NEW GUIDELINES, NEW TREATMENT APPROACH FOR CML

EUROPEAN LEUKEMIANET 2020 RECOMMENDATIONS FOR TREATING CML

CML: chronic myeloid leukemia.


Prescribing information for Iclusig can be found on the last slide.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
NEW DEVELOPMENTS AND FINDINGS PROMPTED THIS FOURTH VERSION OF THE ELN MANAGEMENT RECOMMENDATIONS

GREATER THAN 10% BCR-ABL1 AT 3 MONTHS INDICATES TREATMENT FAILURE AND REQUIRES CHANGE IN TREATMENT

IN CASES OF FAILURE/RESISTANCE, THE CHANGE OF TKI IS MANDATORY, AND MUST BE ACCOMPANIED BY INVESTIGATION OF BCR-ABL1 KD MUTATIONS

TFR IS AN IMPORTANT NEW GOAL OF CML MANAGEMENT

SUMMARY OF RECOMMENDATIONS ABOUT PONATINIB
GREATER THAN 10% BCR-ABL1 AT 3 MONTHS INDICATES TREATMENT FAILURE AND Requires change in treatment

- The monitoring milestones of BCR-ABL1 transcript levels by the IS at 3, 6, and 12 months determine whether the current treatment should be:
  - **(optimal response)**: Continued
  - **(warning)**: Or carefully considered for continuation or change, depending on patients’ characteristics, comorbidities and tolerance
  - **(failure/resistance)**: Changed

### Table 4. Milestones for treating CML expressed as BCR-ABL1 on the IS

<table>
<thead>
<tr>
<th></th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>NA</td>
<td>High-risk ACA, high-risk ELTS  score</td>
<td>NA</td>
</tr>
<tr>
<td><strong>3 months</strong></td>
<td>≤10%</td>
<td>&gt;10%</td>
<td>&gt;10% if confirmed within 1-3 months</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td>≤1%</td>
<td>&gt;1-10%</td>
<td>&gt;10%</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td>≤0.1%</td>
<td>&gt;0.1-1%</td>
<td>&gt;1%</td>
</tr>
<tr>
<td><strong>Any time</strong></td>
<td>≤0.1%</td>
<td>&gt;0.1-1%</td>
<td>&gt;1%, resistance mutations, high-risk ACA</td>
</tr>
</tbody>
</table>

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤ 0.01% (MR4). A change of treatment may be considered if MMR is not reached by 36-48 months. *Loss of MMR (BCR-ABL1 > 0.1%) indicates failure after TFR.

Achieving **MMR** (BCR-ABL1 ≤ 0.1%) predicts a **CML-specific survival close to 100%** as disease progression is uncommon once this level of cytoreduction has been achieved.

**ACA**: additional chromosome abnormalities in Ph+ cells; **ELTS**: EUTOS long term survival score; **ELN**: European LeukemiaNet; **IS**: international scale; **MMR**: major molecular response; **MR4**: deep molecular response; **NA**: not applicable; **TFR**: treatment free remission.
In cases of failure/resistance, the change of TKI is mandatory, and must be accompanied by investigation of BCR-ABL1 KD-mutations.

**First Line**
- **TKIs**
  - Imatinib (brand and generics)
  - Dasatinib (brand, and soon generic)
  - Nilotinib
  - Bosutinib
  - Radotinib (only in South Korea)
- **Interferon α / PEG-IFNα**

**Second Line and beyond**
- If failure/resistance of 1st line treatment, investigation of BRC-ABL1 KD mutations must be done before choosing the therapeutic agent for 2nd line.
- The TKI selection should be guided by the profile of BCR-ABL1 KD-mutations, especially if the T315I mutation is detected.
- In case of intolerance/treatment-related complications, the choice of TKIs in 2nd line depends upon the patient, physician, option of supportive care, and level of response.
- All approved 1st line TKIs and ponatinib are available for 2nd line use.
- Allo-SCT.

- For a patient who is resistant to the initial 2GTKI given either as first or second-line therapy, the chance of achieving a durable response to an alternative 2GTKI is low.

In patients with resistance to a 2GTKI without specific mutations ICLUSIG® is preferred over change of 2GTKI, unless cardiovascular risk factors are present.

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**2GTKI**: second generation tyrosine kinase inhibitor; **KD**: kinase domain; **PEG**: pegylated; **SCT**: stem cell transplantation; **TKI**: tyrosine kinase inhibitor.
In cases of failure/resistance, the change of TKI is mandatory, and must be accompanied by investigation of BCR-ABL1 KD-mutations.

- There are no comparative studies and the choice of TKI should be guided by the sensitivity profile of specific BCR-ABL1 KD-mutations if possible, and, in particular T315I where only ponatinib is efficacious.

- Mutations account for resistance in:
  - 1/3 of resistant CP patients.
  - 2/3 of resistant AP and BP patients.

