Bortezomib, Thalidomide and Lenalidomide: Have They Really Changed the Outcome of Multiple Myeloma?

MICHAEL MIAN[1,2], MARTINA TINELLI[3], ELENA DE MARCH[4], GLORIA TURRI[4], VITTORIO MENEGHINI[3], NORBERT PESCOSTA[1], TAMARA BERNO[4], ALESSANDRA MARABESE[1], PATRIZIA MONDELLO[5], FRANCESCA PATRIARCA[6], GIOVANNI PIZZOLO[3], GIANPIETRO SEMENZATO[4], SERGIO CORTELAZZO[7] and RENATO ZAMBELLO[4]

[1]*Department of Hematology & Center of Bone Marrow Transplantation, Ospedale di Bolzano, Bolzano, Italy;*
[2]*Department of Internal Medicine V (Haematology and Oncology), Medical University of Innsbruck, Innsbruck, Austria;*
[3]*Department of Medicine, Section of Hematology, University Hospital of Verona, Verona, Italy;*
[4]*Department of Medicine, Hematology and Clinical Immunology, Padua University School of Medicine, Padua, Italy;*
[5]*Department of Human Pathology, University of Messina, Messina, Italy;*
[6]*Department of Hematology, University of Udine, Udine, Italy;*
[7]*Unit of Medical Oncology and Hematology, Clinical Institute Humanitas-Gavazzeni, Bergamo, Italy*

Abstract. *Treatment of multiple myeloma (MM) has significantly improved, although the disease remains incurable. Prospective clinical trials evaluating the impact on outcome of new drugs such as proteasome inhibitors or immunomodulating agents are limited since they are not able to reflect the clinical routine and available retrospective data are not detailed enough to directly evaluate the value of new drugs. To address these information gaps, we performed a retrospective real-life analysis. We retrospectively assessed 949 patients treated for multiple myeloma or plasma cell leukemia at three Italian cancer centers in the years 1979-2014. Clinical features at the time of diagnosis were consistent with what was observed in clinical routine. A total of 39% of patients underwent high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). The median overall survival (OS) of the whole group was 5.4 years and ranged from 3.4 years for patients who did not receive at least one of the new drugs compared to 5.9 years in the other patients (p<0.001). The improvement in OS due to administration of new drugs was also observed among different prognostic sub-groups such as age, Durie and Salmon stage, international staging system and renal impairment. Availability of new drugs significantly improved survival of patients who underwent ASCT and also those who did not. In conclusion, we provided evidence that the advent of the new drugs drastically improved the outcome of patients with MM, also in cases with poor risk at the time of diagnosis. ASCT is still of major importance in the treatment of this disease. Nevertheless, MM remains incurable and new therapeutic approaches are warranted.*

Correspondence to: Michael Mian, Department of Hematology & CBMT, Hospital of Bolzano, Via Lorenz Böhler 5, 39100 Bolzano, Italy. Tel: +39 0471908309, e-mail: m.mian@med-sci.eu

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The first case of multiple myeloma (MM) was published in 1844 (1) and, due to the absence of an efficient treatment, disease progression led to a dismal outcome. Treatment of MM has since significantly improved, but it is still considered an incurable disease. The most important steps forward in the management of MM were the introduction of melphalan and prednisone in the late 1960s (2), consolidation treatment with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) in 1987 (3) and finally, in the late 1990s, the identification of non-chemotherapic agents able to induce remission in patients with MM. The first new drugs which in prospective clinical trials proved to improve survival were thalidomide (4), bortezomib (5) and lenalidomide (6). However, patients included in prospective clinical trials are often highly selected and elderly and unfit patients are in particular excluded. This is a major point of criticism in MM, since it is a disease mainly occurring in the elderly and the median age at time of diagnosis is about 65 years. In order to answer these open questions, several research groups performed register-based analyses (7-9). However, due to the lack of detailed clinical data, it was not possible to directly evaluate the impact of such new drugs on the clinical course of these patients but the year of diagnosis was used to estimate the

improvement of survival over time and therefore the possible impact of new drugs. Therefore, these results are biased by improved supportive care over the years and other factors. To our knowledge, only one analysis, that by the Swedish Cancer Registry, has evaluated in detail the impact of the new drugs in clinical routine practice (10). They analyzed the role of the new drugs in the light of ASCT, performing many subgroup analyses; however, a global overview is lacking. In order to close these information gaps, we retrospectively assessed all patients treated in a defined timespan at three major Italian cancer centers.

