Critical Reviews in Oncology / Hematology 120 (2017) 52–59

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Ponatinib in chronic myeloid leukemia (CML): Consensus on patient treatment and management from a European expert panel

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ARTICLE INFO

Keywords:
BCR-ABL1
Chronic myeloid leukemia
Philadelphia chromosome
Ponatinib
Tyrosine kinase inhibitor

ABSTRACT

Five tyrosine kinase inhibitors (TKIs) are currently approved in the European Union for treatment of chronic myeloid leukemia (CML) and all have considerable overlap in their indications. While disease-specific factors such as CML phase, mutational status, and line of treatment are key to TKI selection, other important features must be considered, such as patient-specific comorbidities and TKI safety profiles. Ponatinib, the TKI most recently approved, has demonstrated efficacy in patients with refractory CML, but is associated with an increased risk of arterial hypertension, sometimes severe, and serious arterial occlusive and venous thromboembolic events. A panel of European experts convened to discuss their clinical experience in managing patients with CML. Based on the panel discussions, scenarios in which a CML patient may be an appropriate candidate for ponatinib therapy are described, including presence of the T315I mutation, resistance to other TKIs without the T315I mutation, and intolerance to other TKIs.

1. Introduction

Currently in the European Union (EU), 5 tyrosine kinase inhibitors (TKIs) are approved for use in patients with chronic myeloid leukemia (CML): imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. Because there is considerable overlap in their current EU indications, treatment choices may be complex (Table 1). Physicians have some guidance from labeling and European LeukemiaNet recommendations (Glivec; Sprycel; Tasigna; Bosulif; Iclusig; Baccarani et al., 2013), mainly based on disease-specific factors such as CML phase, mutational status, and line of treatment. However, other features should be taken into consideration, such as patient-specific factors (including comorbidities) and individual TKI safety profiles. Furthermore, the potential value of investigational drugs or drug combinations (Fava et al., 2015; Holyoake and Helgason, 2015), especially those with ongoing clinical trials (eg, ABL001 (Ottmann et al., 2015), dasatinib with nivolumab (Porkka et al., 2014), and nilotinib with ruxolitinib (Gallipoli et al., 2014)) may be taken into account. Thus, additional information from published data and clinical experience may be helpful for treatment selection in patients with CML, especially for those in whom the disease resisted first- or second-line TKI therapy.

Given the overlapping indications of approved TKIs and their differing safety profiles, there is a need for guidance on appropriate use of TKIs including ponatinib, the TKI most recently approved in the EU, within the context of overall management. Therefore, a panel of European experts was convened to discuss these issues. The results of a series of online debates and a live meeting are described in this review. Based on our discussions as members of the panel, we describe scenarios in which a patient with CML in chronic phase (CP-CML) may be an appropriate candidate for ponatinib: presence of the T315I mutation,

Abbreviations: ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; AP-CML, CML in accelerated phase; BP-CML, CML in blast phase; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; CP-CML, CML in chronic phase;; EU, European Union; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response; PACE trial, Ponatinib Ph+ ALL and CML Evaluation trial; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor

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http://dx.doi.org/10.1016/j.critrevonc.2017.10.002
Received 29 March 2017; Received in revised form 26 September 2017; Accepted 3 October 2017

Table 1
Overview of Currently EU-approved TKIs in CML.

	Imatinib (Glivec)	Dasatinib (Sprycel)	Nilotinib (Tasigna)	Bosutinib (Bosulif)	Ponatinib (Iclusig)
Relevant indications	Adult and pediatric patients with: ● Newly diagnosed Ph+ CML for whom bone marrow transplantation is not considered as the first line of treatment ● Ph+ CP-CML after failure of interferon-α therapy, or AP-CML or BP-CML	Adult patients with: ● Newly diagnosed Ph+ CP-CML ● CP-CML, AP-CML, or BP-CML with resistance or intolerance to prior therapy including imatinib ● Lymphoid BP-CML with resistance or intolerance to prior therapy	Adult patients with: ● Newly diagnosed Ph+ CP-CML ● Ph+ CP-CML or AP-CML with resistance or intolerance to prior therapy including imatinib	Adult patients with: ● Ph+ CP-CML, AP-CML, or BP-CML previously treated with 1 or more TKIs and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options	Adult patients with CP-CML, AP-CML, or BP-CML: ● Who are resistant to dasatinib or nilotinib ● Who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate ● Who have the T315I mutation
Key efficacy results in CML from summary of product characteristics	Newly diagnosed Ph+ CML (n = 553 at 84 mo): ● CHR: 96.6% ● MCyR: 88.6% ○ CCyR: 82.5% Ph+ CP-CML after failure of interferon-α therapy (n = 532 at 37 mo): ● CHR: 95% ● MCyR: 65% ○ CCyR: 53% AP-CML (n = 235 at 40.5 mo): ● CHR: 42% ● MCyR: 28% ○ CCyR: 16% BP-CML (n = 260 at 38 mo): ● CHR: 8% ● MCyR: 15% ○ CCyR: 7%	Newly diagnosed Ph+ CML (n = 259 at 60 mo): ● CCyR: 88.0% ● MMR: 76.4% CP-CML in imatinib-resistant or -intolerant (n = 387 at 24 mo): ● CHR: 91% ● MCyR: 62% ○ CCyR: 54% AP-CML in imatinib-resistant or -intolerant (n = 174 at 24 mo): ● CHR: 50% ● MCyR: 40% ○ CCyR: 33% BP-CML in imatinib-resistant or -intolerant (myeloid: n = 109; lymphoid: n = 48 at 24 mo): ● CHR: 26% myeloid; 29% lymphoid ● MCyR: 34% myeloid; 52% lymphoid ○ CCyR: 27% myeloid; 46% lymphoid	Newly diagnosed Ph+ CML (n = 282 [300 mg BID], n = 281 [400 mg BID] at 24 mo) ● CCyR: 86.9% (300 mg); 84.7% (400 mg) ● MMR at 72 mo: 52.5% (300 mg); 57.7% (400 mg) CP-CML in imatinib-resistant or -intolerant (n = 321 at 24 mo): ● CHR: 70% ● MCyR: 51% ○ CCyR: 37% AP-CML in imatinib-resistant or -intolerant (n = 137 at 24 mo): ● CHR: 30% ● MCyR: 30% ○ CCyR: 20%	Ph+ CP-CML with prior imatinib treatment only (n = 266): ● CHR: 85% ● MCyR: 59% ○ CCyR: 48% Ph+ CP-CML with prior imatinib and dasatinib or nilotinib treatment (n = 110): ● CHR: 73% ● MCyR: 41% ○ CCyR: 32% AP-CML with prior treatment of at least imatinib (n = 69): ● CHR: 35% ● MCyR: 35% ○ CCyR: 25% BP-CML with prior treatment of at least imatinib (n = 54): ● CHR: 15% ● MCyR: 30% ○ CCyR: 20%	CP-CML resistant/intolerant to dasatinib or nilotinib (n = 267; T315I, n = 64): ● MCyR: 55% (T315I: 70%) ○ CCyR: 46% (T315I: 66%) ● MMR: 39% (T315I: 58%) AP-CML resistant/intolerant to dasatinib or nilotinib (n = 83; T315I, n = 18): ● MHR: 57% (T315I: 56%) ● MCyR: 39% (T315I: 56%) BP-CML resistant/intolerant to dasatinib or nilotinib (n = 62; T315I, n = 24): ● MHR: 31% (T315I: 29%) ● MCyR: 23% (T315I: 29%)
Key precautions and warnings	Hepatic toxicity, fluid retention, tumor lysis syndrome, hepatitis B reactivation, drug interactions (CYP3A)	Myelosuppression, bleeding, fluid retention, pulmonary artery hypertension, QTc interval prolongation, cardiac adverse reactions, hepatitis B reactivation, drug interactions (CYP3A, proton pump inhibitors, histamine-2 antagonists, antacids)	Myelosuppression, QTc interval prolongation, cardiovascular adverse events, sudden death, fluid retention/edema, hepatitis B reactivation, tumor lysis syndrome, elevated blood lipids, elevated blood glucose, elevated serum lipase, drug interactions (CYP3A4), food effect	Contraindicated in hepatic impairment. Liver function abnormalities, diarrhea/vomiting, myelosuppression, fluid retention, elevated serum lipase, increased risk of infection, QTc interval prolongation, renal impairment, hepatitis B reactivation, drug interactions (CYP3A, proton pump inhibitors)	Myelosuppression, arterial occlusion, venous thromboembolism, congestive heart failure, pancreatitis, hepatotoxicity, bleeding, hepatitis B reactivation, drug interactions (CYP3A)

