European Stop Tyrosine Kinase Inhibitor Trial (EURO-SKI) in Chronic Myeloid Leukemia: Final Analysis and Novel Prognostic Factors for Treatment-Free Remission

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The European Stop Kinase Inhibitors (EURO-SKI) study is the largest clinical trial for investigating the cessation of tyrosine kinase inhibitors (TKIs) in patients with chronic myeloid leukemia in stable deep molecular remission (DMR). Among 728 patients, 434 patients (61%; 95% CI, 57 to 64) remained in major molecular response (MMR) at 6 months and 309 patients of 678 (46%; 95% CI, 42 to 49) at 36 months. Duration of TKI treatment and DMR before TKI stop were confirmed as significant factors for the prediction of MMR loss at 6 months. In addition, the type of *BCR::ABL1* transcript was identified as a prognostic factor. For late MMR losses after 6 months, TKI treatment duration, percentage of blasts in peripheral blood, and platelet count at diagnosis were significant factors in multivariate analysis. For the entire study period of 36 months, multiple logistic regression models confirmed duration of treatment, blasts, and transcript type as independent factors for MMR maintenance. In addition to the duration of treatment, transcript type as well as blasts in peripheral blood at diagnosis should be considered as important factors to predict treatment-free remission.

ACCOMPANYING CONTENT

Appendix
Data Supplement
Protocol

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INTRODUCTION

Chronic myeloid leukemia (CML) serves as a model for targeted cancer therapy, particularly through the development of tyrosine kinase inhibitors (TKIs) targeting the *BCR::ABL1* fusion gene, a molecular hallmark of CML.[1,2] TKIs have significantly improved the prognosis and quality of life for patients with CML.[3,4] Achieving treatment-free remission (TFR) has now become a new goal in CML management, with studies showing that 40%-55% of very good responder patients can successfully discontinue TKI treatment after achieving a deep molecular remission (DMR).[5-7] However, the prognostic indicators for sustained TFR are still not well established.[8-10] The EURO-SKI trial, a comprehensive investigation of TKI discontinuation, aims to shed light on these factors.[11] Here, we present the final analysis of the EURO-SKI trial after 3 years of follow-up and the prognostic factors for short- and long-term molecular response maintenance.

PATIENTS AND METHODS

Adult patients with CML in chronic phase (CP) on TKI treatment for at least 3 years with confirmed DMR (*BCR::ABL1*-transcripts ≤0.01% on the International Scale [IS] for ≥12 months) were eligible. Primary end point was the maintenance of major molecular response (MMR, *BCR::ABL1 [IS]* ≤0.1%) 6 and 36 months after TKI stop (molecular recurrence-free survival [MRecFS]).

Inclusion/exclusion criteria and procedures for this trial were previously published[11] (Data Supplement, online only for summary). The study was registered with ClinicalTrials.gov (identifier: NCT01596114).

RESULTS

Between May 30, 2012, and December 3, 2014, 868 patients with CP CML were screened, with 728 patients included in

TABLE 1. Characteristics of the EURO-SKI Patients

Characteristics	n = 728
Sex, females/males, %	47/53
Age at diagnosis, years, median (range)	52 (11-85)
Blasts in peripheral blood at diagnosis, %, median (range)[a]	0 (0-18)[b]
No. of platelets at diagnosis, 10^9/L, median (range)[c]	435 (72-3,050)
No. of spleen size below costal margin at diagnosis, cm, median (range)[d]	0 (0-32)
Age at TKI stop, years, median (range)	60 (19-89)
Time from diagnosis to TKI stop, years, median (range)	7.7 (3.1-22.6)
Duration of TKI therapy before TKI stop, years, median (range)	7.5 (3.0-14.1)
Duration of TKI therapy before MR[4] was achieved, years, median (range)	1.8 (0-11.7)
Duration of MR[4] before TKI stop, years, median (range)	4.7 (1.0-13.3)
Transcript type, No. (%)	
e13a2	139 (19.1)
e13a2 + e14a2	104 (14.3)
e14a2	323 (44.4)
e13a2 + transcript type other than e14a2	4 (0.6)
Major breakpoint, exact type unknown	158 (21.7)
Treatment before TKI, total number (percent of 728)	376 (51.7)
HU	247 (33.9)
HU + IFN alpha	71 (9.8)
IFN alpha	18 (2.5)
IFN alpha + cytarabine	7 (1.0)
HU + IFN alpha + cytarabine	30 (4.1)
Other (no IFN, no HU)	3 (0.4)

