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Title: TIDEL-II: Frontline use of Imatinib in CML with Early Switch to Nilotinib for Failure to Achieve Time-Dependent Molecular Targets

Running Title: Treatment Results of CML patients from the TIDEL-II Study

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Key points

- Upfront imatinib treatment in CML, with selective nilotinib switching, led to high rates of OS, TFS, EMR and MMR.
- Our strategy may be preferable to universal upfront use of 2nd generation TKIs based on efficacy and toxicity as well as economic concerns.

Abstract

TIDEL-II was designed to optimise outcomes for newly-diagnosed chronic phase chronic myeloid leukemia (CP-CML) patients. Two sequential cohorts enrolled a total of 210 patients, all commencing imatinib 600 mg/day, with a planned dose escalation to 800mg/day for patients with imatinib plasma trough level <1000 ng/mL on day 22 (19%). Patients were then assessed with molecular treatment targets: $BCR-ABL1 \leq 10\%$, $\leq 1\%$ and $\leq 0.1\%$ at 3, 6 and 12 months, respectively. Cohort I patients who failed to achieve targets were escalated to imatinib 800 mg/day (if on 600mg/day), then subsequently switched to nilotinib 400 mg BID for failing the same target 3 months later. Cohort II patients who failed to achieve targets switched to nilotinib directly, as did patients with intolerance or loss of response in either cohort. At 2 years, 55% of study patients remained on imatinib, and 30% were on nilotinib. Only 12% were $>10\%$ $BCR-ABL1$ at 3 months. Confirmed MMR was achieved in 64% and 73% at 12 and 24 months, respectively. MR4.5 at 24 months was 34%. Overall and transformation-free survival was 96% and 95% at 3 years, respectively. This trial supports the feasibility and efficacy of an imatinib-based approach with selective switching to nilotinib. Trial Registration #ACTRN12607000325404.
Introduction

The IRIS study (International Randomised Study of Interferon versus STI-571) reported 8-year overall survival (OS) of 85% in imatinib-treated CP-CML patients in the frontline setting. This is an excellent result, though not all patients benefited equally. In that cohort, 45% discontinued treatment with imatinib, predominantly due to intolerance, drug resistance, or disease progression. The IRIS trial also demonstrated the important correlation between the achievement of time-dependent treatment targets and OS. Early cytogenetic and molecular response to treatment predicted subsequent disease response and event free survival.

Landmark analysis of the IRIS cohort demonstrated superior 5- and 7-year outcomes for patients achieving complete cytogenetic response (CCR) at 12 months and major molecular response (MMR) at 18 months versus those who did not, a finding confirmed subsequently by other cohorts. Based on these results, together with similar findings from other studies, the European Leukemia Net (ELN) recommended in 2009 the achievement of partial cytogenetic response, CCR, and MMR by 6, 12 and 18 months of treatment respectively as being optimal responses for CP-CML patients. The prognostic significance of these targets was confirmed in patients treated with nilotinib and dasatinib in the frontline setting.

To improve outcomes in CP-CML patients, the Australasian Leukaemia and Lymphoma Group (ALLG) conducted the TIDEL-I (Therapeutic Intensification in DE-novo Leukaemia) trial which used a higher imatinib starting dose of 600 mg/day for all patients, and set a series of time-dependent treatment targets. These included complete hematologic response (CHR), major cytogenetic response (MCR), CCR, and \( BCR-ABL1 \leq 0.01\% \) (on the International scale (IS)) at 3, 6, 9, and 12 months, respectively. Patients failing to achieve these targets were treated with an increased dose of 800 mg/day imatinib. The cumulative incidence of MMR was 47% and 73% at 12 and 24 months, respectively. By comparison, the 12 month MMR rate was 40% and 55% at these time-points for the IRIS study.

The TIDEL-II study aimed to optimise treatment outcomes by maximising the number of our patients reaching ELN treatment milestones. Building on our experience from TIDEL-I, in which treatment intensification was delivered based on early treatment targets, we incorporated two additional approaches. Early reports suggested a correlation between
minimum serum imatinib concentration achieved (>1000ng/mL) and the likelihood of achieving CCR/MMR, leading us to escalate the imatinib dose to 800mg/day in patients with trough serum concentration <1000 ng/mL. The second approach consisted of a prompt switch to the more potent tyrosine kinase inhibitor (TKI), nilotinib, for either imatinib intolerance, or a sub-optimal response, as defined by molecular targets. The TIDEL-II targets were intended to be more stringent than the contemporaneous ELN milestones, to allow adequate time for response improvement in order to avoid treatment failures. Based on efficacy and tolerability data from TIDEL-I, we continued to use imatinib at 600 mg/day as initial therapy.

