Opening Remarks

- To submit questions during the webcast, please email CMLwebcast@nccn.org. This is the only online method of communicating questions to the faculty.

- While NCCN is pleased to respond to as many questions as possible during this webinar, NCCN will not be able to respond to your individual questions of a clinical nature after the webinar has concluded. We are also not able to offer recommendations on patient care regarding specific cases.

- Should you need additional assistance please e-mail education@nccn.org or call 215-690-0300 and ask to be connected with someone in the NCCN Conferences and Meetings Department.
Opening Remarks

- To minimize and maximize your screen view, move your cursor over active slides and a tool bar will appear. The far-right option of this tool bar allows you to expand view to full-screen. To exit full-screen, press “Esc” key.

NCCN Webcast

Registration

- If you are participating with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity.

- Lists can be sent to education@nccn.org and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.

- If you have not individually registered, please register at: http://www.cvent.com/d/frqwwv.
Intended Audience
This educational program is designed to meet the educational needs of medical oncologists, community oncologists, oncology fellows, oncology nurses, pharmacists, case managers, and other health care professionals who care for patients with cancer.

Learning Objectives
Following this webcast, participants should be able to:
• Select the appropriate TKI for first-line therapy after considering the risks/benefits of each TKI and individual patient characteristics.
• Describe the prognostic significance of early molecular response milestones and recognize the importance of monitoring molecular response to TKI therapy as outlined in the NCCN Guidelines.
• Summarize the toxicities associated with TKIs and appropriate interventions to manage major side effects and intolerance to treatment.
• Evaluate the factors contributing to non-adherence to TKI therapy and effectively communicate with patients the need to take medication as prescribed.
• Examine the importance of the multidisciplinary care team embracing the patient as a partner in their care and how this patient-centered approach can positively impact long-term health outcomes.

Accreditation Information

Physicians
The National Comprehensive Cancer Network (NCCN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The National Comprehensive Cancer Network designates this live activity for a maximum of 1.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
National Comprehensive Cancer Network is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

NCCN designates this educational activity for a maximum of 1.25 contact hours. Accreditation as a provider refers to the recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity.

Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.
Accreditation Information

Pharmacists

Accreditation Statement

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of Activity: Knowledge

UAN: 0836-0000-15-111-L01-P

Credit Designation: National Comprehensive Cancer Network designates this continuing education activity for 1.25 contact hours (0.125 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

Attention Pharmacists: ACPE and NABP have implemented CPE Monitor as a way to electronically track all ACPE-accredited CPE Units. In order to receive credit for this activity, please enter your six-digit NABP e-profile ID and birth date in the format of MMDD as part of the Overall Evaluation. If you have not already done so, please complete your e-profile at http://www.nabp.net to obtain your NABP e-Profile ID.

To comply with ACPE standards, pharmacists must complete all activity requirements within 30 days of the live event date.

Accreditation Information

Case Managers

This program has been pre-approved by The Commission for Case Manager Certification to provide continuing education credit to CCM® board certified case managers. The course is approved for 1.25 CE contact hours.

Activity code: I00016622

Approval Number: 150002545

To claim these CEs, log into your CE Center account at www.ccmcertification.org.
Accreditation Information

• Certificates will be provided to physicians, nurses, pharmacists, and case managers through completion of an evaluation and post-test.

• All registered participants will receive an e-mail from our CE and Grants Department within 5-7 business days with instructions on how to access this evaluation and post-test at http://education.nccn.org/node/69994. Certificates will be generated automatically upon successful completion of this step.

• Should you not receive an e-mail within 7 days, please contact us at education@nccn.org.

Accreditation Information

• It is required by the ACCME that all educational activities are designed to change participant competence, performance, or patient outcomes.

• To meet this requirement, NCCN asks that all participants complete the outcomes measures described below:

  – The post-test and evaluation as indicated in e-mail you will receive within 5-7 business days of the conclusion of this activity. This is required to receive credits or your certificate of completion. You must be registered in advance to receive credits or certificate. Certificates will be generated automatically upon successful completion of this step.

  • There will be a separate WebEx evaluation at the conclusion of this program, which is optional and does not go to NCCN.

