

Prof. Adam Mead Interview for *Future Oncology*:

Tasigna (Nilotinib) in CML - Treatment-free Remission after nearly 2 years: An interview with Adam Mead.

Bio:

Prof. Mead trained in medicine at the University of Oxford and in hematology at St Bartholomew's Hospital and University College London. In 2007 he completed his PhD, which was focused on the biology of acute myeloid leukemia. He is now Associate Professor of Haematology and MRC Senior Clinical Fellow at the Weatherall Institute of Molecular Medicine, University of Oxford. His research group focuses on myeloid diseases and normal blood stem cell biology. Dr Mead serves as chief investigator for several national and international clinical studies in myeloproliferative neoplasms (MPN) and chronic myeloid leukemia. Additionally, Dr Mead has helped shape the diagnostic and treatment guidelines for MPN in the United Kingdom and serves as the chair of the MPN subgroup of the National Cancer Research Institute.

Keywords:

Chronic myeloid leukemia

Nilotinib

Treatment free remission

Interview questions:

1. Could you please provide a brief summary of your career to date? What triggered your interest in Hematologic Oncology?

I trained in medicine at The University of Oxford, UK, where I spent some time on a haematology attachment with Dr Tim Littlewood, which is when my interest in haematology-oncology was triggered. I then worked with Tim as a house officer (junior doctor) in Oxford, and decided that haematology was the speciality that I would pursue as a career as I particularly liked the integration of academic, laboratory and clinical medicine. I trained in hematology in London, and completed my PhD, which was focused on FLT3 mutations in acute myeloid leukemia, at University College London (London, UK) with Professors David Linch and Rosemary Gale. In 2008 I moved back to Oxford, where I was funded by a Bennett fellowship from Bloodwise (London, UK) to carry out leukemia stem cell research in the laboratory of Professor Sten Eirik Jacobsen. In 2014 I set up my own research group focused on myeloid diseases and normal blood stem-cell biology at the Weatherall Institute of Molecular Medicine funded by a Medical Research Council (MRC) senior clinical fellowship. This allows me to link my clinical work in hemato-oncology, focused on patients with myeloproliferative neoplasms and chronic myeloid leukemia, with stem cell biology research. I currently chair the National Cancer Research Institute MPN clinical research subgroup which helps to shape the diagnostic and treatment guidelines for myeloproliferative neoplasms (MPNs) in the UK and clinical trial portfolios.

2. How have you seen the field of myeloid malignancies develop over your career?

In the field of myeloproliferative neoplasms (MPN) and chronic myeloid leukemia (CML) there has been a dramatic change in diagnostic and treatment approaches in two key ways:

First, is the advent of molecular diagnostics, most notably the discovery of the *JAK2* mutation in patients with MPN in 2005 which has had a huge impact on the field. Molecular monitoring has also transformed the way that we assess treatment responses in CML during this time.

Second, is the development of targeted therapy in CML and MPNs. In CML, the development of Tyrosine Kinase Inhibitors (TKI) – first Imatinib, followed by second generation inhibitors, has transformed the outlook for patients with CML. When I was starting in hematology, CML was a difficult disease to treat and was only manageable in the long term for most patients through allogeneic transplant. Although there was minority of patients that could achieve long term disease control with interferon treatment, for most patients that wasn't a possibility. With the availability of TKI therapies, the vast majority of patients do not require allogeneic transplantation and can be treated in the outpatient clinic with good prospects for long term disease control in most patients. The impact on survival following a diagnosis of CML used to be dramatic when I started in hematology, and now the emerging data suggests that since the introduction of TKIs, life expectancy is similar to that of the normal population in patients who respond well to TKI therapy.

3. At the 22<sup>nd</sup> Congress of the European Hematology Association (EHA) in Madrid (Spain), Novartis announced key data from 2 clinical trials demonstrating Philadelphia-positive (Ph+), chronic myeloid leukemia (CML) patients in the chronic phase (CP) remaining in Treatment-free Remission (TFR\_ almost 2 years following cessation of Tasigna (nilotinib) - could you outline Tasigna's mode of action?

CML is driven by a fusion gene, *BCR-ABL*, which results from damaged chromosomes, the so-called Philadelphia Chromosome. This drives bone marrow stem and progenitor cells to proliferate and in essence, this is what causes the disease. Nilotinib is a second generation TKI that inhibits the *BCR-ABL* fusion gene even more effectively than imatinib, essentially "putting the brake on" and reversing the abnormal proliferation.

4. Why is this particular patient profile (Ph+-CML-CP) a strong target population for the drug?

CML is defined by presence of the Philadelphia chromosome and the *BCR-ABL* fusion gene, which is the target for TKIs. Whilst other cancers and leukemias often carry multiple different genetic mutations, CML is a more "simple" disease that in many cases is probably driven by *BCR-ABL* alone. It is this relative simplicity that has made CML an amazing paradigm for cancer biology over decades. CML is one of the earliest examples of a specific genetic lesion that is associated with a distinct disease which by targeting of that genetic lesion TKIs can have a really dramatic impact. Normal bone marrow cells in normal individuals don't carry the *BCR-ABL* gene, allowing TKIs such as Nilotinib to selectively target the leukemia cells and not the normal bone marrow stem cells which is in essence why they are so incredibly effective.

5. Can you provide our readers with an outline of the ENESTFreedom trial and describe the 96-week TFR rates demonstrated?

