CLINICAL ORAL POSTER PRESENTATIONS
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S170. Oral Presentation**. ASCIMINIB IN HEAVILY PRETREATED PATIENTS (PTS) WITH PHILADELPHIA CHROMOSOME–POSITIVE (PH+) CHRONIC MYELOID LEUKEMIA IN CHRONIC PHASE (CML-CP) SENSITIVE TO TYROSINE KINASE INHIBITOR (TKI) THERAPY**

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EHA Library. Hughes T. 06/13/20; 294990; S170

Background
Asciminib is a novel, specific inhibitor of BCR-ABL1 that targets the myristoyl binding pocket. Its unique mechanism of action is expected to result in improved safety/tolerability compared with available ATP-binding TKIs. In an ongoing Phase I study (NCT02081378), asciminib is being investigated in heavily pretreated pts with Ph+ CML who are relapsed/refractory to or intolerant of TKI therapies. There is increasing interest in improving molecular responses in pts with some, but not deep, response to TKIs.

Aims
Evaluate the safety and efficacy of asciminib monotherapy in pts with baseline *BCR-ABL1*IS ≤ 1%, a population considered to be mainly intolerant of the most recent TKI.

Methods
The study enrolled adults with Ph+ CML in CP or accelerated phase who were relapsed/refractory to or intolerant of ≥ 2 TKIs; informed consent was obtained. Pts were assigned to dose-escalation or -expansion cohorts investigating asciminib monotherapy or combination therapies. For the current analysis, pts enrolled in the monotherapy cohorts (any dose) who had *BCR-ABL1*IS ≤ 1%, regardless of the reason for TKI discontinuation, and did not have a centrally confirmed T315I mutation at baseline were included. The cutoff date was 30 Aug 2019.

Results
In total, 48 pts in 9 dose cohorts (20, 40, 80, 150, 160, and 200 mg twice daily; 80, 120, and 200 mg once daily) were included; all 48 pts had CML-CP, with a median age of 51 y (range, 30-81). One (2.1%, unconfirmed T315I mutation at baseline), 19 (39.6%), and 28 (58.3%) pts received 1, 2, and > 2 TKIs, respectively; 24 pts (50.0%) discontinued TKIs due to both resistance and intolerance, 13 (27.1%) due to intolerance only, and 11 (22.9%) did not report

any prior intolerance. By the cutoff date, 6 pts (12.5%) discontinued treatment due to adverse events (AEs; n = 3: 1 due to chronic kidney disease, 2 due to pancreatic enzyme elevations), progressive disease (n = 2: 1 blast crisis [with unconfirmed T315I mutation at baseline], 1 per investigator decision–increasing *BCR-ABL1* levels), or pt decision (n = 1). Median duration of study treatment exposure was 161 wk (range, 2-271), with 42 pts (87.5%) still on treatment and 36 (75.0%) in major molecular response (MMR) or better at the data cutoff. The most common grade 3/4 AEs (> 10%), regardless of study drug relationship, were lipase increase (27.1%) and hypertension (12.5%). Serious AEs, regardless of study drug relationship, were reported in 16/48 pts (33.3%), with myocardial infarction being the most common (n = 2; 4.2%). Among pts without MMR, MR4, or MR4.5 at baseline, cumulative response rates continued to increase over time, even beyond 48 wk, with 18/24 (75.0%), 16/38 (42.1%), and 18/42 (42.9%) pts achieving MMR, MR4, and MR4.5, respectively (Table 1). Median time to MMR among responders was 30 d. All 18 pts who achieved MMR maintained this level of response or better for ≥ 2 y, apart from 3 whose *BCR-ABL1*IS fluctuated around 0.1% but who were still in MMR at ≈ 60 mo. Among the 6 pts who did not achieve MMR by the cutoff date, 1 pt had *BCR-ABL1*IS > 1%, and 5 remained between *BCR-ABL1*IS 0.1% and 1%. Among pts who achieved MR4 or MR4.5, 9/16 (56.3%) and 10/18 (55.6%), respectively, maintained the response for ≥ 2 y.