  – The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)

• NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at http://education.nccn.org. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail education@nccn.org.
Disclosures

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ACCME, ACPE, and ANCC focuses on financial relationships with commercial interests in the 12-month period preceding the time that the individual is being asked to assume a role controlling content of the CE activity. ACCME, ACPE, and ANCC have not set a minimal dollar amount for relationships to be significant. Inherent in any amount is the incentive to maintain or increase the value of the relationship. The ACCME, ACPE, and ANCC defines “relevant financial relationships” as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.

All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.

Faculty Disclosures

Disclosure of Relevant Financial Relationships

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Faculty Disclosures

Susan L. Buchanan, MS, PA-C has no relevant financial relationships to disclose.

The faculty listed below has disclosed the following relevant financial relationships:

Daniel J. DeAngelo, MD, PhD
ARIAD Pharmaceuticals, Inc.: Consultant Fees/ Honoraria
Bristol-Myers Squibb Company: Consultant Fees/ Honoraria
Novartis Pharmaceuticals Corporation: Consultant Fees/ Honoraria
Pfizer Inc.: Consultant Fees/ Honoraria
Disclosures

NCCN Staff Disclosures
The activity planning staff listed below has no relevant financial relationships to disclose:

Ann Gianola, MA; Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Rose Joyce; Joan S. McClure, MS; Diane McPherson; Melanie Moletzsky; Deborah Moonan, RN, BSN; Liz Rieder; Shannon K. Ryan; Shannon Scarinci; Jennifer McCann Weckesser

The NCCN clinical information team listed below, who have reviewed content, has no relevant financial relationships to disclose:

Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Hema Sundar, PhD

Faculty Biography

Susan Buchanan MS, PA-C, is a Physician Assistant in the Adult Leukemia Program at Dana-Farber/Brigham and Women’s Cancer Center.

Ms. Buchanan earned her master’s degree in health sciences and physician assistant studies from Northeastern University.

Her clinical research focuses on optimizing therapy for adult leukemias, myelodysplastic syndromes, and myeloproliferative disorders. She serves as co-investigator of several ongoing clinical protocols.

Ms. Buchanan is actively involved in advanced practitioner education. She serves as a faculty instructor for courses in hematology and hematologic malignancies at local universities in Boston, including Northeastern University, Massachusetts College of Pharmacy and Health Sciences, and Tufts University School of Medicine. She also is the Education Coordinator for oncology elective clerkships at Dana-Farber/Brigham and Women’s Cancer Center.

Ms. Buchanan is a member of several professional societies, including the Association of Physician Assistants in Oncology, the Advanced Practice Council, the Massachusetts Association of Physician Assistants, and the American Academy of Physician Assistants.
Faculty Biography

Daniel J. DeAngelo, MD, PhD, is Associate Professor of Medicine at Harvard Medical School and Senior Physician for the Adult Leukemia Program at Dana-Farber Cancer Institute.

Dr. DeAngelo earned his medical degree and his doctorate of philosophy in Molecular Genetics from Albert Einstein College of Medicine of Yeshiva University in Bronx, New York. He completed his internship and residency at Massachusetts General Hospital and clinical fellowships in medical oncology and hematology at the Dana-Farber Cancer Institute and Brigham and Women’s Hospital.

Dr. DeAngelo’s clinical research focuses on optimizing therapy for adult leukemias, myelodysplastic syndromes and myeloproliferative disorders. He has authored or coauthored more than 80 original peer-reviewed manuscripts, review articles, and book chapters and has presented his work nationally and internationally.

Dr. DeAngelo is actively involved in a number of professional societies, including the American Society of Hematology and the American Society of Clinical Oncology. Additionally, Dr. DeAngelo is a member of the leukemia core committee for the Cancer and Leukemia Group B (CALGB) and is principal and co-investigator of several ongoing clinical protocols. He also serves as an ad-hoc reviewer for the Therapeutic Advances in Medical Oncology, the New England Journal of Medicine, Blood, the American Journal of Hematology, Clinical Cancer Research, the Journal of Clinical Oncology, the Journal of Gene Medicine, and Leukemia.