Abbreviations: HU, hydroxyurea; IFN, interferon; TKI, tyrosine kinase inhibitor.
[a]Missing data for 141 patients.
[b]Three patients had a blast percentage of >15% at diagnosis.
[c]Missing data for 113 patients.
[d]Missing data for 76 patients.

the baseline analysis (Data Supplement, Fig S1 and Table 1). The first primary end point, MRecFS at 6 months, was achieved by 61% (95% CI, 57 to 64) of patients (null hypothesis of ≤40% rejected, $P < .0001$; for more information and time-to-event analysis, see Fig 1A). The second primary end point, MRecFS at 36 months, was achieved by 46% (95% CI, 42 to 49) of patients (null hypothesis of ≤35% rejected, $P < .0001$; Fig 1A). Molecular recurrence (Fig 1B) and survival statuses (Figs 1B and 1C) were tracked over time, with a 3-year overall survival rate of 98% (95% CI, 97 to 99).

Recovery of DMR After Restarting Therapy

When loss of MMR was observed within 6 months, the probability of a recovery of MR[4] was 28% (95% CI, 23 to 34), 71% (95% CI, 65 to 76), and 85% (95% CI, 80 to 89) by 3, 6, and 12 months, respectively. When loss of MMR was observed after 6 months, the probability of a recovery of MR[4] (*BCR::ABL1 [IS]* ≤0.01%) was 52% (95% CI, 40 to 62), 92% (95% CI, 83 to 96), and 96% (95% CI, 88 to 99) by 3, 6, and 12 months, respectively (Fig 1D). Adverse events of the trial are provided for information purposes in the Data Supplement (Table S5).

Prognostic Factors for MRecFS at 6 Months

The analysis of 6-month data confirmed duration of DMR before TKI discontinuation (odds ratio [OR], 1.126) and duration of treatment (OR, 1.115) as significant factors in maintaining MMR at this time point (Data Supplement, Table S2). Additionally, in 355 patients showing transcript type e14a2, alone or in combination with e13a2, MRecFS at 6 months was 63% (95% CI, 58 to 68), whereas in 106 patients who had only transcript type e13a2, MRecFS at 6 months was 47% (OR, 1.892 95% CI, 38 to 57; $P = .0043$; Data Supplement, Table S2 model 3). Multiple logistic regression models confirmed the significance of these factors (Data Supplement, Table S2 models 4 and 5). For validation of the results in the EURO-SKI trial, a sample of 199 patients with first-line imatinib treatment in the STIM2 trial was considered (Data Supplement, Table S2 models 1′-5′; for patient characteristics, see the Data Supplement, Table S1).

Prognostic Factors for MMR Maintenance Between 6 and 36 Months

Of the 348 patients remaining in MMR or better at 6 months, molecular results at 36 months were not available for 33 patients. In the remaining 315 patients, MRecFS was 76% (95% CI 71-80) at 36 months. For MMR maintenance between 6 and 36 months, the duration of TKI treatment, but not of DMR, emerged as a significant factor. Disease characteristics at diagnosis, peripheral blood blast cells and platelet counts, were also independent significant factors influencing MMR maintenance (Data Supplement, Table S3).

Prognostic Factors for the Entire Trial Period of 36 Months

Analyzing MMR maintenance over the entire 36-month trial revealed four significant factors: duration of TKI treatment, duration of DMR while receiving TKI, peripheral blood blast cells at diagnosis, and transcript type. Patients with transcript type e14a2 (+e13a2) had a higher probability of maintaining MMR over 36 months than e13a2 alone (univariate analysis in the Data Supplement, Table S4, $P = .0051$). Multiple logistic regression models identified various combinations of these factors as predictive of MMR maintenance (Table 2 and for all the details, see the Data Supplement, Table S4).

