SUNDAY, DECEMBER 8, 2019

ORAL ABSTRACTS SESSION: 4:30 PM-6:00 PM

632. Chronic Myeloid Leukemia: Therapy: Clinical Trials and Outcomes

Sunday, December 8, 2019: 4:30 PM-6:00 PM
W308, Level 3 (Orange County Convention Center)
Moderators:
Carlo Gambacorti-Passerini, MD, University of Milano Bicocca and Pia Raanani, MD, Davidoff Cancer Center, Beilinson Hospital

493 An Updated Safety and Efficacy Results of Phase 1 Study of HQP1351, a Novel 3rd Generation of BCR-ABL Tyrosine Kinase Inhibitor (TKI), in Patients with TKI Resistant Chronic Myeloid Leukemia

Qian Jiang, MD

Background: HQP1351, a novel, orally active potent 3rd generation TKI, was designed for treatment of patients with chronic myeloid leukemia (CML) resistant to current TKI-therapies including those with T315I mutation. This is an updated report of the safety and efficacy of HQP1351.

Methods: It is an open-label, dose escalation and expansion phase 1 trial of HQP1351 which was designed to determine maximum tolerated dose (MTD) and to identify dose-limiting toxicities (DLTs) in patients with CML in the chronic phase (CP) or accelerated phase (AP) resistant or intolerant to ≥ 2 prior TKIs or those with T315I mutation after ≥1 prior TKI. HQP1351 was orally administered once every other day (QOD) in 28-day cycles at 11 dose cohorts ranging from 1mg to 60 mg. The eligible patients received continuous treatments until disease progression to AP or BP, developing intolerant toxicity, consent withdrawal, or death. Blood samples were collected at certain time points on Day 1-2 and Day 27-28 during cycle 1 for PK analyses.

Results: From 26 October, 2016 to 27 May, 2019, 101 patients including 87 CP patients and 14 AP patient were enrolled in this study. Seventy-one (70.3%) patients were male. Median duration of follow-up was 12.8 (range, 1.2-31.5) months. Median age was 40 (range, 20-64) years. Median interval from CML diagnosis to starting HQP1351 treatment was 5.8 (range, 0.3-15.2) years. Eighty-three (83.8%) patients received ≥2 prior lines of TKI-therapy. Sixty-two (61.4%) patients harbored T315I mutation. Seventeen patients who initially assigned to the dose escalation cohorts ranging from 1mg to 20 mg moved to 30 mg or higher dose

cohorts via intra-patient dose escalation. Fifty-six patients enrolled in the dose expansion part of the trial, including 30mg,40mg and 50mg dose cohorts. Two out of 3 patients at 60mg dose cohort experienced DLT and 50mg QOD was considered as the MTD.

During the follow-up period, HQP1351 was well-tolerated in each dose cohort with an exception of 60 mg cohort. All patients experienced ≥1 treatment related adverse events (TRAEs), most of the non-hematologic TRAEs were reported as grade 1 or grade 2. The most common hematologic TRAE of grade 3/4 was thrombocytopenia (49.5%). The incidences of TRAEs tended to be dose-dependent. No death and grade 5 AEs occurred. The incidence of common TRAEs (≥ 10% any grade) are summarized in Table1.

HQP1351 showed potent anti-leukemic activities in CML patients. In the 68 evaluable patients with non-CHR at baseline, 63 (92.6%) achieved CHR including 52 out of 55 (94.5%) CP patients and 11 out of 13 (84.6%) AP patients, respectively. In the 95 evaluable patients with non-CCyR at baseline, 56 out of 81 (69.1%) CP patients achieved MCyR including 49 (60.5%) CCyR; and 6 out of 14 (42.9%) AP patients, achieved MCyR including 5 (35.7%) CCyR, respectively. In the 100 evaluable patients, 32 out of 86 (37.2%) CP patients and 5 out of 14 (35.7%) AP patients achieved MMR, respectively. HQP1351 showed highly efficacious in the patients with T315I mutation (Figure A, B). The probability and the depth of response increased with prolonged treatment period (Figure C). As the cut-off date of May 27 2019, 9 patients (5 CP and 4 AP) withdrawn from the study, including progression to AP or BP (n=5), intolerant AEs (n=2), consent withdrawal (n=1), and newly diagnosis of breast cancer (n=1). The progression free survival (PFS) rate at 18-month was 94% in the CP patients and 61% in the AP patients (Figure D).

