Overexpression of the FLT-3 receptor is common in Acute Myeloid Leukaemia (AML) and mutations represent one of the commonest mutations which occur in approximately 30% of adult cases, although less frequent in older patients. The most frequently detected mutation is an Internal Tandem Duplication (ITD) in the juxtamembrane position of the receptor (24%), and a point mutation in the activation loop usually at positive 385 (7%). The mutations are in frame and constitutively activate via STAT5. Mutations are unevenly distributed in FAB and cytogenetic groups. They have highest frequency in Acute Promyelocytic Leukaemia (35-40%), and are associated with a normal karyotypic or trisomy 8. They are less frequent in poor risk karyotypes or in core binding leukaemias. The association with normal karyotype has the additional interest of being associated with mutations of the nucleophosmin 1 mutation in approximately two-thirds of cases. Whether these mutations are themselves leukaemogenic is thought to be unlikely.

The major clinical interest is that the presence of an ITD predicts a significantly increased risk of relapse, but does not reduce the prospect of initial response. The frequent association with the APL subtype, which is highly curable, does not significantly reduce survival. Its impact in that context is difficult to distinguish from the presence of a high white count. Point (TK) mutations do not have an adverse prognosis, and indeed may indicate a favourable feature. The mutation characteristics patients with proliferative disorders ie with high WBC’s and hypercellular marrows. Several agents with pre-clinical in vivo and in vitro activity have been developed. None of the agents who are furthest down the clinical development path are specific for FLT3 mutations. Lestaurtinib (CEP-701) is a small molecule kinase inhibitor which has shown impressive preclinical activity in in vivo models, against cell lines bearing the mutation and against primary cells where it is active against both mutated and non-mutated cases, although at a lower IC against mutants.

In phase I/II studies which recruited mutated AML cases with relapsed disease a maximum tolerated dose was not reached at doses capable of inhibition. Clinical activity was seen as clearance of blasts in approximately half of patients and reduction in bone marrow blasts but no complete remissions. It was suggested that greater benefit would be seen in combination with standard chemotherapy, and some pre-clinical studies suggested
synergy, but also that sequencing of Lestaurtinib was important with the chemotherapy. Antagonism was seen when cells were treated before chemotherapy, whereas simultaneous or sequential administration resulted in synergy.

Two major randomised trials are underway. A potential registration trial in relapsed patients compared chemotherapy (MAC or Ara-C) with or without Lestaurtinib which was given after the course of chemotherapy. This study is close to completing accrual of over 200 patients. An amendment of the UK MRC AML15 Trial assesses CEP-701 in first line use of 80 mgs bid commencing two days after chemotherapy daily until two days before the next course of chemotherapy or for up to four courses. Patients are aged 15-60. Four courses are planned. The toxicity is predominantly gastro-intestinal (nausea) and has caused patients to discontinue therapy or require a dose reduction. Because of interaction with CP3A metabolism azoles tend to potentiate toxicity, and if used dose reduction is usually needed. To be a responder two aspects require to be achieved. Cells have to show sensitivity in \textit{in vitro} testing. Since Lestaurtinib is highly protein bound direct pharmacokinetics are not informative. Levis and colleagues have developed a bioassay of “Plasma Inhibitory Activity”, which demonstrates the extent to which patients’ plasma can dephosphorylate the FLT-3 receptor. Defining these parameters in the context of these prospective trials will be important in assessing efficacy.

The interpretation of inhibitor trials will also require to take into account the relapse risk of individual patients. This depends on whether or not the mutation co-exists with an NPM1 mutation which tends to neutralise the negative impact of FLT3, and what level of FLT3 allelic ratio exists. High level mutations have a greater risk of relapse.

While molecular therapy in AML will be complicated because of the heterogeneous molecular basis of the disease. FLT-3 inhibition is clearly a priority aim for which efficacy will be determined in ongoing randomised trials. Many inhibitory agents are in various stages of development, but none is yet proven to have clinical benefit.