Dr. DeAngelo is a member of the NCCN Chronic Myelogenous Leukemia Panel and Acute Lymphoblastic Leukemia Panel.

Patient Centered Care in Chronic Phase CML — A Multidisciplinary Approach

with Patient/Clinical Case Vignettes

August 7, 2015
CML Prevalence

- US Prevalence is currently ~ 70,000 patients with ~6000 new cases per year.
- Anticipated increase of >10% per year.

Presentation and Clinical Course
Chronic Phase

- 85-90% present in chronic phase
- 50% asymptomatic at presentation
- Symptoms are often non-specific
  - fatigue 80%
  - weight loss 60%
  - abdominal discomfort 40%
  - easy bruising 35%
  - leukostasis, priapism, thrombosis are unusual
Survival in Early Chronic Phase CML

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>230</td>
<td>7</td>
</tr>
<tr>
<td>1990-2000</td>
<td>960</td>
<td>334</td>
</tr>
<tr>
<td>1982-1989</td>
<td>365</td>
<td>265</td>
</tr>
<tr>
<td>1975-1981</td>
<td>132</td>
<td>127</td>
</tr>
<tr>
<td>1965-1974</td>
<td>123</td>
<td>122</td>
</tr>
</tbody>
</table>

Years from referral

Proportion surviving

Patient Centered Approach

- Educating the patient about their disease, milestones, and treatment support
  - in terms they can understand
- Multidisciplinary TEAM of care
  - MD, advanced practitioner, pharmacy, social work, resource specialist, patient and family
- Educators, treatment liaisons, support coordinators, emotional allies
- Maintain life long treatment, monitoring, side effect management and adherence

Patient A: Ms. Smith
What Can We Expect From Front-line Imatinib in chronic phase CML (CP-CML)?

Patient History & Symptoms

• Patient A is a 45yo woman who presents with progressive 7/10 abdominal pain, greater on the left side and 15 lb weight loss over the last 3 months.

• PMH is notable for Type II Diabetes Mellitus, controlled with oral hyperglycemic medication and Factor V Leiden with two documented DVTs within the last 10 years.
Patient History & Symptoms

- At presentation: WBC count 221,000 with a hemoglobin of 11.2 and a platelet count of 361,000.
- Peripheral blood differential shows 2% blasts, 38% pols, 40% bands, 11% metamyelocytes, 14% myelocytes.
- Bone marrow examination revealed chronic phase CML with a classic Philadelphia chromosome involving a reciprocal translocation of chromosome 9 and 22.

IRIS: Overall Survival on First-line Imatinib (ITT principle)

- Estimated rate at 60 months (with 95%CI):
  - CML-related deaths: 4.6% (2-7)
  - All deaths: 10.6% (8-14)

Without CML-related deaths
Overall Survival

Months since randomization

Role of Second-Generation TKIs in First-line Treatment of CP-CML
Nilotinib and Dasatinib

• Nilotinib
  • Developed from imatinib
  • Structure similar; altered to allow for greater ABL1 potency and selectivity
  • 20-50x more potent in vitro
  • Active against some imatinib resistant ABL1 kinase mutants except T315I
  • FDA approved Nov 2007

• Dasatinib
  • Developed as an inhibitor of Src kinase
  • Structure different than imatinib; greater potency; able to bind different conformations
  • ~300x more potent in vitro
  • Active against some imatinib resistant ABL1 kinase mutants except T315I
  • FDA approved June 2006

ENESTnd: Nilotinib vs Imatinib in Newly Diagnosed CP-CML

• Primary endpoint: MMR at 12 mos (defined as ≤ 0.1% BCR-ABL1/ABL1 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

**ENESTnd: Cumulative Incidence of MMR**

![Graph showing cumulative incidence of MMR over time for different treatment groups.](chart1)

*P* values are nominal.

For each arm, the curve stops at the latest time point at which a patient first achieved MMR.