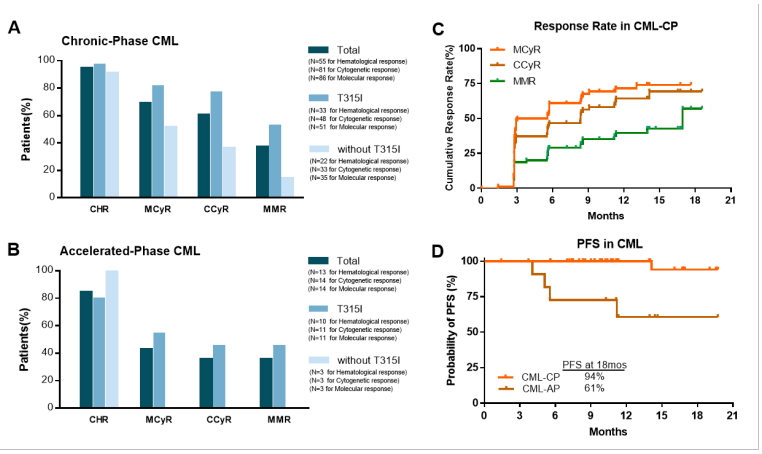
PK analyses indicated an approximately dose proportional increase in exposure (AUC and Cmax) following oral administration of HQP1351 at doses from 1mg to 60 mg. The peak concentration of HQP1351 was reached at 4-8h. The elimination appeared to be linear with a mean terminal T1/2 of 17.5 to 42.5 h. Slight to moderate accumulation was observed on Day 27 following multiple dosing. Reduction of CRkL phosphorylation in PBMCs, a biomarker of BCR-ABL inhibition, has shown to be dose and time dependent in 53 evaluable patients treated with HQP1351.

Conclusions: HQP1351 was well tolerated and exhibited significant and durable antitumor activity in the patients with TKI-resistant CML, including those with T315I mutation. Two pivotal studies of HQP1351 in CML-CP and CML-AP patients with T315I mutation are ongoing in China.

Table1. Treatment Related Adverse Events

	Treated Population (N=101)		
	Any Grade	Grade 3/4	Serious
	number of patients (percent)		
Non hematological AEs			
Skin pigmentation	79 (78.2%)	0	0
Hypertriglyceridaemia	55 (54.5%)	8 (7.9%)	0
AST elevation	37 (36.6%)	3 (3.0%)	0
Proteinuria	35 (34.7%)	5 (5.0%)	0
ALT elevation	34 (33.7%)	2 (2.0%)	0
Bilirubin elevation	34 (33.7%)	1 (1.0%)	0
Hypocalcaemia	34 (33.7%)	0	0
GGT elevation	24 (23.8%)	0	0
Hyponatraemia	23 (22.8%)	0	0
Hyperglycaemia	21 (20.8%)	0	0
Myalgia	21 (20.8%)	0	0
CPK elevation	20 (19.8%)	2 (2.0%)	0
Hypokalaemia	20 (19.8%)	0	0
Pyrexia	18 (17.8%)	7 (6.9%)	1 (1.0%)
Rash	15 (14.9%)	2 (2.0%)	0
Skin mass	10 (9.9%)	1 (1.0%)	0
Hematological AEs			
Thrombocytopenia	76 (75.2%)	50 (49.5%)	6 (5.9%)
Anemia	25 (24.8%)	12 (11.9%)	2 (2.0%)
Leukopenia	21 (20.8%)	20 (19.8%)	0

*Cut-off date was 27May2019



494 The Combination of Nilotinib + Pegylated IFN Alpha 2a Provides Somewhat Higher Cumulative Incidence Rates of MR4.5 at M36 Versus Nilotinib Alone in Newly Diagnosed CP CML Patients. Updated Results of the Petals Phase III National Study.

Franck E Nicolini, MD, PhD

The combination of 2GTKI+pegylated IFN-α (Peg-IFN) is an attractive approach for first-line treatment of CP CML, inducing high rates of deep molecular responses in phase II trials. Thus, we evaluated nilotinib (NIL) alone versus NIL+Peg-IFN in newly diagnosed CP-CML patients (pts) in a randomised phase III trial (PETALs, EudraCT 2013-004974-82).

Newly diagnosed CP CML pts ≤65 y, without prior history of arterial occlusion were randomized 1:1 to get NIL 300 mg BID alone (M0 to M48, arm A) vs Peg-IFN alone for 30 days (M-1→M0) 30 µg/wk as priming, prior to NIL 300 mg BID + Peg-IFN 30 µg/wk 2 wks, upgraded to 45 µg/wk thereafter, for up to 2 y (M0 to M24, arm B) followed by NIL alone for 4 more years unless pts enter treatment-free remission (TFR). The primary endpoint is the rate of MR4.5 by 1 y. As a secondary endpoint, pts reaching MR4.5 ≥2 y are allowed to stop NIL and enter a TFR phase in both arms. The trigger for treatment resumption is loss of MMR. All molecular assessments are centralised, quantifications are expressed as BCR-ABL/ABL1 (IS) in % with ≥32,000 copies of ABL1 as control.