AP-CML, accelerated-phase CML; BID, twice daily; BP-CML, blast-phase CML; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CP-CML, chronic-phase CML; CYP, cytochrome P450; CyR, cytogenetic response; EU, European Union; MCyR, major cytogenetic response; MHR, major hematologic response; MMR, major molecular response; Ph+, Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

resistance to other TKIs without the T315I mutation, and intolerance to other TKIs. Representative case studies are presented. Patients with CML in accelerated phase or blast phase (AP- or BP-CML) are considered in light of their distinct risk-benefit profile, and dosing considerations are discussed.

2. Ponatinib overview

Ponatinib has activity against unmutated and mutated BCR-ABL1, including the T315I mutation present in approximately 15% of patients with TKI-resistant CML (O'Hare et al., 2009; Cortes et al., 2007). In preclinical studies, 40 nM of ponatinib (which is achieved with daily doses ≥30 mg) suppressed the emergence of mutations (O'Hare et al., 2009; Cortes et al., 2012).

Ponatinib demonstrated marked antileukemic efficacy in heavily pretreated patients with CML and Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL) and was approved for treatment of these diseases based on results of the phase 2 Ponatinib Ph + ALL and CML Evaluation (PACE) trial (Cortes et al., 2012; Cortes et al., 2013a). A total of 449 patients were enrolled, 270 with CP-CML, 85 with AP-CML, 62 with BP-CML, and 32 with Ph+ ALL (Cortes et al., 2013a). In patients with CP-CML, 56% had a major cytogenetic response (MCyR) at 1 year, with 46% achieving a complete cytogenetic response (CCyR). In patients with AP-CML and BP-CML, MCyR was observed in 39% and 23% of patients at 6 months, respectively, with CCyR rates of 24% and 18%. In Ph+ ALL patients, 47% had MCyR, with 38% achieving CCyR.

However, the expected benefits of ponatinib treatment must be balanced against the potential risks, including arterial hypertension, which is sometimes severe, and serious arterial occlusive and venous thromboembolic events, which appear to be related to certain pre-existing cardiovascular risk factors, ponatinib dose, or both (Hochhaus et al., 2014; Knickerbocker et al., 2014; Guilhot et al., 2015; Talpaz et al., 2015; Cortes et al., 2015a; Lipton et al., 2016). In the PACE trial, serious arterial and venous occlusive adverse events occurred in 19% and 5% of patients, respectively (Iclusig, 2017).

Regular cardiovascular monitoring is a critical component of managing patients diagnosed with CML, especially those treated with ponatinib (Steegmann et al., 2016). European guidelines on cardiovascular disease prevention can be applied to CML patients to determine a patient's cardiovascular risk group (Table 2; see http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/CVD-Prevention-in-clinical-practice-European-Guidelines-on), and online risk assessment tools (eg, http://www.heartscore.org) can help identify CML patients at high risk of cardiovascular events (Piepoli et al., 2016; Rea et al., 2015). The patient's number of cardiovascular risk factors may be used to determine an appropriate monitoring schedule (Table 3) and all cardiovascular risk factors should be managed aggressively in consultation with primary health care physicians, as well as specialists in cardiovascular medicine and hemostasis.

3. Patients with CP-CML and the T315I mutation

BCR-ABL1 mutations have been detected in approximately 25% to 30% of patients with CP-CML who have resistance to imatinib, based on conventional Sanger sequencing (Soverini et al., 2011; Soverini et al., 2006). The T315I mutation, commonly referred to as the gatekeeper mutation because it controls access to the ATP-binding site (O'Hare et al., 2009), confers resistance to imatinib and to the second-generation TKIs nilotinib, dasatinib, and bosutinib (Soverini et al., 2013). Across studies of patients with CML in various phases, the T315I mutation has been detected in 10% to 27% of patients with resistance-associated mutations (Soverini et al., 2014); however, in trials of dasatinib and nilotinib (with imatinib as a comparator) in newly diagnosed CP-CML patients, the overall frequencies of T315I have been low, at 1% to 7% among patients with a mutational analysis (Hochhaus et al., 2013a; Hughes et al., 2015). Ponatinib has a broad spectrum of activity against most *BCR-ABL1* mutations associated with clinical resistance to imatinib and second-generation TKIs (O'Hare et al., 2009) and is the only approved TKI that has activity against the T315I mutation (Table 1) (Glivec; Sprycel; Tasigna; Bosulif; Iclusig). In some patients with the T315I mutation, alternative treatments such as allogeneic hematopoietic stem cell transplantation (alloHSCT) may need to be considered, based on disease stage, risk factors for adverse events, and comorbidities (Nicolini et al., 2011). Omacetaxine mepesuccinate, an alternative treatment in cases where multiple TKIs have failed, has been shown to result in MCyR in 19% of previously treated CP-CML patients with the T315I mutation, but is not approved in the EU (Cortes et al., 2015b; Cortes et al., 2013b; Synribo, 2017). Another investigational option is interferon-α (Itonaga et al., 2012; Cornelison et al., 2011). Representative cases of patients with CP-CML and the T315I mutation are provided below, along with consensus recommendations from the panel.

Table 2
Cardiovascular risk groups based on 2016 European CVD risk assessment model.

