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# Management of polycythemia vera: A survey of treatment patterns in Italy

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## Abstract

**Objectives:** Polycythemia vera (PV) is an acquired clonal hematopoietic stem cell disorder characterized by the overproduction of red blood cells. It has long been underlined that there are differences in treatment patterns in routine practice. Therapeutic strategies have also expanded, and in recent years the JAK1/JAK2 inhibitor ruxolitinib has emerged as a second-line therapeutic option in patients who are intolerant to or resistant to hydroxyurea. Determining the impact of changes on practice patterns is of interest, especially for aspects that lack detailed guidance for management.

**Methods:** To gain insights into treatment patterns by clinicians treating patients with PV in Italy, we carried out a survey of 60 hematologists and transfusion specialists. The questions covered: treatment of low-risk patients, definition of significant leukocytosis, splenomegaly and excessive phlebotomies, resistance/intolerance to hydroxyurea, use of ruxolitinib, cytoreductive therapy, and vaccines.

**Results:** In general, the results of the survey indicate that there is a large heterogeneity in management of patients with PV across these areas.

**Conclusions:** While helping to provide greater understanding of treatment patterns for patients with PV in Italy, our survey highlights the need for additional clinical studies to obtain more precise guidance for the routine care of patients with PV.

KEYWORDS
management, patterns, polycythemia vera, survey, treatment

## Novelty statements

### What is the new aspect of your work?

Provides data on real-world treatment patterns of polycythemia vera for which there is limited information.

### What is the central finding of your work?

There is a large heterogeneity in management of patients with polycythemia vera.

**What is (or could be) the specific clinical relevance of your work?**
Stresses the need for additional clinical studies to obtain more precise guidance for the routine care of patients with polycythemia vera.

## 1 | INTRODUCTION

Polycythemia vera (PV) is an acquired clonal hematopoietic stem cell disorder characterized by the overproduction of red blood cells, which gives rise to thrombotic and hemorrhagic complications.[1] PV has incidence of about 1 per 100 000 persons with a median age of 61 years at diagnosis.[2,3] Median survival is roughly about 20 years and lower than the age-matched general population.[4] PV has a chronic course, even if a true panmyelopathy may take many years to appear, while the presence of thrombosis is a major risk factor for morbidity and mortality.[3–5]

The Polycythemia Vera Study Group was established in 1967 to develop a standardized approach to diagnosis and treatment of PV. The group studied three treatment regimens (phlebotomy alone, chlorambucil with phlebotomy, and radiotherapy with phlebotomy), and an improvement in survival was seen with phlebotomy.[6] Moreover, the risk of progression to acute leukemia was increased in those treated with chlorambucil and radiotherapy. The PVSG concluded that myelosuppression was required, and hydroxyurea was selected as the best cytoreductive agent.[7,8]

Current first-line recommendations for therapy stratify patients according to risk.[1,9] Low-risk patients have an age ≤ 60 years and no history of thrombotic events, and are generally treated with aspirin and phlebotomy.[1] High-risk patients have an age > 60 years and/or history of thrombosis.[1] High-risk patients are treated with cytoreductive therapy and in addition to aspirin and phlebotomy. Hydroxyurea is now the cytoreductive agent of choice in most patients, although pegylated interferons still remain an important option for first- or second-line treatment.[1]

It has long been highlighted that there are differences in treatment patterns used in routine practice. For example, in a survey in 2002 of 1000 members of the American Society of Hematology (ASH), initial therapy was phlebotomy and most respondents used a target hematocrit of 44% or less, even if a substantial proportion considered targets of ≥50% despite recommendations in place at that time.[10] Most clinicians treated a platelet count of ≥1000 $\times$ $10^9$/L, although some also treated to a lower threshold. Since that survey, there has been much greater understanding in the pathogenesis and classification of PV, which is primarily due to the discovery of the JAK2 V617F mutation and its role in myeloproliferative neoplasms.[11–13] Notwithstanding, a more recent survey in 2016 further highlighted that there were marked differences in target hematocrit and platelet count among different clinicians, even after the discovery of the JAK2 V617F mutation.[14] More recently, in 2016, the World Health Organization (WHO) revised classification criteria for the diagnosis of PV to allow for earlier detection of masked disease.[15] Therapeutic strategies have also expanded, with the approval of the JAK1/JAK2 inhibitor ruxolitinib,[16,17] in patients who are intolerant to or resistant to hydroxyurea. Indeed, in recent years ruxolitinib has emerged as a new second-line therapeutic option.[1] In addition, the optimal target hematocrit target, which has been the subject of debate for more than 30 years, is now confirmed to be ≤45%.[18]

Determining impact of these changes on practice patterns is of interest, especially for aspects that lack detailed guidance for management. To gain insights into treatment patterns by clinicians treating patients with PV in Italy, we carried out a survey of hematologists and transfusion specialists.