- NGS is the recommended technology to detect BCR-ABL1 resistance mutations in patients not responding adequately to TKI.

| Table 5. Recommended tyrosine kinase inhibitors in case of BCR-ABL1 resistance mutations |
|---------------------------------|-------------------------------------------------|
| T315I                           | Ponatinib                                        |
| F317L/V/I/C, T315A              | Nilotinib, bosutinib\(^a\), or ponatinib         |
| V299L                           | Nilotinib or ponatinib                           |
| Y253H, E255V/K, F359V/I/C       | Dasatinib, bosutinib\(^a\), or ponatinib         |

\(^{a}\)There are limited data available regarding mutations associated with clinical resistance to bosutinib in vivo. Some in vitro data suggest that the E255K and, to a lesser extent, the E255V mutation, might be poorly sensitive to bosutinib.

Ponatinib remains the only TKI with activity against the T315I mutant.

AP: accelerated phase; BP: blastic phase; CP: chronic phase; KD: kinase domain; NGS: next generation sequencing; TKI: tyrosine kinase inhibitor.

TFR IS AN IMPORTANT NEW GOAL OF CML MANAGEMENT

- The panel agreed that **TFR is a new significant goal of CML management** that should be discussed with appropriate patients.

- **Treatment may be changed to 2GTKI to improve the depth of response** in selected patients in whom DMR has not been reached:
  - The motivated patient with a high priority for TFR.
  - Younger patients with low or intermediate risk disease.
  - Women who wish to become pregnant.

- **Treatment can be successfully stopped** in some patients if the duration of both treatment and DMR is sufficient to make TFR feasible for potential cure.

### Table 8. Requirements for tyrosine kinase inhibitor discontinuation

<table>
<thead>
<tr>
<th>Mandatory</th>
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</thead>
<tbody>
<tr>
<td>CML in first CP only (data are lacking outside this setting)</td>
</tr>
<tr>
<td>Motivated patient with structured communication</td>
</tr>
<tr>
<td>Access to high quality quantitative PCR using the International Scale (IS) with rapid turn around of PCR test results</td>
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<tr>
<td>Patient’s agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Minimal (stop allowed):</th>
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</thead>
<tbody>
<tr>
<td>First-line therapy or second-line if intolerance was the only reason for changing TKI</td>
</tr>
<tr>
<td>Typical e13a2 or e14a2 BCR-ABL1 transcripts</td>
</tr>
<tr>
<td>Duration of TKI therapy &gt;5 years (&gt;4 years for 2GTKI)</td>
</tr>
<tr>
<td>Duration of DMR (MR^4 or better) &gt;2 years</td>
</tr>
<tr>
<td>No prior treatment failure</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Optimal (stop recommended for consideration):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of TKI therapy &gt;5 years</td>
</tr>
<tr>
<td>Duration of DMR &gt; 3 years if MR^4</td>
</tr>
<tr>
<td>Duration of DMR &gt; 2 years if MR^4.5</td>
</tr>
</tbody>
</table>

2GTKI: second generation tyrosine kinase inhibitor; CML: chronic myeloid leukemia; CP: chronic phase; DMR: deep molecular response; MR^4 and MR^4.5: deep molecular response; TFR: treatment free remission.
SUMMARY OF ELN RECOMMENDATIONS ABOUT PONATINIB

In patients with resistance to a 2GTKI without specific mutations PONATINIB is preferred over change of 2GTKI, unless cardiovascular risk factors are present.

The approved starting dose of ponatinib is 45 mg once daily (Please see SmPC for full licenced posology). However, the panel recommends starting at 30 mg or 15 mg daily for patients with a low degree of resistance or multiple intolerances*; especially those with cardiovascular risk profiles. Patients with the T315I mutation, compound mutations, or progression to an advance phase should receive 45 mg of ponatinib once daily.

If a CCyR or MMR is achieved, the daily dose can be decreased to 15 mg daily followed by careful monitoring. Control of hypertension, hyperlipidemia and diabetes and smoking cessation should be emphasized to possibly reduce the risk of arterial occlusion events (AOE).

Ponatinib remains the only TKI with activity against the T315I mutant.

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*Iclusig® (ponatinib) is indicated in adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. The recommended starting dose is 45 mg of ponatinib once daily. For the standard dose of 45 mg once daily, a 45 mg film-coated tablet is available. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity.2

PRESCRIBING INFORMATION – Iclusig® (ponatinib) film coated tablets

15 mg, 30 mg or 45 mg ponatinib (as hydrochloride)

Contains lactose monohydrate

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See below for how to report adverse reactions.

Legal Category: POM. See Summary of Product Characteristics (SmPC) before prescribing.

Indications:
- Adult patients with:
  - Chronic phase (CP), accelerated phase (AP), or blast phase (BP) chronic myeloid leukemia (CML) who are resistant/intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
  - Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant/intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

Dosage and administration:
Recommended starting dose 45 mg once daily; swallow tablets whole.

Assess and actively manage cardiovascular risk factors before starting treatment and continue throughout treatment; consider other treatment options in patients with prior myocardial infarction (MI), revascuolarisation or stroke (CVA).