Very high risk	Subjects with any of the following: ● Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm, and PAD. Unequivocally documented CVD on imaging includes plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery. ● DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolemia or marked hypertension. ● Severe CKD (GFR < 30 mL/min/1.73 m^2). ● A calculated SCORE ≥10%.
High risk	Subjects with: ● Markedly elevated single risk factors, in particular cholesterol > 8 mmol/L (> 310 mg/dL) (eg, in familial hypercholesterolemia) or BP ≥180/110 mmHg. ● Most other people with DM (with the exception of young people with type 1 DM and without major risk factors who may be at low or moderate risk). ● Moderate CKD (GFR 30–59 mL/min/1.73 m^2). ● A calculated SCORE ≥5% and < 10%.
Moderate risk	● SCORE ≥1% and < 5% at 10 years. Many middle-aged subjects belong to this category.
Low risk	● SCORE < 1%.

ACS, acute coronary syndrome; AMI, acute myocardial infarction; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; PAD, peripheral artery disease; SCORE, Systematic Coronary Risk Estimation; TIA, transient ischemic attack.
Reprinted from: Piepoli MF, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81, by permission of Oxford University Press on behalf of the European Society of Cardiology, http://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/CVD-Prevention-in-clinical-practice-European-Guidelines-on (Piepoli et al., 2016). ARIAD Pharmaceuticals, Inc. was not involved in the development of this ESC Guideline and in no way influenced its content.

Table 3
Potential schedule for cardiovascular monitoring based on number of risk factors.[a]

Evaluation	Baseline	3 months	6 months	12 months	Every 6 months	Every 12 months
No risk factors						
Physical examination[b]	X	X	X	X	X	
LDL-C, HDL-C, TG	X	X	X	X		X
Uric acid, creatinine, K, glucose	X	X	X	X		X
Blood pressure	X	X	X	X	X	
ECG	X	X (as clinically indicated)				
Echocardiogram	X	X (as clinically indicated)				
1–3 risk factors						
Physical examination[b]	X	X	X	X	X	
HbA_{1c}	X	X	X	X	X	
LDL-C, HDL-C, TG	X	X	X	X		X
Uric acid, creatinine, K, glucose	X	X	X	X		X
Blood pressure	X	X	X	X	X	
ECG	X			X		X
Echocardiogram	X	X (as clinically indicated)				
Edinburgh Claudication Questionnaire[c] (Leng and Fowkes, 1992)	X			X		X (24 months)
> 3 risk factors						
Physical examination[b]	X	X	X	X	X	
HbA_{1c}	X	X	X	X	X	
LDL-C, HDL-C, TG	X	X	X	X		X
Uric acid, creatinine, K, glucose	X	X	X	X		X
Blood pressure	X	X	X	X	X	
ECG[d]	X		X	X	X	
Echocardiogram[d]	X	X (as clinically indicated)				
Edinburgh Claudication Questionnaire[c,d] (Leng and Fowkes, 1992)	X			X		X
Inferior limb and carotid ultrasound (Doppler) scan[d,e]	X			X		X

ECG, electrocardiogram; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; K, potassium; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
[a] Based on schedule used at St Orsola-Malpighi Hospital, Bologna, Italy. Courtesy of Gianantonio Rosti.
[b] Physical examination should include peripheral pulses.
[c] If Edinburgh result is positive, determine ankle-brachial index (ABI); if ABI is < 0.9, refer patient to a vascular surgeon.
[d] Within context of referral to cardiovascular specialist.
[e] If carotid ultrasound (Doppler) scan is positive, refer patient to a vascular surgeon.

3.1. Patient 1

Patient 1 is a 38-year-old female patient with an intermediate Sokal risk score who received nilotinib as first-line treatment for CP-CML and achieved CCyR without major molecular response (MMR) after 3 months. Loss of cytogenetic response was detected after 6 months of nilotinib treatment, and the T315I mutation was detected. No cardiovascular risk factors or comorbidities were present at that time. Ponatinib was initiated as second-line treatment.

The panelists agreed that ponatinib was an appropriate choice for this patient, because she had developed the T315I mutation and she did not have any cardiovascular risk factors or comorbidities (Table 2). They agreed that they would treat with ponatinib before eventually proceeding to alloHSCT. Most panelists agreed that the patient could continue to receive ponatinib over a prolonged period, depending on response and tolerability, and that the patient should be monitored for development of cardiovascular risk factors such as hypertension, arterial occlusive events, and other adverse events. Ponatinib was associated with an estimated 3-year overall survival rate of 63% in patients with CP-CML and the T315I mutation in a pooled analysis of phase 1 and phase 2 (PACE) trials (Baccarani et al., 2015). Most importantly, responses were durable, with 83% and 81% of T315I patients estimated to maintain MCyR and CCyR, respectively, after 3 years of ponatinib treatment. Hence, ponatinib is not specifically viewed as a bridge to transplantation, but rather may be used for a prolonged period of time if well tolerated (Nicolini et al., 2015). Although Patient 1 was young and had experienced early second-generation TKI failure, most panelists did not endorse proceeding with alloHSCT without first trying ponatinib treatment, unless the patient expressed an informed preference for alloHSCT. Nevertheless, given the patient's age, it is recommended that HLA typing be conducted at the time of resistance and detection of the T315I mutation (Baccarani et al., 2013). The patient's Sokal risk group at diagnosis may help guide the decision of proceeding to transplantation during response to ponatinib, with transplantation indicated if signs of ponatinib failure or intolerance are observed.

3.2. Patient 2

Patient 2 is a 67-year-old man with low Sokal risk score who received imatinib as first-line treatment for CP-CML for 5 years, until secondary resistance developed. Dasatinib was initiated as second-line treatment, but after 2 years the T315I mutation was detected while the patient was in cytogenetic relapse. No alloHSCT donor was available. The patient had arterial hypertension and myocardial infarction 9 years ago, with stenting of the right coronary artery, and has been regularly monitored for cardiovascular problems since that time. Ponatinib was initiated as third-line treatment.

Most of the panelists agreed that ponatinib was an appropriate choice for this patient in terms of expected efficacy, because he had developed the T315I mutation. However, because of prior myocardial infarction, this patient is at high risk of a serious arterial occlusive event with ponatinib (Table 2). Thus, the patient should undergo a complete cardiovascular evaluation followed by appropriate secondary preventive measures before ponatinib initiation, with close cardiovascular monitoring during treatment. A planned dose reduction after the achievement of a response milestone could be considered (this

possibility is discussed in a later section titled "6. Dosing considerations for ponatinib use in patients with CP-CML"). Other treatment options for this patient are limited and not without risk. They include omacetaxine mepesuccinate (Cortes et al., 2015b; Cortes et al., 2013b; Synribo, 2017) or interferon-α combined with a TKI (Itonaga et al., 2012; Cornelison et al., 2011) or used alone prior to resumption of a second-generation TKI after disappearance of the T315I-mutated clones. A 3-cohort clinical trial (AP24534-14-203; NCT02467270) is currently ongoing with the goal of comparing the efficacy and safety of 3 different starting doses of ponatinib (15 mg, 30 mg, and 45 mg, with reductions to 15 mg upon achievement of MCyR) in patients resistant to at least 2 TKIs. Investigational drugs under development in clinical trials should also be considered.