DISCUSSION

We previously demonstrated that stopping TKI therapy is feasible and safe when applying predefined criteria, and decentralized but standardized molecular monitoring.[11-13] The final analysis of the EURO-SKI trial demonstrates that

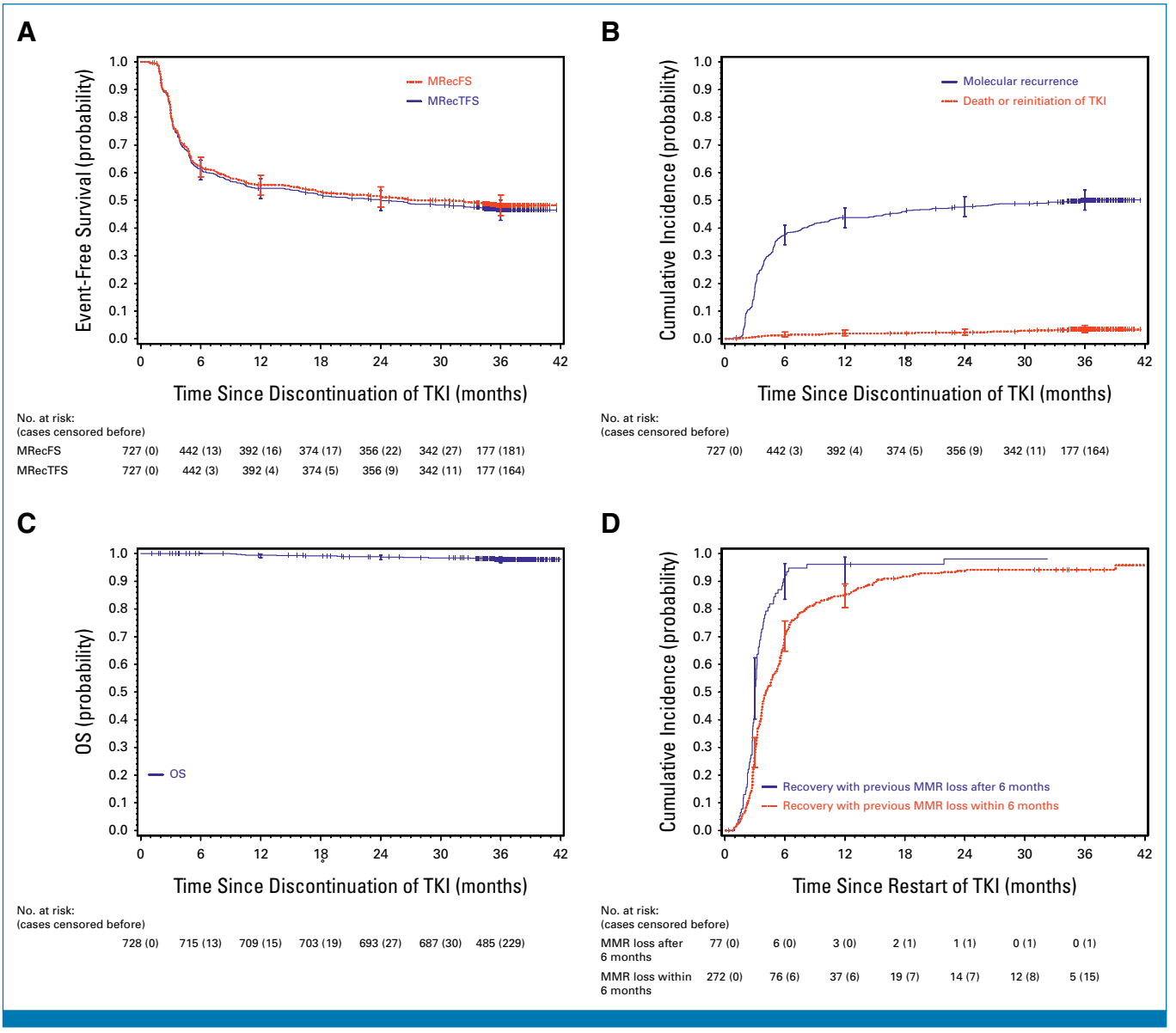

FIG 1. (A) MRecFS and MRecTFS after TKI discontinuation. Of 713 available patients (six patients without molecular result at 6 months; nine patients had TKI restart without previous loss of MMR), 434 remained in MMR during the first 6 months. Thus, also in the final analysis, the null hypothesis was rejected ($P < .0001$). For the second primary end point, MRecFS rate at 36 months, 678 patients could be analyzed (33 patients were without molecular result; 17 patients restarted TKI without loss of MMR). Three hundred nine patients (46% [95% CI, 42 to 49]) were in MMR or better; thus, the null hypothesis of 35% or lower was rejected ($P < .0001$). For the time-to-event analysis, 727 patients were evaluable. One patient lacked follow-up information on molecular status. Median follow-up for MRecFS was 36 months (IQR, 36-37). MRecFS was 62%, 56% and 48% by 6, 12, and 36 months, respectively. When the 17 cases with reinitiation of TKI without previous MMR loss were also counted as an event, MRecTFS was 61%, 54%, and 46% at 6, 12, and 36 months, respectively. Bars at 6, 12, 24, and 36 months indicate the upper and lower limits of the 95% CIs for the estimated incidences. (B) Cumulative incidence of molecular recurrence (loss of MMR) and death or restart of TKI therapy after TKI discontinuation without loss of MMR. Cumulative incidence of MRec was 38%, 44%, and 50% at 6, 12, and 36 months, respectively. Twenty-four patients experienced an event competing against loss of MMR: 17 patients had a reinitiation of TKI, of whom two later died while still in MMR; seven