Two hundred pts were randomized (99 in A, 101 in B), 130 M and 35 F in each arm, median age of 46 (18-66) y. Median follow-up is 43.8 (34.3–55.9) Mo. Results are analysed in intention-to-treat. Sokal and EUTOS LTS scores were H in 25% and 2.5%, Int. in 33% and 16.5% and L in 42% and 81% pts respectively equally balanced. Median age is 46 (18-66) y, 18 pts (9%) had ACAs, all pts have a “Major” BCR transcript. CHR was obtained in 9.6% of pts at M0 (in B) and 88% of pts in A

and 90.4% of pts in B at M1. CCyR rates at M3 were 63% vs 75% in A and B (p=ns), and BCR-ABL1 ≤1% at M6 were 87% in A vs 93% in B (p=ns). By M12, the rates of MMR were 68.1% vs 70.1% (p=0.44), MR4 were 34% vs 47.5% (p=0.041), MR4.5 were 15.9% vs 21.5% (p=0.049), MR5 11.7% vs 23.71% (p=0.023), in A vs B respectively. By M36 the rates of MMR were 83% vs 86.6% (p=0.31), MR4 were 70.2% vs 71.13% (p=0.50), MR4.5 were 37.2% vs 49.5% (p=0.05), MR5 33% vs 42.3% (p=0.12), in A vs B respectively The overall cumulative incidence of MR4.5 is superior in B (54.6 [43.7-65.5]%) vs A (44 [31.5-54]%) close to significance (unilateral Fisher test, p=0.05, see Figure).

Seven patients were mutated by Sanger in A (5 Y253, 1 E255K, 1 T315I) vs 2 in B (2 T315I). One pt (A) progressed toward AP and then myeloid BC with a Y253H mutation, is still alive in CMR on Ponatinib. Twenty nine (29%) pts were withdrawn from study in A (toxicity 9, cancer 3, resistance 14, investigator decision 2, lost for FU 1) vs 26 (26%) pts for B (toxicity 13, resistance 8, investigator decision 5), 1 pt died from cervix cancer (A). Median overall doses of NIL delivered by M36 were 600 mg/d in both arms (p=ns). The median overall dose of Peg-IFN delivered in B by M24 was 37.5 mg/wk. The overall rate of grade 3-4 hematologic toxicities was 22%; with 2% and 7% thrombocytopenia, 4% and 6% neutropenia, and 1% and 1% pancytopenia in A vs B respectively. Major grade 3-4 non-hematologic toxicities consisted in 9% of cardiac disorders in A (2 coronaropathies, 1 myocardial infarction, 2 thoracic pains, 2 atrial fibrillation, 1 bradycardia, 1 palpitations, 1 pericarditis) vs 8% in B (2 coronaropathies, 1 myocardial infarction, 3 atrial fibrillation, 1 palpitations, 1 pericarditis), 4% vascular disorders in A (1 thrombophlebitis + PE, 1 transient ischemic attack, 1 PAOD, 1 carotid stenosis) vs 3% in B (1 thrombophlebitis, 1 PAOD, 1 transient ischemic attack). Three % of gastro-intestinal disorders were observed in A (2 pancreatitis, 1 anal fissure) vs 6% in B (2 pancreatitis, 1 anal fissure, 1 abdominal pain, 2 cholecystectomies); 5% auto-immune disorders in B (1 recurrent pericarditis, 2 hemolytic anemia, 1 ITP, 1 thyroiditis); 5 and 8 pregnancies (2 pts + 3 partner Arm 1, 3 pts + 5 partner Arm B), despite recommended contraceptive methods. Secondary tumours were diagnosed in 4% (1 breast, 1 cervix, 1 thyroid, 1 neuroendocrine) in A vs 2% of pts (1 neuroendocrine and 1 testis) in B. Of note 8% psychiatric episodes were reported in B pts (2 unsuccessful suicide attempts), vs 2% in A. We observed 9% lipase elevations in A, 6% in B, 2% cholestatic episodes in A, 6% in B; 3% of transaminase elevations in A vs 2% in B. Infections were detected in 3% A vs 7% in B.

