS. Cancer Facts & Figures 2014.

Treatment Goals

- Maintain remission
- Prevent progression to accelerated phase (AP) or blast phase (BP)
- Minimize therapy-related toxicity

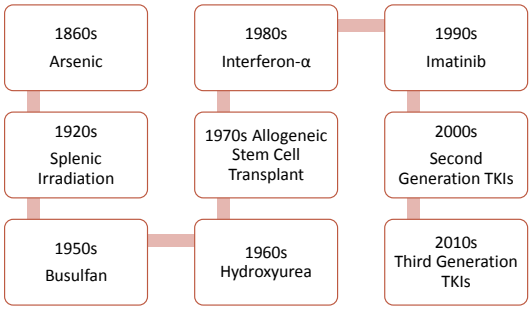
Fausel C. JMCP. 2007;13(Suppl S-a):S8-S12.

Measuring Treatment Response

Complete Hematologic Response (CHR)
•Complete normalization of peripheral blood counts with leukocyte count <10 cells x10^9/L •Platelet count <450 cells x10^9/L •No immature cells in peripheral blood •No signs/symptoms of disease with disappearance of palpable splenomegaly
Cytogenetic Response
•Complete (CCyR): No Ph-positive metaphases •Partial (PCyR): 1-35% Ph-positive metaphases •Major (MCyR): 0-35% Ph-positive metaphases (complete + partial) •Minor: >35% Ph-positive metaphases
Molecular Response
•Complete: no detectable BCR-ABL mRNA by QPCR (IS) •Major (MMR): •BCR-ABL transcripts 0.1% by QPCR (IS) OR •≥3-log reduction in BCR-ABL mRNA from standardized baseline

NCCN. Chronic Myelogenous Leukemia. V3.2014. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

Treating CML: A Perspective



Hehlmann R, et al. Ann Hematol. 2005;84:487-97.

Tyrosine Kinase Inhibitors (TKIs)

- Bind BCR-ABL ATP-binding site
  - Inhibit cellular growth
  - Induce apoptosis
- 1st line treatment options
  - Imatinib (Gleevec®)
  - Dasatinib (Sprycel®)
  - Nilotinib (Tasigna®)

Fausel C. JMCP. 2007;13(Suppl S-a):S8-S12.

Drug Resistance in CML

- 20-30% of patients fail to respond to imatinib or experience disease relapse after initial response
  - 37-52% of these patients do not have a response to 2nd generation TKIs
- Classifying resistance
  - Primary (intrinsic)
  - Secondary (acquired)

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.

BCR-ABL Independent Resistance Mechanisms

- Pharmacokinetics and oral bioavailability
  - Variability in drug exposure
  - Variability of CYP450 enzyme system (CYP 3A4)
  - Drug binding (via α_1-acid glycoprotein)
- Inadequate intracellular concentrations
  - Concentrations affected by transporters involved in drug influx and efflux

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.

BCR-ABL Independent Resistance Mechanisms

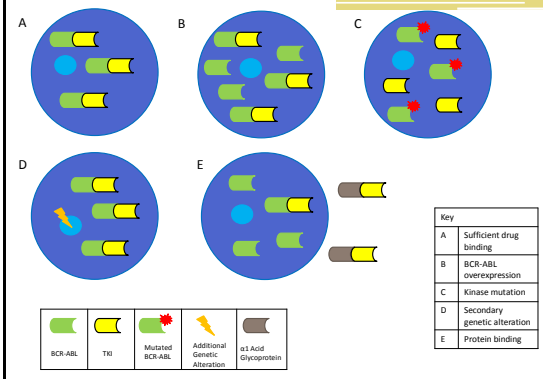
- Activation of alternative signaling pathways
- Clonal evolution
  - Acquisition of additional chromosomal abnormalities
- Stem cell persistence

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.

BCR-ABL Dependent Resistance Mechanisms

- BCR-ABL duplication and amplification
- BCR-ABL kinase domain point mutations
- Mutations outside kinase domain

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.



Adapted from: von Bubnoff N, et al. Leukemia. 2003;17:829-38.

BCR-ABL Kinase Point Mutations

- Over 100 distinct point mutations identified
- Mutations in kinase domain of BCR-ABL
  - Alter amino acid residues needed for direct contact with TKI
  - Prevent BCR-ABL from assuming the inactive conformation required for imatinib binding

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.

BCR-ABL Kinase Point Mutations

- Frequency increases with sequential TKI therapy
- Mutations may vary by disease phase
  - T315I, E255K/V, Y253F often found in patients with accelerated phase/blast crisis
- Locations
  - Imatinib binding site
  - Phosphate binding (P) loop/ATP binding site
  - Activation (A) loop
  - Catalytic loop

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.