patients died without loss of MMR or reinitiation of therapy. Bars at 6, 12, 24, and 36 months indicate the upper and lower limits of the 95% CIs for the estimated incidences. (C) OS. Three-year OS was 98% (95% CI, 97 to 99). Apart from the above-mentioned nine patients with death in MMR, eight patients died after loss of MMR. However, seven of eight patients had regained MMR before death. In 15 cases, death was in CP and considered unrelated to CML; in two cases, cause of death was unknown. Bars at 6, 12, 24, and 36 months indicate the upper and lower limits of the 95% CIs for the estimated incidences. (D) Cumulative incidences of recovery of MR4 after loss of MMR. Bars at 3, 9, and 12 months indicate the upper and lower limits of the 95% CIs for the estimated incidences. CP, chronic phase; MMR, major molecular response; MRecFS, molecular recurrence-free survival; MRecTFS, molecular recurrence- and treatment-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor.

TABLE 2. Multiple Logistic Models With Significant Factors for the Probability to Maintain MMR 36 Months After TKI Stop

	EURO-SKI				STIM2			
Multiple Models	N	OR	95% CI	*P*	N	OR	95% CI	*P*
Model A								
Duration of TKI treatment, years	413	1.127	1.038 to 1.224	.0043	175	1.216	1.059 to 1.396	.0057
Blasts in peripheral blood, %	413	0.882	0.800 to 0.972	.0116	175	0.767	0.592 to 0.994	.0447
Model B								
Duration of TKI treatment, years	392	1.106	1.019 to 1.200	.0163	158	1.270	1.092 to 1.478	.0019
Transcript, e14a(+e13a2) *v* e13a2	392	2.090	1.254 to 3.484	.0047	158	3.089	1.398 to 6.826	.0053
Model C								
DMR duration under TKI, years	413	1.119	1.022 to 1.225	.0149	175	1.289	1.083 to 1.533	.0042
Time to DMR under TKI, years	413	1.142	1.016 to 1.284	.0261	175	1.145	0.966 to 1.357	.1176
Blasts in peripheral blood, %	413	0.881	0.800 to 0.972	.0112	175	0.778	0.602 to 1.006	.0558

