Title
Contemporary insights into the pathogenesis and treatment of chronic myeloproliferative neoplasms.

Permalink
https://escholarship.org/uc/item/7283q01n

Journal
Leukemia & lymphoma, 57(7)

ISSN
1042-8194

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Publication Date
2016-07-01

DOI
10.1080/10428194.2016.1185783

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Peer reviewed
Contemporary insights into the pathogenesis and treatment of chronic myeloproliferative neoplasms

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Abstract

This review is based on the deliberations at the 5th John Goldman Colloquium held in Estoril on 2nd October 2015 and the 9th post-ASH International Workshop on chronic myeloid leukemia (CML) and BCR-ABL\textsuperscript{-}negative myeloproliferative neoplasms (MPN) which took place on the 10th-11th December 2014, immediately following the 56th American Society of Hematology Annual Meeting. It has been updated since and summarizes the most recent advances in the biology and therapy of these diseases, in particular updates of genetics of MPN, novel insights from mouse MPN models, targeting CML stem cells and its niche; clinical advances include updates on JAK2 inhibitors and other therapeutic approaches to BCR-ABL\textsuperscript{-}negative MPNs, the use of alpha interferons, updates on tyrosine kinase inhibitors (TKI) randomized trials in CML, TKI cessation studies, and optimal monitoring strategies.

Keywords

Molecular genetics; myeloid leukemias and dysplasias; stem and primitive progenitor cells

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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at http://dx.doi.org/10.1080/10428194.2016.1185783.
Introduction

The myeloproliferative neoplasms (MPN) are clonal hematopoietic diseases characterized by recurrent genomic alterations, the details of which are still unfolding. CML is characterized by a consistent cytogenetic abnormality, the Philadelphia (Ph) chromosome and the exclusive presence of the BCR-ABL1 fusion gene; in contrast, the BCR-ABL1-negative MPNs are characterized by mutually exclusive Janus kinase 2 (JAK2), calreticulin (CALR), and myeloproliferative leukemia virus oncogene (MPL) mutations. These mutations are often accompanied by other mutations which, though less specific, may have prognostic significance (Figure 1).[1–5] Moreover, the precise contribution of inherited factors remains poorly understood.[6] Clonal evolution and transformation to leukemia have revealed multiple acquired gene mutations, such as TP53, during progression.[7] Indeed, the genomic complexity of these and related disorders, such as systemic mastocytosis (SM), and the possible prognostic and predictive implications for therapy, are only beginning to be examined in considerable detail. Novel therapies for several subtypes of MPNs, including type I and II JAK2 inhibitors, anti-fibrotic agents for myelofibrosis (MF), midostaurin for SM, and numerous combination therapies are now in clinical trials. In CML, topical issues include optimal TKI choice for first-line therapy, the role of molecular response in altering TKI therapy, and the role of TKI cessation.[8] New therapeutic modalities are being pursued for patients with resistant mutations, while strategies to produce a more profound and rapid disease response are under investigation. Here, we summarize some of these important developments in MPN biology and treatment, as discussed and presented at the 5th John Goldman CML Colloquium in Estoril, Portugal and the 9th Annual Post-ASH workshop, immediately following the 56th American Society of Hematology meeting in San Francisco, USA.

Updates on genetics and biology from mouse MPN models

The development of genetically faithful murine models of MPNs has been an important component of investigating disease biology and facilitating a platform for testing new therapeutic strategies. Previous studies have characterized JAK2^{V617F} and MPL^{W515K/I} mutation in murine models.[9–11] The recent identification of a third driver mutation, the CALR mutation, in essential thrombocythemia (ET) and MF have promoted the evaluation of this mutation in a murine model.[12] A retroviral transduction model demonstrated that expression of either mutation variants in CALR, type 1, a 52-bp deletion (p.L367fs*46 or del52) or type 2, a 5-bp TTGTC insertion (p.K385fs*47 or ins5), in mouse bone marrow leads to a MPN mimicking ET.[5] The MPN induced by CALRdel52 was more pronounced and progressed to MF after six months, with disease transplantable to secondary recipients. Figure 2 depicts some current conceptual thoughts on the progression of MPNs.