**Patients and methods**

**Patient enrolment**

TIDEL-II is a single arm prospective open label trial enrolling CP-CML patients aged >16 years within 6 months of diagnosis. Exclusion criteria included known HIV infection, pregnancy, renal or hepatic dysfunction (creatinine and bilirubin ≥1.5x ULN, ALT, AST, ALP, GGT ≥ 2.5 x ULN), past history of pancreatitis, or QTc >480 msec. Patients with myocardial infarction <12 months from CML diagnosis or those with other clinically significant uncontrolled heart disease (eg unstable angina, congestive heart failure) were also excluded. Up to 6 months of prior treatment with hydroxyurea or anagrelide was permitted. The study was carried out with approval of Human Research Ethics Committees and in accordance with the Declaration of Helsinki.

**Treatment**

The TIDEL-II treatment schema is illustrated in supplementary figure S1. Two sequential cohorts of 105 patients each were enrolled. All patients started treatment with imatinib 600 mg/day. An imatinib plasma trough level was taken on day 22, 24 hours after a previous imatinib dose. A level of <1000 ng/mL determined if a patient dose-escalated to 800 mg/day or, if this dose could not be tolerated, the maximum tolerable dose was given. All patients then had to meet a series of specific time-dependent molecular targets, defined as $BCR-ABL1$ of ≤ 10%, ≤ 1% and ≤ 0.1% (IS) at 3, 6 and 12 months, respectively. These targets have subsequently been adopted by the ELN as optimal treatment responses to frontline TKI
treatment in 2013.\textsuperscript{17} Cohort 1 patients who failed to achieve their molecular targets were
dose-escalated to imatinib 800 mg/day; those who failed to achieve that target after a further
3 months were switched to nilotinib 400 mg BID. Patients who were unable to dose-escalate
imatinib after failing to achieve a time-dependent molecular response switched to nilotinib
without further delay. Contemporaneously, the TOPS study was published and demonstrated
a lack of benefit for using imatinib 800mg/day versus 400mg/day for CP-CML in terms of
MMR achievement, and that 800mg/day was difficult to maintain.\textsuperscript{18} After enrolling 105 patients
to cohort 1, a protocol amendment allowed subsequent TIDEL-II patients to switch directly to
nilotinib for failure to achieve TIDEL-II targets. Imatinib dose-escalation was retained only for
patients with low imatinib trough levels in cohort 2. Patients from either cohort meeting the
loss of response criteria (see definition below) were switched from imatinib to nilotinib 400 mg
BID.

In either cohort, patients who experienced grade III/IV or persistent grade II non-haematologic
imatinib toxicity were subjected to review by the study management committee (SMC).
Imatinib and nilotinib dose reductions were permitted for toxicity management.

Monitoring
Blood counts and biochemistry assessments were performed weekly for four weeks and at 3
months, then quarterly thereafter. Bone marrow biopsies for morphologic and cytogenetic
examination were performed locally at diagnosis, at 6 and 12 months after imatinib
commencement, and in the event of treatment failure. *BCR-ABL1* transcripts were measured
monthly for the first 3 months, then at 3-monthly intervals. Assays were performed centrally at
an international reference laboratory (SA Pathology, Adelaide) using methodology previously
published.\textsuperscript{19,20} Testing for *BCR-ABL1* kinase domain mutations\textsuperscript{21} was triggered when a >2-
fold rise in transcript level was detected, when a patient met the loss of response criteria or
for failure to achieve TIDEL-II molecular targets.

End points and statistical procedures
The primary end point was confirmed MMR (*BCR-ABL1* ≤ 0.1% IS) at 12 months (± 4 weeks),
documented by 2 *BCR-ABL1* qRT-PCR results of ≤0.1% IS on 2 consecutive occasions 3
months apart. The date of achievement of MMR was then considered to be the date of the first of the two qRT-PCR results ≤0.1%. This endpoint was calculated on an intention to treat basis: patients with missing values, or having withdrawn from study were scored as failures. The Clopper-Pearson exact method was used to calculate 95% confidence intervals (CI). Molecular responses were also calculated using the cumulative incidence function with study discontinuation for any reason as a competing risk. Complete molecular response (CMR) was defined as 2 consecutive measurements of undetectable BCR-ABL1 within 3 months using qRT-PCR sensitivity of ≥4.5 log, also backdated to the first of the two measurements, as for MMR. MR\(^4\) and MR\(^4.5\) were previously defined. A BCR-ABL1 result of ≤1% was considered a surrogate for CCR based on a strong correlation between the two as previously published. Patient numbers in the two cohorts was not powered to allow for any comparisons and this was therefore not attempted.