**ENESTnd: Progression to AP/BC**

![Graph showing progression to AP/BC for different treatment groups.](chart2)

Since the 5-year data cutoff, 1 new progression to AP/BC on study was reported in the nilotinib 300 mg BID arm; this patient had a low Sokal risk score at baseline, achieved BCR-ABL ≤ 10% at 3 months, and discontinued core treatment due to neutropenia ≈ 5 years before progression to AP/BC was reported.

Dasatinib vs Imatinib in Treatment-naive CML: DASISION (CA180-056)

- **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

**Randomized**

- Dasatinib 100 mg QD (n = 259)
- Imatinib 400 mg QD (n = 260)

*N* = 519
108 centers
26 countries

Follow-up 5 years


DASISION: Cumulative MMR Rates Over Time

- **By 1 year**: 28%
- **By 2 years**: 46%
- **By 3 years**: 46%
- **By 4 years**: 55%
- **By 5 years**: 60%

Cortes et al. ASH 2014 Abstract #152

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### DASISION: Overall Survival and Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg QD (n=259)</th>
<th>Imatinib 400 mg QD (n=260)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths, n</td>
<td>26</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Estimated 5-year OS, % (95% CI)</td>
<td>91 (87–94)</td>
<td>90 (85–93)</td>
<td>1.01 (0.58–1.73)</td>
</tr>
<tr>
<td>Estimated 5-year PFS, % (95% CI)</td>
<td>85 (80–89)</td>
<td>86 (80–89)</td>
<td>1.06 (0.68–1.66)</td>
</tr>
</tbody>
</table>

- Causes of death were cardiovascular disease (2 dasatinib, 1 imatinib); disease progression (9 dasatinib, 17 imatinib); infection (11 dasatinib, 1 imatinib); other malignancy, septic shock and cardiac failure, multi-organ failure, and whole body swelling (1 each dasatinib); stem cell transplantation complications and unknown (2 each imatinib); severe chest pain, clinical deterioration and decrease in performance status, and fatal bleeding (1 each imatinib)

On-study treatment and in follow-up after discontinuation of randomized treatment.

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Cortes et al. ASH 2014, Abstract #152

### Summary of the DASISION and ENESTnd Studies

<table>
<thead>
<tr>
<th></th>
<th>DASISION (18 months)</th>
<th>ENESTnd (24 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imatinib</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>CCyR</td>
<td>80%</td>
<td>85%</td>
</tr>
<tr>
<td>MMR</td>
<td>41%</td>
<td>57%</td>
</tr>
<tr>
<td>On Therapy</td>
<td>81%</td>
<td>80%</td>
</tr>
<tr>
<td>AP/BP CML</td>
<td>3.5%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Shah et al., ASH 2010; Hughes et al., ASH 2010
Defining Response or Lack of Response

NCCN Recommendations for Response Monitoring

<table>
<thead>
<tr>
<th>Hematologic Analysis</th>
<th>Cytogenetic Analysis BM</th>
<th>Molecular Analysis IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
</tr>
<tr>
<td>Every 3 months</td>
<td>If QPCR IS is not available</td>
<td>Every 3 months until CCyR</td>
</tr>
<tr>
<td></td>
<td>At 3 and 6 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If not in MMR &amp; lack of CCyR at 3 months</td>
<td>CCyR Confirmed</td>
</tr>
<tr>
<td></td>
<td>At 12 months</td>
<td>Every 3 months for 3 years</td>
</tr>
<tr>
<td></td>
<td>If not in MMR &amp; lack of CCyR at 12 months</td>
<td>Every 3-6 months thereafter</td>
</tr>
<tr>
<td></td>
<td>At 18 months</td>
<td></td>
</tr>
</tbody>
</table>

Perform Repeat Analysis Anytime the Following Occurs

Rising levels of BCR-ABL transcript (1 log increase) without an MMR
Rising levels of BCR-ABL transcript (1 log increase) with an MMR

Molecular Response: Definition

- **Complete** = undetectable *BCR-ABL1* transcript
  - depends upon sensitivity of assay

- **Major** = *BCR-ABL1/ABL1* ≥ 3-log reduction from standardized baseline

- What is a 3-log reduction?
  - Baseline is in reference to institution or reference lab’s **NOT** patient’s baseline
  - IRIS Trial: 37% to 0.037% (3-log reduction)
  - International Scale (IS): 100% at diagnosis, 3-log reduction therefore 0.1%
  - Must use same lab since “housekeeping” genes are different in each lab
  - Must use same ‘source’