## 2 | MATERIALS AND METHODS

The MPN Lab was established in March 2018 to study the management of myelofibrosis and PV at 18 hematology centers in Italy. The results of the first survey were published in 2020 and described diagnosis, stratification, and management of patients with myelofibrosis patients in real-world settings.[19] A second survey with 27 questions was later used to evaluate criteria used to identify resistant and intolerant myelofibrosis patients, the role of allogeneic transplant, and clinicians' perceptions of new therapies. A third online survey with 19 questions described herein was developed with closed answers about the management of patients with PV and carried out from June to September 2021 (Table S1). The authors themselves responded to the survey and also invited additional Italian hematologists and transfusion specialists to participate via email. All respondents had direct experience in the management of PV patients and replies were collected anonymously. As in the prior surveys, the questionnaire was distributed via internet, and responses were collected by an external agency. Given the restrictions related to the COVID-19 pandemic, the authors met online to discuss the results. Herein, we present the results of the survey summarized by descriptive statistics.

## 3 | RESULTS

The survey was divided into subareas and presented data from each question as below. A total of 60 participants completed the survey. Of these, 48 (80.0%) were hematologists and 12 (20.0%) were transfusionists. It should be noted that in Italy, transfusionists also have an important role in PV because they perform phlebotomies and, in many centers, can also prescribe or adjust cytoreductive therapy. Of note, the survey contained no questions regarding variant allele frequency of the JAK2 V617F, since the survey also involved smaller centers where allelic burden is not routinely assessed.

### 3.1 | Treatment of low-risk patients

The first two questions regarded treatment of low-risk patients. In considering the question of in which low-risk patients should cytoreduction be considered, a range of responses were seen (Figure 1A). Most considered progressive leukocytosis (71.7%) and massive thrombocytosis (76.7%) to be driving criteria, although progressive splenomegaly in the absence of disease progression, persistent symptoms despite good disease control, and excessive number of phlebotomies were also cited by more than half of participants. In the next question regarding which low-risk patients in need of cytoreduction should be preferably treated with IFN-α rather than hydroxyurea or other cytoreductive agents, 73.3% replied that the patient's desire for paternity/maternity was considered. Fewer responders said that any patient without a contraindication to IFN-α should be treated with that agent (26.7%), while some cited age < 40 years (40.0%) and age < 60 years (25.0%).

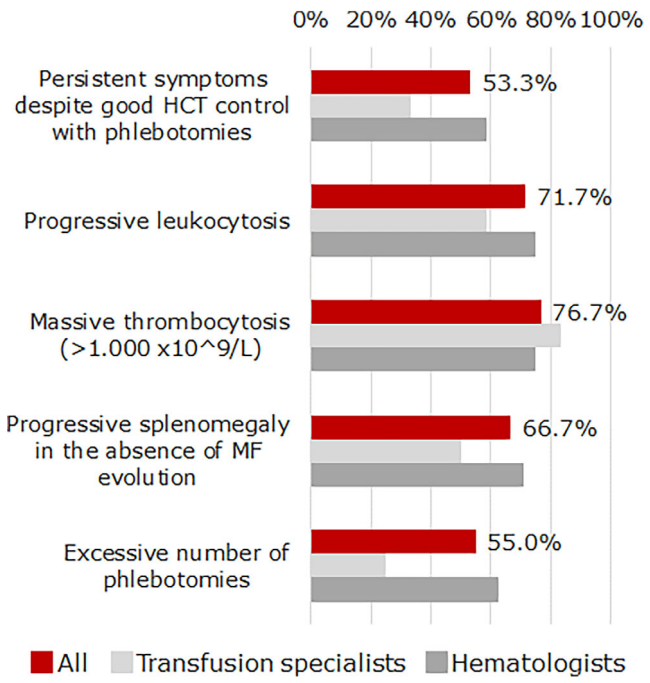


**FIGURE 1** In which low-risk PV patient should cytoreduction be considered? (Multiple responses possible). PV, polycythemia vera.