Studies assessing the role of mutations in epigenetic regulator genes in MPN disease initiation and progression show EZH2 loss-of-function that promotes megakaryopoiesis and contributes synergistically to JAK2^{V617F}-initiated MPN and accelerated primary MF.[13] Skoda and colleagues also found that TET2 loss-of-function enhanced MPN phenotype, but led to early exhaustion when transplanted at limiting dilution. Mullally and colleagues confirmed the synergism between TET2 and JAK2 in initiating MPN, using a JAK2
conditional knock-in mice model crossed to TET2 mutant (null) mice.[14] Other investigators reported that in the context of JAK2<sup>V617F</sup> expression, loss of EZH2 inhibits erythropoiesis and accelerates the development of MF in JAK2<sup>V617F</sup> knock-in mice, with extensive bone marrow fibrosis in the bone marrow and spleen at 24 weeks.[15] The mechanisms by which mutations in splicesome protein SRSF2 contribute to diverse myeloid malignancies through mutant-specific effects on exon recognition have also been established by work conducted by Abdel-Wahab et al.[16] Briefly, SRSF2 contributes to both constitutive and alternative splicing by binding to exonic splicing enhancer (ESE) sequences within pre-mRNA. In its wildtype form, SRSF2 recognizes both C- and G-rich ESE motif sequences with equal avidity.[17] In contrast, forms of SRSF2 bearing mutations at the Proline 95 residue (as seen in patients with myeloid leukemia) have a skewed RNA binding and splicing preference such that mutant protein preferentially binds to and promotes splicing of C-rich ESEs.[18] This altered RNA binding/splicing preference results in a number of downstream effects on RNA splicing including promotion of an exon inclusion event in EZH2 mRNA which promotes downregulation of EZH2 protein expression. Collectively these observations suggest how nonspecific mutations interact with the currently known MPN driver mutations and converge to affect the hematopoietic phenotype and the prognosis in some cases.

Chen et al. analyzed the gene expression profiles (GEP) of JAK2<sup>V617F</sup>-positive MPNs and observed an increased expression of the RECQL5 helicase, which plays a role in DNA replication fork stability, in JAK2-mutant erythroblasts from MPN patients.[19] Similar findings were observed in JAK2<sup>V617F</sup> knock-in mice. Notably, shRNA-mediated downregulation of RECQL5 rendered cells from JAK2<sup>V617F</sup> knock-in mice more susceptible to apoptosis induced by hydroxyurea. Increased double-strand breaks were noted, as were increased stalled replication forks.[20] This effect was rescued by re-introduction of a shRNA-resistant RECQL5 construct. These data suggest that upregulation of RECQL5 in JAK2<sup>V617F</sup>-expressing cells may serve to protect these cells from DNA damage-induced cell death, which may potentially be exploited for therapeutic gain as a potential down-stream target.

In CML, Koschmieder, Schemionek, and colleagues provided updates on the inducible transgenic murine stem cell leukemia (SCL) transactivator protein (tTA) model, first developed in 2005, which has been instrumental in defining CML stem cell characteristics and providing insights in the biology and progression of the disease.[21,22] By studying primitive Lin<sup>−</sup>/Sca-1<sup>−</sup>/c-Kit<sup>+</sup> (LSK) cell GEP in this model, it was established that MTSS1, a scaffolding protein, is down-regulated in CML stem cells by a mechanism which involves both kinase-dependent and -independent effects. Mice deficient in MTSS1 develop aggressive long-latency lymphomas. Overexpression of MTSS1 in murine CML stem cells inhibits cell migration in vitro as well as myeloid cell growth and leukemia in vivo. Interestingly, the candidacy of MTSS1 as a potent tumor suppressor has also been demonstrated in normal karyotype AML patients.[23] More recently, a novel murine model capable of simulating progression of human CML, in particular transformation to myeloid blast crisis, has been engineered.[24] This should enable a better understanding of the molecular pathogenesis of blast crisis and inform on candidate therapeutic targets.
Novel approaches to treatment of Ph-negative MPNs