Patients and Methods

We retrospectively assessed all patients treated for MM or plasma cell leukemia at the Hospital of Bolzano, the University Hospitals of Verona, and Padova in the years 2004-2014, 1979-2012 and 1986-2013, respectively. Patients with diagnosis of smouldering myeloma, monoclonal gammopathy of undetermined significance and amyloidosis were excluded. Diagnosis was performed according to international criteria (11), and staging according to Durie and Salmon (12) or the international scoring system (ISS) (13) or both. Treatment initiation was based in most cases on the CRAB (14) criteria. Data were acquired by retrospective evaluation of patient files and consisted of clinical parameters at diagnosis, administration of bortezomib, thalidomide and lenalidomide (Revlimid®), high-dose chemotherapy followed by ASCT and survival information. In the present analysis bortezomib, thalidomide and Revlimid® were defined as new drugs. Since fluorescence *in situ* hybridization data were available only in a minority of the patients, this information was not assessed.

The ethical committee of Bolzano approved the present analysis (no. 39/2013). Since data collection was performed anonymously, no informed consent was required.

Chi-square test was performed to assess the significance of differences between categorical variables. OS was defined as the time from diagnosis until last follow-up or death from any cause and was plotted as a curve using the Kaplan–Meier method. Log-rank test was employed to assess the impact of categorical variables on survival. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software v.17.0.1 (SPSS, Chicago, IL, USA).

Results

Patient inclusion. Overall, 949 patients were assessed. All patients treated in the three participating centers in the above-mentioned time periods were included without performing any selection in order to provide a true-to-life analysis. However, due to missing data, 69 patients had to be excluded from further analyses, hence 880 were considered as evaluable.

Clinical characteristics at the time of diagnosis. The most important clinical characteristics assessed at the time of diagnosis are summarized in Table I. As expected, most patients were aged between 60 and 74 years, with an overall median age of 65 (range=22-97) years. Only a minority of patients presented exclusively with extramedullary disease (4%) and in the whole cohort, only 2% of patients had plasma-cell leukemia at the time of diagnosis. Most patients presented with advanced Durie and Salmon stage, while only a minority had an ISS of 3. Renal impairment, defined according to Durie and Salmon, was registered in 15% of cases. Of course, the distribution of positive and negative prognostic factors was non-homogeneous between those patients who underwent the new drugs or not, since in the early years of their use in clinical routine, patients with negative prognosticators were preferably directed to the new treatment modalities, while, for example, the very elderly, received mainly treatments without at least one of the investigated drugs due to their low life expectancy (data not shown).

Treatment. As expected, since MM is not yet curable, the assessed patients underwent a median of two treatment lines ranging between 1 and 11 lines. Patients were treated according to the guidelines of the single centers. Since all three centers are involved in clinical research, some of the included patients underwent at least one of the investigated drugs in the setting of experimental protocols and outside clinical routine. Twenty-six percent did not receive any of the three new drugs, while 22% at least one only in first line, 28% only in second/higher line and 24% as in first and higher treatment lines. ASCT was performed in 39% and mostly only once (55%). Due to the high rate of expected severe side-effects without the security of a definitive cure of disease (15), allogeneic stem cell transplantation was only delivered to selected patients (3%), hence specific sub-group analysis was not performed.

Survival. The median follow-up of the whole group was 3 years (range=1 month-28 years). The median OS of the whole group was 5.4 years. Those patients who did not receive at least one of the new drugs achieved a median OS of 3.4 years compared to 5.9 years in the other ($p<0.001$; Figure 1A). The year of diagnosis did not influence the clinical course (Figure 1B).