### 3.2 | Definition of significant leukocytosis

Considering evaluation of leukocytosis, when asked if this was assessed differently according to smoking habit, 56.7% referred "yes." Among those responding "no," 23.1% said >15 × $10^9$/L, 38.5% >15 × $10^9$/L confirmed after 6 months of follow-up, 19.2% >20 × $10^9$/L, and 19.2% >20 × $10^9$/L confirmed after 6 months of follow-up. Among those responding "yes," for non-smokers 23.1% referred >15 × $10^9$/L, 64.7% >15 × $10^9$/L confirmed after 6 months of follow-up, 2.9% >20 × $10^9$/L, and 11.8% >20 × $10^9$/L confirmed after 6 months of follow-up. For smokers, the percentages for the same cutoffs were 11.8%, 14.7%, 14.7%, and 58.8%, respectively.

### 3.3 | Definition of splenomegaly and excessive phlebotomies

The results for definition of splenomegaly are shown in Figure 2A (note that more than one response was possible). The majority referred that they consider the presence of splenomegaly-related symptoms, regardless of spleen size, as a criterion to identify clinically meaningful splenomegaly (25% chose this option alone); fewer percentages of respondents said that they considered the presence of a palpable spleen at 5–15 cm. In considering the definition of excessive number of phlebotomies, the majority (61.7%) said that any number was excessive if the procedure was not well tolerated, while 50.0% said more than one phlebotomy per month was considered excessive (Figure 2B).

### 3.4 | Resistance/intolerance to HU

When asked which toxicities or lack of responses they were willing to tolerate to continue HU in fit patients, a large variety of responses