A loss of response event is defined as any of the following: loss of confirmed complete hematological or major cytogenetic response; cytogenetic clonal evolution; a confirmed >5-fold rise in BCR-ABL1 level from nadir to a level >0.1% resulting in loss of MMR; a >2-fold rise from nadir in BCR-ABL1 level to a level >10%; detection of >50% mutant BCR-ABL1; or disease transformation to accelerated phase / blast crisis (AP/BC). The durations of OS and transformation free survival (survival without AP/BC; TFS) were estimated using the Kaplan-Meier method. Transformation events include AP/BC observed for patients who discontinued study.

Results

Overall response

Between November 2007 and March 2011, 210 patients were enrolled from 27 centres around Australia and New Zealand. Baseline characteristics are summarised in Table 1. All CI’s quoted below are 95% CI’s.

The number of patients achieving confirmed MMR and CMR in each of the cohorts is summarised in Table 2. Overall, 134 patients (64%; CI, 56-72%) achieved confirmed MMR at 12 months, increasing to 153 (73%; CI, 67-79%) at 24 months. The rates of MR\(^4.5\) were 19%
and 34% at 12 and 24 months respectively. Confirmed CMR was achieved in 24 patients (11%; CI, 6.8-15%) at 12 months and in 52 patients (25%; CI, 19-31%) at 24 months. The cumulative incidence of achieving MMR and CMR are shown in Figure 1.

With a median follow up of 40 months, seven BC cases were observed (3.5%). Six patients transformed whilst on study (at 3.5, 4, 5, 9, 12 and 34 months). One additional patient transformed to BC at 18 months after withdrawing from TIDEL-II at 12 months. No transformation to accelerated phase was observed. TFS was 95% (CI, 92-98%) at 3 years (Figure 2). Six additional patients died during the study from non-CML related causes. The overall survival was 96% at 3 years (CI, 94-99%). Events such as transformation and death are summarised in supplementary tables S1-2. Patients with high risk Sokal scores were noted to have inferior OS, TFS and achievement of MMR, though these differences did not reach statistical significance (supplementary figure S2). Kinase domain mutations were detected in eleven patients (supplementary table S3). Additional cytogenetic abnormalities at baseline were detected in only 8 patients and did not lead to statistically significant inferior outcomes (supplementary table S4)

Treatment received by patients together with the discontinuation rate is summarised in table 3 and supplementary figure S3. Of the 134 patients in MMR at 12 months, 111 (83%) continued with imatinib therapy and 23 (17%) had been switched to nilotinib therapy. Of the 153 patients in MMR at 24 months, 111 (73%) were assigned to imatinib whereas 42 were assigned to nilotinib (27%). Of the 71 patients in MR4.5 at 24 months, 49 (69%) only had imatinib treatment.

### Imatinib dose escalation for low trough levels at day 22 (supplementary figure S4)

At day 22, 40 (19%) of the patients (19 from cohort 1 and 21 from cohort 2) recorded imatinib trough levels <1000 ng/mL. Dose was escalated for 31/40 patients at a median of 43 days (31-187). Twenty remained on this dose until the 12 month time-point, two de-escalated to imatinib 400mg/day, 2 had withdrawn and seven switched to nilotinib (intolerance, n=2; failure to achieve target, n=5). The other 9 patients had imatinib 400-600mg/day as maximum tolerated dose: five switched to nilotinib directly either for intolerance or for failing their 3 and
6 months targets (n=2, 2 and 1 respectively). One withdrew at 9 months, one patient later
dose escalated at 13 months for failing to achieve MMR and 2 achieved MMR on 600mg/day
imatinib. At 24 months, 28/40 (70%) achieved MMR; 15 of the 40 patients were still on
imatinib 800 mg/day, 4 on 400-600 mg/day imatinib, 14 on nilotinib, and 7 had withdrawn from
study.

**Early molecular response and outcome**

The 25 patients (12%) who failed to achieve an early molecular response (EMR; BCR-ABL1
≤10% at 3 months) had inferior OS, TFS, and decreased probability of achieving MMR
(Figures 3A-C). Six of these patients achieved MMR at 24 months (24%). Ten of the 25
patients had imatinib plasma trough level <1000ng/mL at day 22. At 6 months, 16 of these 25
patients had BCR-ABL1 <10% (6 patients <1%), 6 had BCR-ABL1 >10%, 3 had already
withdrawn, (1 from blast crisis). At 12 months, 18/25 patients remained on study, 5 patients
having achieved MMR. At 24 months 6/25 patients (24%) were in MMR (2 on imatinib 800
mg/day and 4 on nilotinib) and 10/25 patients had withdrawn from the study: 3 each due to
blastic transformation, failure to comply with protocol treatment, and failure to achieve
satisfactory therapeutic responses (either MMR or CCR), and one died from infection. In
contrast, 91% of patients who achieved BCR-ABL1 ≤1% at 3 months subsequently achieved
confirmed MMR at 24 months. In those with BCR-ABL1 between 1-10%, the 24-month rate of
MMR was 75%. Treatment assignments for patients failing TIDEL-II time dependent targets
and subsequent molecular outcomes for other time-points are described in figure 4.