Table 1: Cumulative Molecular Response Rates

Pts With Response, n (%)[a]	By Week 8	By Week 24	By Week 48	Overall[b]
MMR (N = 24)	10 (42)	11 (46)	12 (50)	18 (75)
MR^4 (N = 38)	6 (16)	10 (26)	12 (32)	16 (42)
$MR^{4.5}$ (N = 42)	4 (10)	9 (21)	12 (29)	18 (43)

[a] n is calculated based on number of pts (N) evaluable for response and without that response level at baseline. One pt had an F319L mutation detected at baseline.

[b] As of the cutoff date of 30 Aug 2019.

Conclusion

Asciminib monotherapy was well tolerated and showed promising clinical activity in pts with baseline *BCR-ABL1*IS ≤ 1%, with 75.0% remaining on therapy and in MMR at the data cutoff. These results support further investigation of asciminib in pts who did not reach an optimal treatment outcome and discontinued TKIs.

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S171 Oral Presentation. MAJOR MOLECULAR RESPONSE IS THE THRESHOLD FOR NGS ANALYSIS AND RESISTANT BCR-ABL1 MUTATION DETECTION IN CML

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EHA Library. Machova Polakova K. 06/13/20; 294991; S171

Background

In chronic myeloid leukemia (CML), the advantages of sensitive BCR-ABL1 kinase domain (KD) mutation detection promote the use of next generation sequencing (NGS). Early recognition of an emerging resistance to tyrosine kinase inhibitor (TKI) therapy associated with BCR-ABL1 KD mutations is important for successful patient (pt) management. Previous studies suggested that fluctuating levels of BCR-ABL1 transcript levels around 0.1 %IS (unstable major molecular response – MMR) during TKI therapy may be an early indicator for mutation testing.

Aims

The aim of this EUTOS study was to take advantage of NGS to investigate the role of BCR-ABL1 KD mutations in CML pts with unstable MMR on TKI therapy.

Methods

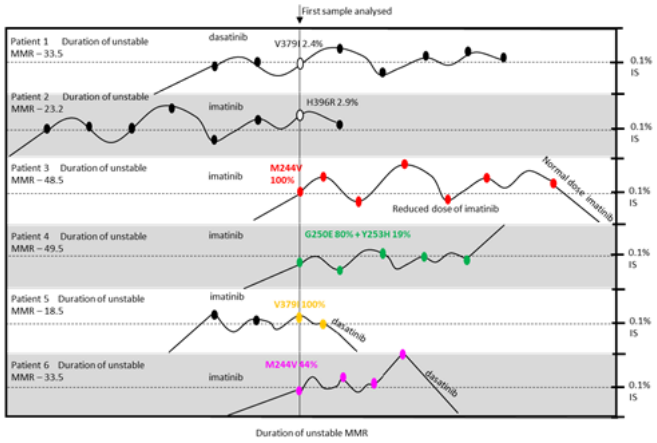
A total of 90 pts with unstable MMR on TKI therapy were divided into 2 groups. Group A (14/90) included pts on TKI therapy (1st line, n=13; 5th line, n=1) who had initially achieved deep molecular response (DMR), but BCR-ABL1 transcripts had subsequently increased to the levels of unstable MMR. Group B (76/90) consisted of pts who had achieved no better response to TKIs (1st line, n=53; 2nd or subsequent line, n=23) than unstable MMR. NGS of the BCR-ABL1 KD was performed in duplicate on an Illumina MiSeq. The NextGene software (Softgenetics) and the in-house bioinformatic tool NextDom were applied for data processing, error filtering and mutation calling at significant levels (median 1.5 % of a particular mutation in total BCR-ABL1 transcripts, range 1.0-3.7 %; p-value ≤0.05).

Results

In Group A, NGS has so far been performed in 11/14 pts and mutations have been detected in 6/11 (54%). Mutations were confirmed by NGS analysis in subsequent follow-up samples in 4/11 pts (36%). Pts with M244V and V379I mutations were switched to dasatinib and achieved DMR (Figure 1). Another pt with M244V mutation maintained unstable MMR for 18 months as long as imatinib dose was reduced due to intolerance, but obtained DMR after the full dose was restored. Pt with G250E and Y253H remained in MMR for 10 months, followed by a 1-log BCR-ABL1 increase. Two pts with low-level mutations remain in unstable MMR. The low-level mutations were detected in one of the

duplicates only and were not confirmed in subsequent analyses. In Group B, 65/76 pts were sequenced so far and variants were detected in 9/65 (14%). The pt with confirmed T315I during unstable MMR subsequently relapsed to blast crisis in one month. Imatinib-resistant mutations were detected in 4 pts, who were swichted to a 2nd generation TKI and achieved stable MMR or better with a median follow-up of 12 months (range, 6-18). Finally, 4 pts with low-level variants detected in one of the duplicates remain in unstable MMR with a median follow-up of 68.5 months (range, 33-144).

