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Eltrombopag for myelodysplastic syndromes or chronic myelomonocytic leukaemia with no excess blasts and thrombocytopenia: a French multicentre retrospective real-life study

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Summary

Despite a moderate prevalence in low-risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML), thrombocytopenia remains a risk of severe bleeding and therapeutic options are still limited. There are only a few studies with eltrombopag (ELT), a thrombopoietin receptor agonist, in those patients. In this retrospective multicentre study, ELT was used in 50 patients with MDS and 11 with CMML, with no excess of marrow blasts and platelet counts of $<50 \times 10^9$/l in a 'real-life' situation. Platelet response occurred in 47 (77%) patients. The median (range) duration of response was 8 (0–69) months. None of the eight still responders who discontinued ELT had relapsed, at a median (range) of 16 (6–23) months after ELT discontinuation. Although 36% of the patients were anti-coagulated or anti-aggregated only 10% of patients had Grade ≥3 bleeding events. Thrombotic events were observed in six (10%) patients, who all but one had a medical history of arterial or venous thrombosis. Progression to acute myeloid leukaemia occurred in four (7%) patients. In this first 'real-life' study, ELT was effective and generally well tolerated in patients with MDS/CMML without excess blasts.

Keywords: eltrombopag, thrombocytopenia, myelodysplastic syndromes, chronic myelomonocytic leukaemia, real-life.

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Introduction

Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia (CMML) are clonal myeloid haematological malignancies characterised by ineffective haematopoiesis resulting in peripheral cytopenia, a risk of progression to acute myeloid leukaemia (AML) and, in the case of CMML, possible myeloproliferation.[1,2] While treatment of higher-risk MDS (HR-MDS) mainly aims at modifying the disease course, treatment of lower-risk MDS [LR-MDS, low risk and intermediate-1 risk, according to the International Prognostic Scoring System (IPSS)][3] is mainly aimed at correcting cytopenias.[4] Anaemia is generally the predominant cytopenia in LR-MDS, but thrombocytopenia may predominate over anaemia (or may even be isolated) in 10–15% of patients with LR-MDS. Thrombocytopenia in LR-MDS is mainly due to ineffective platelet production, but increased peripheral destruction of autoimmune origin may be present.[5] Platelet function defects are often associated.[6]

Options to improve thrombocytopenia in patients with LR-MDS are limited. Platelet transfusions are associated with a short-term effect.[6] Androgens can help increase (generally transiently) the platelet count, but may expose patients to thrombotic events or stimulate underlying prostate cancer in those elderly patients. Immune thrombocytopenia (ITP)-like treatments sometimes have transient efficacy.[7] Azacitidine has relatively limited effects in LR-MDS with thrombocytopenia, and is not approved for this indication in Europe.

In patients with CMML without excess of marrow blasts, thrombocytopenia may also be prominent, and often includes peripheral destruction of autoimmune origin, but its treatment, as for MDS, is difficult.[8]

More recently, two thrombopoietin receptor agonists (TPO-RAs), romiplostim and eltrombopag (ELT) have been

developed and approved for the treatment of ITP and for ELT acquired severe aplastic anaemia. Both drugs yield 30–50% platelet responses in relatively selected LR-MDS included in clinical trials,[9–17] but there are no or very limited reports of their use in LR-MDS outside of clinical trials.

Eltrombopag is an orally bioavailable, small non-peptide that binds to the transmembrane region of the TPO receptor.[18] The binding site on the receptor does not compete with TPO, which differs from romiplostim binding. Only two clinical trials, to our knowledge, have been performed in LR-MDS with ELT monotherapy[11,16] and one in CMML (but seven of nine patients had an excess of bone marrow blasts).[19]

The main objective of the present study was to assess the efficacy and safety profile of ELT in thrombocytopenia related to MDS and CMML with no excess blasts (EB), in a 'real-life' context.

Patients and methods

Following Institutional Review Board (IRB) approval, we collected data from patients with MDS and CMML treated with ELT between January 2011 and January 2019, and included in the 'Groupe Francophone des Myélodysplasies' (GFM) registry of patients with MDS. Inclusion criteria were: (1) MDS or chronic myelomonocytic leukaemia with leucocytes <13 g/l [according to World Health Organization (WHO) 2016 classification][20], (2) <5% bone marrow blasts, (3) treatment with ELT outside of a clinical trial, (4) platelet count of $\leq 50 \times 10^9$/l at the onset of ELT.