NOTE. A total of 561 patients with first-line imatinib treatment were evaluable for the entire 36 months in the EURO-SKI trial. Three significant multiple logistic regression models were identified: model A with duration of TKI treatment plus blasts, model B with duration of TKI treatment plus transcript type, and model C with time to DMR and duration of DMR while receiving TKI plus blasts. Because of correlations and different sample sizes, the three models are not statistically comparable. Univariate analysis and details of multivariate analysis are given in the Data Supplement (Table S4; model A, B, C counterpart to model 5, 6, 7 and 5′, 6′, 7′).

Abbreviations: DMR, deep molecular remission; EURO-SKI, European Stop Kinase Inhibitors; OR, odds ratio; STIM2, second Stop Imatinib study; TKI, tyrosine kinase inhibitor.

the initial objectives were met as the MRecFS of 61% at 6 months and 46% at 36 months are significantly above the prespecified cutoffs. In the preliminary analysis, the duration of treatment and DMR before TKI cessation were the significant factors to predict loss of MMR at 6 months.[11] We confirm these factors as beneficial for staying in MMR at 6 months as well as the finding that every additional year of DMR (TKI) is associated with a probability increase of around 3% to maintain MMR at 6 months. When modeling, a significant influence of interferon pretreatment was removed. In addition to our previous report, the transcript type e14a2 was favorable for MMR maintenance. Its statistical significance was confirmed in the STIM2 validation sample. Prognostic influence of the *BCR::ABL1* transcript type was noticed in previous studies. Patients with transcript e14a2 had a higher 3-year probability of TFR than those with transcript e13a2. However, the effect of different PCR efficiencies remains unclear in this setting.[14]

About 80% of MRec after stopping TKI occur within the first 6 months with kinetics of *BCR::ABL1* reascension clearly different compared with those after 6 months.[12] Regarding MRec between 6 and 36 months, the duration of TKI treatment, but not of DMR, was a significant factor for the probability to maintain MMR. The mechanisms underlying early and late loss of MMR are probably not the same. In addition, in the EURO-SKI trial, with peripheral blast cells and platelet counts, characteristics of the disease at diagnosis were independent significant factors associated with MMR maintenance between 6 and 36 months. These two factors are part of the Sokal score, reported as prognostic in some studies, for example, the STIM1 study.[15] However, age at diagnosis and spleen size had no prognostic meaning and it is advisable to examine the single factors rather than a scoring system not developed for prognosis of TFR maintenance. The two significant factors reflect intrinsic characteristics of CML that continue to influence outcome in the off-therapy situation long after diagnosis.

Investigating MMR maintenance for the whole trial period of 3 years, four prognostic factors were identified in the EURO-SKI trial and successfully validated in the STIM2 trial: duration of TKI treatment and DMR while under treatment, peripheral blood blast cells at diagnosis, and transcript type. Notably, validation in the STIM2 trial was accomplished for two multiple prognostic models comprising duration of TKI treatment and either blasts in peripheral blood or transcript type. The next step would be to establish a EURO-SKI score if possible.

AFFILIATIONS

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EQUAL CONTRIBUTION

F.-X.M., M.P., J.R., and S.S. contributed equally to this work.

PRIOR PRESENTATION

The interim analysis was published in Lancet Oncology (19:747-757, 2018). Data from the final analysis were presented in part at the congress of the European Hematology Association (EHA) in virtual June 2012, and EHA, Frankfurt (Germany) 8-11 June 2023, ASH Atlanta (Georgia US) 10-14 December 2021.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