Despite several promising novel non-transplant therapies, the notion of achieving long-term remission, and potential cure, has remained elusive for most, if not all, patients with Ph-negative MPNs. Current treatment options include interferon-alpha (IFN-α), JAK inhibitors, which can target the active (type I) or inactive (type II) conformation of JAK2, immunomodulatory drugs, telomerase inhibitors, HSP90 inhibitors, anti-fibrotic agents, pan-histone deacetylase inhibitors such as panobinostat, PI3-kinase inhibitors, hedgehog pathway SMO inhibitors, used either alone or in combination with type I JAK2 kinase inhibitors.[25–37] Ruxolitinib, a type I JAK 1/2 inhibitor, accords a qualified benefit to some patients with MF and PV, alleviating symptom burden and improving survival modestly, but having a limited effect on JAK2 mutant allele; in contrast, molecular responses, albeit not complete, have been observed in CALR-mutant MF treated with IFN-α.[26,38] This therefore begs the question of the mechanism of efficacy of the current JAK kinase inhibitors. Previous studies had shown that the significant reduction in spleen size and amelioration of symptoms in MPN patients was associated with a reduction in circulating inflammatory cytokine levels. Levine and others have demonstrated the mechanistic basis for inflammatory cytokine production in MPN models.[39,40] First, different MPN populations, including stem/progenitor cells and differentiated MPN-expanded progeny, can produce cytokines and contribute to the inflammatory milieu that drives MPN pathology. Second, single cell profiling shows that there is marked heterogeneity in inflammatory cytokine production in MPN cells, and that many MPN cells acquired a poly-functional phenotype which allows for secretion of many different cytokines in parallel. Third, the STAT3 transcription factor is a key mediator of inflammatory cytokine production. Most importantly, profiling and genetic studies show that activated JAK2-STAT3 signaling in MPN, mutant cells and in nonmutant cells contributes to inflammatory cytokine production, and that JAK inhibitors achieve therapeutic efficacy by blocking cytokine production from both populations. It was also observed that persistent JAK2 activation in cells selected under increasing concentrations of JAK2 inhibitors are cross-resistant to all type I TKIs but still dependent on JAK2.[41] These cells reactivate the JAK-STAT pathway through transactivation of JAK2 by other kinases. As such, genetic studies show that elimination of JAK2 leads to dramatic molecular responses, and demonstrates an absolute requirement for JAK2 in MPN cells.[42] In efforts to improve inhibition of JAK2 activation, efforts are now assessing the role of type II JAK inhibitors, which inhibit JAK2 in the inactive conformation. One such JAK inhibitor, NVP-CHZ868, has been tested in JAK2V617F mutant and MPL mutant cells, as well as MPN cells which harbored acquired resistance to type I JAK inhibitors. JAK2 and MPL mutant cells were sensitive to NVP-CHZ868 and displayed attenuation of JAK-STAT signaling. Furthermore, NVP-CHZ868 suppressed JAK-STAT signaling in type I JAK-inhibitor-persistent cells, in addition to a reduction in the mutant allelic ratio, and clinical trials are now in progress.[43]

It is also possible to target JAK2 by other downstream pathways activated by JAK2V617F, for example by targeting the MEK pathway. To test this hypothesis, JAK2V617F transgenic mice were treated with a JAK inhibitor (NS-018), MEK inhibitor (PD325901), or combination of the two.[44] Notably, a lower proportion of mice treated with the MEK inhibitor alone or in
combination with NS-018 demonstrated advanced bone marrow fibrosis. Treatment with PD325901 was also associated with increased bone marrow cellularity, but had no effect on spleen size when given as a monotherapy.