Figure 1 Scheme illustrates mutation detection in patients at the time of unstable MMR. For the imagination the group A of patients is presented.



Legend: Unstable MMR is depicted by the wavy black line of BCR-ABL1 transcript corresponding to 0.1% IS ± 0.16 (the uncertainty of measurement); the ≥1log increase or decrease of BCR-ABL1 is depicted by the black line; dashed line illustrates the 0.1% IS level of BCR-ABL1; black dots represent the BCR-ABL1 measurement of unstable MMR; coloured dots depict a mutation detected by NGS; empty dots depict variants that have been detected in one parallel only.

Conclusions. Our data suggest that loss of DMR followed by BCR-ABL1 increase to the level of MMR is an early indicator for NGS mutation testing. In contrast, the probability of mutation detection in pts who do not achieve better response than unstable MMR seems to be low. MMR is the level of measurable residual disease above which NGS of BCR-ABL1 can successfully be performed. However, mutation testing in MMR samples should be done in duplicate and results should be evaluated carefully. It is unclear whether low-level variants detected only in one of the duplicates of the investigated sample can be artefacts that occur during processing of low-copy BCR-ABL1 samples. Hence, follow-up testing in subsequent samples should be performed to monitor mutation kinetics.

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S172 Oral Presentation. INTERIM ANALYSIS FROM THE OPTIC TRIAL, A DOSE-RANGING STUDY OF 3 STARTING DOSES OF PONATINIB

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EHA Library. Cortes J. 06/13/20; 294992; S172

Background

In PACE (NCT01207440), heavily pretreated patients with chronic-phase chronic myeloid leukemia (CP-CML) demonstrated deep, lasting responses to ponatinib; long-term follow-up showed increasing rates of arterial occlusive events (AOEs).

Aims

We present the first interim analysis results from OPTIC (NCT02467270), evaluating the association between ponatinib exposure, efficacy, and safety, and response-based dose-reduction in patients with CP-CML.

Methods

This ongoing, multicenter, randomized phase 2 trial enrolled patients with CP-CML resistant or intolerant to ≥2 tyrosine kinase inhibitors (TKIs) or with a T315I mutation to receive ponatinib at a starting dose of 45 mg (cohort A), 30 mg (B), and 15 mg (C) qd. Doses were reduced to 15 mg qd on achievement of ≤1% BCR-ABL1IS at any time in cohorts A and B. Primary endpoint: ≤1% BCR-ABL1IS at 12 months; secondary endpoints include cytogenetic response, molecular responses and rates of AOEs, venous thromboembolic events, and adverse events. The results are descriptive at this interim analysis and will be inferential by adjusting multiplicity across 3 cohorts at the final analysis.

Results

Enrollment was completed with 283 patients randomized (A/B/C: n=94/95/94); median age 48 y (18–81 y). 26% had hypertension history; 2/43/55% received 1/2/≥3 TKIs; 40% had ≥1 baseline mutations, with 23% T315I. One patient in cohort B never started treatment and was not included in the safety population. At the interim analysis data cutoff (20 Jul 2019), 162 patients (57%) (n=57/51/54) remained on study treatment. Among 282 patients in the safety population, median duration of exposure was ≈1 year (A/B/C, 12.9/11.2/11.0 months). At 12 months, 39% (95% CI, 27.6, 50.6), 27% (17.6, 39.1), and 26% (16.5, 38.6) for A, B, and C, respectively, achieved ≤1% BCR-ABL1IS. Additional efficacy results are presented in the Table. Dose reductions due to efficacy (A/B): 35/21%. Most common treatment-emergent adverse events in all patients (any grade/≥3): thrombocytopenia 39/27%, neutropenia 25/17%. Most common any-grade adverse events (≥25%) by cohort: A, thrombocytopenia

(44%), neutropenia (29%); B, thrombocytopenia (38%), hypertension (31%); C, thrombocytopenia (36%). AOEs/serious AOEs were reported by (A, B, C) 5%/2%, 4%/3%, and 1%/0%. Dose reductions due to treatment-emergent adverse events (A/B/C): 44/31/28%; discontinuations due to treatment-emergent adverse events: 18/15/14%. There were 4 (1.4%) on-study deaths; 2 cases of sudden death in A and 2 cases of pneumonia in C; no deaths were due to AOEs.