The data collected in the study are not available to others. 868 CML patients were preregistered, from 61 European centers, that is,11 countries. 140 patients were excluded and finally 728 patients were eligible. The data were checked with sites and cleaned. The database was transferred first from Poitiers to Bordeaux and then to Munich. The data were analyzed by Markus Pfirrmann. The list of data include date of diagnosis, sex, age, all further parameters to calculate Sokal EURO and EUTOS scores, initial cytogenetic results and type of BCR-ABL1 transcript, treatment (duration, drug, dose, indications for dose, and treatment changes), date of CCR, MMR, and MR4 • Quantification of BCR-ABL1 transcripts in a EUTOS-CMR laboratory • Complete blood count, • Clinical examination • Comorbidity assessment with the Adult Comorbidity Evaluation-27 (ACE-27) • Samples as described in Annex 2 for substudies • QoL assessment (Annex 4), anytime between informed consent and last day of TKI V. 2. 3. Follow-up (see summary Annex 2). • Visits for clinical follow-up made every 3 months and will contain a clinical exam of the patient and the reporting of events that have occurred and treatment that have been implemented since last visit. Follow-up for residual disease (quantification of BCR-ABL transcripts with RTQ-PCR of peripheral blood) and a blood test performed every month in the first 6 months, every 1.5 months in month 7-12, and every 3 months from the second year on.

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Investigators are listed in Appendix Tables A1 and A2 (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

European Stop Tyrosine Kinase Inhibitor Trial (EURO-SKI) in Chronic Myeloid Leukemia: Final Analysis and Novel Prognostic Factors for Treatment-Free Remission

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Travel, Accommodations, Expenses: Novartis

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Honoraria: Abbvie, Roche, Bristol Myers Squibb/Sanofi
Consulting or Advisory Role: Abbvie, AstraZeneca/Greece, Novartis
Research Funding: Roche (Inst), AstraZeneca/Greece (Inst), Abbvie (Inst)

Antonio Almeida
Honoraria: Novartis, Bristol Myers Squibb/Celgene, Abbvie
Consulting or Advisory Role: Novartis, Celgene
Speakers' Bureau: Novartis, Celgene
Travel, Accommodations, Expenses: Bristol Myers Squibb

Jiri Mayer
Research Funding: BeiGene, Roche

Henrik Hjorth-Hansen
Honoraria: Incyte, Novartis
Research Funding: Austrian Orphan Pharma (Inst), Pfizer (Inst)

Jeroen J.W.M. Janssen
Honoraria: Amgen (Inst), Novartis (Inst)
Consulting or Advisory Role: Novartis (Inst)
Research Funding: Bristol Myers Squibb Foundation (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Servier (Inst)
Other Relationship: Novartis (Inst), Astellas Pharma (Inst), Alexion Pharmaceuticals (Inst), Janssen Oncology (Inst), Servier (Inst), Jazz Pharmaceuticals (Inst)

Satu Mustjoki
Consulting or Advisory Role: DAAN Biotherapeutics, Novartis
Speakers' Bureau: Bristol Myers Squibb
Research Funding: Novartis (Inst), Pfizer (Inst), Bristol Myers Squibb (Inst)

Joaquin Martinez-Lopez
Honoraria: Janssen Oncology, BMSi
Research Funding: Bristol Myers Squibb/Celgene (Inst)

Katerina Machová Poláková
Honoraria: Angelini
Research Funding: Novartis

Gert Ossenkoppele
Consulting or Advisory Role: Roche, Bristol Myers Squibb, Abbvie/Genentech, Astellas Pharma, Gilead Sciences, SERVIER, Jazz Pharmaceuticals
Research Funding: Janssen (Inst), Celgene (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Roche

Gabriel Etienne
Consulting or Advisory Role: Novartis, Pfizer, Incyte
Speakers' Bureau: Novartis, Incyte

Tim H. Brümmendorf
Honoraria: Novartis (Inst), Pfizer, Roche, Gilead Sciences, Merck KGaA, ARIAD
Consulting or Advisory Role: Novartis, Pfizer, Gilead Sciences
Research Funding: Repeat Diagnostics (Inst), Novartis (Inst), Pfizer (Inst)
Patents, Royalties, Other Intellectual Property: Patent on the combination of Imatinib with Hypusination inhibitors