Mutational Analysis

- Direct sequencing (DS)
  - Used by ~80% of laboratories
  - Detects mutations present in ≥20% of Ph+ cells
- Challenges
  - Lack of standardization between laboratories
  - Under-utilization

Soverini S, et al. Leukemia Research. 2014;38:10-20.

Timing of Mutational Analysis

NCCN Guidelines

Chronic Phase
- With inadequate initial response, defined as <u>failure to achieve</u>
  - PCyR at 3 and 6 months
  - BCR-ABL/ABL ≤ 10% (IS) at 3 and 6 months
  - CCyR at 12 and 18 months
- Loss of response
  - Hematologic or cytogenetic relapse
  - 1 log increase in BCR-ABL transcript levels and loss of MMR

Disease progression to AP or BP

NCCN. Chronic Myelogenous Leukemia. V3.2014. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

BCR-ABL Kinase Point Mutations

Mutation	Imatinib	Bosutinib	Dasatinib	Nilotinib
G250E				
Y253F				
E255K				
E255V				
M351T				
F359V				
T3151				

Key: Sensitive; Moderately Resistant; Resistant; Highly resistant

Adapted from Redaelli S, et al. Am J Hematol. 2012;87(11):E125-8.

T315I Mutation

- Accounts for ~14% of detected mutations
- Single nucleotide mutation
  - Threonine to isoleucine substitution at amino acid 315
  - Prevents TKI localization within ATP binding pocket
- Confers resistance to 1st and 2nd generation TKIs
- Treatment options
  - Ponatinib (Iclusig®)
  - Omacetaxine mepesuccinate (Synribo®)
  - Allogeneic hematopoietic stem cell transplantation (HSCT)

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.

Ponatinib (Iclusig®)

- Granted accelerated approval December 2012
- Pan-BCR-ABL TKI
  - Also inhibits VEGFR, FGFR, PDGFR, EPH and SRC kinases as well as KIT, RET, TIE2 and FLT3

Iclusig [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc; 2014.

Ponatinib (Iclusig®)

- Initial dose: 45 mg once daily
- Administered without regard to food
- Drug interactions
  - Reduce dose to 30 mg daily when administered with strong CYP3A4 inhibitors
  - Avoid antacids/proton pump inhibitors

Iclusig [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc; 2014.

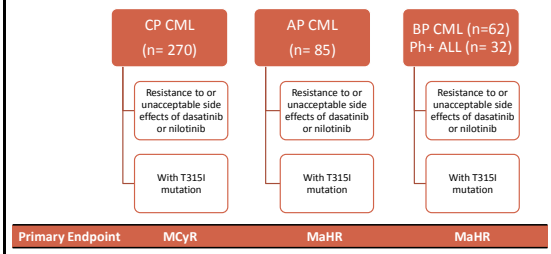
Ponatinib (Iclusig®)

- Ponatinib Ph-positive ALL and CML Evaluation (PACE)
  - Open-label, multinational phase II trial
  - 449 heavily pre-treated patients with CML or Ph-positive ALL
    - Resistant/intolerant to dasatinib or nilotinib
  - Ponatinib 45 mg orally once daily

Cortes JE, et al. NEJM. 2013;369(19):1783-96.

PACE

- Six cohorts



Cortes JE, et al. NEJM. 2013;369(19):1783-96.

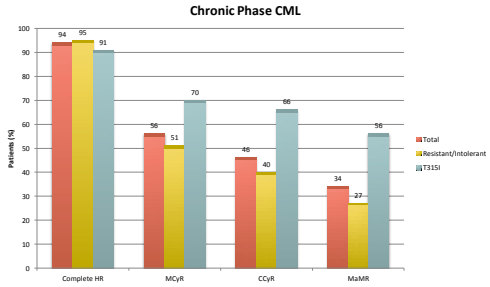
PACE: Patient Characteristics

- Median age: 59 years (range 18-94)

Characteristic		CP CML (n=270)	AP CML (n=85)	BP CML (n=62)	Ph+ ALL (n=32)
Previous TKI use (# drugs)	≥2	252 (93%)	80 (94%)	59 (95%)	26 (81%)
	≥3	161 (60%)	51 (60%)	37 (60%)	13 (41%)
Resistance		214 (84%)	74 (92%)	59 (97%)	27 (90%)
Unacceptable side effects only		40 (16%)	6 (8%)	2 (3%)	2 (7%)

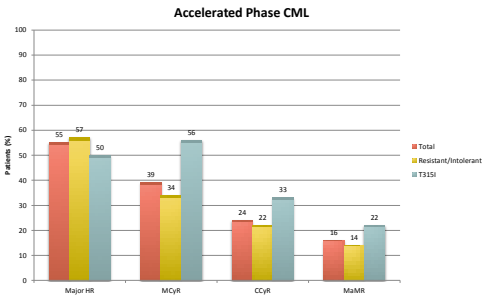
Cortes JE, et al. NEJM. 2013;369(19):1783-96.