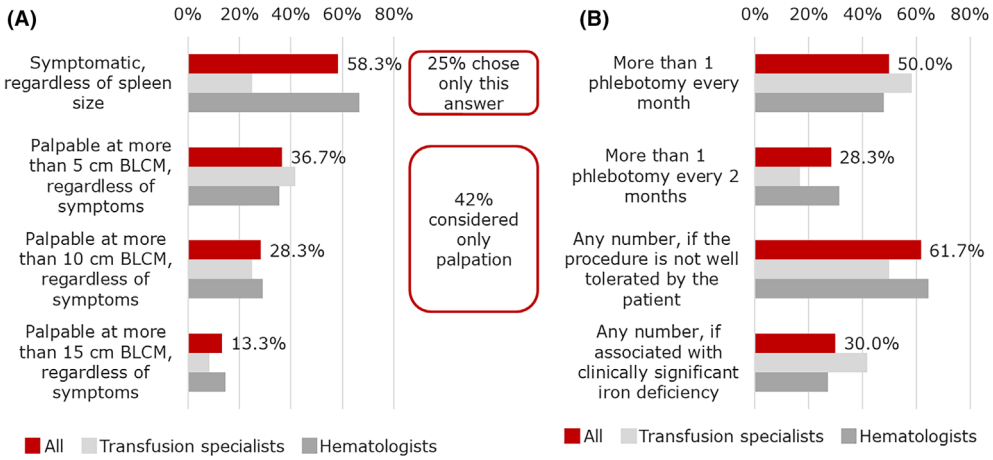


**FIGURE 2** Definition of splenomegaly (A) and excessive number of phlebotomies (B)

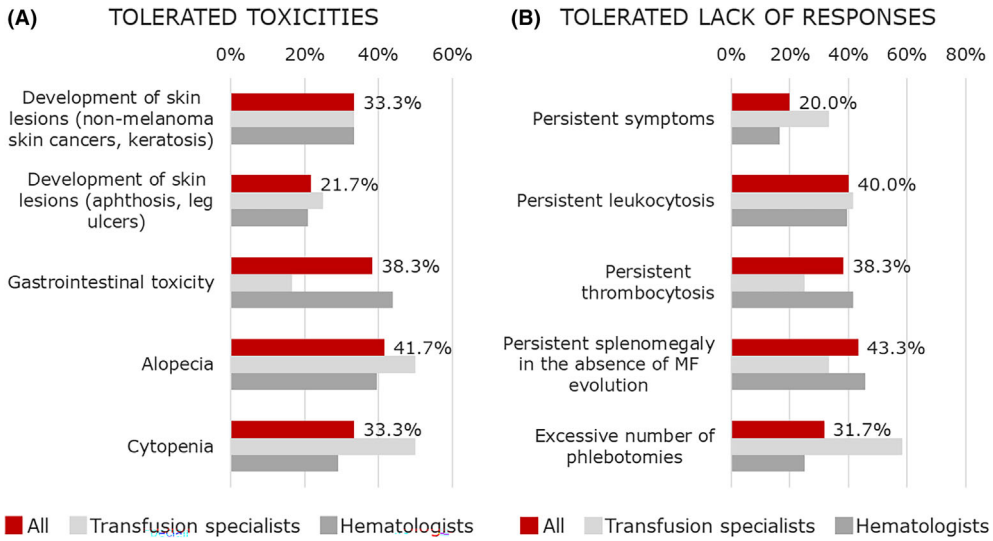


**FIGURE 3** Which toxicities or lack of responses are you willing to tolerate to continue HU in fit patients?

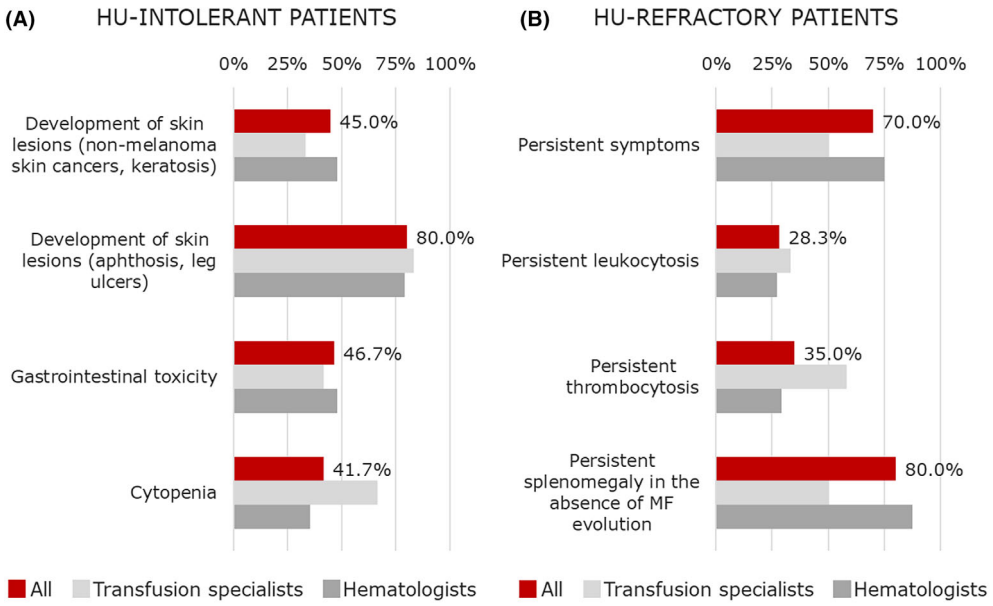


**FIGURE 4** Aspects considered in patients who are preferentially candidates for ruxolitinib over other cytoreductive therapies in case of HU intolerance (A) or HU refractoriness (B)

were given (Figure 3). When asked if they usually use HU at a dose of 2 g/day before switching to second-line therapy in the absence of toxicity, 43.3% replied that they do.

In considering which Hydroxyurea (HU)-intolerant/refractory patients are preferable candidates for ruxolitinib over other cytoreductive drugs, the large majority (80.0%) referred skin lesions such as aphthosis and leg ulcers; less than 50% referred other skin lesions such as non-melanoma skin cancer, gastrointestinal toxicity, and cytopenia (Figure 4A). Most respondents considered persistent splenomegaly (80.0%) and persistent symptoms (70%) in HU-intolerant patients who are preferable candidates for ruxolitinib over other cytoreductive drugs (Figure 4B).

## 3.5 | Use of ruxolitinib

A few questions regarded the use of ruxolitinib. Almost one-half (45.0%) said that there are specific clinical situations in which they do

