UK Interim Expert Opinion on Discontinuing Tyrosine Kinase Inhibitor Treatment in Clinical Practice for Treatment-Free Remission in Chronic Myeloid Leukaemia

This interim expert opinion document has been developed following consultation with a UK CML expert panel and with the support and funding of Novartis Oncology UK.

The intended purpose of this document is to provide medical education, upon unsolicited request, via the Novartis UK Medical team (Novartis Medical Affairs and Medical Information).

This interim expert opinion document is dated 01 August 2017 and remains valid only until such time as pending updates to European LeukemiaNet (ELN) CML recommendations and/or British Society for Haematology (BSH) CML guidelines are published.

Treatment-Free Remission Overview:

To date more than 2000 Chronic Myeloid Leukaemia (CML) patients have discontinued tyrosine kinase inhibitor (TKI) treatment within clinical studies of treatment-free remission (TFR)[1,2]. Studies have included discontinuation in patients following treatment on imatinib, nilotinib or dasatinib[1-11]. Safety and efficacy reports from these studies are in agreement that the discontinuation of TKI therapy for TFR in select CML patients with a deep and sustained molecular response appears to be achievable[1,2].

Within these clinical studies ~40-60% of patients had a molecular recurrence requiring TKI re-initiation. A majority of recurrences occurred within six months following discontinuation; however more recent studies show later molecular recurrences continue to occur, highlighting the need for ongoing frequent molecular monitoring. To date, all patients who re-initiated treatment remained sensitive to TKI treatment, and re-achieved a deep molecular response in the majority of cases[1-11].

A “TKI withdrawal syndrome” has been described in later studies with rates of ~15-40% and includes symptoms of musculoskeletal pain (often proximal), myalgia, arthralgia, and bone pain. These events were mostly low grade and generally self-limiting, resolving within 12 months, although some events continued beyond one year [5, 8-13].

Stopping TKI treatment to attempt TFR has until now been recommended only within a clinical trial setting where strict eligibility criteria are employed and frequent monitoring is ensured.

Nilotinib is the only approved TKI for the treatment of CML to include TFR efficacy and safety data, entry requirements and management for nilotinib discontinuation, within the summary of product characteristics (SmPC) (updated 5th June 2017)[14]. When considering discontinuation of nilotinib in patients treated first or second line (following imatinib), reference should be made to the specific requirements detailed within the current SmPC[14].

Tasigna® (nilotinib) Summary of Product Characteristics

The first formal expert evidence based guidelines on TKI discontinuation in mainstream clinical practice, outside of clinical trials, was recently produced by the American National Comprehensive Cancer Network (NCCN) in February 2017[15]. Updated evidence based European LeukemiaNet (ELN) CML recommendations and British Society for Haematology (BSH) CML guidelines are currently pending.

The following is the interim expert panel opinion on TKI discontinuation and management for TFR in clinical practice in the UK:

The panel is of the opinion that discontinuation of TKI treatment could be attempted within mainstream clinical practice in select patients if all stringent criteria are applied as described below. It is important that the molecular monitoring capabilities and requirements prior to and during TKI discontinuation are ensured. The risks (including TKI withdrawal symptoms) and benefits of TFR, and the requirement for increased frequency of monitoring, should be clearly discussed with potential eligible patients. The panel recommends that any patient being considered for TKI discontinuation should be discussed first at local multidisciplinary team (MDT), or with a regional CML specialist. In addition, if there is a failure to meet all the criteria described below, this should be discussed at local MDT, or with a regional CML specialist. The final decision to discontinue TKI in attempting TFR should only be made following discussion between the treating clinician and patient, with the patient being fully supportive of this decision.

The expert panel is of the opinion that <u>ALL</u> of the following eligibility and management criteria should be followed when attempting TKI discontinuation for TFR:

- Adult (≥ 18 years) first Chronic Phase CML (CP-CML) patient.
- On an approved TKI therapy for at least three (but preferably five) years prior to TKI discontinuation.
- No prior history of Accelerated Phase or Blast Phase CML.
- No prior history of resistance to any TKI (and no prior detection of known BCR-ABL1 kinase domain mutations).
- No prior transplant.
- A patient treated on a TKI second line following prior first line intolerance may be considered if all the remaining criteria are fulfilled.
- Any Sokal risk group may be considered if all the remaining criteria are fulfilled.
- A confirmed expression by the laboratory of typical BCR-ABL1 transcript type at diagnosis (e13a2/b2a2 and/or e14a2/b3a2), e.g. by qualitative Polymerase Chain Reaction (PCR).
- Access to a laboratory that provides BCR-ABL1 real-time quantitative PCR (RQ-PCR) results expressed on the International Scale (IS) with a sensitivity of at least MR4.5 (BCR-ABL1 IS ≤0.0032%).
- A sustained deep molecular response of at least MR4 (BCR-ABL1 IS ≤0.01%) throughout the last 24 months prior to discontinuation, verified by a minimum of four consecutive (at least 3 months apart) RQ-PCR results (including an RQ-PCR result taken shortly prior to discontinuing TKI).
- The laboratory should be informed a patient is discontinuing TKI, requiring increased frequency of molecular monitoring (RQ-PCR) and timely results (a maximum turnaround time for results of 2 weeks).
- Molecular monitoring (RQ-PCR) and full blood differentials following discontinuation of TKI is required monthly for the first year, every two months in the second year, every three months in third and subsequent years (indefinitely).
- Re-initiation of TKI treatment must occur within one month of a loss of major molecular response (MMR) at a single RQ-PCR test, i.e. BCR-ABL1 IS >0.1% IS.
- Re-initiation of the TKI should be at the standard recommended dose as per SmPC, or at the maximum tolerated dose for the patient.
- Re-initiated patient must have monthly RQ-PCR until MMR (BCR-ABL1 IS ≤0.1%) is achieved and confirmed, and then every three months thereafter.
- Re-initiated patient not re-achieving MMR by six months on TKI should have BCR-ABL1 kinase domain mutation testing performed, and should be discussed at local MDT or with the regional CML expert.
- Musculoskeletal pain, myalgia, arthralgia and bone pain ≥Grade 3 or <Grade 3 persisting for ≥ 6months during TKI discontinuation should be discussed at the local MDT or with the regional CML specialist.

Dated 01 Aug 2017: This interim document is valid only until such time as pending updates for European (ELN) CML recommendations and/or UK (BSH) CML guidelines are published. The expert opinion (page 2) is that of the CML expert panel listed (page 3).

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Expert Panel	Role	Institution
Prof Richard Clark	Consultant Haematologist	Royal Liverpool University Hospital
Prof Mhairi Copland	Consultant Haematologist	The Beatson West of Scotland Cancer Centre, Glasgow
Dr Andrew Goringe	Consultant Haematologist	University Hospital of Wales, Cardiff
Prof Brian Huntly	Consultant Haematologist	Addenbrooke's Hospital, Cambridge University Hospitals
Dr Dragana Milojkovic	Consultant Haematologist	Hammersmith Hospital, Imperial College London
Prof Adam Mead	Consultant Haematologist	The Churchill Hospital, Oxford University Hospitals
Dr Graeme Smith	Consultant Haematologist	St James's University Hospital, Leeds
Ms Sandy Craine	Patient Advocate Representative	UK CML Support
Prof Nick Cross	Director National Genetics Reference Laboratory – Wessex	NGRL (Wessex) Salisbury NHS Trust.

This interim consensus expert opinion document has been developed following consultation with a UK CML expert panel and with the support and funding of Novartis Oncology UK.

Adverse Events during treatment and discontinuation should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard

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