PACE: Efficacy



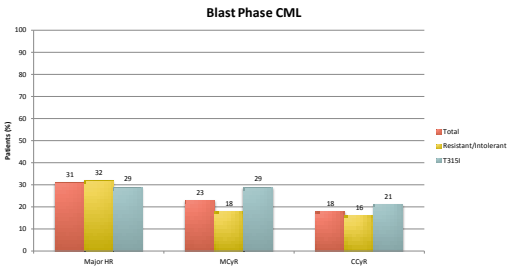
Cortes JE, et al. NEJM. 2013;369(19):1783-96.

PACE: Efficacy



Cortes JE, et al. NEJM. 2013;369(19):1783-96.

PACE: Efficacy



Cortes JE, et al. NEJM. 2013;369(19):1783-96.

PACE: Two Year Follow-Up

	CML-CP			CML-AP	CML-BP
	MCyR (%)	CCyR (%)	MMR (%)	MaHR (%)	MaHR (%)
Resistant/Intolerant to dasatinib or nilotinib	56	48	31	62	32
T315I mutation	72	70	58	61	29
Total	60	54	38	61	31

Cortes JE, et al. Proc ASH. 2013; Abstract 650.

PACE: Hematologic Toxicity

- Thrombocytopenia (37%)
- Neutropenia (19%)
- Anemia (13%)

Cortes JE, et al. NEJM. 2013;369(19):1783-96.

PACE: Nonhematologic Toxicity

- Rash
- Dry skin
- Abdominal pain
- Headache
- Increased lipase
- Constipation
- Fatigue
- Myalgia
- Arthralgia
- Nausea
- Increased ALT
- Hypertension
- Increased AST
- Pancreatitis
- Dyspnea

Cortes JE, et al. NEJM. 2013;369(19):1783-96.

Ponatinib: Boxed Warnings

- Heart failure
- Hepatotoxicity
  - Liver function tests at baseline, then monthly
- Arterial and venous thrombosis/occlusions
  - Myocardial infarction
  - Stroke
  - Thrombosis

Iclusig [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc; 2014.

FDA Alert

- October 31, 2013
  - Ponatinib marketing and sales suspended
  - Vascular events
    - Phase 2 trial: 24%
    - Phase 1 trial: 48%
  - May continue in patients responding to therapy and for whom benefits > risks
- December 20, 2013
  - New safety measures implemented

Iclusig [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc; 2014.

Ponatinib: Safety Measures

- Limited indications
  - Adult patients with T315I-positive CML (CP, AP, or BP) or T315I-positive Ph+ ALL
  - Adult patients with CP, AP, or BP CML or Ph+ ALL for whom no other TKI therapy is indicated
- Revised
  - Warnings and Precautions
  - Dosage and Administration recommendations
  - Patient Medication Guide
- Iclusig REMS
- ARIAD's post market investigations will further evaluate dose selection, drug exposure, treatment response, and toxicity

U.S. Food and Drug Administration. [2013, December 20] FDA Drug Safety Communication. Retrieved from: http://www.fda.gov/Drugs/DrugSafety/ucm379554.htm

Ponatinib: Dose Modifications

Modification Indication	Laboratory Results	Recommendation
Myelosuppression	ANC < 1,000/mm^3 Platelets < 50,000/mm^3	1st occurrence at: Interrupt ponatinib, resume at 45 mg daily after count recovery (ANC > 1,500/mm^3 PLT ≥ 75,000/mm^3)
		2nd occurrence: Interrupt ponatinib, resume at 30 mg daily dose after count recovery
		3rd occurrence: Interrupt ponatinib, resume at 15 mg daily dose after count recovery

Iclusig [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc; 2014.