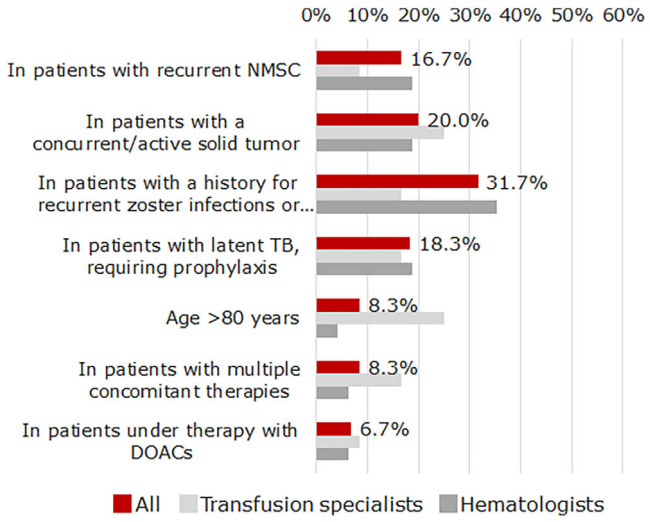


**FIGURE 5** Clinical situations for which there is a lack of confidence in using ruxolitinib

not feel confident in using ruxolitinib. A variety of reasons were given among those responding "yes" (Figure 5). The responses included recurrent tumors, history of herpes zoster or other clinically meaningful infections, age, and concomitant therapies. Regarding use of ruxolitinib, 60.0% said that they withdraw the drug in patients with severe infections.

### 3.6 | Cytoreductive therapy and vaccines

Finally, vaccinations in patients undergoing cytoreduction were explored. While 65.0% said that they never consider cytoreductive therapy a contraindication for vaccines, 33.3% responded that they consider cytoreductive therapy a contraindication for all attenuated vaccines, and 1.7% a contraindication for all vaccines.

## 4 | DISCUSSION

The present survey helps to provide greater understanding of treatment patterns for patients with PV in Italy among hematologists and transfusion specialists. For low-risk patients, there were variable responses in the criteria to be used to consider how patients should be considered candidates for cytoreduction, even if the majority did cite massive thrombocytosis and progressive leukocytosis. This is interesting since current guidelines state that extreme thrombocytosis does not warrant cytoreductive therapy.[1] Indeed, guidelines state that in the presence of platelets >1000 $\times$ $10^9$/L, screening for ristocetin cofactor activity is advised and consideration be given to withhold aspirin therapy if the result shows <20% activity. In general, cytoreductive therapy is not advised in low-risk patients.[1] Notwithstanding, considering cytoreductive therapy in low-risk patients, most said that the desire for paternity/maternity would be a criterion for IFN use. This indicates that there is clear regard for therapeutic choice in pregnant women and those of childbearing potential as noted by other authors.[20–22]

Regarding leukocytosis, this is typically defined as >15.0 $\times$ $10^9$/L, although a clear cutoff value is lacking. According to a recent systematic review, cutoffs used for the definition of leukocytosis ranged from 9.5 $\times$ $10^9$/L to 25.0 $\times$ $10^9$/L in PV, as further evidence that there is no well-established cutoff value.[23] In line with this, herein, the cutoff values considered for leukocytosis were highly variable with almost 40% considering 20.0 $\times$ $10^9$/L. Around one-half also considered smoking habit in the evaluation of leukocytosis. Some respondents also considered persistent leukocytosis (>6 months) as an additional criterion. Persistent leukocytosis in patients with PV has been previously associated with disease evolution, but not thrombotic events.[24] However, discrepant data has been reported. In a real-world analysis of 1565 patients with PV, a significant association between an increased white blood cell count of 8.5 $\times$ $10^9$/L and thrombotic events was noted.[25] According to the European LeukemiaNet 2021 recommendations, patients with PV and age < 60 years with no history of thrombotic events should start cytoreductive drug therapy if at least one of the following criteria are met: strict intolerance to phlebotomy, symptomatic progressive splenomegaly, persistent leukocytosis (>15 $\times$ $10^9$ white blood cells per L), progressive leukocytosis (≥100% increase if baseline is <10 $\times$ $10^9$ cells per L or ≥50% increase if baseline is >10 $\times$ $10^9$ cells per L), extreme thrombocytosis (>1500 $\times$ $10^9$ platelets per L), inadequate hematocrit control needing phlebotomy, persistently high cardiovascular risk, and persistently high symptom burden.[26] Recombinant interferon alfa is recommended for cytoreduction in these patients.[26]

In the present survey, almost 60% of respondents referred that splenomegaly requiring cytoreduction is defined by symptoms, regardless of spleen size. The remainder referred that a spleen palpable at more than 5–15 cm would be considered as splenomegaly in need of cytoreduction. There is now both controlled and uncontrolled evidence that supports phlebotomy for all patients with PV, suggesting that some clinicians may be undertreating PV.[9] At present, there is little guidance on what should be considered an excessive number of phlebotomies.[1,9] However, the majority held that any number is excessive if not well tolerated. One-half considered more than one every month to be excessive. In this regard, a hematocrit <45% has been associated with fewer cardiovascular deaths and major thrombotic events, suggesting that more intensive cytoreductive therapy should be preferred.[18]