3.3. Patient 3

Patient 3 is a female aged 53 years with a high Sokal score who experienced treatment failure following nilotinib as first-line treatment for CP-CML and dasatinib as second-line treatment. The patient has both T315I and F317L (compound) mutations. She also has diabetes mellitus that is well controlled.

Primarily because chances of responding to TKIs are rather low in patients with particular compound mutations (Deininger et al., 2016), and also because this patient has an elevated risk of cardiovascular events because of diabetes (a less critical factor), the panelists agreed that they would not have selected ponatinib as a treatment choice for this patient, unless other treatment options were exhausted. They agreed that the patient should undergo alloHSCT if a suitable donor is available and that experimental drugs in clinical trials (eg, ABL001 Ottmann et al., 2015) should be considered. Of note, most patients with CP-CML and compound mutations detected by next-generation sequencing responded to ponatinib in the phase 2 PACE trial; 16 (64%) of 25 patients achieved MCyR by 1 year (Deininger et al., 2016). A separate report showed that several compound mutants including the T315I mutation were resistant to ponatinib in vitro and in patients with advanced disease (Zabriskie et al., 2014).

4. Patients with CP-CML and resistance to other TKIs without the T315I mutation

Ponatinib has shown efficacy in patients with CP-CML who are resistant to dasatinib or nilotinib, without having the T315I mutation (Cortes et al., 2012, 2013a; Parker et al., 2016). These patients may have mutations other than T315I, or no identifiable *BCR-ABL1* mutations. While the appropriateness of ponatinib is clear in some of these cases, many cases are ambiguous. The panelists were sometimes divided regarding the preferred course of treatment in the following representative cases.

4.1. Patient 4

Patient 4 (female, age 71 years) received imatinib as first-line treatment for CP-CML for 2 years, until resistance developed. Dasatinib was initiated as second-line treatment, but after 1 year precapillary pulmonary hypertension developed. The patient then received nilotinib as third-line treatment. Cytogenetic response on nilotinib was not sufficient, with 80% Ph + metaphases 9 months later. No mutation was detected. The patient has controlled diabetes mellitus, controlled arterial hypertension, and rate-controlled atrial fibrillation, and is receiving warfarin.

The panelists agreed that alloHSCT is not an option for this patient because of comorbidities and advanced age and most agreed that ponatinib would be an appropriate choice for this patient because her leukemia is not well controlled, she has received 3 prior TKIs, and her risk factors for cardiovascular complications are controlled. Bosutinib, a dual BCR-ABL1 and SRC kinase inhibitor like dasatinib, is another treatment option approved for patients with resistance to prior TKIs. In a phase 1/2 study of bosutinib that included patients with CP-CML who had previously received imatinib followed by dasatinib and/or nilotinib, MCyR and CCyR occurred in 32% and 24% of evaluable patients, respectively (Khoury et al., 2012). CCyR was attained by 1 (33%) of 3 patients who had previously been treated with all 3 TKIs (imatinib, dasatinib, and nilotinib). However, responses were not necessarily durable; although the probability of retaining MCyR at 2 years was 86% in responders with nilotinib resistance and 76% in responders with dasatinib intolerance, it was 34% in patients with dasatinib resistance and 50% in the 2 responders with nilotinib intolerance and prior treatment with all 3 TKIs. Finally, recent data suggest a risk of pulmonary hypertension recurrence on bosutinib therapy (Riou et al., 2016). Investigational drugs in clinical trials (eg, ABL001 Ottmann et al., 2015) should also be considered for patients with resistance to multiple TKIs and increased cardiovascular risk. This patient has an increased risk of experiencing an arterial occlusive event while taking ponatinib due to her history of hypertension and diabetes (Table 2). Thus, although from an efficacy point of view ponatinib is the most appropriate option (please see "3. Patients with CP-CML and the T315I mutation" ["3.1. Patient 1"] for ponatinib efficacy data), the patient should undergo a complete cardiovascular evaluation prior to initiating ponatinib treatment, appropriate primary preventive measures should be taken, and close cardiovascular monitoring should be performed during treatment. This patient's advanced age is not a contraindication for any TKI therapy. The clinical response rates in elderly patients treated with imatinib are generally like those in younger patients, although elderly patients may experience a higher rate of adverse events (Latagliata et al., 2005, 2011).

4.2. Patient 5

Patient 5 is a 45-year-old female with CP-CML and intermediate Sokal risk score who experienced treatment failure with first-line nilotinib and with second-line dasatinib. No BCR-ABL1 mutation was detected. The patient has a very high cardiovascular risk profile, with obesity (body mass index = 33 kg/m^2), uncontrolled diabetes, arterial hypertension, a history of venous thrombosis of the leg, and a family history of myocardial infarction (maternal, at age 53 years).

The panelists were divided over whether this patient should undergo alloHSCT as soon as possible. Cardiovascular problems can follow the lipid dysregulation that is common after alloHSCT (Rovó and Tichelli, 2012), and patients with a reduced cardiac ejection fraction are of concern. While bosutinib could be tried before ponatinib, not all panelists would have chosen this option, because bosutinib may not be effective in patients in whom both nilotinib and dasatinib have failed; this was not investigated in trials that led to approval of bosutinib, and responses may not be durable (Khoury et al., 2012). Some panelists thought that the patient could be given a trial of ponatinib, while managing risk factors as much as possible. In any case, a thorough discussion with the patient and research into investigational drugs would be warranted due to this patient's high risk of cardiovascular events with ponatinib. Investigational drugs under development in clinical trials should also be considered, but uncontrolled comorbid conditions may be a serious hurdle to enrollment.

4.3. Patient 6

Patient 6 (male, age 64 years) received nilotinib as first-line treatment for intermediate-risk (by Sokal and Hasford risk calculations) CP-CML and achieved optimal response from months 3 to 18. The patient then lost MMR, with a 0.5% BCR-ABL1 transcript level according to the International Scale (BCR-ABL1^{IS}). Nilotinib treatment was continued because the patient remained in CCyR. Three months later, quantitative polymerase chain reaction indicated 4.2% BCR-ABL1^{IS}. Bone marrow analysis indicated that the patient remained in CP-CML, and bone marrow cytogenetics indicated 7% Ph + metaphases. The E255K mutation was detected. The patient has a high

body mass index (32 kg/m^2) and mild hypertension (grade 1).

The E255K mutation is one of the most common mutations conferring resistance to imatinib (Ursan et al., 2015) and is notoriously difficult to treat. In the phase 2 PACE trial, 75% (6/8) of CP-CML patients with the E255K mutation at baseline achieved CCyR with ponatinib treatment (Cortes et al., 2013a). Dasatinib, nilotinib, and bosutinib have relatively modest efficacy in patients with the E255K mutation, but can be successful in some cases (Müller et al., 2009; Hughes et al., 2009; Khoury et al., 2011). Other options to be considered in this scenario include alloHSCT, depending on donor availability, and investigational drugs. The panelists agreed that dasatinib and ponatinib are appropriate treatment options for this patient. Some panelists thought that ponatinib could be tried first because of its effectiveness against the E255K mutation (Cortes et al., 2013a), while others favored dasatinib because of the patient's high cardiovascular risk profile.