The ENESTFreedom study, which we took part in in Oxford, recruited patients with chronic phase CML who had been treated with front line Nilotinib for at least 2 years and achieved a deep molecular remission, defined as an MR 4.5. Once on the study, patients had to have an additional year of consolidation nilotinib treatment to ensure that they were in a stable MR4.5, so essentially patients had to have a minimum of 3 years on Nilotinib and to have a sustained deep molecular remission (MR 4.5) during that consolidation phase. Patients with a sustained MR4.5, were eligible to stop the Nilotinib treatment, so called treatment-free remission. Patients were then very closely followed, initially once a month, and assessed for any evidence of the disease re-occurring at the molecular level.

The results of the ENESTFreedom trial, presented at EHA showed, showed that after a minimum of 96 weeks follow-up, the estimated rate of successful treatment-free remission (TFR) was 50.9%; meaning that approximately half of patients treated on front-line Nilotinib and achieving a stable MR4.5 could successfully stop the treatment. Most relapses at the molecular level occurred within the first 6 months after treatment discontinuation and later relapses were infrequent.

6. The second trial, ENESTop, looked at 96-week TFR rates with Tasigna in the second-line (as opposed to ENESTFreedom, which looked at the drug in the first-line); can you briefly describe the trial protocol and highlight any differences in molecular durability or safety profiles compared with the first trial?

The ENESTop trial was a study that again took patients with chronic phase CML, but the difference with ENESTFreedom was that these patients firstly had to have three years of TKI therapy before going on the study. Crucially, these patients received first-line Imatinib treatment, before they were switched to Nilotinib treatment at some point during their disease course. To be eligible for the study, patients needed to have achieved a deep molecular remission similarly defined as for ENESTFreedom (MR 4.5). Once on the study, the design of ENESTop and ENESTFreedom are very similar; patients who achieved MR4.5 on second-line Nilotinib entered a consolidation phase for one year and as long as they maintained their deep molecular remission, they then stopped the treatment and then went into the TFR phase.

This is an interesting population because these are patients who switched from first-line Imatinib to second-line Nilotinib treatment, making it quite a distinct population relative to those patients who had first-line Nilotinib. At 96 weeks from the start of the TFR phase, 53% of patients remained in TFR. So the data is essentially very similar to the ENESTFreedom, despite the fact that this trial enrolled patients receiving Nilotinib as second-line treatment.

The ENESTop and ENESTFreedom trials also contributed to the field in that the vast majority of the patients that did relapse after the treatment was stopped were shown to regain their molecular remission quickly after reinitating the treatment. That is an important consideration for patients of course, not only whether they might be able to successfully stop the treatment but also whether it is safe to do so. For the most part, apart from isolated cases, the data from these and other studies is reassuring that this is a very safe approach for patients that have achieved deep molecular remission.

The second aspect in relation to safety is the occurrence of a withdrawal reaction after the treatment has stopped. Some patients develop a musculoskeletal withdrawal reaction after the

treatment is discontinued and the ENESTop and ENESTfreedom trials describe that although such reactions do occur in a subgroup of patients, it is usually transient and manageable. So again the data is supportive that this is safe approach for patients.

7. What would say would be the reason behind any discrepancies seen in using Tasigna as a first- or second-line treatment, with regards to drug efficacy?

When you are using a drug in the second-line, it is in patients who have failed first-line treatment, usually with imatinib. That can be for a number of reasons, such as patient preference, but it is more likely intolerance to the first-line treatment, i.e side effects or a lack of an optimal response to the first line treatment. Patients with lack of response to first line imatinib are an inherently more challenging group to treat, and most data up to now would suggest that patients failing first line imatinib due to resistance are unlikely to achieve TFR, even when they have achieved MR4.5.

8. Given the durable molecular response rates and safety profiles of the drug demonstrated in these trials, concretely what do these results mean for CML patients on Tasigna?

There is accumulating evidence from a number of studies, not just ENESTFreedom & ENESTop but a number of studies from over quite a few years now, demonstrating that patients who achieve a stable, deep molecular remission on TKI treatment can attempt TFR. For patients with CML this is of course a huge step forward. It's the difference between being told you have to have lifelong treatment compared to a realistic chance that if you achieve a deep remission, you can stop the treatment, hopefully, permanently. The data looks very promising that as long there is no evidence of molecular relapse in the first 6 months, then it's very unlikely that the disease will relapse later.

9. Though the drug has already been approved by global agencies since the last decade, what do these developments signify for the drug moving forwards?

These developments mean that attempting TFR can now move from a phase when this was only done as part of clinical trials, to a phase where this is part of more routine clinical practice. It is important to point out that TFR is not restricted to patients on Nilotinib. The data is very robust for Nilotinib thanks to the ENEST studies, but there is also similar data for some other TKI treatments. Patients achieving stable deep molecular remission can now face the real prospect of being able to stop the treatment and achieve long term TFR. As second generation TKIs such as Nilotinib are more effective at achieving deep molecular remission than first-line treatment with Imatinib, this now becomes a significant consideration to take into account when deciding which first line treatment to use for patients.

10. Where do you see the field of CML management in a decade?

I would say that even though these results are exciting and contribute to a growing body of data demonstrating that subgroups of CML patients are able to successfully stop treatment, the reality is there are still major challenges in CML; most patients are not eligible for TFR and therefore cannot stop treatment. In many patients who attempt TFR, the leukemia begins to grow back. I think the challenge of the next 10 years is to understand what is different about the patients who respond so well to these treatments that they are able to stop TKI compared to those who are not able to stop the treatment. If we can understand more about these difference, then that might lead the way towards more effectively treating the disease and allowing more patients to stop.

I expect that in 10 years' time, there will be a range of even more advance treatments coming through that increase the likelihood of achieving these deep molecular remissions and successfully stopping the treatment – that's the goal!