The improvement in OS was also observed among different prognostic sub-groups. Younger patients especially benefited from the ND (<60 years, $p=0.017$ and 60-74 years, $p=0.007$), while among the elderly, the improvement was limited (76-84 years, $p=0.095$). Despite these improvements, age maintained its significant impact on survival ($p<0.001$; Figure 2A). Patients across all stages according to Durie and Salmon had a significant survival advantage from the new drugs (stage 1 $p=0.001$, stage II $p=0.008$ and stage III $p>0.001$). This led to a narrowing of the survival curve of patients affected by stage II and III disease, while the OS difference between those with limited and advanced-stage disease

Table I. *Clinical characteristics at time of diagnosis and their impact on overall survival, treatment details and follow-up of 880 patients.*

Parameter	N	Valid	Percentage
Year of diagnosis		876	
1979-1995	24		3
1996-2005	314		36
2006-2015	538		61
Median age at diagnosis years (range)		64 (22-97)	
Age groups at diagnosis, years		876	
<60	285		32
60-74	412		47
75-84	157		18
≥85	22		3
Disease extent		855	
Only medullary disease	726		85
Only extramedullary disease	35		4
Medullary and extramedullary disease	94		11
Plasma cell leukemia	16	868	2
Durie and Salmon stage		830	
1	221		27
2	143		17
3	466		56
Renal insufficiency	127	841	15
ISS		378	
1	195		52
2	94		25
3	89		23
Administration of new drugs		870	
No new drugs	223		26
First-line only	194		22
Second-/higher line only	245		28
First-and second-/higher line	208		24
Drug combinations		874	
BTL	89		25
BT	147		10
BL	106		17
TL	12		12
B	113		1
T	159		13
L	26		18
ASCT	335	856	39
Number of ASCTs		335	
1	185		55
2	147		44
3	3		1
Allogeneic stem cell transplantation	26	867	3
Deaths	481	876	55
Second neoplasia	49	762	6

ISS, International Staging System; B, bortezomib; T, thalidomide; L, lenalidomide; ASCT, autologous stem cell transplantation; n.a., not applicable.

remained highly statistically significant ($p<0.001$; Figure 2B). Moreover, patients with renal impairment significantly benefited from introduction of the new drugs into clinical routine ($p=0.003$). Nevertheless, the OS improvement was not sufficient to abolish the negative impact of renal dysfunction on survival, therefore the OS of patients with end-organ damage was still significantly inferior to that of those without ($p<0.001$; Figure 2C). As the ISS was introduced in 2005, it was available only for 378 patients (43%; Table I). The new drugs were able to improve only the OS of patients with ISS 2 ($p<0.001$), while this was not the case for those with stage I ($p=0.725$) and stage III ($p=0.285$) disease. Therefore, in the era of new drugs the curves of ISS I and ISS II patients narrowed, while the negative impact of ISS III was still