Numerous clinical trials with type I JAK inhibitors and also other novel agents, as monotherapy or in combination are in progress. Two monotherapy phase 3 trials (PERSIST-1 and -2) assessing the JAK2/FLT3 inhibitor pacritinib (SB1518) have now been completed, and the initial results from PERSIST-1 demonstrate impressive efficacy and safety.[45] Pacritinib decreased MF-related symptoms and spleen volume in 41% and 25% of evaluable patients, respectively, including those with significant baseline thrombocytopenia (<50,000/μl). The drug does not appear to have a significant negative impact on hemoglobin or platelet count and the most relevant side effect of note, so far, is grade 3 diarrhea, which occurred in <5% of the study cohort. Unfortunately, on 16 February 2016, the US Food and Drug Administration (FDA) placed a full clinical hold on all pacritinib trials following concerns about the drug’s safety in view of excessive cardiovascular adverse events, including deaths.[46] Another JAK2 inhibitor, momelotinib (CYT387) has demonstrated significant activity in MF patients with a favorable impact on disease-associated anemia, though peripheral neuropathy has been observed; two randomized phase 3 trials are ongoing, including a randomized comparison with ruxolitinib in newly diagnosed patients.[47]

Lastly for patients with SM, which remains a difficult disease to treat, midostaurin (PKC412), a multikinase inhibitor, which targets the most common mutation in SM, KIT816V, has now been tested in a phase 2 trial.[48] The overall response rates were 60%, with most being major responses. Median overall survival was 24.1 months. 44% major response rate was reported in mast cell leukemia patients. Grade 3 and 4 drug-related events included leukopenia, uncomplicated and febrile neutropenia, thrombocytopenia, anemia, vomiting, fatigue, and lipase/amylase elevations. Other candidate therapies in SM include brentuximab vedotin, based on the notion of mast cells expressing aberrant CD30, and ibrutinib to target the BTK pathway.[49,50]

**Genetic insights into MPN risk stratification**

Genomic data is now increasingly being garnered and integrated scoring systems to better assess individual patients’ risks are being developed.[51,52] The Mutation-Enhanced International Prognostic Scoring System (MIPSS) stratified prognosis of MF patients based on the dynamic international prognostic scoring system (DIPSS) or DIPSS-plus, as well as mutations previously demonstrated to have prognostic significance (Figure 3).[53] The study identified both clinical factors and mutations which were associated with inferior survival. These factors were assigned weighted-averse points and four risk groups with distinct survival curves were delineated. The Genetics-Based Prognostic Scoring System (GPSS) utilizes cytogenetic data as well as mutations associated with impaired survival in previous studies. Factors such as high-risk karyotype, presence of ASXL1 mutations and triple-negative status (negative for JAK2/MPL/CALR mutations), among other factors, was used to derive a hazard-ratio based risk scoring system.[54] Thus, these studies demonstrate the
feasibility of integrating clinical, cytogenetic, and diagnostic molecular studies into comprehensive risk-assessment tools.

The impact of CALR mutations, either alone or in the presence of other nonspecific mutations, on some of the prognostic scores and treatment for MPN patients is being assessed.\[5\] In patients with ET, the presence of CALR mutations does not appear to affect the International Prognostic Score for the risk of thrombosis (IPSET-thrombosis) in terms of thrombotic risk.\[55\] It is possible, though not certain, that CALR mutations affect younger cohorts who have had fewer thrombotic events.\[5\] Current observations in ET patients also suggest that the presence of CALR mutations appear not to affect the efficacy of hydroxyurea or interferon alpha, though responses are inferior in the presence of multiple mutations.

Efforts to study the impact of somatic mutations on phenotypic features and survival by genotyping hematopoietic colonies or by means of NGS also reveal striking findings. Skoda et al. showed the presence of two or more mutations to significantly lower the overall survival and risk for leukemic transformation, whilst Green and colleagues demonstrated the phenotypic impact of the order of acquisition of JAK2 and TET2 mutations.\[56–58\] They observed that the prior mutation of TET2 influenced not only the clinical features and response to ruxolitinib, but also the biology and clonal evolution.