Clinical data at baseline included patient demographics, Revised International Prognostic Scoring System (R-IPSS) parameters, bleeding complications, platelet transfusion dependence status and prior treatments for MDS and/or thrombocytopenia. Comorbidities that could influence the bleeding risk, and/or thrombotic events were also noted. During follow-up, ELT dose modifications, adverse events, bleeding symptoms, disease progression [International Working Group (IWG) 2006 criteria] and survival were assessed.

The primary endpoint was platelet response [haematological improvement-platelet (HI-P)], according to the IWG 2006 response criteria.[21] We also reported other haematological responses [HI-erythroid (HI-E), HI-neutrophil (HI-N)] when available, safety and tolerability, bleeding and thrombotic events.

Data were expressed as median [interquartile range (IQR) or 95% confidence interval (CI)] or mean [standard deviation (SD)] for quantitative variables and number (%) for categorical variables. Overall survival (OS) rate was calculated with the Kaplan–Meier method. The median follow-up was calculated using reverse censoring method on GraphPad Prism (version 7.0.0 for Windows; GraphPad Software, San Diego, CA, USA). The chi- square test was used to compare OS of the patient group to expected survival as estimated from the R-IPSS scoring system. A $P < 0{\cdot}05$ was considered statistically significant. Observations with missing values were deleted in this analysis with the assumption that they were missing at random. Data analysis was done with JMP® software (SAS Institute Inc., Cary, NC, USA). For univariate analysis we used the Mann–Whitney and Fisher's exact tests.

This study was approved by the IRB, in accordance with the French data protection authority [MR004, Commission Nationale de l'Informatique et des Libertés (CNIL)].

Results

Baseline features

From the 5423 patients included in the GFM registry before January 2019, 61 satisfying inclusion criteria were identified (50 with MDS and marrow blasts <5%, 11 with CMML-0). Their baseline characteristics are listed in Table I. In all, 11 (18%) of those patients had a Grade 3–4 bleeding history of <6 months before the onset of ELT. The median (IQR) time from diagnosis to ELT onset was 7 (1–26) months. At the onset of ELT, the median (IQR) baseline platelet count was 21 (12–38) $\times 10^9$/l; with platelet transfusion dependency in 44% of the patients. Of note, 25 (41%) patients had thrombocytopenia as single cytopenia.

Karyotype was predominantly normal ($n = 37$, 63%; two patients without cytogenetic data). Only one patient had a complex cytogenetic profile (Table I). Isolated del(20q), was observed in five patients. Mutational analysis by next-generation sequencing (NGS) was not recorded.

All patients had a WHO performance status of <3. Regarding potential additional bleeding risk factors, 22 (36%) patients were treated by anticoagulant or anti-aggregating agents. Indications for anticoagulants and/or anti-aggregating agents were as follows: ischaemic heart disease (13 patients), atrial fibrillation (six), stroke (three), arteriopathy (three) and vein thrombosis (one). These agents were discontinued at ELT initiation in 12 (55%) patients, due to thrombocytopenia (mean platelet count 29×10^9/l) and could be restarted after HI-P in five patients. In addition, 14 (23%) patients had a thrombotic history [ischaemic heart disease (five), stroke (three), pulmonary embolism (two), splenic thrombosis (two), deep vein thrombosis (one) and lower limb arteriopathy (one)].

Overall, 35 (57%) patients had received prior treatments for thrombocytopenia, including steroids ($n = 24$, 39%) with a response rate of 46%, and danazol ($n = 18$, 30%) with eight (44%) responses. Four patients had previously received romiplostim and were switched to ELT due to lack of response (one), splenic thrombosis (one), large variation in platelet counts (one) and transient presence of circulating blasts (one).

Concomitant treatments for MDS/CMML at the onset of ELT were erythropoietin (EPO) alone (15 patients, 25%) or

Table I. Baseline patient characteristics.