Ponatinib: Dose Modifications

Modification Indication	Laboratory Results	Recommendation
Hepatotoxicity	Elevation AST or ALT > 3 x ULN (≥ grade 2)	Occurrence at 45 mg: Interrupt ponatinib and monitor hepatic function Resume ponatinib at 30 mg after recover to grade 1 (< 3x ULN)
		Occurrence at 30 mg: Interrupt ponatinib and resume at 15 mg after recovery to grade ≤ 1
		Occurrence at 15 mg: Discontinue ponatinib
	Elevation of AST or ALT ≥ 3 x ULN WITH bilirubin > 2 x ULN and alkaline phosphatase < 2 x ULN	Discontinue ponatinib

Iclusig [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc; 2014.

Ponatinib: Dose Modifications

Modification Indication	Laboratory Results	Recommendation
Pancreatitis and elevation of lipase	Asymptomatic grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction
	Asymptomatic grade 3 or 4 elevation of lipase (> 2 x ULN) Asymptomatic radiologic pancreatitis (grade 2)	Occurrence at 45 mg: •Interrupt ponatinib and resume at 30 mg after recovery to grade ≤ 1 Occurrence at 30 mg: •Interrupt ponatinib and resume at 15 mg after recovery to grade ≤ 1 Occurrence at 15 mg: •Discontinue ponatinib
	Symptomatic grade 3 pancreatitis	Occurrence at 45 mg: •Interrupt ponatinib and resume at 30 mg after complete resolution of symptoms and recovery of lipase elevation to ≤ grade 1 (< 1.5 x ULN) Occurrence at 30 mg: •Interrupt ponatinib and resume at 15 mg after complete resolution of symptoms and recovery of lipase elevation to ≤ grade 1 Occurrence at 15 mg: •Discontinue ponatinib
	Grade 4 pancreatitis	Discontinue ponatinib

Iclusig [prescribing information]. Cambridge, MA: Ariad Pharmaceuticals, Inc; 2014.

Omacetaxine Mepesuccinate (Synribo®)

- Granted accelerated approval October 2012
  - CML in CP or AP after failure of 2 or more TKIs
- Synthetic homoharringtonine (HHT)
  - Reversible protein translation inhibitor
    - Inhibition of proteins regulating proliferation and cell growth
    - Induces apoptosis in CML stem cells
  - Provides activity regardless of BCR-ABL mutation status

Synribo [prescribing information]. North Wales, PA: Teva Pharmaceuticals US, Inc. 2014.

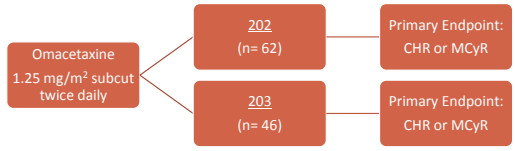
Omacetaxine Mepesuccinate (Synribo®)

- Dosing
  - Induction
    - 1.25 mg/m^2 subcut BID x 14 days of 28-day cycle
  - Maintenance
    - 1.25 mg/m^2 subcut BID x 7 days of 28-day cycle

Synribo [prescribing information]. North Wales, PA: Teva Pharmaceuticals US, Inc. 2014.

Omacetaxine 202/203

- Open-label, multinational phase II trials
  - 202: CML with T315I mutation
  - 203: CML resistant and/or intolerant to 2 or more TKIs



Cortes J, et al. Blood. 2012;120:2573-80.
Cortes J, et al. Am J Hematol. 2013;88:350-4.

202/203: Patient Characteristics

	Study 202 (n= 62)	Study 203 (n=46)
Median age, years (range)	56 (26-83)	58 (20-78)
Number of Prior TKIs, n (%)		
1	16 (26)	7 (15)
2	30 (48)	12 (26)
≥3	16 (26)	27 (59)

Cortes J, et al. Blood. 2012;120:2573-80.
Cortes J, et al. Am J Hematol. 2013;88:350-4.

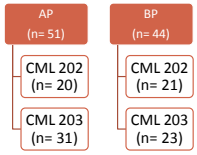
202/203: Efficacy

Response	Study 202 (%)	Study 203 (%)
CHR	77	67
MCyR	23	22

Cortes J, et al. Blood. 2012;120:2573-80.
Cortes J, et al. Am J Hematol. 2013;88:350-4.

Omacetaxine in Advanced CML

- Pooled analysis of Omacetaxine 202 and 203 studies
  - Primary endpoint: MHR
- Patients in advanced phase CML



Khoury HJ, et al. Leukemia & Lymphoma. 2014;Early Online:1-8.

Pooled Analysis: Efficacy

Response	AP (%)	BP (%)
MHR	37	9
MCyR	4	0
MHR (Patients with T315I)	55	10

Khoury HJ, et al. Leukemia & Lymphoma. 2014;Early Online:1-8.