- CCyR = ~1-log reduction

---

8-year Probability of Survival Based on 3-month PCR Data

![Graph showing survival probability over time](Marin et al., JCO 2012;30(3):232-238)
Goals of Therapy and Assessing Response

- Landmarks of response in CML:

  - CHR
  - CCR
  - MMR
  - CMR

  "Complete Molecular Response"; qPCR (-); Undetectable BCR-ABL transcripts

  Established Landmarks; Unambiguously Defined

  Dependent on Assay Sensitivity; Ambiguous

Figure 2a. PFS According to BCR-ABL Level at 3 Months

Dasatinib 100 mg QD
84% had ≤10% BCR-ABL

Imatinib 400 mg QD
64% had ≤10% BCR-ABL

Jabbour et al., Blood 2014;123(4):494-500
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)

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

When to check for ABL TKD mutation and switch therapy:
  - loss of response (hematologic or cytogenetic relapse) or disease progression to AP/BP
  - confirmed 1-log increase in BCR-ABL1 transcript and loss of MMR

Stopping TKI not recommended; 68/100 who had 2 y CMR had molecular relapse but all responded to re-challenge*

NCCN Criteria for Failure to TKI Therapy

• No PCyR response at 3 and 6 months (Ph >35%)
• BCR-ABL1/ABL1 >10% by QT-PCR (IS) at 3 and 6 months
• Less than CCyR response at 12 or 18 months
• Cytogenetic relapse or hematologic relapse
• Lack of MMR at 18 months is not failure

*Mahon et al, ASH 2013, Abstract 255.
**Resistance Work-Up**

Failure to reach milestones or loss of response

- Non-compliance or drug-drug interactions?
- Laboratory error or imprecision?

No

Diagnostic Work-Up
- Physical exam
- Marrow biopsy with karyotyping
- *BCR-ABL* mutation screen

---

**ABL Kinase Inhibitor Resistance**
Mechanisms of Resistance to Imatinib

- BCR-ABL Kinase domain mutations
- BCR-ABL amplification / increased expression
- Ph+ Clonal Evolution
- Decreased Drug Exposure
  - Decreased amount/activity of influx protein OCT-1
  - Increased P-glycoprotein (ABCB1 / MDR1) efflux
  - α1 Acid Glycoprotein sequestration
- Other mechanisms
  - Src-related (Lyn) kinase over-expression
  - Autocrine GM-CSF based JAK-2/STAT-5 activation
  - HSP70 overexpression; p53 mutations; PI3K/Akt/mTor activation
  - Quiescent stem cells (persistence)

Incidence of BCR-ABL Mutations After Imatinib Failure

T315I, G250A, Y253F, E255D, M351T are found in >10% of patients with mutations

14 mutations make 80% of all mutations
T315I mutation is the most common mutation

Diamond and Melo, Leukemia and Lymphoma 2011;52 Suppl 1:12-22
Traffic light system identifying ABL kinase domain mutation sensitivity to TKIs (adapted from O’Hare et al, 2007). N=native (unmutated)

### Treatment Options Based on ABL Kinase Domain Mutation Status

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>Ponatinib, omacetaxine, clinical trial or stem cell transplant</td>
</tr>
<tr>
<td>V299L</td>
<td>Consider ponatinib or nilotinib</td>
</tr>
<tr>
<td>T315A</td>
<td>Consider ponatinib or nilotinib or bosutinib or imatinib</td>
</tr>
<tr>
<td>F317L/V/I/C</td>
<td>Consider ponatinib, or nilotinib or bosutinib</td>
</tr>
<tr>
<td>Y253H, E255K/V, F359V/C/I</td>
<td>Consider ponatinib, or dasatinib or bosutinib</td>
</tr>
<tr>
<td>Any other mutation</td>
<td>Consider ponatinib or nilotinib or dasatinib or bosutinib or high-dose imatinib</td>
</tr>
</tbody>
</table>