Characteristic	Value
Total number of patients	61
Age, years, median (IQR)	77 (71–82)
Sex, *n* (%)	
Male	41 (67)
Female	20 (33)
Interval from MDS diagnosis, months, median (IQR)	8 (2–25)
WHO 2016 classification, *n* (%)	
SLD-MDS	16 (25)
SLD-MDS-RS	1 (2)
MLD-MDS	28 (46)
MLD-MDS-RS	4 (7)
MDS-U	1 (2)
CMML-0	11 (18)
Revised IPSS (for 50 patients with MDS), *n* (%)	
Very low	4 (8)
Low	36 (72)
Intermediate	8 (16)
High	1 (2)
Very high	1 (2)
CMML-specific Prognostic Scoring System (for 11 patients with CMML), *n* (%)	
Low risk	6 (55)
Intermediate-1	3 (27)
Unknown	2 (18)
R-IPSS cytogenetic risk group, *n* (%)	
Very good	8 (13)
Good	42 (69)
Intermediate	7 (12)
Poor or very poor	2 (3)
Unknown	2 (3)
Platelet transfusions, *n* (%)	
Dependent	27 (44)
Independent	34 (56)
Platelet count, $\times 10^9$/l, median (IQR)	21 (12–38)

CMML, chronic myelomonocytic leukaemia; IQR, interquartile range; MDS(-U), myelodysplastic syndromes (unclassifiable); MLD-MDS, MDS with multilineage dysplasia; R-IPSS, Revised International Prognostic Scoring System; RS, ring sideroblasts; SLD-MDS, MDS with single lineage dysplasia; WHO, World Health Organization.

with granulocyte-colony stimulating factor (G-CSF; four) and steroids (one).

Eltrombopag disposition

The starting dose of ELT was 25 mg/day in nine (15%) patients, 50 mg/day in 44 (72%), 75 mg/day in seven (12%) and 300 mg/day in one. The dose was increased in 37 (61%) patients, with a mean (SD) maximal dose of 80 mg/day (45).

With a median follow up of 21 months (95% CI 14·1–29), the median (range) duration of treatment was 10 (0–70) months. Six (10%) patients were exposed to ELT for ≤1 month. Overall, 32 (53%) patients discontinued ELT before the end of follow-up: 15 (25%) for primary or secondary failure, 13 (21%) for disease progression (suspected or proved), for prolonged response (two, after 6 and 37 months on ELT), for allergy (one) and after physician's decision (one, after 1·5 months on treatment). After discontinuation of ELT, five patients were switched to romiplostim and among them, three responded to romiplostim (one partial response and two complete responses).

Response to ELT

Platelet response (HI-P according to IWG 2006 criteria)[21] was observed in 47 (77%) patients, with a median (IQR) time to response of 30 (15–39) days. The median (IQR) dose of ELT to obtain HI-P was 50 (50–75) mg/day. In the 27 platelet transfusion-dependent patients, 19 (70%) achieved transfusion independency. Two of the four patients who switched from romiplostim to ELT reached HI-P (without recurrence of side-effects), but the patient who stopped romiplostim for lack of response did not respond to ELT. Among 47 responders to ELT, 13 relapsed (all on therapy). The median (range) duration of response was 8 (0–69) months. None of the eight still responders who discontinued ELT had relapsed, at a median (range) of 16 (6–23) months after ELT discontinuation.

Of the 12 patients with haemoglobin <100 g/l who did not receive an EPO-stimulating agent (ESA), four (33%) obtained an erythroid response (HI-E), while of the six patients with an absolute neutrophil count of $<1 \times 10^9$/l who did not receive G-CSF, two (33%) obtained a neutrophil response (HI-N).

During ELT therapy, nine major bleeding events occurred in six (10%) patients all with MDS, including intracranial (two patients), intestinal (one), oral (two) and urinary tract (one) bleeding. All bleeding episodes occurred before platelet response. Among those six patients, four had started ELT with a platelet count of $<20 \times 10^9$/l, four were platelet transfusion dependent and two received concomitant anticoagulant treatment. Three patients had a platelet response after a major bleeding episode. One patient with intracranial bleeding at presentation died after AML transformation 1-month after ELT initiation.

Comparisons between responders and non-responder patients are summarised in Table II. The duration of response to ELT is shown in Fig 1.

There was a trend for better response rate to ELT in MDS/CMML with very low and low R-IPSS ($P = 0{\cdot}019$), while no other predictive factor of response was seen.

Adverse events

Thrombotic events. Thrombotic events occurred in six (10%) patients, and in three of them events were similar to those preceding ELT onset. Acute coronary syndrome (ACS) was reported in two patients (one of them had concomitant

Table II. Characteristics of responders and non-responders to eltrombopag.