5. Patients with CP-CML who are intolerant to other TKIs

When a patient experiences unacceptable adverse events with a given TKI, a choice to switch to another treatment must be made. Patients with nonhematologic intolerance to one TKI generally do not experience the same nonhematologic intolerance with another TKI (Khoury et al., 2012; Cortes et al., 2016; Cortes et al., 2011; Khoury et al., 2016; Neelakantan et al., 2014; Kobayashi et al., 2011; Garcia-Gutierrez et al., 2015; Kantarjian et al., 2013; Hochhaus et al., 2013b). In contrast, patients with hematologic intolerance to one TKI are likely to experience hematologic intolerance with another TKI, in general. Bosutinib is a possible option for patients with intolerance to the other approved TKIs in many cases, due to the relatively low incidence of severe hematologic adverse events in clinical trials (Gambacorti-Passerini et al., 2014). In the examples provided below, various cases of intolerance to TKIs are presented.

5.1. Patient 7

Patient 7 (female, age 64 years) received imatinib as first-line treatment for CP-CML and experienced recurrent grade 3/4 neutropenia and other cytopenia, which required dose reduction, treatment interruption, and granulocyte colony–stimulating factor support. The patient was then given nilotinib as second-line treatment, but similar hematologic toxicity subsequently developed.

The panelists generally agreed that this patient is likely to experience hematologic intolerance with further TKIs. Because the reserve of normal hematopoietic stem cells may be exhausted, some panelists endorsed alloHSCT as the best option, whereas other panelists suggested that trying another TKI (eg, dasatinib, bosutinib, or ponatinib) would be preferable. All panelists agreed that if alloHSCT is not possible, another TKI may be used to maintain the hematologic response for as long as possible, with bosutinib being the TKI of choice for most panelists due to the relatively low incidence of grade 3/4 neutropenia and thrombocytopenia with bosutinib (Gambacorti-Passerini et al., 2014).

5.2. Patient 8

Patient 8 is a 62-year-old female who received imatinib as first-line treatment for intermediate Sokal risk CP-CML and achieved MMR after 18 months. Because of chronic grade 1/2 nausea with imatinib 400 mg daily, treatment was switched to nilotinib and the favorable response was maintained. During nilotinib treatment, the patient developed hypercholesterolemia, requiring administration of statins, and then 2 episodes of transient ischemic attack. Nilotinib treatment was discontinued and aspirin use was initiated. The patient has had arterial hypertension, well controlled with a low-sodium diet and drug therapy, since age 56.

Because this patient has a recent history of ischemic events and has not yet received other reasonable treatment options, the panelists agreed that options other than ponatinib should be considered. The panelists suggested considering dasatinib or bosutinib. Some panelists suggested reinitiating imatinib treatment at a reduced dose of 300 mg daily together with adequate supportive care whenever needed and then changing the TKI if imatinib is not effective or tolerable at a lower dose.

6. Dosing considerations for ponatinib use in patients with CP-CML

Dose intensity correlates with the level of response to and toxicity from ponatinib treatment (Hochhaus et al., 2014; Knickerbocker et al., 2014). In the absence of data from a large, dose-ranging study, the panelists discussed appropriate starting and maintenance doses of ponatinib. The recommended starting dose of ponatinib is currently 45 mg once daily. Dose modifications or interruption of dosing should be considered for the management of adverse events (Iclusig, 2017). Panelists' opinions regarding dose modifications are off-label and are provided based solely on their clinical experience. The expert panel agreed that it is difficult to provide a general dosing strategy for all patients, as the strategy may differ according to resistance versus intolerance to previous therapy at baseline, comorbidities, response to the initial dose of ponatinib, adverse events during treatment, and other variables. They agreed that dosing should be determined following assessment of expected benefits and risks based on CML characteristics, *BCR-ABL1* mutation status, and cardiovascular risk. Most panelists preferred to initiate ponatinib treatment in CP-CML patients at 30 mg/day, even in patients with low cardiovascular risk. Some preferred to start at 45 mg/day and reduce the dose to 30 mg/day after the achievement of MCyR or BCR-ABL1^{IS} $\leq$10%, and others preferred to reduce it to 30 mg/day after achievement of CCyR or BCR-ABL1^{IS} $\leq$1%. Most panelists supported reducing the dose to 15 mg/day after the achievement of BCR-ABL1^{IS} $\leq$1%.

Regarding patients with a moderate or high cardiovascular risk profile (eg, controlled diabetes or hypertension; Table 2), most panelists supported starting ponatinib at a dose of 30 mg/day and reducing to 15 mg/day after achievement of CCyR or MMR. It was generally agreed that patients who have not achieved MCyR at 30 mg ponatinib could have their dose escalated to 45 mg with careful management of the cardiovascular risk. Some panelists suggested that a ponatinib dose of 15 mg/day could be introduced and escalated according to response and tolerability in patients with a low level of CML burden and cardiovascular risk factors.

Although some data suggest that lower doses of ponatinib are associated with a lower risk of cardiovascular events, the best dose or dosing schedule remains unknown. A recent multivariate analysis predicted that each 15 mg/day decrease in average ponatinib dose intensity would reduce the risk of an arterial occlusive event by approximately 33% (Dorer et al., 2016). Long-term prospective studies are needed to investigate long-term maintenance of response and safety in patients who started ponatinib treatment at doses lower than the indicated starting dose of 45 mg once daily. In the context of imatinib treatment, patients receiving a lower dose eventually achieved the same long-term responses as patients receiving a higher dose (Baccarani et al., 2014), and the same could be true with other TKIs. A prospective dose-ranging trial in patients with refractory CML, mentioned in the discussion of Patient 2, should provide further insight.

7. Use of ponatinib in patients with AP-CML or BP-CML

The poor prognosis in patients with advanced CML shifts the risk-benefit balance in favor of using more effective treatments, because cardiovascular risk factors carry less weight relative to the risk of death from CML. The panelists agreed that ponatinib should be considered in patients with advanced CML (both AP-CML and BP-CML) as a second-

or third-line treatment after dasatinib or nilotinib failure, regardless of the presence of the T315I mutation. They would also choose ponatinib as a second-line treatment after any TKI failure in patients with advanced CML with the T315I mutation. The panelists further agreed that ponatinib may be an appropriate option for, and that alloHSCT may be avoided in, some patients with AP-CML, depending on whether the disease presents in AP-CML or progresses from CP-CML under treatment. In the phase 2 PACE study, 55% of AP-CML patients achieved major hematologic response by 6 months, the median duration of major hematologic response was 12 months, and the estimated rate of overall survival at 12 months was 84% (Cortes et al., 2013a). The panelists agreed that they would always prepare to proceed with alloHSCT, if possible, for patients with BP-CML. While ponatinib monotherapy was associated with major hematologic response in 31% of BP-CML patients in the phase 2 study, responses were not durable; the median duration was 5 months, which is within the range of duration of hematologic response observed in previously treated patients receiving dasatinib or bosutinib (Cortes et al., 2013a, 2008; Gambacorti-Passerini et al., 2015). The estimated rate of overall survival at 12 months was 29% and median overall survival was 7 months (Cortes et al., 2013a). Ponatinib combined with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone chemotherapy was shown to be highly effective in a phase 2 study in patients with Ph+ acute lymphoblastic leukemia, with MMR and undetectable disease achieved by 100% and 78% of patients, respectively (Jabbour et al., 2015). After a median follow-up of 26 months, the 2-year rates of complete remission, event-free survival, and overall survival were 97%, 81%, and 80%, respectively. Further studies are needed to determine whether ponatinib combined with chemotherapy may be an effective approach in patients with BP-CML.