The combination of NIL + Peg-IFN seems to provide somewhat higher MR4.5 rates by M36 in newly diagnosed CP CML pts without inducing significant higher toxicities than NIL alone. Whether this will translate in higher TFR rates is under evaluation. Final updated results at M36 will be presented

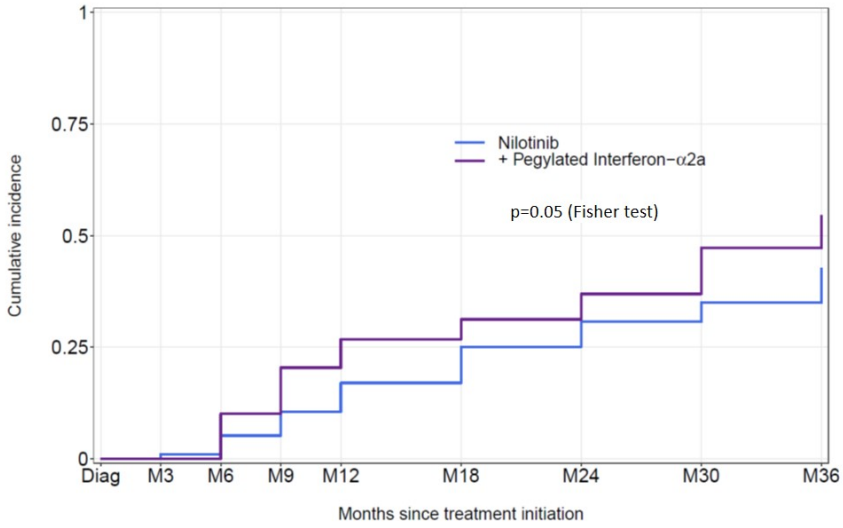


Figure: Overall Cumulative Incidence of MR4.5 over time

495 Nilotinib Vs Nilotinib Plus Pegylated Interferon α (Peg-IFN) Induction and Nilotinib or Peg-IFN Maintenance Therapy for Newly Diagnosed BCR-ABL1 Positive Chronic Myeloid Leukemia Patients in Chronic Phase (TIGER Study): The Addition of Peg-IFN Is Associated with Higher Rates of Deep Molecular Response

Andreas Hochhaus, MD

Introduction: The TIGER (CML V)-study* (NCT01657604) is a multicenter, randomized phase III trial to evaluate efficacy and tolerability of nilotinib (NIL) 2*300mg/d monotherapy vs NIL 2*300mg/d + pegylated interferon α2b (Peg-IFN) 30-50µg/week as first line therapy for chronic myeloid leukemia (CML) patients (pts) in chronic phase and discontinuation of therapy after Peg-IFN maintenance (Figure).

Methods: In August 2012, recruitment started with a pilot phase, aiming to validate the recommended dose of Peg-IFN. 25 pilot phase patients were treated with the combination of NIL 2*300 mg daily and Peg-IFN (30-50µg/week according to tolerability and commenced after ≥6 weeks NIL monotherapy). During the main phase of the study, 692 newly diagnosed pts were randomized between NIL 2*300 mg/d and NIL/Peg-IFN combination according to the outcome of the pilot phase.

Results: Within 5 years, a total of 717 pts (429 male; median age 51 years, range 18-85; 12.9% EUTOS high risk) were recruited from 109 sites in Germany, Switzerland, and the Czech Republic. 702 pts with typical BCR-ABL1 transcripts (97.9%) were eligible for molecular follow-up assessments according to the

international scale (IS). Fifteen pts (2.1%) expressed atypical BCR-ABL1 transcripts. 692 pts were randomized after EUTOS risk stratification to receive NIL monotherapy (n=353) or NIL/PEG-IFN combination therapy (n=339). Median observation time since recruitment was 41 months. Up to now, 477 pts concluded the induction phase by achieving a confirmed major molecular response, MMR (BCR-ABL1 transcript levels ≤0.1% IS, which qualified for entering the maintenance phase of the study using NIL or Peg-IFN monotherapy. During the maintenance phase, 199 pts achieved or sustained MR4 (BCR-ABL1 ≤0.01% IS) for at least one year and then discontinued all therapy.

While the rate of MMR at 12 and 18 mo – the first primary endpoint of the study - was not different between the treatment arms, adding Peg-IFN to upfront NIL significantly improved rates of MR4 and MR4.5, BCR-ABL1 ≤0.0032% IS) (Table). In competing risk analysis, median time to MMR was 5.7 vs 5.4 mo, to MR4 20.9 vs 12.5 mo, and to MR4.5 33.8 vs 23.2 mo for NIL vs NIL/Peg-IFN, respectively.

After NIL discontinuation, during Peg-IFN maintenance therapy, rate of molecular recurrence (BCR-ABL1 >1% IS) after 18 mo was 28%. From 199 pts who discontinued all therapy, 63 experienced a molecular relapse (BCR-ABL1 >0.1%). Relapse free survival by 18 mo after treatment discontinuation was 61% in the total cohort. By protocol, it is too early to assign relapse rates to the randomized treatment arm.