Month 12 BCR-ABL1^{IS} Ratio,[a] n (%)	45 mg n=75	30 mg n=73	15 mg n=68
≤10%	38 (50.7)	31 (42.5)	30 (44.1)
≤1%	29 (38.7)	20 (27.4)	18 (26.5)
≤0.1% (MMR)	11 (14.7)	13 (17.8)	13 (19.1)

MMR, major molecular response.
[a]Population includes all patients who are randomized and for whom BCR-ABL1^{IS} can be measured at baseline. Those who are still on treatment but have not achieved 12 months were excluded. Those with ≤1% BCR-ABL1^{IS} or better result at baseline were considered as failure.

Conclusion

Results from this OPTIC interim analysis show a trend toward dose-dependent efficacy and safety, and may provide a refined understanding of the ponatinib benefit:risk profile and its relation to dose. Mature data from continued follow-up may support an alternate dosing regimen for patients with CP-CML.

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S173 Oral Presentation. DASATINIB PLUS PEG-INTERFERON ALPHA 2B COMBINATION IN NEWLY DIAGNOSED CHRONIC MYELOID LEUKEMIA: 48-MONTHS RESULTS OF A PHASE 2 STUDY ON BEHALF OF THE FRENCH GROUP OF CML (FI-LMC)

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EHA Library. ROY L. 06/13/20; 294993; S173

Background

Sustained deep molecular response (DMR) achievement is a prerequisite for future TKIs cessation attempts, a new goal for CP-CML pts. Combination of Pegylated-Interferon alpha (Peg-IFN) with TKIs has been reported to induce high rates of DMR, despite some substantial toxic effect.

Aims

This phase II trial investigates the combination of Dasatinib (DAS) a 2G-TKI and Peg-IFNa2b in pts with newly diagnosed CP-CML (Eudract Number 2012-003389-42).

Methods

Newly diagnosed Ph+ CP-CML pts, aged from18 to 65 were recruited in 25 centers. They started DAS 100 mg/d first, andPeg-IFNa2b was associated to DAS at M3 (when counts of plts>100x10^9/L, ANC>1.5x10^9/L, lymphocytes<4.0x10^9/L), until M24. DAS was continued (ELN criteria), for the 5-y duration of the study. The primary endpoint was the rate of $MR^{4.5}$ by 12 months. Other endpoints included responses rates and safety. Molecular analyses were centralized until M24 and expressed according to the international scale (IS).

Results

81 pts were enrolled between October 2013 and July 2014. 79 pts were analyzed in intention-to-treat (1 death related to CML and 1 screening failure, before any study treatment uptake). Median age was 48y (20-65). Sokal and ELTS scores were intermediate in 39% and 29% and high in 17% and 5%,

respectively. Single additional cytogenetic abnormalities were found in 11% of pts. At M3, 18 pts (23%) were not eligible to Peg-IFN (neutropenia 56%, thrombocytopenia 28%, as in the protocol): among them, 7 pts (39%) discontinued DAS before M24, mainly due to an unsatisfactory response. 61 pts (77%) started Peg-IFNa2b at 30 µg/week. 48 (79%) and 37 (61%) pts have continued the Peg-IFN at M12 and M24, respectively.

During the combination, 67 hematological AEs occurred in 44 pts. Neutropenia was the main issue (61%, half grade 3 and 3% grade 4). Neither severe anemia nor thrombocytopenia was observed. 59 pts experienced at least an extra-hematological AE (n=370), but few grades 3 (4%) and no grade 4. Despite neutropenias, infections (14% of AEs) were not severe. General, musculo-skeletal, nervous system, and psychiatric AEs expected with Peg-IFN, were usually low grade and manageable. Grade 2 immune disorders were reported in 8 pts (13%): 6 thyroiditis, 1 cutaneous lupus-like syndrome, and 1 Raynaud syndrome. Gastro-intestinal AEs included grade 3 diarrhea or vomiting in 3 pts, anal fistula, and fissure in 2 pts. 4 grade 2 pleural effusions were reported. A grade 2-dyspnea was recorded in 7 pts without evidence of pulmonary, cardiac disorder, and pulmonary hypertension. 3 pts developed a benign lymph node hyperplasia after M18, which resolved after study treatment discontinuation. One patient with DAS (Peg-IFN stopped 11 months earlier) was diagnosed at M27 with a bilateral optic neuropathy.

