

and Common Terminology Criteria for Adverse Events (CTCAE) liver-related laboratory tests and categories. Those with grade ≥ 3 ALT/AST elevation were evaluated for rate of resolution to grade ≤ 1 ALT/AST, and recurrence of the event at any time on study. Patients were grouped by use of IDELA alone or as part of a combination regimen.

Results: Among patients with any disease type or regimen (N=1073), the incidence of any grade ALT/AST elevation was 51%, and the incidence of grade ≥ 3 ALT/AST elevation was 14% (Table). Of patients with transaminase elevation, 73% (398/543) experienced grade 1 or grade 2 events. The incidences of grade ≥ 3 ALT/AST elevations, and outcomes for patients with grade ≥ 3 ALT/AST elevation (Table) were comparable whether IDELA was used alone or in combination. 92% of patients with grade ≥ 3 ALT/AST elevation were managed with dose interruption and achieved resolution to grade ≤ 1 . The majority (69%) of patients with subsequent IDELA rechallenge experienced no recurrence of the event; of events that did recur, the vast majority (94%) resolved in the analysis time period.

Summary/Conclusions: These data support the management of ALT/AST elevation with IDELA using dose interruption at grade 3 with reintroduction after resolution at the discretion of the treating physician. Studies Included in this Analysis: 101-02: NCT00710528; 101-07: NCT01088048; 101-08: NCT01203930; 101-09: NCT01282424; 101-10: NCT01306643; 101-11: NCT01393106; 101-99 (extension): NCT01090414; GS-US-312-0116: NCT01539512; GS-US-312-0117 (extension): NCT01539291; GS-US-312-0119: NCT01659021

Chronic myeloid leukemia - Clinical 1

P227

DE-ESCALATION OF TYROSINE KINASE INHIBITOR THERAPY IS SAFE IN CHRONIC MYELOID LEUKAEMIA IN DURABLE MOLECULAR RESPONSE (\geq MR3 FOR ≥ 12 MONTHS): INITIAL RESULTS IN THE BRITISH DESTINY STUDY

R Clark^{1,*}, F Polydoros², J Apperley³, C Pocock⁴, G Smith⁵, R Salim⁶, T Coffey², S O'Brien⁷, L Foroni³, M Copland⁸

¹Haematology/MCCM, ²Liverpool Clinical Trials Unit, University of Liverpool, Liverpool, ³Haematology, Hammersmith Hospital, London, ⁴Haematology, Kent & Canterbury Hospital, Canterbury, ⁵Clinical Haematology, St James University Hospital, Leeds, ⁶Haematology, Royal Liverpool University Hospital, Liverpool, ⁷Northern Institute for Cancer Research, University of Newcastle, Newcastle, ⁸Paul O'Gorman Leukaemia Research Centre, University of Glasgow, Glasgow, United Kingdom

Background: Some chronic myeloid leukaemia (CML) patients with prolonged and deep molecular remissions on tyrosine kinase inhibitor (TKI) therapy can discontinue treatment. However, study of this has been restricted to patients in stable MR4 (BCR-ABL1 < 0.01%), and it is not known whether some patients in stable major molecular response (MR3; BCR-ABL < 0.1%) but not MR4 can discontinue treatment. In addition, it is plausible that while some patients might not be able to completely discontinue TKI therapy, they may be able to maintain good molecular remissions on TKI doses that are less than standard, with concurrent improvement in any TKI-related adverse events; this has not been previously investigated.

Aims: The British DESTINY study is examining the safety and efficacy of initially de-escalating therapy to half the standard TKI dose (*i.e.* imatinib 200mg daily, nilotinib 200mg twice daily, or dasatinib 50mg daily) for 12 months, then stopping altogether.

Methods: Entrants must be in stable MR3 or better, on all PCR results (minimum of 3) in the preceding 12 months, and must have received TKI for at least 3 years, and not switched TKI (except that a single switch was permitted if solely due to intolerance). The primary endpoint is loss of MR3; monthly molecular monitoring is carried out centrally.

Results: During 16 months recruitment to April 2015, 174 patients (male 98; female 76) were recruited after giving informed consent by 20 sites. At entry, 125 (72%) were in MR4 and 49 (28%) in MR3 but not MR4; 148 were receiving imatinib, 16 on nilotinib and 10 on dasatinib. During 12 months of de-escalation in the first 100 patients, no deaths, disease progressions or losses of cytogenetic response have been seen, though 7 serious adverse events have occurred (6 Grade 3+), all unrelated to TKI. Thirteen patients reported 14 new events of musculoskeletal disorders since decreasing TKI therapy (all Grade 1), comprising pain, stiffness or cramps in the joints, legs, chest, neck and/or back (13) with one additional event of arthritis. Individual side effects (lethargy, diarrhoea, rash, nausea, periorbital oedema, hair thinning) all improve in the first 1-2 months of de-escalation but not significantly thereafter, though the FACT-BRM or EQ-5D Quality of Life data are already optimal at trial entry, suggesting that TKI side effects in entrants do not impact Quality of Life. During the de-escalation phase in the first 100 patients there have been 7 molecular relapses (defined as loss of MR3 on 2 consecutive samples), occurring during the second (1 case), third (2), seventh (1) and eighth (3) month of de-escalation. Four of these were in the 31 patients in MR3 but not MR4 at trial entry, giving a relapse rate of 12.9%; similarly 3 of 69 patients (4.3%) relapsed in the 'MR4 at entry' group. No relapses have occurred in the quartile with the shortest duration of prior TKI treatment (less than 4.8 years), while 3 of the 7 relapses have occurred in the quartile with the longest pre-entry TKI treatment (>10.2 years). All 7 patients have regained at least MR3 within 4 months of resumption of standard dose TKI. Overall, 26 (84%) 'MR3 but not MR4' and 64 (93%) 'MR4 at entry' patients have proceeded to the stopping phase.

Summary/Conclusions: In this first DESTINY trial report focussed on de-escalation, halving the standard TKI dose for 12 months in CML patients in at least MR3 appears safe, does not compromise disease control, and is associated with a rapid improvement in side effects. Mild musculoskeletal symptoms may occur in about 13% of patients.

P228

LONG-TERM EFFICACY AND SAFETY OF PONATINIB IN HEAVILY PRETREATED LEUKEMIA PATIENTS: 4-YEAR RESULTS FROM THE PIVOTAL PHASE 2 PACE TRIAL

JE Cortes^{1,*}, J Pinilla-Ibarz², PD le Coutre³, R Paquette⁴, C Chuah⁵, FE Nicolini⁶, JF Apperley⁷, HJ Khoury⁸, M Talpaz⁹, M Baccarani¹⁰, S Lustgarten¹¹, FG Haluska¹¹, F Guilhot¹², MW Deininger¹³, A Hochhaus¹⁴, TP Hughes¹⁵, NP Shah¹⁶, HM Kantarjian¹

¹The University of Texas MD Anderson Cancer Center, Houston, TX, ²H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, United States, ³Charité Universitätsmedizin Berlin, Berlin, Germany, ⁴Ronald Reagan UCLA Medical