Frequencies of adverse events after 24 mo of therapy were 90 and 92% (grade 1-5) and 36 and 42% (grade 3-5) for NIL vs NIL/Peg-IFN, respectively. Adverse events of special interest (all grades) were fatigue in 34.6 vs 40.4%, thrombocytopenia in 13.3 vs 18.9% and elevation of the alanin aminotransferase (ALAT) in 11.0 vs 18.9% of pts in the NIL vs NIL/Peg-IFN arms, respectively. Fifteen pts (2.1%) progressed to accelerated phase or blast crisis; 22 pts (3.1%) received an allogeneic stem cell transplantation, 10 of them after disease progression. In total, 22 pts (3.1%) died, 16 during the induction phase, 4 in the maintenance phase and 2 in treatment free remission. Four deaths were related to CML, 3 to vascular complications.

Conclusions: This per protocol interim analysis demonstrates feasibility of the first-line treatment with NIL 2*300 mg/d combined with PEG-IFN 30-50 µg/week. Peg-IFN, when added upfront to NIL further increases the rates of MR4 and MR4.5, which may translate into higher rates of treatment free remission.

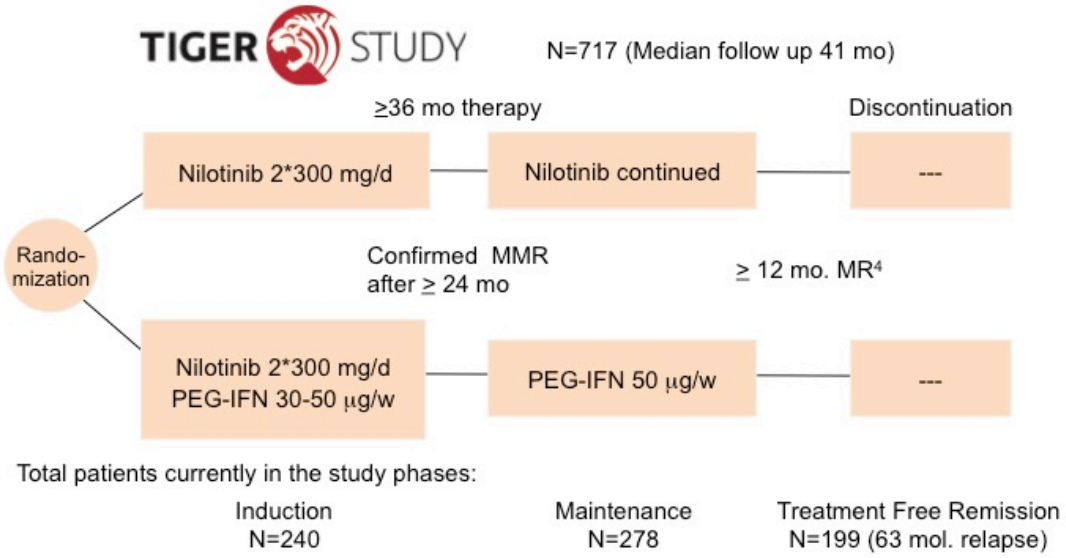


Figure: Study design

Table: Molecular response (intention-to-treat analysis, censored at stem cell transplantation)

	Nilotinib	**Nilotinib + Peg-IFN**	p
Response at 12 mo % (95% CI)			
MMR	77.0 (72.0 – 81.5)	82.6 (77.8 – 86.7)	0.085
MR^4	32.6 (27.5 – 38.0)	48.4 (42.6 – 54.1)	<0.001
$MR^{4.5}$	18.6 (14.5 – 23.3)	32.2 (27.0 – 37.8)	<0.001
Response at 18 mo % (95% CI)			
MMR	81.9 (77.0 – 86.0)	86.5 (82.0 – 90.2)	0.13
MR^4	39.6 (34.1 – 45.4)	49.0 (43.1 – 54.9)	0.022
$MR^{4.5}$	23.1 (18.5 – 28.3)	32.6 (27.3 – 38.4)	0.0097

CI confidence interval

496 Dose Optimization in Elderly CML Patients Treated with Bosutinib after Intolerance or Failure of First-Line Tyrosine Kinase Inhibitors

Fausto Castagnetti, MD, PhD

Background and Rationale. Bosutinib (BOS), dasatinib (DAS) and nilotinib (NIL) are 2nd generation TKIs with similar second-line efficacy. The use of DAS and NIL may be burdened by pulmonary, infectious, cardiovascular and metabolic complications; these complications are more frequent and more clinically relevant in the elderly. BOS could represent an important therapeutic option in elderly patients intolerant to or failing a first-line TKI, but the dose of 500 mg OAD may be higher than necessary.

Aims. All TKIs have been tested at a fixed initial dose, with dose adjustment in case of toxicity or treatment failure. On the contrary, the aim of our study was to evaluate in elderly CML patients if second-line BOS was effective and better tolerated at doses lower than 500 mg OAD, beginning with 200 mg OAD, then increasing the dose to 300 OAD or 400 mg OAD according to the molecular response, to find the minimum effective dose.