Cumulative incidence of $MR^{4.5}$ by 12 months were 28 % (IC95%: 19–39) for the entire cohort and 33% (IC95%: 23–46) for the Peg-IFN eligible pts. Also, for the entire cohort (n=79), MR^3, MR^4 or $MR^{4.5}$ rates were 65%, 35% and 25% at M12, 77%, 58%, and 38% at M24, and 88%, 63% and 36,5% at M36. For DAS+Peg-IFN pts (n=61), rates were higher at M12, M24 and M36: 73%, 85%, 95% in MR^3, 39%, 65%, 69% in MR^4 and 31%, 44%, 41% in $MR^{4.5}$. At last follow-up, rates of pts who have achieved a sustained DMR>= 2y were 32% in $DMR^{4.5}$ and 42% in DMR^4 (36% and 47% for DAS+Peg-IFN pts).

Conclusion

In conclusion, the study exhibits a manageable toxicity with the combination of DAS+Peg-IFN as starting therapy for CML. A high rate of early and sustained DMR was achieved, leading these patients as potential candidates for further TKI discontinuation attempt.

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S174 Oral Presentation. HIGH LEVEL OF SUCCESSFUL TKI DISCONTINUATION OUTSIDE CLINICAL TRIALS - A POPULATION-BASED STUDY FROM THE SWEDISH CML REGISTRY

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EHA Library. Flygt H. 06/13/20; 294994; S174

Background

Tyrosine Kinase Inhibitor (TKI) discontinuation in chronic phase CML is being implemented in clinical routine, but little is known about patients stopping TKI outside of clinical trials. Studies have shown that 40-50% of patients with a deep molecular response (DMR, defined as MR4.0 or lower on the International Scale) could successfully discontinue TKI. Most relapses occur within 12 months, and re-initiation of TKI treatment has been shown effective with most patients regaining DMR. In the updated (2019) Swedish Guidelines for CML, stopping TKI can now be considered in patients treated with a TKI ≥5 years and in MR4.0 or better for two years. In Sweden, >95% of patients diagnosed with CML are reported to the national CML registry, making it a unique source of population-based data (Hoglund et al., Blood, 2013). The Swedish Prescribed Drug Register is held by the Swedish National Board of Health and Welfare, and contains data on all prescribed drugs dispensed in Sweden since 2005.

Aims

To retrospectively identify and characterize CML patients diagnosed 2007-2015 and stopping treatment with TKI ≥1 month. Further aims were describing the proportion of CML patients stopping treatment due to DMR, the incidence of discontinuation attempts outside of clinical trials, and the proportion of patients still treatment-free at time of evaluation.