CML 202/203: Hematologic Toxicity

Toxicity (all grades)	CML 202 (%)	CML 203 (%)
Thrombocytopenia	79	67
Anemia	66	54
Neutropenia	50	50
Pancytopenia	26	17
Leukopenia	21	20
Lymphopenia	18	-

Cortes J, et al. Blood. 2012;120:2573-80.
Cortes J, et al. Am J Hematol. 2013;88:350-4.

CML 202/203: Nonhematologic Toxicity

Toxicity (all grades)	CML 202 (%)	CML 203 (%)
Diarrhea	40	44
Nausea	34	30
Fatigue	29	24
Headache	18	20
Asthenia	27	20
Pyrexia	29	20
Epistaxis	15	17
Injection site erythema	21	17
Pain in extremity	11	17
Peripheral edema	13	15
Vomiting	-	15

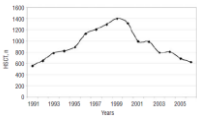
Cortes J, et al. Blood. 2012;120:2573-80.
Cortes J, et al. Am J Hematol. 2013;88:350-4.

Omacetaxine: Dose Modifications

Modification Indication	Laboratory Results	Recommendation
Myelosuppression	ANC < 500/mm³ or Platelets < 50,000/mm³	Delay start of next cycle until ANC > 1000 and platelets ≥ 50,000 **AND** Reduce number of treatment days by 2 days
Nonhematologic Toxicity		Manage symptomatically and interrupt/delay treatment until toxicity resolves

Synribo [prescribing information]. North Wales, PA: Teva Pharmaceuticals US, Inc. 2014.

Allogeneic HSCT



- Remains only curative therapy
- NCCN recommendations
  - BP at diagnosis
  - T315I/other BCR-ABL mutations resistant to TKIs
  - Intolerance to all TKIs
- 5-year survival rates following matched-related HSCT
  - CP: 75%
  - AP: 40%
  - BP: 10%

Image: Gratwohl A, et al. Haematologica. 2010;95(4):637-643.
NCCN. Chronic Myelogenous Leukemia. V3.2014. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

Future Directions…

- TKIs
  - XL228
    - Potent multi-target kinase inhibitor
  - Rebastinib (DCC-2036)
    - Switch control inhibitor
    - Induces/stabilizes inactive ABL conformation
- Aurora Kinase Inhibitors
  - Danusertib
    - Activity against all known aurora kinases in addition to BCR-ABL tyrosine kinase

Jabbour EJ, et al. Clinical Lymphoma, Myeloma & Leukemia. 2013;5:515-29.
Bose P, et al. Leukemia Research Reports. 2013;2:18-20.

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Omacetaxine
Potency relative to imatinib	1	325-fold	30-fold	20-fold	>400-fold	-
Target ABL conformation	Inactive	Active and inactive	Inactive	Active	Inactive	-
Activity against T315I	None	None	None	None	Highly active	Active
Dose	400 mg daily	100 mg daily	300 mg BID	500 mg daily	45 mg daily	1.25 mg/m² BID x 14 days
Metabolism	CYP3A4	CYP3A4	CYP3A4	CYP3A4	CYP3A4	Not CYP3A4
Activity against CML stem cells	None	None	None	None	Unknown	Unknown
Main toxicities	Pancytopenia, periorbital and peripheral edema, rash, nausea, diarrhea, transaminitis, cramps, skin discoloration	Pancytopenia, pleural effusions, headache, QT prolongation, rash, diarrhea, bleeding	Transaminitis, clinical and laboratory pancreatitis, pancytopenia, hyperglycemia, QT prolongation, diarrhea, rash, electrolyte abnormalities	Diarrhea, pancytopenia, transaminitis, edema, rash	Arterial thrombosis, HTN, clinical and laboratory pancreatitis, transaminitis, pancytopenia, rash	Pancytopenia, infections, injection site erythema, diarrhea
Price ($)	6,395/month	8,582/month	9,735/month	8,181/month	9,580/month	23,280/14 days

Adapted from: Frankfurt O, et al. Clin Cancer Res. 2013;19:5828-34.

Question 1

- When given concomitantly with strong CYP3A4 inhibitors, ponatinib should initially be dosed at 15 mg by mouth daily
  - A. True
  - B. False

Question 2

- BCR-ABL mutational analysis testing is appropriate when
  - A. Patients fail to achieve adequate initial response
  - B. Patients lose response to therapy
  - C. Patients progress to accelerated phase or blast phase
  - D. All of the above

Question 3

- Patients receiving omacetaxine mepesuccinate are transitioned to maintenance dosing once a hematologic response is achieved
  - A. True
  - B. False

Questions?

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