Characteristic	Responders (%) $n = 47$	Non-responders (%) $n = 14$	P
Sex, *n* (%)			
Male	27 (58)	7 (50)	0·64
Female	20 (42)	7 (50)	
Age, years, mean (SD)	77 (8)	72 (13)	0·18
Bone marrow blasts >2%, *n* (%)	15 (32)	7 (50)	0·34
Cytogenetics, *n* (%)			
Normal	29 (62)	8 (57)	0·62
Isolated del(20q)	5 (11)	0	Not calculable
R-IPSS cytogenetic score >1	6 (13)	3 (21)	
R-IPSS category, *n* (%)			
Very low and low risk	38 (81)	8 (57)	0·019
Intermediate risk	8 (17)	3 (21)	0·91
High and very high risk	0	2 (14)	Not calculable
Unknown	1	1	
Platelet count, $\times 10^9$/l, median	25	16	0·14
Platelet transfusion dependence, *n* (%)	20 (43)	7 (50)	0·62
Haemoglobin, g/l, median	110	90	0·21
RBC transfusion dependence, *n* (%)	2 (4)	2 (14)	Not calculable
Dose of eltrombopag at initiation, mg/day, mean (SD)	51 (11)	61 (68)	0·13

RBC, red blood cell; R-IPSS, Revised International Prognostic Scoring System.

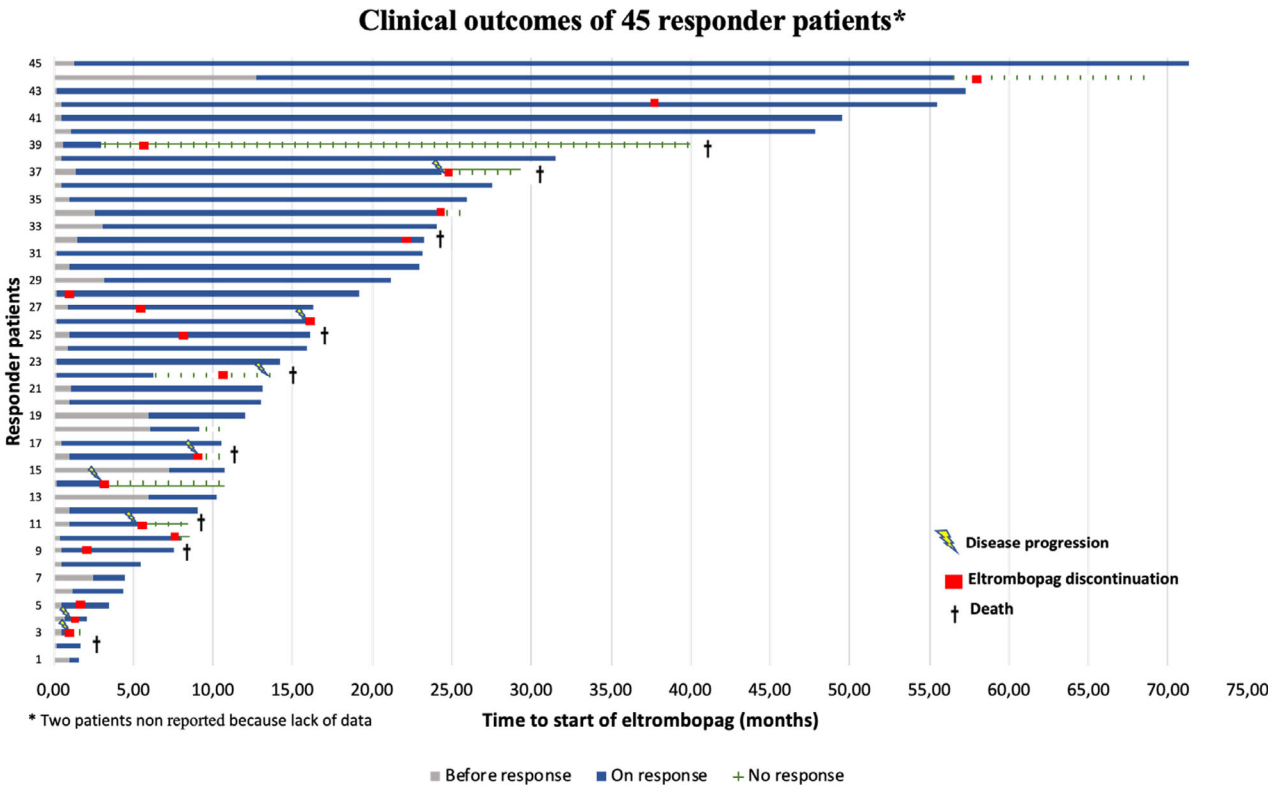

Fig 1. Response duration in responders. [Colour figure can be viewed at wileyonlinelibrary.com]