**Optimal treatment of patients with CML**

Though the standard starting daily dose of imatinib is 400 mg for newly diagnosed patients in the chronic phase, the optimal dose is unknown.\[59\] Several single-arm studies suggest that higher doses, from 600 to 800 mg daily, might give better results with a greater proportion of patients achieving complete cytogenetic responses (CCyR) and major molecular responses (MMR; also referred to as MR\(^3\)-signifying a 3 log reduction of the BCR-ABL\(^1\) transcripts compared to baseline).\[60\] Such studies also suggest better progression-free survival and transformation-free survival but with potentially more side effects, particularly myelosuppression. Amongst randomized studies, the TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity) study showed imatinib 800 mg to induce MR3 more rapidly than imatinib 400 mg, but at one year there was no statistically significant difference.\[61\] In contrast, Hehlmann presented persuasive evidence from the recent randomized German (CML IV) study that optimized high-dose imatinib allows for most patients to achieve a complete molecular responses (defined at a 4.5 log reduction of the BCR-ABL\(^1\) transcripts compared to baseline or MR\(^{4.5}\)) and this may provide an improved therapeutic basis for treatment discontinuations (Figure 4).\[62\] A subset analysis from this randomized study also showed a greater benefit for patients older than 65 years of age.\[63\] It is also of some interest that in the German CML IV study the median daily dose of imatinib was actually 628 mg, lending additional support to the 600 mg dose strategy. Regardless of the dose of imatinib, the current safety analysis of imatinib is quite impressive, with no potentially serious long-term side-effects noted after 10-years or more continuous use in over 1500 patients.\[64,65\]
The next-generation TKIs, nilotinib and dasatinib, entered studies in 2004 to treat patients with CML who were resistant/refractory or intolerant to imatinib. Current results suggest that the efficacy, but not the toxicity, of both drugs in the second-line setting is fairly similar, with about 45% of the patients achieving CCyR and a four year overall survival of 78%. Though these results are impressive, it is of note that only a third of the responding patients remained on nilotinib or dasatinib at five years, which means that two-thirds of patients require a further change of therapy. Both drugs entered clinical trials for first-line therapy of the newly diagnosed patient in 2006, and the latest updated results are summarized in Table 1. Having met the primary end-points and many of the secondary end-points, both drugs were licensed for first-line use in patients with CML in the chronic phase in 2010. Compared to imatinib 400 mg, nilotinib and dasatinib, render earlier and higher molecular response rates, in particular faster and deeper molecular responses (MR3, MR4, and beyond), that in turn appear to decrease the rates of progression to the advanced phases of CML.[68,69] Discontinuation rates for disease progression or treatment failure for any cause appears to be similar at around 33–38% at three years for both drugs, with the caveat that the definitions of progression and the duration of follow-up prior to censoring in these two large studies were not uniform. It is notable that currently there is no survival advantage for either drug to be used for first-line therapy of a newly diagnosed patient with CML in chronic phase, despite the superior early molecular responses and the subsequent MR4.5 responses.[70] Additionally, in contrast to the earlier reports, the longer follow-up of DASISION and ENESTnd raise significant concerns for the associated vascular occlusive events with nilotinib (10% with nilotinib 300 mg; 15.9% with nilotinib 400 mg), and pulmonary hypertension (6%) with dasatinib; of note is the notion of ‘sudden cardiac death’ reported in a few of the earlier nilotinib studies appear not to have been borne in the more recent larger studies.[71]

The third and newest of the next-generation TKIs, bosutinib, currently licensed for second-line use, has now been tested for first-line use and found to have a similar efficacy to nilotinib and dasatinib in terms of the molecular results, and the risk of transformation to the advanced phases.[72] Last but not least, ponatinib, a third generation TKI, resulted in 46% CCyR (40% without T315I; 66% with T315I) and 34% MR3 (27% without T315I; 56% with T315I) when used in the second-line setting, in a phase 2 study (PACE), leading to the drug being licensed for second line use in 2012 and a phase 3 randomized study (EPIC) commenced.[73,74] In early 2013, significant concerns were raised with regard to thrombotic events, in particular arterial, and the drug use suspended. It is of note that at the time of termination of this study, 7% of the ponatinib cohort had experienced arterial thrombotic events, described as ‘serious’ in all except one patient. In 2014, despite the serious thrombotic risks, it was relicensed exclusively for the treatment of adult patients with T315I-positive CML in all phases or T315I-positive Ph-chromosome positive ALL and adult patients with CML in all phases or Ph-chromosome positive ALL who were resistant and/or refractory to imatinib, dasatinib or nilotinib. Though the precise mechanisms of ponatinib-induced vascular occlusive events remain an enigma, recent observations from a retrospective analysis of the PACE data, suggest a direct relationship of ponatinib dose and frequency of such vascular events.[75]
Candidate drugs being developed against the T315I mutation include ABL001, a BCR-ABL1 inhibitor that targets the myristoyl pocket of the ABL1 kinase. Data presented showed the drug to selectively inhibit growth of CML and Ph\(^+\)ALL cell lines. In a xenograft model utilizing the KCL-22 cell line, treatment with either nilotinib or ABL001 as single agents resulted in tumor regression, with subsequent tumor relapse and the acquisition of point mutations. However, mice treated with combination of nilotinib and ABL001 achieved tumor regression without relapse in the time frame of the study.[76] Another drug of interest is ABT-199, a BCL2 inhibitor. Combination therapy with ABT-199 and TKIs in patients with CML in advanced phases resulted in synergistic killing of patient-derived cells.[77]