**Outcomes of patients switching from imatinib to nilotinib**

Seventy-eight patients failed TIDEL-II targets. Fourteen patients remained on imatinib therapy
(13 on 800mg/day), 12 of them achieved MMR, at 24 months. Ten withdrew from study
without further intervention. Fifty-four subsequently switched to nilotinib at a median of 7
months (range, 2-19) after study commencement. Twenty-one of these patients (39%) were in
MMR at 24 months. Nineteen additional patients switched to nilotinib secondary to imatinib
toxicity without failing any targets, at a median of 3 months after study commencement (range
2-16), 5 doing so before 3 months. Six patients had already achieved MMR at the time of
switch. At 24 months, 18 of these 19 patients were in MMR (95%). Altogether, 73 patients
switched to nilotinib for either intolerance or failure to achieve TIDEL-II targets, 33 of which achieved MMR at 24 months. An additional 5 patients switched to nilotinib after loss of response to imatinib between 8-23 months (4 lost MMR, 1 lost CCR); 4 subsequently re-established MMR by 24 months.

**Adverse events**

Grade III/IV adverse events (AE) are listed in supplementary table S5. These are similar in spectrum to those reported in other studies using imatinib and nilotinib treatment. Events attributed to the two drugs in this study are not directly comparable, as nilotinib exposure occurs subsequently to imatinib and only selected patients (37% at 24 months). Cytopenia, especially at the commencement of study treatment, was the most common severe AE associated with imatinib. Biochemical abnormalities and allergic skin reactions were common with both imatinib and nilotinib treatment, the former including elevated serum liver or pancreatic enzymes for both drugs, as well as hypophosphatemia for imatinib and hyperbilirubinemia for nilotinib. Interestingly, grade III/IV lipase and amylase elevations were seen with imatinib as well as nilotinib. Arthralgia, gastrointestinal disturbances as well as edema were also commonly reported with imatinib. Vascular disease (involving coronary, cerebral and/or peripheral arteries) was reported in 13 patients (6.2%) resulting in 5 deaths, as summarised in supplementary table S6. Most of these patients had pre-existing vascular disease or significant vascular risk factors.

**Discussion**

The optimal frontline treatment of CML-CP patients remains unclear. Imatinib has been the standard of care since its introduction, associated with high overall survival and low risk of toxicity associated with major morbidity.\(^2\) In contrast, second generation TKIs such as nilotinib and dasatinib lead to faster and deeper molecular responses,\(^{29,30}\) lower risks of AP/BC transformation, and in the case of nilotinib, lower risk of acquired kinase domain mutations.\(^{31}\) Second generation TKIs are often preferred in patients with high Sokal or Hasford risk scores, or when a high priority is placed on the rapid achievement of deep molecular responses.\(^{32}\) However, outstanding questions remain over the long term safety profile of these drugs. Although severe adverse events such as vascular disease\(^{33-35}\) or
pulmonary toxicities\textsuperscript{36,37} occur uncommonly with second generation TKIs, these events lead to significant morbidity when they do occur. These toxicities may, in part, contribute to the lack of significant differences in overall survival between patients treated with imatinib and those receiving either nilotinib or dasatinib, despite the clear differences in AP/BC transformation rates.\textsuperscript{29,30}

TIDEL-II represents a strategy that incorporated both imatinib and, where needed, a second generation TKI into a treatment schema for frontline treatment of CML-CP patients. Overall, TIDEL-II treatment led to MMR rates of 64\% by 12 months, rising to 73\% by 24 months. The 3-year OS and TFS are 96\% and 95\%, respectively. These results compare very favourably with other current frontline TKI studies in CML-CP patients, including the frontline use of nilotinib or dasatinib.\textsuperscript{29,30}

TIDEL-II is a novel treatment strategy in many respects. Firstly, patients started treatment with imatinib 600mg/day, and modulated this dose according to serum imatinib trough levels, achievement of molecular targets, and tolerability. The overall effect of our individualized approach to imatinib administration led to 111 of the total 210 patients achieving MMR at 24 on imatinib (53\%), out of the 153 patients that achieved this end-point. Although most clinical studies select 400mg/day as the imatinib dose, an optimal dose for imatinib has never been established. The French SPIRIT study demonstrated superior MMR achievement with imatinib 600mg/day versus 400mg/day, though in the randomised TOPS study, MMR at 12 months was no different between patients randomised to imatinib 400mg/day versus 800mg/day.\textsuperscript{18,38} The German CML IV study also randomized patients to these 2 imatinib doses, and found the higher dose well tolerated with a tolerability adapted approach, and demonstrated superior achievement of MMR/MR\textsuperscript{4} at 24 months with 800mg/day imatinib.\textsuperscript{39} The higher median dose density achieved in the German study may have contributed to the differences not seen in TOPS.