Dosing considerations for patients with advanced disease were discussed by the expert panel; it should be reiterated that the panelists' opinions regarding dose modifications are off-label, and their opinions are provided based on their clinical experience. The panelists suggested maintaining a 45 mg/day dose until alloHSCT, if possible, depending on response, and some panelists proposed that the dose could be reduced to 30 mg/day following CCyR or MMR in patients with significant cardiovascular risk. In any case, a patient with advanced CML requiring ponatinib treatment should be seen in a center with expertise in CML, if possible, and cardiovascular risk factors should always be managed aggressively during ponatinib therapy.

8. Conclusions

Ponatinib has shown efficacy in patients who have received prior TKIs, and the risk-benefit balance should always be evaluated for an individual patient. Based on the discussions of an expert panel assembled from various EU institutions, important factors to consider when deciding to initiate ponatinib treatment include disease state, mutational status, line of treatment, reason for change of therapy (intolerance or resistance), and specific comorbidities. Results from ongoing clinical trials, including a dose-ranging study with ponatinib (NCT02467270), are expected to provide further information regarding the benefit-risk balance in ponatinib-treated patients.

Conflict of interest statement

MCM has shares in and is employed by the Institute for Hematology and Oncology (IHO GmbH); has received consultant fees and fees for speakers bureaus from ARIAD, Bristol-Myers Squibb, Novartis, and Pfizer; and has received research support from ARIAD, Bristol-Myers Squibb, and Novartis.

FC has received consultant fees and fees for speakers bureaus from ARIAD, Bristol-Myers Squibb, Novartis, and Pfizer.

HHH has served as chairman of the Nordic CML Study Group, which has received support from Bristol-Myers Squibb, Merck, Novartis, and Pfizer, and has received honoraria from ARIAD, Bristol-Myers Squibb, Janssen, and Novartis.

JJWMJ has received honoraria from and has served as a speaker for ARIAD, Bristol-Myers Squibb, and Pfizer; has served on advisory boards for ARIAD and Pfizer; and has received research support from Novartis.

DM has received honoraria from ARIAD, Bristol-Myers Squibb, Novartis, and Pfizer.

DR has received fees from ARIAD, Bristol-Myers Squibb, Incyte, Novartis, and Pfizer.

GR has received fees from ARIAD, Bristol-Myers Squibb, Incyte, Novartis, and Pfizer.

Acknowledgments

The online debates and live follow-up meeting were sponsored by ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. Professional medical writing assistance for this publication was provided by Pamela Barendt, PhD, of Peloton Advantage, LLC, Parsippany, New Jersey, USA, and funded by ARIAD Pharmaceuticals, Inc. All authors contributed to the writing and revision of all drafts, approved the final manuscript, and decided to submit the paper for publication.

References

Baccarani, M., Deininger, M.W., Rosti, G., Hochhaus, A., Soverini, S., Apperley, J.F., et al., 2013. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 122 (6), 872–884.

Baccarani, M., Druker, B.J., Branford, S., Kim, D.W., Pane, F., Mongay, L., et al., 2014. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: final update from the Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) study. Int. J. Hematol. 99 (5), 616–624.

Baccarani, M., Mauro, M.J., Cortes, J.E., Hochhaus, A., Hughes, T.P., Guilhot, F., et al., 2015. Long-term follow-up of ponatinib efficacy and safety in patients (pts) with the T315I mutation in the phase 1 and phase 2 (PACE) trials [abstract]. Haematologica 100 (Suppl. 1), 65.

Bosulif [summary of product characteristics]. Pfizer Limited, Sandwich, United Kingdom, 2017, March 30, 2017.

Cornelison, A.M., Welch, M.A., Koller, C., Jabbour, E., 2011. Dasatinib combined with interferon-alfa induces a complete cytogenetic response and major molecular response in a patient with chronic myelogenous leukemia harboring the T315I BCR-ABL1 mutation. Clin. Lymphoma Myeloma Leuk. 11 (Suppl. 1), S111–S113.

Cortes, J., Jabbour, E., Kantarjian, H., Yin, C.C., Shan, J., O'Brien, S., et al., 2007. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. Blood 110 (12), 4005–4011.

Cortes, J., Kim, D.W., Raffoux, E., Martinelli, G., Ritchie, E., Roy, L., et al., 2008. Efficacy and safety of dasatinib in imatinib-resistant or -intolerant patients with chronic myeloid leukemia in blast phase. Leukemia 22 (12), 2176–2183.

Cortes, J.E., Hochhaus, A., le Coutre, P.D., Rosti, G., Pinilla-Ibarz, J., Jabbour, E., et al., 2011. Minimal cross-intolerance with nilotinib in patients with chronic myeloid leukemia in chronic or accelerated phase who are intolerant to imatinib. Blood 117 (21), 5600–5606.

Cortes, J.E., Kantarjian, H., Shah, N.P., Bixby, D., Mauro, M.J., Flinn, I., et al., 2012. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N. Engl. J. Med. 367 (22), 2075–2088.

Cortes, J.E., Kim, D.W., Pinilla-Ibarz, J., le Coutre, P., Paquette, R., Chuah, C., et al., 2013a. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N. Engl. J. Med. 369 (19), 1783–1796.

Cortes, J.E., Nicolini, F.E., Wetzler, M., Lipton, J.H., Akard, L., Craig, A., et al., 2013b. Subcutaneous omacetaxine mepesuccinate in patients with chronic-phase chronic myeloid leukemia previously treated with 2 or more tyrosine kinase inhibitors including imatinib. Clin. Lymphoma Myeloma Leuk. 13 (5), 584–591.

Cortes, J., Kim, D.W., Pinilla-Ibarz, J., le Coutre, P.D., Paquette, R., Chuah, C., et al., 2015a. Ponatinib efficacy and safety in heavily pretreated leukemia patients: 3-year results of the PACE trial [abstract]. Haematologica 100 (Suppl. 1), 64.

Cortes, J.E., Kantarjian, H.M., Rea, D., Wetzler, M., Lipton, J.H., Akard, L., et al., 2015b. Final analysis of the efficacy and safety of omacetaxine mepesuccinate in patients with chronic- or accelerated-phase chronic myeloid leukemia: results with 24 months of follow-up. Cancer 121 (10), 1637–1644.

Cortes, J.E., Lipton, J.H., Miller, C.B., Busque, L., Akard, L.P., Pinilla-Ibarz, J., et al., 2016. Evaluating the impact of a switch to nilotinib on imatinib-related chronic low-grade adverse events in patients with CML-CP: the ENRICH study. Clin. Lymphoma Myeloma Leuk. 16 (5), 286–296.