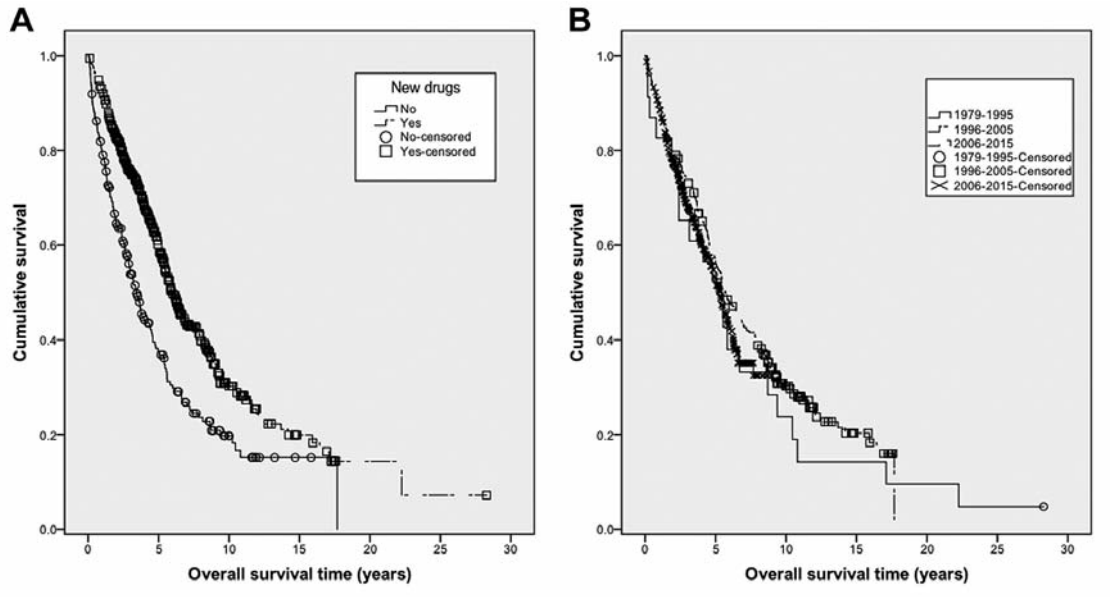

Figure 1. *Overall survival according to the administration of new drugs (A) and to the year of diagnosis (B).*

statistically significant ($p<0.001$; Figure 2D). Due to the low occurrence of plasma cell leukemia (2% in the whole cohort) it was not possible to draw any conclusions. Nevertheless, despite the low number of observed cases, the negative impact of plasma cell leukemia was overwhelming, leading to a statistically significant survival difference in the era of new drugs ($p<0.001$; Figure 2E). The presence of additional extramedullary disease is also a known negative prognosticator and indeed, when compared to patients with disease limited to the bone marrow, despite the positive impact of the new drugs, it remains a very negative factor ($p=0.006$).

The new drugs significantly improved survival of patients who underwent ASCT ($p=0.001$) and those who did not ($p<0.001$). However, they were not able to outdo the positive impact of high-dose chemotherapy followed by stem cell infusion ($p<0.001$; Figure 2F).

Secondary neoplasia. Due to the relatively low number of secondary neoplasias (49/762; 6%) and the high number of treatment sub-groups (7), we were not able to evaluate if a specific treatment modality was significantly associated with a higher occurrence of other tumors. However, the percentage of secondary non-plasma cell neoplasia was about 6% (35/562) among patients who underwent therapy with at least one of the new drugs and 7% (14/196) among those who did not receive them. When comparing patients who had treatment with Revlimid® to those who did not, no important difference in frequency was observed [5% (11/202) *versus* 7% (25/360), $p>0.05$].

Discussion

Over the last 170 years, treatment of MM has dramatically changed. Especially in the last 15-20 years, many new drugs were introduced and, at least in prospective clinical trials, they were an important step forward. However, these trials were limited by patient selection and published real-life data use the year of diagnosis as a surrogate marker for new drugs and are registry-based (7-9) and therefore, except for the Swedish Cancer Registry one (10), not detailed enough. Herein, we show that bortezomib, thalidomide and Revlimid® are able to improve survival among most prognostic sub-groups, confirming the positive impact of new drugs in a true clinical setting.

The strengths of this analysis were the large number of patients assessed, the relatively long-term follow-up, its 'real-life' nature and treatment in a multicenter setting. Apart from the limits common to every retrospective analysis, a central pathology review was not performed. However, all participating centers demonstrated a lengthy experience in myeloma diagnosis and management, as well as the active involvement of expert hemopathologists.

Overall, except for stage according to the ISS, the clinical features at the time of diagnosis are consistent with what observed in clinical routine (16). In contrast to the original analysis by Greipp *et al*. where about one-third of patients were assigned to each ISS risk group (13), herein 52% had stage 1 disease. This can easily be explained by the fact that in the participating centers the ISS was initially applied mainly in clinical trials and only later on it was assessed in clinical routine. Since many trials exclude patients with