Considering resistance and intolerance to HU, in the REVEAL study on 1381 patients with PV, the most common reasons for HU discontinuations and interruptions were adverse events/intolerance (37.1% and 54.5%, respectively) and lack of efficacy (35.5% and 22.1%, respectively). In all, 18.6% of patients discontinued HU.[27] Thus, while adverse events are frequent, in daily practice only about 20%–40% of the respondents to the present survey were willing to tolerate specific adverse events in fit patients. Also from REVEAL, the most common maximum daily HU doses were 1000 mg (30.6%) and 500 mg (30.1%), and only 6.4% received ≥2 g/d. The dose of hydroxyurea is normally titrated to keep platelet count in the normal range. Herein, 43.3% replied that they usually use HU at a dose of 2 g/day before switching to second-line therapy in the absence of toxicity, indicating that there is no clear standard of treatment. The modified ELN criteria state that the need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/day or a maximum tolerated dose are among the criteria for HU resistance/intolerance.[28] Among criteria for intolerance, most considered the development of various leg ulcers and persistent splenomegaly as criteria for HU resistance/intolerance in line with the modified ELN criteria.[28]

Considering the use of ruxolitinib, about one-half referred that there are patients in whom they would not feel confident in prescribing ruxolitinib, even if the particular patient profile varied. Of these, about one-third said that they would not feel confident in prescribing ruxolitinib to patients with a history of recurrent zoster or other clinically meaningful infections. Age was a factor in only a small percentage of participants. Due to the immunosuppressive effects of ruxolitinib, patients are an increased risk of infections.[29] More than half of the respondents also said that they would temporarily discontinue ruxolitinib in the presence of a severe infection, while there were diverse responses regarding the contraindication for vaccines in PV patients receiving cytoreductive therapies.

Among the limitations of the present survey, there is the relatively small number of participants and the potential for self-selection bias. As a consequence, it may not necessarily be thoroughly representative of routine practice, even if there is a very limited number of publications with which to compare the results seen herein. In addition, there are few questions involving ropeginterferon alfa-2b given the limited clinical experience with this drug at the time of the survey, even if some prescribers had used it on a compassionate basis starting in 2019. Likewise, there were no questions on the issue of iron deficiency in PV, which is of relevance in light of the emergence of hepcidin mimetic agents and other novel therapeutic strategies such as JAK inhibitors, ropeginterferon alfa-2b, and histone deacetylase inhibitors, as well as MDM2 and LSD1 inhibition.[30,31] A similar survey could also be carried out in the future when there is greater experience in prescribing it. At the same time, however, the survey does reveal that there is a large heterogeneity in management of patients with PV. Overall, the results of the present survey indicate that there is considerable heterogeneity in management of PV in routine practice, which may suggest that educational programs could be of value in improving the consistency of treatment of PV.

## AUTHOR CONTRIBUTIONS

*Conceptualization*: Giuseppe Alberto Palumbo, Massimo Breccia, Alessandra Iurlo, Paola Guglielmelli, Francesca Palandri. *Methodology*: Giuseppe Alberto Palumbo, Claudia Baratè, Massimiliano Bonifacio, Elena Maria Elli, Novella Pugliese, Elena Rossi, and Francesca Palandri; *Writing – original draft*: Giuseppe Alberto Palumbo and Francesca Palandri. *Writing – review and editing*: all authors. All authors have read and agreed to the published version of the manuscript.

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## CONFLICTS OF INTEREST

Giuseppe A. Palumbo has received honoraria from Abbvie, Amgen, AstraZeneca, Celgene, and Novartis and has participated at advisory boards for AOP, AstraZeneca, BMS, Celgene, Janssen, and Novartis. Massimo Breccia received honoraria from Novartis, Pfizer, Incyte, and Celgene. Claudia Baratè received honoraria from Novartis, Abbvie, and Janssen. Elena Maria Elli has participated at advisory boards for Abbvie and Novartis. Alessandra Iurlo received honoraria from Novartis, Pfizer, Incyte, BMS, and Celgene. Francesca Palandri has received honoraria from and has served on speakers' bureaus for Novartis. The remaining authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data presented in this study are available in this article.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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