Andreas Burchert
Honoraria: Novartis, Incyte, Astellas Pharma
Consulting or Advisory Role: Pfizer, Gilead Sciences
Research Funding: Novartis (Inst), AOP Orphan Pharmaceuticals (Inst), Incyte (Inst)

Delphine Réa
Honoraria: Incyte, Novartis, Pfizer
Consulting or Advisory Role: Novartis, Pfizer, Incyte, Terns Pharmaceuticals
Travel, Accommodations, Expenses: Novartis

Philippe Rousselot
Honoraria: Incyte
Research Funding: Incyte (Inst), Pfizer (Inst)
Travel, Accommodations, Expenses: Pfizer

Franck E. Nicolini
Honoraria: Novartis France, Incyte, Pfizer
Consulting or Advisory Role: Novartis, Kartos Therapeutics
Speakers' Bureau: Novartis, Incyte
Research Funding: Incyte (Inst), Novartis France (Inst)
Travel, Accommodations, Expenses: Novartis, Pfizer

Johan Richter
Stock and Other Ownership Interests: AstraZeneca

Susanne Saussele
Honoraria: Novartis, Pfizer, Incyte, Roche
Research Funding: Novartis (Inst), BMS GmbH & Co KG (Inst), Incyte (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. EURO-SKI Clinical Investigators

Country	City	Institution	Investigator
Czech Republic	Brno	Department of Internal Medicine, Hematology and Oncology, Masaryk University and University Hospital Brno	Jiri Mayer, MD
Czech Republic	Hradec Kralové	4th Department of Internal Medicine—Hematology, University Hospital	Jaroslava Voglová, MD
Czech Republic	Olomouc	Department of Hemato-Oncology, Palacký University Olomouc, Faculty of Medicine and Dentistry	Prof. Edgar Faber, MD
Czech Republic	Prague	Institute of Hematology and Blood Transfusion	Hana Klamova, MD
Denmark	Odense	Department of Hematology, Odense University Hospital, Odense, Denmark;	Hanne Vestergaard, MD
Finland	Helsinki	Hematology Research Unit Helsinki, University of Helsinki and Helsinki University Hospital Comprehensive Cancer Center	Perttu Koskenvesa, MD
France	Bordeaux	Bergonié Cancer Institute, INSERM UMR1312 Inserm, University of Bordeaux	Francois-Xavier Mahon, MD
France	Bordeaux	Centre Régional de Lutte Contre le Cancer de Bordeaux et du Sud-Ouest, Bordeaux, France	Gabriel Etienne, MD
France	Clermont-Ferrand	Hématologie Biologique and EA 7453 CHELTER, CHU Estaing and Université Clermont Auvergne	Marc G. Berger, MD
France	Le Chesnay	Department of Hematology, Centre Hospitalier de Versailles, INSERM UMR 1184, Université Versailles Paris Saclay	Philippe Rousselot, MD
France	Lyon	Center Léon Bérard	Franck E. Nicolini, MD
France	Marseille	Paoli-Calmettes Institute	Aude Charbonnier, MD
France	Nice	Service d'Hématologie Clinique, Centre Hospitalier Universitaire de Nice	Laurence Legros, MD
France	Paris	Service d'Hématologie Adulte and INSERM UMR-1160, Hôpital Saint-Louis	Delphine Réa, MD
France	Poitiers	INSERM CIC 1402, CHU de Poitiers	François Guilhot, MD
France	Rennes	Service d'Hématologie Adulte, CHU de Rennes	Martine Escoffre-Barbe, MD
France	Toulouse	University Institute of Cancer Toulouse-Oncopole, University Hospital	Françoise Huguet, MD
France	Tours	Hématologie et Thérapie Cellulaire, CHU de Tours	Prof. Emmanuel Gyan, MD
Germany	Aachen	Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, Medical Faculty, RWTH Aachen University	Tim Henrik Brümmendorf, MD
Germany	Freiburg	Department of Hematology, Oncology and Stem Cell Transplantation, Medical Center University of Freiburg	Cornelius Waller, MD
Germany	Heilbronn	Onkologische Schwerpunktpraxis Heilbronn	Jolanta Dengler, MD
Germany	Jena	Klinik für Innere Medizin II, Universitätsklinikum Jena	Andreas Hochhaus, MD
Germany	Mannheim	Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University	Susanne Saußele, MD
Germany	Marburg	Department of Hematology, Oncology and Immunology, Philipps University Marburg Faculty of Medicine	Andreas Burchert, MD
Germany	Würzburg	Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg	Volker Kunzmann, MD
Greece	Athens	Hellenic Society of Haematology	Maria N. Pagoni, MD
Greece	Athens	Laikon General Hospital, National and Kapodistrian University of Athens	Panayiotis Panayiotidis, MD
The Netherlands	Amsterdam	Department of Hematology, Amsterdam UMC, Location VUMC	Jeroen J.W.M. Janssen, MD, Gert Ossenkoppele, MD
The Netherlands	Dordrecht	Internal Medicine, Albert Schweitzer Hospital	Peter E. Westerweel, MD
The Netherlands	Rotterdam	Department of Hematology, Erasmus MC Cancer Institute, University Medical Center	Georgine E. de Greef, MD
Norway	Tromsø	Department of Hematology, University Hospital of North Norway	Franz Gruber
Norway	Trondheim	St Olavs Hospital HF	Henrik Hjorth-Hansen, MD
Portugal	Lisbon	Faculdade de Medicina, Universidade Católica Portuguesa	Antonio Almeida, MD
Spain	Madrid	Hospital 12 de Octubre, CNIO, i+12, Department of Medicine Univ. Complutense	Joaquin Martinez-Lopez, MD