Methods. A prospective phase 2 single-arm multicenter study has been designed by the GIMEMA CML Working Party (NCT02810990). Study design: all patients started with 200 mg OAD for 2 weeks ("run-in" period), then the dose was increased to 300 mg OAD; after 3 months, patients with BCR-ABLIS transcript ≤ 1% continued 300 mg OAD, while in patients with transcript > 1% the dose is furtherly increased to 400 mg OAD. In responsive patients, BOS dose was maintained, 300 mg or 400 mg OAD. Key inclusion criteria: > 60 yrs old, chronic phase CML, intolerance or failure of any first-line TKI (2013 ELN criteria), absence of T315I or V299L mutation. Sixty-three patients have been enrolled. The primary endpoint was the proportion of patients in MR3 at 1 year. Definitions: MR3, BCR-ABLIS < 0.1%; MR4, BCR-ABLIS < 0.01% with > 10.000 copies; MR4.5, BCR-ABLIS < 0.0032% with > 32.000 copies.

Results. Median age: 73 yrs (range 60-90). Age distribution: 60-69 yrs, 18 pts (29%); 70-79 yrs, 31 pts (49%); > 80 yrs, 14 pts (22%). Sokal score at diagnosis: low 19%, intermediate 49%, high 32%. Reasons for switching to BOS: intolerance 63%, resistance 37%. First-line TKI: imatinib 83%, DAS 11%, NIL 6% (same TKI distribution in intolerant and resistant patients). Median follow-up: 9 mos (range 1-30). Overall, 10/63 patients had a dose-increase to 400 mg OAD, 49/63 to 300 mg OAD, while 4/63 continued on BOS 200 mg OAD without any dose increase. At baseline, 13 patients were already in MR3. The MR3 rates by 3 and 6 months were 43% and 56%, respectively. The cumulative rate of patients achieving or maintaining a MR3 by 12 months was 60% (65% in intolerant and 52% in resistant patients, p = 0.31). Interestingly, only 21% of patients > 80 yrs old achieved or maintained a MR3 (p < 0.001, compared to younger patients). Patients achieving MR4 or MR4.5 were 38% and 19%, respectively. Overall, 22%, 27% and 11% of patients had 1 log, 2 logs or > 3 logs reduction from baseline BCR-ABLIS

transcript level. Selected adverse events: cardiac ischemia, 2 patients; pericardial effusion, 2 patients; no pleural effusions. Events leading to permanent treatment discontinuation: 2 unrelated deaths, 7 adverse events (3 hypertransaminasemia, 1 nephrotoxicity, 1 diarrhea, 1 skin rash, 1 myalgia/fatigue), 3 unsatisfactory responses (without progressions). Fifty-one out of 63 patients are still on BOS at the last contact: 6 on 400 mg OAD, 34 on 300 mg OAD, 11 on 200 mg OAD.

Conclusions. A gradual dose increase, based on prospective molecular monitoring, allowed the great majority of enrolled patients (approximately 70%) to remain on treatment with BOS 300 mg OAD or less, achieving a major molecular response (MR3) in 60% of the cases. These results trial showed that, in elderly patients intolerant to or failing a first-line TKI, BOS may be highly effective and better tolerated at a dose lower than 500 mg OAD, namely at 300 mg OAD.

497 FLAG-IDA and Ponatinib in Patients with Blast Phase Chronic Myeloid Leukaemia: Results from the Phase I/II UK Trials Acceleration Programme Matchpoint Trial

Mhairi Copland, PhD, MBBChir, FRCP, FRCPath

Background: The outcome of patients with blast phase chronic myeloid leukaemia (CML) remains extremely poor despite the advent of tyrosine kinase inhibitors (TKIs), and the majority of blast phase patients have already failed the currently licensed TKIs during the chronic phase. Currently there is no standard therapy for patients with blast phase CML, but most will receive 2 or 3 courses of chemotherapy or a TKI, followed by stem cell transplantation (alloSCT). In the PACE clinical trial of ponatinib, 23% of patients with blast phase CML achieved major cytogenetic response, with overall survival of 20% at 12 months. To date, there has been no prospective evaluation of salvage chemotherapy in combination with ponatinib.