The effect of 600mg/day imatinib as the starting dose can also be demonstrated in the rate of EMR (BCR-ABL1 \( \leq 10\% \) at 3 months). Failure to achieve EMR correlates with inferior PFS, OS and MMR achievement, irrespective of the TKI used for front-line treatment.\textsuperscript{4,9,10,12,14,26,40}
Patients starting treatment with either dasatinib or nilotinib are more likely to achieve EMR compared to standard dose imatinib. The imatinib starting dose of 600mg/day, and dose escalation for low imatinib trough levels, have likely contributed to our low EMR failure rate of 12%, which compares favourably to that seen in the 300mg BID arm of ENESTnd (9%)\(^{12}\) and dasatinib treated patients in DASISION (16%).\(^{13}\) In contrast, 33-36% of patients in the imatinib 400mg OD arm in these two studies failed to achieve EMR. Higher starting doses of imatinib have also been associated with a reduced rate of EMR failure in the SWOG S0325 study.\(^{41}\)

We postulated that imatinib 800mg/day may be beneficial for selected patients, such as those failing to achieve milestone responses, though in practice only 9 of our 28 patients mandated for dose escalation based on target failure alone stayed on this dose until 24 months. We also hypothesised that dose escalation may be relevant in patients with low imatinib trough levels, based on retrospective data showing a correlation between achievement of CCR/MMR and a serum trough imatinib level >1000ng/mL.\(^{15}\) This link was corroborated by a sub-analysis of the IRIS study,\(^{16}\) though the clinical utility of imatinib serum levels has never been validated prospectively. In the 40 TIDEL-II patients with imatinib trough <1000ng/mL, only 15 achieved MMR on imatinib 800mg/day at 24 months. Taken together, ~11% of patients can maintain imatinib 800mg/day and achieve MMR on this dose, suggesting that the importance of high dose imatinib may be secondary to therapy switching based on intolerance or failure to reach molecular targets.

Secondly, TIDEL-II allowed patients to switch from imatinib to nilotinib, which enabled an additional 32 patients (15% overall) to achieve MMR. Patients were allowed to switch for three reasons: imatinib intolerance, failure to achieve time dependent molecular targets or loss of response. Although switching TKIs for these reasons is a standard practice outside of clinical studies, patients in studies focused on a single TKI who switch drugs are usually regarded as therapeutic failures, withdrawn from study and their subsequent outcome not reported. Incorporating this intervention within the TIDEL-II schema allowed us to observe “real-world” treatment outcomes incorporating transition to second-line therapy.
Overall, 30% of TIDEL II patients switched to nilotinib. For patients with imatinib intolerance, the outcome was generally favourable. In contrast, the benefit of nilotinib switching in patients who failed to achieve early TIDEL-II targets is not clearly demonstrated in our cohorts. This is a likely consequence of our low EMR failure rate. In the 300mg BID arm of the ENESTnd trial, continuing nilotinib treatment in the 9% of patients with EMR failure led to a 24 month MMR rate of 29%.12 These patients are likely to have a degree of intrinsic TKI resistance through poorly understood mechanisms. It is reasonable to speculate that the 12% of TIDEL-II patients who failed to achieve EMR may have a similar degree of treatment resistance to a second generation TKI, and nilotinib switching in this group of patients resulting in a 24 months confirmed MMR rate of 24% is therefore unsurprising. Furthermore, early transformations in these patients with relative TKI resistance suggests that even interventions as early as 3 months may be too late to have a clinically meaningful impact on underlying disease biology. For our 7 blast crisis cases, 3 occurred in the first 6 months, and only 1 had an opportunity to receive the more potent TKI. However, it is doubtful that upfront dasatinib or nilotinib therapy would have prevented many of these early transformations, given the similar rate of transformation for nilotinib and dasatinib treated patients compared to TIDEL-II.12,13

TIDEL-II patients failing later time-dependent targets had better outcomes compared to those who failed to achieve EMR. Although patients with BCR-ABL1 >1% at 6 months also had a low probability of achieving MMR at 24 months, BCR-ABL1 <1% (CCR equivalent) is still achievable in this group using our approach. In contrast, interventions were more successful for those patients failing to achieve BCR-ABL1 ≤0.1% at 12 months: 67% of these patients achieved MMR at 24 months (12 months after intervention). Furthermore, the overall strategy of TIDEL-II led to an MR4.5 rate of 34% at 24 months, compared to 25% in the 300mg BID arm of the ENESTnd study.42 Of the 71 patients who achieved confirmed MR4.5, 49 received only imatinib (23% overall). Nilotinib switching allowed an additional 22 patients (10% overall) to achieve this end-point. A deep molecular response is an increasingly valued treatment goal, associated with improved survival43,44 and acting as a platform for cessation studies aimed at treatment-free remissions.45,46 Results of our 12 month intervention and our overall MR4.5 rates are consistent with the results of the ENESTcmr study,47 which demonstrated
achievement of deeper molecular responses subsequent to therapy switching from imatinib to nilotinib in patients who had achieved CCR but not MR4.5.