Note: Bosutinib approved as second/third line drug based (n=546) on 26 week MCyR rates: imatinib failures-34%; imatinib f/b nilotinib or dasatinib failures-27%

How Do You Choose The Subsequent Generation TKIs

- Disease characteristics
  - CML-BC: favor dasatinib (?) and combinations

- Mutations
  - T315I → ponatinib
  - Nilotinib IC$_{50}$ > 150nM → avoid
  - Dasatinib IC$_{50}$ > 3nM → avoid
  - Bosutinib also hits F359 and T315L

- Other health issues
  - Hypertension, CHF, lung problems, COPD → avoid dasatinib
  - Severe diabetes, pancreatitis history → avoid nilotinib
  - QTc problems → be cautious with all TKIs(?)
  - Vascular disease, diabetes, etc. caution with nilotinib and ponatinib
Patient B: Ms. Miller

What to do with a Newly Diagnosed Patient with CML?

Patient History & Symptoms

- 55 yo woman who underwent a routine yearly exam at PCP office and was found to have elevated WBC count of 64,000.
- A bone marrow examination demonstrated Philadelphia chromosome in 20 out of 20 metaphases. No other cytogenetic aberrations.
- PMH is notable for:
  - moderate cirrhosis of liver
  - multiple hospital admissions for pancreatitis
  - heavy alcohol use; 1/2 liter of vodka daily for 10+ years
### NCCN Guidelines 2015

**WORKUP**
- H&P, including spleen size by palpation (cm below costal margin)
- CBC with differential, platelets
- Chemistry profile
- Bone marrow aspirate and biopsy
  - Morphologic review
  - Percent blasts
  - Percent basophils
- Cytogenetics
  - RQFRA
  - Quantitative RT-PCR (QPCR) using International Scale (IS)
  - (blood or bone marrow)
- Determine risk score (See Risk Calculation Table CML-0)
- HLA testing, if considering allogeneic HCT

**PRIMARY TREATMENT**
- Chronic phase CML
- Advanced phase CML
- Ph positive or BCR-ABL positive
- Ph negative and BCR-ABL negative
- Discussion of treatment options including:
  - Tyrosine kinase inhibitor (TKI)
  - Role of HCT
  - Clinical trial

* Sokal or Hasford risk score.


---

### CML Response Monitoring and Milestones

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

NCCN Guidelines 2015

ELN 2013 CP-CML Treatment Recommendations

1st line
- Intolerance to 1st TKI
  - IM, NIL, DAS
- Failure of 1st line IM
  - NIL, DAS, BOS, PON
- Failure of 1st line NIL/DAS
  - DAS/NIL, BOS, PON

2nd line
- Intolerance to 1st TKI
  - IM, NIL, DAS

3rd line
- Failure of, and/or intolerance to 2 TKIs
  - Any of the remaining TKIs

Any line, T315I mutation
- PON


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NCCN Guidelines for CML Recommend to Evaluate Patient Comorbidities Prior to Treatment Selection

• NCCN Considerations When Prescribing TKI Therapy for CML Patients

<table>
<thead>
<tr>
<th>Agent not preferred for patients with the following conditions</th>
<th>Dasatinib 100 mg daily</th>
<th>Imatinib 400 mg daily</th>
<th>Nilotinib 300 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung disease, risk of developing pleural effusions</td>
<td></td>
<td>Intermediate or high risk score*</td>
<td>Arhythmiyas, heart disease, pancreatitis, hyperglycemia</td>
</tr>
</tbody>
</table>

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“I lost my job so I can’t afford my TKI right now.”
Adherence Rates and Outcomes: CML

- Patients with chronic phase CML treated with imatinib for median of 60 months and in CCyR (N=67) were monitored for adherence to imatinib using MEMS for a 3-month period in a prospective study conducted by Marin et al.²
- Patients on this study were subsequently followed for median of 19 months. Adherence to imatinib ≥85% correlated with loss of CCyR during this follow-up period (P<0.0001) as depicted in this graph¹.