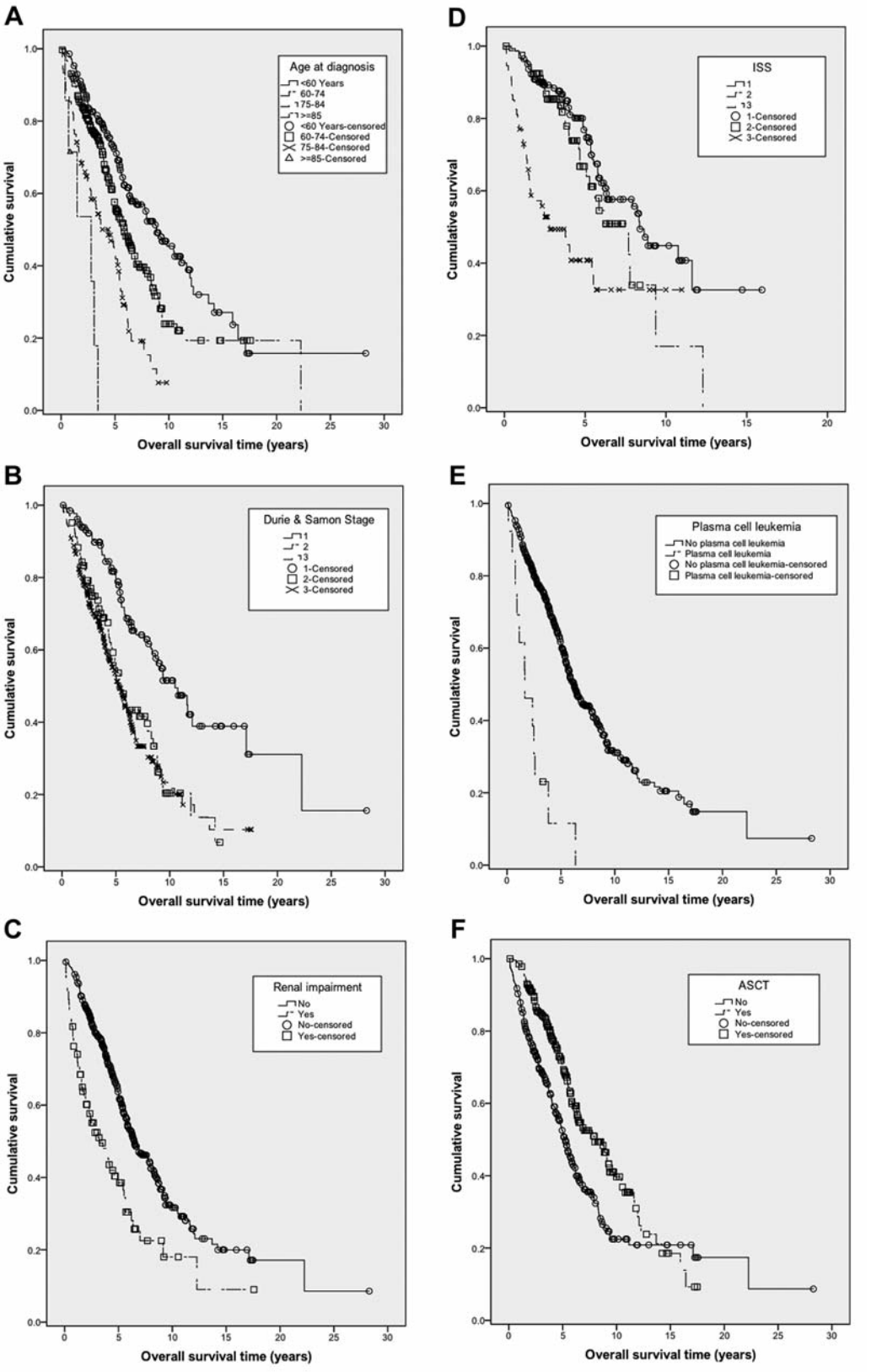

Figure 2. *Overall survival according to age (p<0.001) (A), Durie and Salmon stage (p<0.001) (B), renal impairment (p<0.001) (C), ISS score (p<0.001) (D), plasma-cell leukemia (p<0.001) (E) and to ASCT (p<0.001) (F) in patients who underwent therapy with at least one of the investigated drugs.*

unfavorable disease, the higher percentage of stage 1 cases in the present analysis was not unexpected. Another expected difference compared to prospective trials was a more representative age distribution. Clinical studies often select patients by age (6, 17) or fitness/life expectancy (5), hence survival data of such cohorts only rarely reflect real-life situations.