Methods: MATCHPOINT is a seamless Phase I/II trial to determine the optimal dose of ponatinib in combination with conventional chemotherapy (fludarabine, cytarabine, idarubicin and G-CSF; FLAG-IDA) for the treatment of CML in blast phase. An efficient Bayesian design, EffTox, which utilises both efficacy and toxicity to select desirable doses for subsequent patient cohorts, was used. Given the observed patient outcomes and the investigators' prior beliefs, the next cohort's dose is chosen adaptively to optimize the risk-benefit trade-off between efficacy and toxicity. The initial ponatinib dose was 30mg daily, commenced on day 1 of FLAG-IDA chemotherapy. Where possible, ponatinib was given continuously during the remission-induction phase, but ponatinib therapy was interrupted from day 28 of each cycle if haematologic recovery had not occurred. Patients received one or two cycles of FLAG-IDA chemotherapy plus ponatinib at the allocated dose level, and then proceeded to alloSCT followed by ponatinib maintenance. The co-primary outcome measured toxicity (dose-limiting toxicity; DLT) during the first therapy cycle and efficacy (clinical response; haematologic or cytogenetic) after the first cycle.

Results: A total of 17 patients were recruited between March 2015 and May 2018. Eight presented with de-novo blast phase CML and 9 had progressed on TKI. Eight patients had additional cytogenetic abnormalities and 3 had BCR-ABL kinase domain mutations (E255K x2 and T315I x1) at study entry. Nine and 8 patients commenced 1 or 2 cycles of FLAG-IDA + ponatinib, respectively. Of these, 16 patients were evaluable for the primary analysis. Treatment-related mortality (TRM) occurred in 3 patients during remission-induction (cardiomyopathy x1, pulmonary haemorrhage x1 and marrow aplasia x1). During cycle 1, 4/16 patients experienced a DLT (raised ALT x1, fulminant cardiomyopathy x1, cerebral sinus vein thrombosis x1, elevated amylase x1). Eleven of 16 (69%) patients achieved a clinical response, defined as either complete haematologic (3 patients) or cytogenetic response (1 minor and 9 major [2 partial and 7 complete]). Five patients achieved major molecular remission after cycle 1. All patients were recommended to be dosed at the 30mg dose, which was defined as the optimal dose for ponatinib with FLAG-IDA. Nine patients proceeded to alloSCT (7 myeloablative and 2 reduced intensity). Four patients developed acute GvHD (grades 2-4) and 3 had CMV reactivation. Four patients re-started ponatinib maintenance post alloSCT, and de-escalated to 15mg if major molecular remission was maintained. Overall 1-year survival was 45.8% (95% CI 26.9-77.7%), estimated using Kaplan Meier.

Summary/Conclusion: We report the first prospective trial of ponatinib and conventional chemotherapy for blast phase CML. The EffTox model combined Phase I and II, and delivered efficiency in determining the trial's optimal dose. This innovative statistical model has the potential to be applied in other rare malignancies. We confirm that FLAG-IDA + ponatinib 30mg, is a tolerable combination in blast phase CML, with promising response and survival. Post-transplant ponatinib was well tolerated and no excess toxicity was observed when ponatinib was used both pre- and post alloSCT. The combination of ponatinib and FLAG-IDA represents a potentially important advance in the treatment of blast phase CML, a rare complication which currently has a very poor outcome.

498 Pregnancy Management in CML Patients: To Treat or Not to Treat? Report of 224 Outcomes of the European Leukemia Net (ELN) Database

Elisabetta Abruzzese, MD

Pregnancy in CML patients (pts) is becoming a reality due to the increase in information from published cases or larger multicentric database (GIMEMA and ELN). Interferon (IFN) has been used during pregnancy, but little is known about the use of tyrosine kinase inhibitors (TKIs), which should be stopped early due to their teratogenic effects.

Female pts can ideally plan a pregnancy if they are in a deep, stable, molecular response (DMR=MR≥ 4, ≤0.01%IS) and treatment free remission (TFR)

parameters  are satisfied. Molecular remission can be maintained throughout the pregnancy, but how to proceed if the remission is rapidly lost, or if the patient is not in DMR, or when CML is discovered during pregnancy?

To address these questions, we analyzed more than 300 pregnancies registered through the ELN database. Pts completing pregnancy were grouped as follow:

1) pts diagnosed with CML while pregnant

2) pts in DMR

3) pts with ≤MR3 (≥ 0.1%IS)

In 47 patients CML was diagnosed during pregnancy, 21 during the 1st trimester, 15 in the 2nd , and 11 in the 3rd (range 3-38 wk). Sixteen patients were not treated until delivery, 15 were treated with IFN; 19 with Imatinib (IM), 12 in the 2nd trimester (>16 wk), and 7 in the 3rd. Forty-eight children were born (one set of twins). Three were preterm (35-37 wk), and one pregnancy is ongoing. No births defects were observed. Seven newborns had a low birth weight (< 2.5 Kg) 6 of them were exposed to IM at late pregnancy and 3 were preterm. Follow-up was uneventful. The majority of pts achieved ≥ MR3 after starting TKI. Two pts died: 1 in blast crisis (BC) after 9 years, but she was not adherent to treatment; 1 of transplant complication (resistant to>2TKI).