**Conclusions**

Current results epitomize the remarkable success story of CML, a genetically simple cancer, in contrast to all other MPNs, where only a qualified success has been noted in a rare subtypes, SM and myelofibrosis. Treatment for CML today involves a choice of three first-line orally administered drugs and two effective second-line therapies that should be used based on a number of factors, including the cost of drug, associated side-effects, and indeed drug access. Currently there is little difference in the pricing structure of the licensed first-line drugs, but this should change dramatically once generic imatinib becomes increasingly available. Regardless of the initial choice of TKI, the vast majority of patients achieve a durable CCyR, with a lifespan approaching that of the general population. In most instances the medication must be continued indefinitely, and a principal challenge now is to develop strategies to stop TKIs safely and effectively.

In patients with MF, stem cell transplantation remains the most effective treatment for those eligible to receive it. Sadly this accounts for a small minority and there is clearly an urgent need to develop effective therapies. The licensing of ruxolitinib for the treatment of high-risk patients with MF and polycythemia (PV) represent an important advance in the treatment of these diseases, but for the most part, these remain qualified. There is some uncertainty as to the drug’s precise effect on the disease biology in a manner to accord an improvement in survival. Efforts based on targeting multiple molecular pathways, in addition to JAK-STAT, are now assessing the role of combining ruxolitinib with other drugs, including IFN-a. Furthermore, clinical trials assessing the efficacy of the type II JAK inhibitors are now in progress. A principal challenge is to establish the prognostic and predictive impact of the numerous mutations described in efforts to better identify drug targets and understand the impact of the microenvironment and the ‘inflammation’ in the pathogenesis of these diseases.

**Acknowledgements**

Myers Squibb Oncology for support towards the 9th Post-ASH workshop. RVE was the recipient of the 2015 Janet Rowley Award.

References


Figure 1.
(Black & white) Somatic mutations in MPNs – distribution of somatic mutations among 382 polycythemia vera (PV), 311 essential thrombocythemia (ET) and 203 primary myelofibrosis (PMF) patients. The shades of gray indicate the mutational status.
Figure 2.
Conceptual thoughts on the progression of MPNs.
**Figure 3.**
The mutation-enhanced international prognostic scoring system (MIPSS).

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR* (95% CI)</th>
<th>P</th>
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<td>Age &gt;60yrs</td>
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<td>Hb &lt;100g/L</td>
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<td>PLT &lt;200x10^9/L</td>
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<td>Triple Negativity</td>
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<td>SRSF2 mutation</td>
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* HR=Hazard ratios for mortality
Figure 4.
German CML IV study – optimized high-dose imatinib.
Table 1.
Summary of data from different studies comparing dasatinib or nilotinib to imatinib at five years.

<table>
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<tr>
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<th>Dasatinib 100 mg qd n = 259</th>
<th>Imatnib 400 mg qd n = 260</th>
<th>Imatinib 400 mg qd n = 283</th>
<th>Nilotinib 300 mg bid n = 282</th>
<th>Nilotinib 400 mg bid n = 281</th>
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<td>MMR at five years</td>
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<td>Overall progression to AP/BC</td>
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<td>18 (7.3%)</td>
<td>20 (7.5%)</td>
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<td>6 (2.1%)</td>
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<td>Overall survival</td>
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