Adherence Rates and Outcomes: CML

- In the prospective, observational ACADIO study, poor adherence is associated with suboptimal responses and lower rates of complete cytogenetic response (CCyR) in 169 patients treated with imatinib³.
- At follow-up (~90 days after baseline), nonadherence measure of pill count was calculated as the percentage of pills not taken of imatinib prescribed for a 90-day observation period.

³ Prospective, observational, multicenter (54 centers in Belgium), noninterventional study with assessments taken at 3 time points—baseline (screening visit) and follow-up (~90 days later). A total of 180 patients who met the eligibility criteria (age ≥14 years, diagnosed with CML, and treated with imatinib for at least 30 days) completed the study with evaluable data.

Strategies for Potentially Improving Adherence

- Identify poor adherence by looking for potential indicators of nonadherence\(^1\)
  - Missed appointments
  - Lack of response to medication
  - Missed refills
- Ask about barriers (patient’s knowledge of disease; patient’s understanding of benefits, risks, and proper use of treatment; patient’s access to appointments, pharmacy, medications; etc.) to adherence\(^1\)
- Identify potential side effects of treatment and if they may impact patients’ ability to adhere to therapy\(^2\)
- Emphasize value of the regimen and importance of adherence\(^1\)
- Elicit patients’ feelings about ability to follow regimen\(^1\)
- Provide simple, clear instructions and simplify the regimen as much as possible\(^1\)
- Encourage use of a medication-taking system\(^1\)
- Obtain help from family, friends, and community services\(^1\)


Q&A Session

To submit questions to the faculty, email CMLwebcast@nccn.org.
Resources

• NCCN Guidelines® for CML
  NCCN.org

• NCCN Guidelines for Patients®: CML
  NCCN.org/patients

• NCCN Clinician/Patient Communication Tool:
  Tests and Treatment Responses In Chronic Phase CML
  Enclosed in Webcast Handout

Please Remember:

• If you participated with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity. Lists can be sent to education@nccn.org and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.

• If you have not individually registered, please register at:

• An e-mail will be sent within 5-7 business days with instructions on how to login to complete post-test and evaluation. These must be completed in order to receive a CE certificate. Contact education@nccn.org should you not receive this e-mail within 5 business days.

• For notification of upcoming NCCN educational events:
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OVERVIEW

Chronic myelogenous leukemia (CML) is the cancer of blood-forming cells in the bone marrow. CML is a slow growing cancer that causes an increase in the number of white blood cells. CML is caused by the reciprocal translocation between chromosomes 9 and 22. The BCR gene located on chromosome 22 and the ABL1 gene located on chromosome 9 join together to form the BCR-ABL1 fusion gene. This translocation also creates a longer chromosome 9 and a shorter chromosome 22, which is called the Philadelphia (Ph) chromosome. CML occurs in three different phases (chronic, accelerated, and blast phase) and is usually diagnosed in the chronic phase. Tyrosine kinase inhibitor (TKI) therapy with small molecules that target the BCR-ABL1 protein is the standard of care for all patients with newly diagnosed chronic phase CML.

TESTS

Bone marrow cytogenetics detects and measures the number of cells in the bone marrow that contain the Ph chromosome. It is performed at diagnosis to establish the disease phase. Fluorescence in-situ hybridization (FISH) on a peripheral blood specimen using dual probes for the BCR and ABL genes can be used, if collection of bone marrow is not possible. Quantitative reverse transcriptase polymerase chain reaction (QPCR) is the most sensitive test that detects and measures the BCR-ABL1 gene in a peripheral blood specimen. QPCR should be done at diagnosis to establish the BCR-ABL1 transcript levels at baseline. BCR-ABL1 kinase domain mutational analysis detects new mutations in the BCR-ABL1 gene that may occur during treatment for CML. Mutational analysis helps to select an alternate TKI therapy when CML is not responding to a particular TKI therapy.