Deininger, M.W., Hodgson, J.G., Shah, N.P., Cortes, J.E., Kim, D.W., Nicolini, F.E., et al., 2016. Compound mutations in BCR-ABL1 are not major drivers of primary or secondary resistance to ponatinib in CP-CML patients. Blood 127 (6), 703–712.

Dorer, D.J., Knickerbocker, R.K., Baccarani, M., Cortes, J.E., Hochhaus, A., Talpaz, M., et al.,

2016. Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients. Leuk. Res. 48, 84–91.
Fava, C., Morotti, A., Dogliotti, I., Saglio, G., Rege-Cambrin, G., 2015. Update on emerging treatments for chronic myeloid leukemia. Expert Opin. Emerg. Drugs 20 (2), 183–196.
Gallipoli, P., Cook, A., Rhodes, S., Hopcroft, L., Wheadon, H., Whetton, A.D., et al., 2014. JAK2/STAT5 inhibition by nilotinib with ruxolitinib contributes to the elimination of CML CD34+ cells in vitro and in vivo. Blood 124 (9), 1492–1501.
Gambacorti-Passerini, C., Brümmendorf, T.H., Kim, D.W., Turkina, A.G., Masszi, T., Assouline, S., et al., 2014. Bosutinib efficacy and safety in chronic phase chronic myeloid leukemia after imatinib resistance or intolerance: minimum 24-month follow-up. Am. J. Hematol. 89 (7), 732–742.
Gambacorti-Passerini, C., Kantarjian, H.M., Kim, D.W., Khoury, H.J., Turkina, A.G., Brümmendorf, T.H., et al., 2015. Long-term efficacy and safety of bosutinib in patients with advanced leukemia following resistance/intolerance to imatinib and other tyrosine kinase inhibitors. Am. J. Hematol. 90 (9), 755–768.
Garcia-Gutierrez, V., Martinez-Trillos, A., Lopez Lorenzo, J.L., Bautista, G., Martin Mateos, M.L., Alvarez-Larran, A., et al., 2015. Bosutinib shows low cross intolerance, in chronic myeloid leukemia patients treated in fourth line. Results of the Spanish compassionate use program. Am. J. Hematol. 90 (5), 429–433.
Glivec [summary of product characteristics], 2017. Novartis Europharm Limited, Camberley, United Kingdom, January 16, 2017.
Guilhot, F., Khoury, H.J., Baccarani, M., Hochhaus, A., Hughes, T.P., Lipton, J.H., et al., 2015. Elevated blood pressure (BP) and adverse events of hypertension (HTN) in phase 1, 2, and 3 trials of ponatinib in leukemia [abstract]. Haematologica 100 (Suppl. 1), 692.
Hochhaus, A., Saglio, G., Larson, R.A., Kim, D.W., Etienne, G., Rosti, G., et al., 2013a. Nilotinib is associated with a reduced incidence of BCR-ABL mutations vs imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Blood 121 (18), 3703–3708.
Hochhaus, A., Cortes, J.E., Kim, D.-W., Pinilla-Ibarz, J., le Coutre, P.D., Paquette, R., et al., 2013b. Efficacy and safety of ponatinib following failure of dasatinib in patients (pts) with chronic phase chronic myeloid leukemia (CP-CML) in the PACE trial [abstract 1498]. Blood 122 (21), 1498.
Hochhaus, A., Pinilla-Ibarz, J., Kim, D.-W., le Coutre, P.D., Paquette, R., Chuah, C., et al., 2014. Clinical impact of dose modification and dose intensity on response to ponatinib (PON) in patients (pts) with Philadelphia chromosome-positive (Ph+) leukemias [abstract]. J. Clin. Oncol. 32 (15(Suppl.)), 7084.
Holyoake, T.L., Helgason, G.V., 2015. Do we need more drugs for chronic myeloid leukemia? Immunol. Rev. 263 (1), 106–123.
Hughes, T., Saglio, G., Branford, S., Soverini, S., Kim, D.W., Müller, M.C., et al., 2009. Impact of baseline *BCR-ABL*mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. J. Clin. Oncol. 27 (25), 4204–4210.
Hughes, T.P., Saglio, G., Quintas-Cardama, A., Mauro, M.J., Kim, D.W., Lipton, J.H., et al., 2015. *BCR-ABL1* mutation development during first-line treatment with dasatinib or imatinib for chronic myeloid leukemia in chronic phase. Leukemia 29 (9), 1832–1838.
Iclusig [summary of product characteristics]. 2017. ARIAD Pharma Ltd, Leatherhead, United Kingdom, February 1, 2017.
Itonaga, H., Tsushima, H., Hata, T., Matsuo, E., Imanishi, D., Imaizumi, Y., et al., 2012. Successful treatment of a chronic-phase T-315I-mutated chronic myelogenous leukemia patient with a combination of imatinib and interferon-alfa. Int. J. Hematol. 95 (2), 209–213.
Jabbour, E., Kantarjian, H., Ravandi, F., Thomas, D., Huang, X., Faderl, S., et al., 2015. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol. 16 (15), 1547–1555.
Kantarjian, H.M., Cortes, J.E., Kim, D.-W., Pinilla-Ibarz, J., le Coutre, P.D., Paquette, R., et al., 2013. Efficacy and safety of ponatinib following failure of nilotinib in patients with chronic phase chronic myeloid leukemia (CP-CML) in the PACE trial [abstract 2738]. Blood 122 (21), 2738.
Khoury, H.J., Cortes, J.E., Gambacorti-Passerini, C., Kim, D.-W., Zaritskey, A., Hochhaus, A., et al., 2011. Activity of bosutinib by baseline and emergent mutation status in Philadelphia chromosome-positive leukemia patients with resistance or intolerance to other tyrosine kinase inhibitors [abstract]. Blood 118 (21) abstract 110.
Khoury, H.J., Cortes, J.E., Kantarjian, H.M., Gambacorti-Passerini, C., Baccarani, M., Kim, D.W., et al., 2012. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 119 (15), 3403–3412.
Khoury, H.J., Goldberg, S.L., Mauro, M.J., Stone, R.M., Deininger, M.W., Bradley-Garelik, M.B., et al., 2016. Cross-intolerance with dasatinib among imatinib-intolerant patients with chronic phase chronic myeloid leukemia. Clin. Lymphoma Myeloma Leuk. 16 (6), 341–349.
Knickerbocker, R., Dorer, D.J., Haluska, F.G., Baccarani, M., Cortes, J.E., Hochhaus, A., et al., 2014. Impact of dose intensity of ponatinib on selected adverse events: multivariate analyses from a pooled population of clinical trial patients [abstract]. Blood 124 (21) abstract 4546.
Kobayashi, Y., Sakamaki, H., Fujisawa, S., Ando, K., Yamamoto, K., Okada, M., et al., 2011. Lack of non-hematological cross intolerance of dasatinib to imatinib in imatinib-intolerant patients with Philadelphia chromosome positive chronic myeloid leukemia or acute lymphatic leukemia: a retrospective safety analysis. Int. J. Hematol. 93 (6), 745–749.