The risk of Arterial Occlusive Events is likely to be dose-related. Consider dose reduction to 15 mg for CP-CML patients who achieve a Major Cytogenetic Response; consult the SmPC for full details of risk benefit and recommended monitoring of response.

Discontinue in case of disease progression or severe adverse reactions (ADRs); also, if Complete Haematological Response does not occur by 12 months.

Dose modifications, or interruptions, should be considered for haematological and non-haematological toxicities; consult the SmPC for full details of all recommended dose modifications.

Contraindications: Hypersensitivity to ponatinib or excipients.

Warnings and precautions: Important ADRs: refer to SmPC for full details of recommended monitoring and management.

Myelosuppression: Perform Full Blood Count every 2 weeks for the first 3 months and then monthly as clinically indicated.

Most severe events occurred in first 3 months; overall, events occurred more frequently in AP-CML, BP-CML or Ph+ ALL than CP-CML.

Arterial Occlusion: Intermittent treatment immediately.

Serious reactions including MI, CVA and retinal artery occlusion have occurred in 20% of patients in the Phase 2 PAC trial of icalug (see SmPC for full details); events occurred more frequently in elderly patients and those with history of ischaemia, hypertension, diabetes, or hyperlipidaemia.

Venous thromboembolism: Intermittent treatment immediately.

Serious reactions including retinal vein occlusion have occurred in 5% of patients.

Hypertension: Monitor and manage throughout treatment; may increase risk of arterial thrombotic events including renal artery stenosis.

Treatment-emergent events have occurred, including hypertensive crisis.

Anaeumy and artery disuctions: This risk should be considered in patients with hypertension or history of anaeumy. VEGF pathway inhibitors may promote the formation of anaeumy

Conective Heart Failure: Consider discontinuing treatment if severe.

Fatal events have occurred, related to prior vascular occlusive events.
Pancreatitis and serum lipase: Check serum lipase fortnightly for 2 months and then periodically.

Frequency of events is greater in the first 2 months. Caution in patients with history of pancreatitis or alcohol abuse.

Hepatotoxicity: Perform LFTs before and during treatment.

Hepatic failure (including fatal outcome) has been observed, mostly in first year of treatment.

Haemorrhage: Intermittent treatment if serious or severe.

Most severe events, including gastrointestinal haemorrhage and subdural haematoma, occurred more frequently in AP-CML, BP-CML or Ph+ ALL. Caution with use of anti-clotting agents.

Risk of Hepatitis & reactivation: Test for HBV before treatment.

Reactivation has occurred following icalug treatment. Consult with hepatologist if serology is positive.

Severe Cutaneous Adverse Reaction (SCARs).

Severe skin reactions (such as Stevens-Johnson Syndrome) have been reported with some BCR-ABL TKIs.

Reversible Reversible Encephalopathy Syndrome (PRES).

Post-marketing cases of PRES have been reported in icalug-treated patients.

Effects on ability to drive and use machines.

Lethargy, dizziness and blurred vision have occurred. QT prolongation.

A clinically significant effect on QT cannot be excluded.

Drug interactions: See SmPC for details of all interactions.

Avoid treatment with icalug and strong CYP3A inducers if possible. Caution when treating with strong CYP3A inhibitors; consider 30 mg starting dose of icalug.

Pregnancy and breastfeeding: Advise pregnant and/or breastfeeding women to avoid treatment.

Any histories of alcohol intake should be discontinued.

Undesirable effects: Reporting suspected ADRs is important to continue monitoring the benefit-risk of icalug. Healthcare professionals are asked to report suspected ADRs via the Yellow Card Scheme. Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

Most common serious ADRs (see SmPC for details of all ADRs). Pneumonia, CVA, coronaary artery disease, peripheral arterial occlusive disease, pancreatitis, pyrexia, abdominal pain, anaemia, angina, decreased platelet count, febrile neutropaenia, hypertension, MI, atrial fibrillation, CCF, sepsis, cellulitis, acute kidney injury, UTI, increased lipase.

Other very common ADRs.

Upper respiratory tract infection, decreased neutrophil count, dyspepsia, cough, diarrhoea, decreased appetite, nausea, vomiting, constipation, increased ALT/AST, peripheral oedema, rash, dry skin, pruritis, pain incl. back, bone & extremities, arthralgia, myalgia, muscle spasms, fatigue, headache, dizziness, asthenia.

Quantities and Marketing Authorisation numbers:

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Marketing Authorisation number</th>
</tr>
</thead>
<tbody>
<tr>
<td>45 mg dose</td>
<td>30 tablets EU/1/11/839/004</td>
</tr>
<tr>
<td>30 mg dose</td>
<td>30 tablets EU/1/11/839/006</td>
</tr>
<tr>
<td>15 mg dose</td>
<td>30 tablets EU/1/11/839/005</td>
</tr>
<tr>
<td>Cost: 45mg x 30 tablets £5050; 30mg x 30 tablets £5050; 15mg x 30 tablets £2525.</td>
<td></td>
</tr>
</tbody>
</table>


For further information phone: 0800-0002-7423.

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Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Incyte immediately by phoning the EU universal free phone number 00-800-0002-7423.