TREATMENT RESPONSES

Monitoring response to TKI therapy is one of the key management strategies of CML. Hematological response measures normalization of the blood counts, particularly white blood cell counts. Cytogenetic response measures the decrease in the number of bone marrow cells that have the Ph chromosome. Molecular response measures the decrease in the number of cells in the peripheral blood that contain the BCR-ABL1 gene. QPCR is the only test capable of monitoring molecular response to TKI therapy after the patient has achieved complete cytogenetic response (CCyR). QPCR should be performed in a lab that uses the International Scale (IS) that was established to standardize the measurement of molecular response across different laboratories. In the QPCR (IS), results are expressed as the ratio of BCR-ABL1 gene transcripts to the number of control gene transcripts (BCR, ABL1, or GUSB). Laboratories with no access to QPCR (IS) may establish their own standardized baseline, based on a large number of pre-treatment samples. Molecular response is then measured as the log-reduction of BCR-ABL1 transcripts from the standardized baseline (not a reduction from the actual baseline level in an individual patient).
# TREATMENT RESPONSE CRITERIA

<table>
<thead>
<tr>
<th>Hematologic Response</th>
<th>Complete Hematologic Response (CHR)</th>
<th>Peripheral blood counts and platelet counts completely normal; No blasts or immature cells in the peripheral blood and no signs or symptoms of disease including no enlarged spleen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic Response</td>
<td>Complete Cytogenetic Response (CCyR)</td>
<td>No Ph chromosome is detectable in bone marrow cytogenetics</td>
</tr>
<tr>
<td></td>
<td>Partial Cytogenetic Response (PCyR)</td>
<td>1%–35% of cells have the Ph chromosome on bone marrow cytogenetics</td>
</tr>
<tr>
<td></td>
<td>Major cytogenetic response (MCyR)</td>
<td>0%–35% of cells have the Ph chromosome on bone marrow cytogenetics</td>
</tr>
<tr>
<td>Molecular Response</td>
<td>Complete Molecular Response (CMR)</td>
<td>No $BCR-ABL1$ transcripts are detectable in peripheral blood by QPCR using IS</td>
</tr>
<tr>
<td></td>
<td>Early molecular response (EMR)</td>
<td>$BCR-ABL1 \leq 10%$ by QPCR using IS at 3 or 6 months</td>
</tr>
<tr>
<td></td>
<td>Major molecular response (MMR)</td>
<td>$BCR-ABL1 \leq 0.1%$ by QPCR using IS or at least a 3-log reduction in the $BCR-ABL1$ transcript levels from the standardized baseline (if QPCR using IS not available)</td>
</tr>
</tbody>
</table>
# Monitoring Response to TKI Therapy and Mutational Analysis

<table>
<thead>
<tr>
<th>TEST</th>
<th>TEST SAMPLE</th>
<th>AT DIAGNOSIS</th>
<th>RESPONSE MILESTONES</th>
<th>ANYTIME DURING THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>QPCR (IS)</td>
<td>Peripheral Blood or Bone Marrow</td>
<td>✓</td>
<td><strong>BCR-ABL1/ABL1 ≤10% by QPCR using IS or PCyR on Bone Marrow Cytogenetics</strong></td>
<td>Repeat QPCR (IS) in 1–3 months if there is 1-log increase in <strong>BCR-ABL1</strong> transcript levels <em>with</em> a MMR</td>
</tr>
<tr>
<td>Bone marrow Cytogenetics</td>
<td>Bone Marrow</td>
<td>✓</td>
<td>If QPCR using IS not available</td>
<td>If there is no CCyR or MMR</td>
</tr>
<tr>
<td><strong>BCR-ABL1 kinase domain mutation analysis</strong></td>
<td>Peripheral Blood or Bone Marrow</td>
<td></td>
<td><strong>BCR-ABL1/ABL1 &gt;10% by QPCR using IS</strong> or Lack of PCyR on bone marrow cytogenetics</td>
<td>If not in MMR and lack of CCyR at 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-log increase in <strong>BCR-ABL1</strong> transcript levels <em>without</em> a MMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any sign of loss of response (hematologic or cytogenetic relapse)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-log increase in <strong>BCR-ABL1</strong> transcript levels <em>and</em> loss of MMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Disease progression to accelerated or blast phase</td>
</tr>
</tbody>
</table>
REFERENCES

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Chronic Myelogenous Leukemia, Version 1.2015.