In the present analysis, 39% of patients underwent high-dose chemotherapy followed by ASCT, which is very similar to the analyses of the Swedish Cancer Registry (10), suggesting a similar treatment approach over large parts of Europe.

The median OS of the whole group was 5.4 years and ranged from 3.4 years for patients who did not receive at least one of the new drugs to 5.9 years for other patients ($p<0.001$). A similar improvement was recorded by Turesson *et al*. (8) over several decades, and by other authors (7), but none of them were able to show directly that this was attributable to the administration of new drugs. In contrast to these trials, we were not able to show a correlation between the year of diagnosis and improvement of survival. This can be explained by the fact that in the participating cancer centers, new drugs were already available in the 1990s due to clinical trials.

The improvement in OS due to the administration of new drugs was also observed among different prognostic sub-groups such as age, Durie and Salmon stage, ISS and renal impairment. Up to now, this fact has only been described for age and creatinine, while to our knowledge, no real-life data were available regarding the other parameters. Especially younger patients benefited from the new drugs, while among the elderly the improvement was limited. However, we did not assess the dose intensity of treatment. Since in elderly patients a dose reduction or early treatment suspension is often required due to toxicity, these limited improvements might be attributed to this. The negative impact of advanced age on the clinical course of patients with MM was also described in other register-based trials which considered the year of diagnosis as a surrogate marker for new treatments (7, 8), as well as in the analysis by Liwing *et al*. (10). Overall, the advent of new drugs was able to improve OS of most age subgroups, but age maintained its significant impact on survival even in the era of new drugs.

In line with the analysis of the Swedish Cancer Registry (10), patients with renal impairment also significantly benefited from the introduction of the new drugs into clinical routine. Nevertheless, the OS improvement was not sufficient to abolish the negative impact of renal dysfunction on survival, explaining why the OS of patients with renal end-organ damage was still significantly inferior to those without.

None of the previously mentioned register-based analyses evaluated the impact of disease stage on OS (7, 8, 10). In the present analysis, patients across all stages according to Durie and Salmon had a significant survival advantage from the new drugs, leading to a narrowing of the survival curved of patients affected by stage II and III disease. Since this staging system reflects the presence of compromised end-organ function, the fact that the outcome of stage II and III patients is still poor might suggest that treatment should be initiated before the presence of such damage in order to improve the outcome – in line with what we observed regarding renal impairment. This supports the recently change of paradigms in the management and therapy of MM, favoring earlier treatment initiation (18). On the other hand, in the era of new drugs, the curves of ISS I and ISS II patients narrowed, while the negative impact of ISS III was still statistically significant. Since the ISS better reflects the tumor mass, this observation also suggests that earlier treatment initiation could improve OS of patients with MM.

The new drugs significantly improved survival of patients who underwent ASCT and those who did not, confirming that ASCT outcomes are improved by induction treatments with new drugs (19). Of course, due to the limits of data assessment of the present study, we cannot say which patients underwent new drugs in the setting of a first-line treatment but since in recent years in particular, bortezomib and thalidomide have become an essential part of first-line treatment, the majority of patients might belong to this group. However, despite the clear OS improvement, the new drugs were not able to better the positive impact of high-dose chemotherapy followed by stem cell infusion, which still represents the current standard-of-care, confirming previously published data (19).

Some trials reported a rather high rate of secondary neoplasia after myeloma treatment, especially after lenalidomide, raising major safety concerns (20). In the present trial, the number of secondary neoplasias was within the expected range. However, due to the high number of treatment subgroups and the retrospective nature of this analysis, we were not able to evaluate whether a specific treatment modality was associated with a higher occurrence of other tumor types. Overall, the percentage of secondary non-plasma cell neoplasias was similar in patients who underwent treatment with new drugs and those who did not, as well as those who underwent Revlimid® and those who did not.

In conclusion, in this real-life analysis, we showed that the advent of new drugs has drastically improved the outcome of patients with MM, even in cases with a poor risk at the time of diagnosis. Despite these positive impacts, ASCT is still of major importance in the treatment of this disease. Nevertheless, MM remains incurable and new therapeutic approaches are warranted.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in regard to this study.

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