For the vast majority of CML patients, the TIDEL II approach leads to excellent outcomes. Future efforts should be directed at early identification of high risk patients (especially those destined to experience early disease transformation), and the development of experimental strategies targeted at this population. Ideally, prognostic biomarkers of sufficient discriminatory ability should be implemented at diagnosis. Clinical scoring systems such as the Sokal index, Hasford and EUTOS scores continue to have relevance for CML patients and may be useful in combination with emerging biomarkers in the derivation of a new prognostic score. Better salvage therapies targeted at high risk patients may improve outcomes in these patients and spare unnecessary additional toxicity for the 60-80% of patients who do well with current regimens.

In conclusion, TIDEL-II represents a novel and effective treatment option for the management of treatment naïve CML-CP patients. Although imatinib is effective treatment for many, we recognised that some patients will need a more potent kinase inhibitor. In contrast, using second generation TKIs upfront universally may lead to increased long-term toxicity. TIDEL-II allows a cohort of patients to commence treatment on imatinib, with the majority achieving EMR and MMR while remaining on a drug with long term safety data. The strategy allows selection of patients who are less sensitive or are intolerant to imatinib, switching them over to nilotinib in a time-dependent manner to minimise treatment failure. Given the increasing availability of generic imatinib in many countries over the next decade, the TIDEL-II strategy is particularly attractive when the increasing economic burden of CML therapy is considered. We note that molecular monitoring may not be available or commonly practiced in some countries, which may limit application of strategies such as TIDEL-II. However, successive technological improvements will improve access to these assays, making such risk-adapted sequential agent strategies feasible. We believe strategies such as TIDEL-II may be preferable to the universal use of second generation TKIs as frontline treatment, and formal comparative studies between the strategies are warranted.
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D.T.Y. is a PhD candidate at the University of Adelaide and this work is submitted in partial fulfilment of the requirement for the PhD. D.T.Y. receives PhD scholarship funding form the Leukaemia Foundation of Australia and the Royal Adelaide Hospital Research Foundation A R Clarkson Scholarship. D.T.Y. received a CRTI training award from ASH. T.P.H. is a National Health and Medical Research Council Practitioner Fellow.

The data has been presented in part at ASH 2011, 2012, 2013; and EHA 2012 and 2013.

Authorship Contribution

D.T.Y. supervised conduct of the study, contributed patients, gathered and analysed the data, made the figures and wrote the manuscript. M.P.O. & A.K.M. supervised conduct of the study, contributed patients and reviewed the manuscript. D.L.W. designed the study and reviewed the manuscript. S.B. designed the study, analysed molecular data and reviewed the manuscript. Jo.B. analysed molecular data and reviewed the manuscript. M.K. Je.B. & A.H. gathered and analysed the data and reviewed the manuscript. S.I., D.K.H., M.H., A.P.S., R.F., C.K.A., Y.L.K., Ju.T., C.J.F., Jo.T., D.M.R., contributed patients and reviewed the manuscript.

C.T. supervised the conduct of the study and reviewed the manuscript. A.P.G. & T.P.H.
designed the study, supervised conduct of the study, contributed patients, served on the study management committee and reviewed the manuscript.

**Conflict-of-Interest Disclosures**

D.T.Y. received research funding from Novartis and BMS; received honoraria from and participated in advisory boards of Novartis and BMS. D.L.W. & D.K.H. received research funding from Ariad, CSL, Novartis and BMS; received honoraria from and participated in advisory boards of Novartis and BMS. S.B. received research funding from Ariad, Novartis, Otsuka and BMS; received honoraria from and participated in advisory boards of Ariad, Novartis, Qiagen and BMS. A.P.S. acted as a consultant for Novartis, Bristol-Myers Squibb, and Pfizer; and received honoraria from Novartis and BMS. C.K.A., A.P.G. & A.K.M. had participated in advisory boards of Novartis and BMS. D.R.M. received research funding from Novartis; had received honoraria from and participated in advisory boards of Novartis and BMS. T.P.H. received research funding from Ariad, CSL, Novartis and BMS; received honoraria from and participated in advisory boards of Ariad, Pfizer, Novartis and BMS. The remaining authors declare no competing financial interests.
References