severe anaemia and medical history of ACS prior to ELT onset). One patient died on treatment from ischaemic stroke (a previous ischaemic stroke had occurred before ELT initiation and aspirin had been discontinued due to thrombocytopenia). One patient presented with hand ischaemia. Two patients had pulmonary embolism, one with preceding deep vein thrombosis (treated concomitantly by ESA and with a history of pulmonary embolism). One of them was known to have positive anti-cardiolipin antibodies and one had a circulating anticoagulant. Complete data were available for four patients, in whom the thrombotic event(s) occurred in the first month after ELT initiation (two patients) or after ~1 year of exposure (two). At the time of the thrombotic event, the platelet count was normal for two patients and $<20 \times 10^9$/l for the remaining two.

Other side-effects. Other adverse events were skin allergy (one patient), major thrombocytosis (one) and pulmonary hypertension (one).

Disease progression

Disease progression (according to IWG criteria) was identified in 10 (16%) patients after a median (range) of 7 (1–24) months. Seven (70%) of the progressions were observed within the first year of treatment, including five at <6 months. Two patients evolved to MDS EB-1, two to MDS EB-2, one to CMML-1, one to CMML-2 and four to AML. ELT was stopped in all of them, with no reversibility to <5% marrow blasts after discontinuation.

Survival

With a median follow-up of 21 months (95% CI 14·1–29), 19 patients (31%) had died: eight from infection; two from intracranial bleeding (both had progressive disease); two from ischaemic stroke (one on treatment but with a similar ischaemic stroke before ELT initiation and one after a switch to romiplostim); three from heart failure; two from AML transformation, one from multiple myeloma and one without available information. Four of the patients who died were still on treatment (with non-progressive disease). The median OS was 40 months and was significantly longer in patients who responded to ELT (median not reached *versus* 14 months, $P = 0{\cdot}005$).

Discussion

In this 'real-life' study, ELT proved effective and generally safe in thrombocytopenic MDS and CMML without excess of marrow blasts. HI-P was reached in 77% of the patients, a somewhat higher rate than in two recent clinical trials,[11,16] which reported response rates of 47% and 44% respectively. Some differences in baseline characteristics could explain our higher response rate, as Oliva *et al.*[11] and Vicente *et al.*[16] included a significant proportion of patients with a higher MDS risk profile (excess of marrow blasts or high/very high R-IPSS). The median dose of ELT to obtain HI-P was the same in our present study and the Oliva *et al.*[11] trial, 50 mg/day, but we observed a longer median time to reach platelet response, potentially due to less frequent blood counts available in a retrospective study. In agreement with previous studies, response to ELT was associated with less severe bleeding events.

In previous studies with ELT in MDS, follow-up was 2 and 15 months in Oliva *et al.*[11] and Vicente *et al.*[16] series respectively. The median follow-up was 21 months in our present series, and the median (range) response duration was 8(0·5–70+) months, with a >6 months response in 26 patients. Interestingly, eight patients in whom ELT was discontinued while still in response had not relapsed, at a median (range) of 16 (6–23) months. These results are in agreement with Vicente *et al.*[16] study (four of 10 patients with persistent response after ELT discontinuation, with a median of 15 months off drug) suggesting the possibility of ELT discontinuation without relapse. There are no clear explanations for this phenomenon, observed in aplastic anaemia,[22] but several hypotheses can be discussed, including an iron-chelating effect of ELT,[23] which could stimulate normal haematopoiesis and thus megakaryopoiesis; or an immunomodulatory effect of ELT (modulation of T-regulatory cells, restore Fcγ receptor balance in phagocytes),[24] which could reduce excessive intramedullary apoptosis. Restoration of normal megakaryopoiesis could stabilise the medullary stroma despite drug withdrawal, but this remains a hypothesis.