(continued on following page)

TABLE A1. EURO-SKI Clinical Investigators (continued)

Country	City	Institution	Investigator
Sweden	Linköping	Department of Hematology and Department of Clinical and Experimental Medicine, Linköping University	Kourosh Lotfi, MD
Sweden	Lund	Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital	Johan Richter, MD
Sweden	Stockholm	Division of Hematology, Department of Medicine, Karolinska University Hospital and Karolinska Institutet	Leif Stenke, MD
Sweden	Uppsala	Department of Medical Science and Division of Hematology, University Hospital	Ulla Olsson-Strömberg, MD, Stina Söderlund, MD

TABLE A2. Investigators in Laboratories

Country	City	Laboratory	Investigator
Czech Republic	Praha	Institute of Hematology and Blood Transfusion, Department of Molecular Genetics	K. Machova Polakova
Finland	Turku	Hospital District of Southwestern Finland, TYKSLAB -Lab. of Molecular Genetics	V. Kairisto M. Ridanpaa K. LundanTuija V. Juvonen
Finland	Helsinki	Hematology Research Unit Helsinki and Translational Immunology Research Program, University of Helsinki and Helsinki University Comprehensive Cancer Center, and ICAN Digital Precision Cancer Medicine Flagship	S. Mustjoki
France	Bordeaux	University Hospital of Bordeaux, Laboratory of Hematology, Hôpital Haut Lévêque, Pessac, France	F.X. Mahon F. Robbesyn S. Dulucq
Germany	Jena	Universitätsklinikum Jena, Klinik und Poliklinik für Innere Medizin II	A. Hochhaus P. LaRosee
Germany, analyses also for Denmark, Greece, and the Netherlands	Mannheim	Universitätsmedizin Mannheim, III. Medizinische Klinik, Wissenschaftliches Labor	M.C. Müller C. T. Dietz S. Saussele A. Fabarius
Portugal	Lisbon	Instituto Português de Oncologia de Lisboa Francisco Gentil, Laboratório de Hemato-oncologia	J. Diamond
Spain	Barcelona	Hospital Clínic de Barcelona, Unitat d'Hematopatologia	D. Colomer
Sweden, analyses also for Norway	Lund	Lund University Hospital, Department of Clinical Genetics	H. Ehrencrona P. Johnels