Table 1: Baseline characteristics and follow up

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<td>49 (17-79)</td>
<td>48.5 (16-81)</td>
</tr>
<tr>
<td>Female</td>
<td>51 (49%)</td>
<td>41 (39%)</td>
<td>92 (44%)</td>
</tr>
<tr>
<td>Median follow up in months (range)</td>
<td>50 (40-65)</td>
<td>32 (24-40)</td>
<td>40 (24-65)</td>
</tr>
<tr>
<td>Sokal risk score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>23%</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>32%</td>
<td>30%</td>
<td>31%</td>
</tr>
<tr>
<td>Low</td>
<td>41%</td>
<td>50%</td>
<td>46%</td>
</tr>
<tr>
<td>Unknown</td>
<td>4%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>
Table 2: Molecular responses at 12 and 24 months in cohorts 1 and 2. Please note, patients who achieved deeper molecular responses are not excluded from the calculation of less stringent molecular responses. For instance, 134 patients achieved confirmed MMR at 12 months in total, of which 39 has achieved MR4.5 at 12 months.

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>12 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawn</td>
<td>7 , 6.6 (2.1-12)</td>
<td>8 , 7.6 (2.8-13)</td>
<td>15 , 7.1 (3.6-11)</td>
</tr>
<tr>
<td>BCR-ABL1 &gt;1.0% IS</td>
<td>6 , 5.7 (1.5-11)</td>
<td>6 , 5.7 (1.5-11)</td>
<td>12 , 5.7 (2.6-8.8)</td>
</tr>
<tr>
<td>BCR-ABL1 ≤1.0% IS</td>
<td>92 , 88 (82-94)</td>
<td>91 , 87 (81-93)</td>
<td>183 , 87 (82-92)</td>
</tr>
<tr>
<td>Confirmed MMR^</td>
<td>69 , 66 (57-75)</td>
<td>65 , 62 (53-71)</td>
<td>134 , 64 (56-72)</td>
</tr>
<tr>
<td>BCR-ABL1 ≤0.0032% IS</td>
<td>16 , 15 (8-22)</td>
<td>23 , 22 (14-30)</td>
<td>39 , 19 (14-24)</td>
</tr>
<tr>
<td>BCR-ABL1 ≤0.001% IS</td>
<td>13 , 12 (5.8-18)</td>
<td>18 , 17 (10-24)</td>
<td>31 , 15 (10-20)</td>
</tr>
<tr>
<td>Confirmed CMR^</td>
<td>11 , 10 (4.3-16)</td>
<td>13 , 12 (5.8-18)</td>
<td>24 , 11 (6.8-15)</td>
</tr>
<tr>
<td><strong>24 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawn</td>
<td>16 , 15 (8.2-22)</td>
<td>16 , 15 (8.2-22)</td>
<td>32 , 15 (10-20)</td>
</tr>
<tr>
<td>BCR-ABL1 &gt;1.0% IS</td>
<td>0 , 0</td>
<td>2 , 1.9 (0-4.7)</td>
<td>2 , 1.0 (0-2.4)</td>
</tr>
<tr>
<td>BCR-ABL1 ≤1.0% IS</td>
<td>89 , 85 (78-92)</td>
<td>87 , 83 (76-90)</td>
<td>176 , 84 (79-89)</td>
</tr>
<tr>
<td>Confirmed MMR^</td>
<td>80 , 76 (68-84)</td>
<td>73 , 70 (61-79)</td>
<td>153 , 73 (67-79)</td>
</tr>
<tr>
<td>BCR-ABL1 ≤0.0032% IS</td>
<td>36 , 34 (25-43)</td>
<td>35 , 33 (24-42)</td>
<td>71 , 34 (28-40)</td>
</tr>
<tr>
<td>BCR-ABL1 ≤0.001% IS</td>
<td>32 , 30 (21-39)</td>
<td>34 , 32 (23-41)</td>
<td>66 , 31 (25-37)</td>
</tr>
<tr>
<td>Confirmed CMR^</td>
<td>23 , 22 (14-30)</td>
<td>29 , 28 (19-37)</td>
<td>52 , 25 (19-31)</td>
</tr>
</tbody>
</table>

^Patients who have withdrawn prior to the specified time-point are included as failures to achieve the relevant response

^A number of responses at both the CMR and MMR level at 24 months could not be confirmed due to missing values at the subsequent time-point.
Table 3: Assigned therapy and treatment discontinuations at follow up of 24 mos

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imatinib assigned at 24 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400mg</td>
<td>64 (61%)</td>
<td>51 (49%)</td>
<td>115 (55%)</td>
</tr>
<tr>
<td>600mg</td>
<td>9 (9%)</td>
<td>13 (12%)</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>800mg</td>
<td>37 (35%)</td>
<td>32 (31%)</td>
<td>69 (33%)</td>
</tr>
<tr>
<td><strong>Nilotinib assigned at 24 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawn at or before 24 months</td>
<td>16 (15%)</td>
<td>16 (15%)</td>
<td>32 (15%)</td>
</tr>
<tr>
<td>AE</td>
<td>3</td>
<td>4</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Progression to AP/BC^</td>
<td>2</td>
<td>3</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Death*</td>
<td>3</td>
<td>3</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Therapeutic failure#</td>
<td>4</td>
<td>3</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Other+</td>
<td>7</td>
<td>3</td>
<td>10 (5%)</td>
</tr>
</tbody>
</table>