Moreover, our present results confirmed the possibility of HI-E and HI-N with ELT in MDS, both observed in one-third of our present platelet responders. Vicente *et al.*[16] also described responses on the erythroid and neutrophil lineage in 36% and 12% of the patients respectively. This observation was also made in aplastic anaemia.[22,25] Such responses could potentially be explained by 'off-target' effects of ELT (including iron chelation and immunomodulation) that could restore and/or stimulate normal haematopoiesis.[26,27]

Switching between the two available TPO-RAs had not been explored in MDS. This switch had been evaluated in ITP,[28] with a response rate of 60% to the second TPO-RA when the switch was made for lack of response to the first, regardless of the direction of the switch. Recent data showed similar results in aplastic anaemia.[29] In our present study, four patients were previously treated by romiplostim: one did not respond to either romiplostim or ELT, and two who previously responded to romiplostim also responded to ELT. In addition, five patients were switched from ELT to romiplostim and among them, three (60%) responded to romiplostim.

In our present study, very low/low R-IPSS category seemed to be associated with better response to ELT, but no other prognostic factors of response were seen.

A potential concern when using TPO mimetics is the risk of MDS progression or transformation to AML. We observed disease progression in 17% of the patients (including AML transformation in four), figures similar to those observed by Oliva *et al.*[11] in both ELT- and placebo-treated patients, and concordant with the 'natural' evolution of LR-MDS.[1] In a recent meta-analysis in MDS,[30] a potential increased risk of disease progression with TPO mimetics was likewise not confirmed. The risk of progression with ELT was found to be higher in CMML, but in a series where many patients initially had an excess of marrow blasts.[19] Our present data are more reassuring (only two progressions without AML transformation).

The toxicity profile of ELT was comparable with that observed in previous studies. The main ELT-related adverse events were a relatively low incidence of thrombotic events; however, higher than observed in the Oliva *et al.*[11] or Vicente *et al.*[16] controlled clinical trials. However, most of our present patients who experienced thromboembolic events had a history of similar complications and those patients were probably excluded from the controlled clinical trials of Oliva *et al.*[11] and Vicente *et al.*[16] Our present results suggest caution with the indication of ELT in patients with a thromboembolic history.

Our present study has inherent limitations considering its retrospective design, possible missing data and reduced and non-homogeneous follow-up.

Conclusion

Overall, we have reported for the first-time real-life data about ELT in patients with low-risk MDS and CMML with thrombocytopenia. We confirmed that ELT is effective with a sustained effect on platelet counts reduction in the platelet transfusion burden and in severe bleeding. The effect of ELT was often prolonged after drug discontinuation. The tolerance profile was favourable in this population with no excess of blast, but a previous history of thrombosis remains a major risk factor for thrombotic events on treatment.

Author contributions

Thibault Comont performed research, analysed results and wrote the paper; Mathieu Meunier provided clinical care, performed research and analysed results; Amina Cherait, Clemence Santana, Thomas Cluzeau, Bohrane Slama, Kamel Laribi, Jean-Thomas Giraud, Sophie Dimicoli, Ana Berceanu, Lenaïg Le Clech, Pascale Cony-Makhoul, Berangere Gruson, Jose Torregrosa, Laurence Sanhes, Vincent Jachiet, Marie-Agnes Azerad, Ahmad Al Jijakli, Emmanuel Gyan, Clement Gaudin, Jonathan Broner, Claire Guerveno, Thierry Guillaume provided clinical care and reviewed the paper; Odile Beyne-Rauzy and Pierre Fenaux reviewed the paper and contributed equally to this work.

Conflict of interest

Thibault Comont received honoraria and/or research or educational support from AbbVie, AstraZeneca, Bristol Myers Squibb (Celgene), Novartis and Takeda. Emmanuel Gyan received research support from Novartis; Thomas Cluzeau received honoraria and/or research or educational support from Abbvie, Agios, Alexion, Amgen, Aprea, Arog, Bristol Myers Squibb (Celgene) Jazz, Kartos, Novartis, Sanofi. Kamel Laribi has received in the last 24 months personal fees for participating to advisory boards or consulting from: Abbvie, Jansen, Beigene, BMS/Celgene, Astellas, Sandoz, Iqone, Novartis. Jonathan Broner and Laurence Sanhes received educational support from Novartis Odile Beyne-Rauzy received research support from Novartis and educational grant from Bristol Myers Squibb (Celgene). Pierre Fenaux has received honoraria and/or research support from Celgene, Janssen, AbbVie, Jazz, Novartis, Roche and Aprea. All other authors have no conflicts of interest to declare.

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