Latagliata, R., Breccia, M., Carmosino, I., Sarlo, C., Montefusco, E., Mancini, M., et al., 2005. Elderly patients with Ph+ chronic myelogenous leukemia (CML): results of imatinib mesylate treatment. Leuk. Res. 29 (3), 287–291.
Latagliata, R., Breccia, M., Castagnetti, F., Stagno, F., Luciano, L., Gozzini, A., et al., 2011. Dasatinib is safe and effective in unselected chronic myeloid leukaemia elderly patients resistant/intolerant to imatinib. Leuk. Res. 35 (9), 1164–1169.
Leng, G.C., Fowkes, F.G., 1992. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. J. Clin. Epidemiol. 45 (10), 1101–1109.
Lipton, J.H., Chuah, C., Guerci-Bresler, A., Rosti, G., Simpson, D., Assouline, S., et al., 2016. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. Lancet Oncol. 17 (5), 612–621.
Müller, M.C., Cortes, J.E., Kim, D.W., Druker, B.J., Erben, P., Pasquini, R., et al., 2009. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting *BCR-ABL* mutations. Blood 114 (24), 4944–4953.
Neelakantan, P., Rezvani, K., May, P., Gerrard, G., Marco, B., Paliompeis, C., et al., 2014. Excellent outcome after repeated changes of tyrosine kinase inhibitor therapy for chronic myeloid leukaemia in complete cytogenetic response due to minor side effects. Br. J. Haematol. 164 (4), 608–610.
Nicolini, F.E., Basak, G.W., Soverini, S., Martinelli, G., Mauro, M.J., Müller, M.C., et al., 2011. Allogeneic stem cell transplantation for patients harboring T315I BCR-ABL mutated leukemias. Blood 118 (20), 5697–5700.
Nicolini, F.E., Basak, G.W., Kim, D.W., Olavarria, E., Pinilla-Ibarz, J., Apperley, J.F., et al., 2015. The impact of ponatinib versus allogeneic stem cell transplant (SCT) on outcomes in patients with chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with the T315I mutation [abstract]. Blood 126 (23) abstract 480.
O'Hare, T., Shakespeare, W.C., Zhu, X., Eide, C.A., Rivera, V.M., Wang, F., et al., 2009. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell 16 (5), 401–412.
Ottmann, O.G., Alimena, G., DeAngelo, D.J., Goh, Y.T., Heinrich, M.C., Hochhaus, A., et al., 2015. ABL001, a potent, allosteric inhibitor of BCR-ABL, exhibits safety and promising single-agent activity in a phase I study of patients with CML with failure of prior TKI therapy [abstract]. Blood 126 (23) abstract 138.
Parker, W.T., Yeung, D.T., Yeoman, A.L., Altamura, H.K., Jamison, B.A., Field, C.R., et al., 2016. The impact of multiple low-level *BCR-ABL1* mutations on response to ponatinib. Blood 127 (15), 1870–1880.
Piepoli, M.F., Hoes, A.W., Agewall, S., Albus, C., Brotons, C., Catapano, A.L., et al., 2016. European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur. Heart J. 37 (29), 2315–2381.
Porkka, K., Mauro, M.J., Lipton, J.H., Mahon, F.X., Strauss, L.C., Geese, W.J., et al., 2014. An open-label, phase 1b, dose-escalation study (CA180-373) of dasatinib plus nivolumab, an investigational anti-programmed cell death 1 (PD-1) antibody, in patients (pts) with previously treated chronic myeloid leukemia (CML) [abstract]. J. Clin. Oncol. 32 (15 (Suppl.)) abstract TPS7119.
Rea, D., Mirault, T., Raffoux, E., Boissel, N., Andreoli, A.L., Rousselot, P., et al., 2015. Usefulness of the 2012 European CVD risk assessment model to identify patients at high risk of cardiovascular events during nilotinib therapy in chronic myeloid leukemia. Leukemia 29 (5), 1206–1209.
Riou, M., Seferian, A., Savale, L., Chaumais, M.-C., Guignabert, C., Canuet, M., et al., 2016. Deterioration of pulmonary hypertension and pleural effusion with bosutinib following dasatinib lung toxicity. Eur. Respir. J. 48 (5), 1517–1519.
Rovó, A., Tichelli, A., 2012. Cardiovascular complications in long-term survivors after allogeneic hematopoietic stem cell transplantation. Semin. Hematol. 49 (1), 25–34.
Soverini, S., Colarossi, S., Gnani, A., Rosti, G., Castagnetti, F., Poerio, A., et al., 2006. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on Chronic Myeloid Leukemia. Clin. Cancer Res. 12 (24), 7374–7379.
Soverini, S., Hochhaus, A., Nicolini, F.E., Gruber, F., Lange, T., Saglio, G., et al., 2011. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood 118 (5), 1208–1215.
Soverini, S., De Benedittis, C., Machova Polakova, K., Brouckova, A., Horner, D., Iacono, M., et al., 2013. Unraveling the complexity of tyrosine kinase inhibitor-resistant populations by ultra-deep sequencing of the BCR-ABL kinase domain. Blood 122 (9), 1634–1648.
Soverini, S., Branford, S., Nicolini, F.E., Talpaz, M., Deininger, M.W., Martinelli, G., et al., 2014. Implications of BCR-ABL1 kinase domain-mediated resistance in chronic myeloid leukemia. Leuk. Res. 38 (1), 10–20.
Sprycel [summary of product characteristics], 2017. Bristol-Myers Squibb Pharma EEIG, Uxbridge, United Kingdom, July 7, 2017.
Steegmann, J.L., Baccarani, M., Breccia, M., Casado, L.F., Garcia-Gutierrez, V., Hochhaus, A., et al., 2016. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia 30 (8), 1648–1671.
Synribo [package insert], 2017. Teva Pharmaceuticals USA, Inc, North Wales, PA, June 2017.
Talpaz, M., Cortes, J.E., Kantarjian, H.M., Shah, N.P., Bixby, D.L., Flinn, I.W., et al., 2015. Minimum follow-up of 4 years for ongoing patients with chronic-phase chronic myeloid leukemia (CP-CML) in a phase trial of ponatinib [abstract]. Haematologica 100 (Suppl. 1), 65–66.
Tasigna [summary of product characteristics], 2017. Novartis Europharm Limited, Camberley, United Kingdom, July 19, 2017.
Ursan, I.D., Jiang, R., Pickard, E.M., Lee, T.A., Ng, D., Pickard, A.S., 2015. Emergence of BCR-ABL kinase domain mutations associated with newly diagnosed chronic myeloid leukemia: a meta-analysis of clinical trials of tyrosine kinase inhibitors. J. Manag. Care Spec. Pharm. 21 (2), 114–122.
Zabriskie, M.S., Eide, C.A., Tantravahi, S.K., Vellore, N.A., Estrada, J., Nicolini, F.E., et al., 2014. BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia. Cancer Cell 26 (3), 428–442.