Seventy five pts had 80 pregnancies in DMR. Six were in TFR (no therapy) for more than 12 mo, while 8 stopped TKI in order to conceive (2-8 mo before conception). Twenty two pts were treated during pregnancy: 12 with TKI (8 IM, 4 nilotinib, NIL) 1 in the 1st trimester (never stopped IM), 7 in the 2nd and 4 in the 3rd; 10 pts received IFN. Eighty one children were born (6 patients had 2 pregnancies, 1 had twins) with one baby born preterm (wk 35). No births defects were observed and two pregnancies are ongoing. Fifty eight pregnancies were carried without any CML treatment. Twenty six maintained DMR, 28 ≤ MR3 and considered in "treatment free pregnancy" (TFP), and 5 had >10% transcript levels at delivery, considered as high tumor burden (HTB). None of the patients progressed after pregnancy, 4 patients maintained TFR. Four patients did not return to MR3 <12 months after restarting TKI; 3 were switched to a more potent TKI rapidly achieving ≥ MR3, while 1 pt, who did not, is in hematologic remission after 3 years.

Pts belonging to ≤MR3 do not satisfy TFR criteria, and were discouraged from starting a pregnancy. However 95 pregnancies (90 pts) were reported; 29 had stopped TKI prior to conception (5 of them had HTB at pregnancy onset). Fifty eight (61%) were treated with IFN (20), TKIs (35), or HU (3). Thirteen patients were treated with IM during 1st trimester (10 throughout the pregnancy). Among the untreated pts, 6 were surprisingly in DMR at delivery, 20 were in TFP, and 11 had HTB. Two babies were born with polydactyly and hypospadias (IFN treatment since 1st trimester), and 2 exhibited a non-closed foramen ovale (IM during 2-3rd trimester) which was considered unlikely to be related to treatment. Four pts progressed in BC and died after pregnancy but all were not compliant to therapy.

This is the first, large, multicenter report focusing on treatment during pregnancy. Results suggest that CML patients can pursue a normal life including planning a family, with several caveats. Based on the different situations examined, treatment with IFN is confirmed safe. In contrast TKIs should not be used during pregnancy. Selected TKIs, specifically IM and NIL which have little placental transfer, can be started after organogenesis. Pts at onset can delay therapy without jeopardizing the future CML outcome. If therapy during pregnancy is deemed necessary, IFN can induce and maintain hematologic remission, or, if introduced earlier, preserve molecular remission after TKI interruption, while TKIs can reduce HTB. Caution should be taken when considering stopping TKI prior to conception due to the possibility of losing response, while an early stop (at first positive pregnancy test, 4-5 wk) could be considered. Detailed results, mother and child follow up and practical management will be presented.

Fig.1 Trend of pregnancies in CML patients

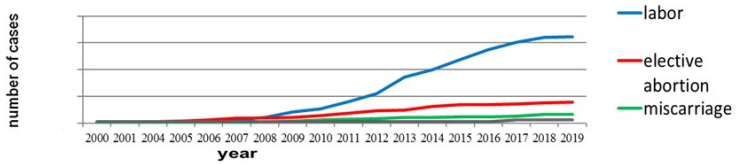


Table 1- Patients characteristics

	number of cases pts, n,/ babies born,n	TKI stopped,n			Therapy type*	Therapy start (per trimester) N=nilotinib			MR @delivery				Progression in BP,n
		Yes	TFR (>12mo)	@ FPT	*(some patients received >1 treatment)	1st	2nd	3rd	DMR	≤MR3		HTB (>10%IS)	
										MR3	TFP		
Pts diagnosed with CML while pregnant	47/48	NA	NA	NA	IFN	9	5	1	NA	NA			1
					TKI		12	7	NA	NA			
					Other (HU)	0	2	2	NA	NA			
pts in DMR (≤0.01% IS)	75/81	8	6	66	IFN	1	6	3	26	9	19	5	0
					TKI	1	7(2N)	1					
					Other (HU)	0	1	0					
pts with ≤MR3 (≥0.1%IS)	90/95	29	2	64	IFN	1	19	0	6	8	12	11	4
					TKI	13 (3+10)[1]	21(6N)	1					
					Other (HU)	0	1	2					

Legend:

prg=pregnancy. **TKI stopped, n**= number of pts who stopped TKI and timing (**Yes**=stopped 2-8 mo before pregnancy in order to conceive "treatment free"; **TFR**= patients in treatment free remission for >12 months before conception; **@FPT**= treatment was stopped at first positive pregnancy test, generally between 3-5 wk gestation). **IFN**=interferon A. **TKI**= tyrosine chinase inhibitor (imatinib or nilotinib only). **HU**= hydroxyurea. **TFP**=Treatment Free Pregnancy=patients who could complete the pregnancy not in MR3, but treatment free.