^Progression to AP/BC as a primary cause of withdrawal

*Death as primary cause of withdrawal

#Failure to achieve milestone responses or loss of response, aside from transformation to AP/BC

+The 10 patients in this category discontinued because of protocol violations, as follows: failure to comply with therapy (n=3); consent withdrawal (n=3); pregnancy or failure to apply contraception (n=3) and development of long QTc affecting ability to switch to nilotinib (n=1).
Figure Legends

Figure 1. **Molecular responses** a) Cumulative incidence for achievement of confirmed MMR (BCR-ABL1 ≤0.1% on 2 successive occasions); and b) confirmed CMR. Point estimates at 12 and 24 months are 60.9% (95% CI, 53.9-67.2%) and 78.1% (95% CI, 71.8-83.1%) respectively for MMR. Point estimates at 12 and 24 months are 9.0% (95% CI, 5.6-13.4%) and 25.2% (95% CI, 19.6-31.3%) respectively for CMR. The differences between confirmed MMR/CMR measured in the cumulative incidence function versus that used in endpoint calculation note in Table 2 is due to a wider visit window defined in the latter.

Figure 2. **Survival curves calculated using the Kaplan-Meier estimate.** a) overall survival; b) transformation free survival.

Figure 3. **Outcomes stratified by a patient’s BCR-ABL1 at 3 months in subgroups >10%, ≤ 10% to >1% versus ≤ 1%.** A) Cumulative incidence for achievement of MMR, excluding 29 patients who achieved MMR prior to day 100. The differences between the 3 groups are statistically significant, \( P < 0.001 \) for each pair-wise comparison; b) Overall survival by Kaplan-Meier and c) Transformation free survival. The survival differences between the 3 groups did not reach statistical significance for the survival analyses.

Figure 4: **Treatment assignments and molecular outcomes for patients failing TIDEL-II treatment targets.** The proportion of patients with an imatinib trough level of <1000ng/mL at day 22 is denoted by numbers in brackets. Abbreviations: C1 – cohort 1; C2 – Cohort 2; T – Total; IM 600 – Imatinib 600mg/day; IM 800 – Imatinib 800mg/day; NIL – Nilotinib; IM 400 – imatinib 400mg/day; W – withdrawn from TIDEL-II, and molecular responses not recorded. Outcomes for the 25 patients who failed to achieve their 3-month molecular target of BCR-ABL1 ≤10% has been described in the body of the article. Excluding the 25 patients who failed their 3-month target, 23 of the remaining 185 patients (11%) failed to achieve BCR-ABL1 <1% at 6 months. Fifteen switched to nilotinib by 12 months either directly or after a trial of imatinib 800 mg/day; another 3 remaining on imatinib 800 mg/day, and 5 have withdrawn. At 24 months, 9 of the 23 had withdrawn (3 each from toxicity, non-adherence, and treatment
failure). Of the remaining 14 patients, 2 remained on imatinib 800 mg/day and 12 on nilotinib, and all had BCR-ABL1 <1%. Overall, 6 of the 23 patients had MMR at 24 months (26%), only one doing so on escalated-dose imatinib. The 24 month MMR rate in this group is similar to patients with BCR-ABL >10% at 3 months. Of the 159 patients who achieved their 3 and 6 month TIDEL-II targets and had not withdrawn from the study before 12 months, 30 had BCR-ABL1 \( \geq 0.1\% \) at 12 months. At 24 months, 20 of these 30 patients (67%) had achieved and maintained MMR (10 on nilotinib, 9 on imatinib 800 mg/day and one on imatinib 600 mg/day). Of the remainder, 6 had achieved and maintained BCR-ABL1 \( \leq 1\% \); the other 4/30 withdrew from the study (two with nilotinib-resistant mutations). Forty patients had trough imatinib levels <1000ng/mL at day 22, 20 of whom subsequently failed one of the TIDEL-II molecular targets and are included in this diagram. This group of patients make up 40%, 13% and 23% of patients failing to achieve their 3, 6 and 12 month targets respectively. The other 20 patients all achieved MMR at 12 months, 15 of them having done so on imatinib 800mg/day, 2 on imatinib 600mg/day and 3 on nilotinib (supplementary figure S4).
Cumulative incidence of confirmed MMR

Cumulative incidence of confirmed CMR

Fig. 1A

Fig. 1B
TIDEL-II: frontline use of imatinib in CML with early switch to nilotinib for failure to achieve time-dependent molecular targets

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