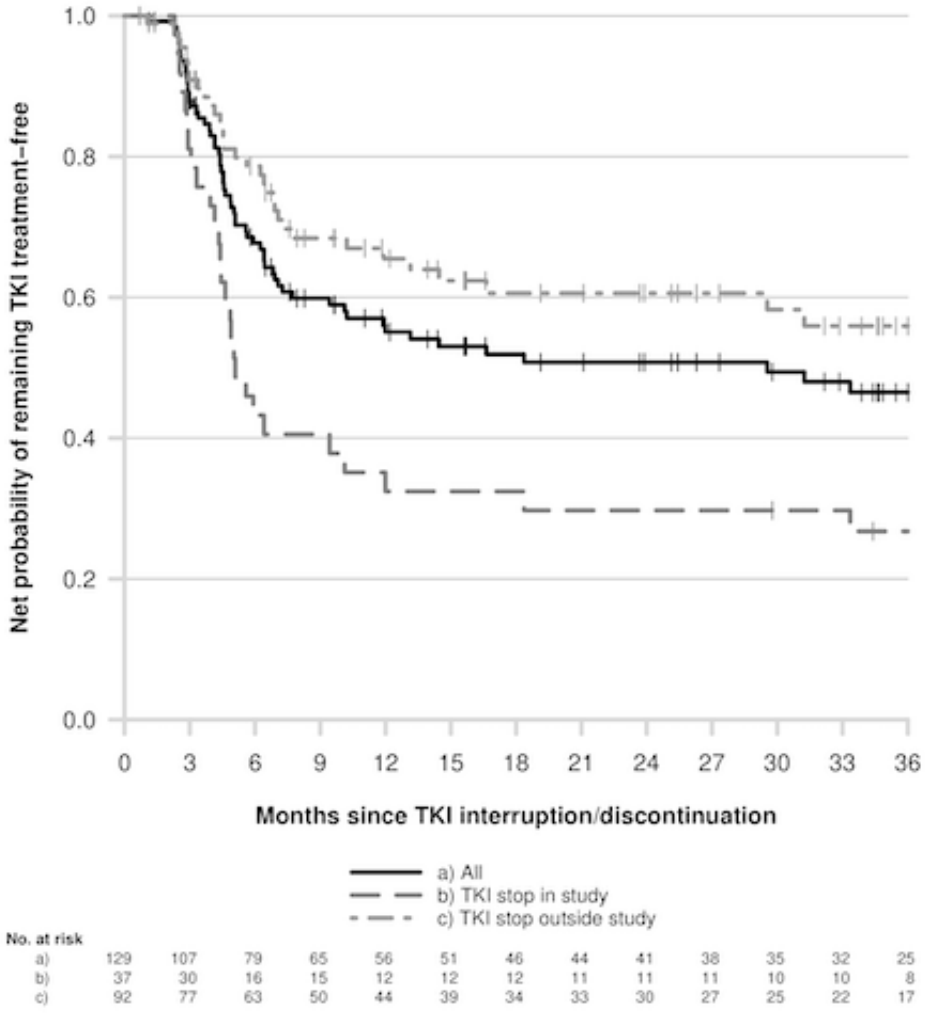
Methods

Patients diagnosed with CML between 2007-2015 were identified using the Swedish CML registry, and a TKI stop-form was sent to reporting clinicians. Only patients with a TKI-interruption ≥1 month were reported. Information collected included stop date, reason for stop, stop in a clinical trial, TKI re-initiation and reason and date for re-initiation. Information on last TKI prior to stop was collected from the Swedish Prescribed Drug Register. To allow for an adequate follow-up time, patients diagnosed between 2007-2012 were selected for further analysis, focusing on those discontinuing due to DMR.

Results

Between 2007-2012, 584 pts were diagnosed with CML. Information on TKI interruption was available in 548, of which 234 had a reported TKI interruption ≥ 1 month. Reasons for interruption were DMR in 131 (56%), adverse events in 43 (18%), allo-SCT in 31 (13%) and other in 29 (12%). Of the 131 pts

discontinuing due to DMR (22% of all pts from this period), 29% (N=38) stopped in a clinical study (EURO-SKI and ENEST-Freedom) while 70% (N=92) stopped outside a study. Median time from diagnosis to TKI stop in a study was 4.2 years (IQR: 3.6-5.2), and 6.0 years (IQR: 4.0-7.5) outside study. Last TKI was imatinib in 63.2% and 48.9%, nilotinib in 23.7% and 29.3% and dasatinib in 13.2% and 21.7% for pts in study and outside study respectively. At time of evaluation, 64 pts (48.9%) had re-initiated TKI treatment at a median 0.4 years (IQR 0.3-0.6) after stopping TKI. Date of last follow-up was between Mar 2018 and Nov 2019, with a median follow-up time from stop of 2.9 yrs (IQR: 1.2-5.1). Net probability of remaining TKI treatment-free is shown in the figure.



Conclusion

With a median follow-up of 9 years from diagnosis, TKI treatment was stopped in DMR in 24% of 548 evaluable CML patients, in a population-based setting. The majority stopped TKI outside clinical trials despite lack of recommendations in national guidelines at the time. Of those stopping TKI outside a study, the probability of remaining TKI treatment-free at 22 months was 61%. The reasons for higher TFR rate outside studies may be longer duration of therapy before stop and/or more frequent use of 2nd generation TKIs in this group.