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Second primary malignancies in multiple myeloma: an overview and IMWG consensus

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Background: Therapeutic advancements following the introduction of autologous stem cell transplantation and 'novel' agents have significantly improved clinical outcomes for patients with multiple myeloma (MM). Increased life expectancy, however, has led to renewed concerns about the long-term risk of second primary malignancies (SPMs). This review outlines the most up-to-date knowledge of possible host-, disease-, and treatment-related risk factors for the development of SPMs in patients with MM, and provides practical recommendations to assist physicians.

Design: A Panel of International Myeloma Working Group members reviewed the most relevant data published in the literature as full papers, or presented at meetings of the American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, or International Myeloma Workshops, up to June 2016. Here, we present the recommendations of the Panel, based on this literature review.

Results: Overall, the risk of SPMs in MM is low, multifactorial, and partially related to the length of patients' survival and MM intrinsic susceptibility. Studies suggest a significantly increased incidence of SPMs when lenalidomide is administered either following, or concurrently with, oral melphalan. Increased SPM incidence has also been reported with lenalidomide maintenance following high-dose melphalan, albeit to a lesser degree. In both cases, the risk of death from MM was significantly higher than the risk of death from SPMs, with lenalidomide possibly providing a survival benefit. No increase in SPM incidence was reported with lenalidomide plus dexamethasone (without melphalan), or with bortezomib plus oral melphalan, dexamethasone, or thalidomide.

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Conclusion: In general, the risk of SPMs should not alter the current therapeutic decision-making process in MM. However, regimens such as lenalidomide plus dexamethasone should be preferred to prolonged exposure to lenalidomide plus oral melphalan. SPM risk should be carefully discussed with the patient in the context of benefits and risks of different treatment options.

Key words: multiple myeloma, second primary malignancy, SPM, risk factors, lenalidomide, International Myeloma Working Group

introduction

The potential for patients originally diagnosed with multiple myeloma (MM) to develop solid or hematologic second primary malignancies (SPMs) has long been recognized. Forty-five years ago, Dr Robert Kyle and co-workers described the subsequent development of acute myeloid leukemia (AML) in four patients who had received prolonged melphalan treatment for MM or systemic amyloidosis [1]. Nine years later, other researchers reported a greater-than-expected incidence of AML (14 cases, 3.8%) among 364 patients with MM treated with low-dose melphalan in combination with other alkylating agents [2].

Subsequent Medical Research Council (MRC) studies strengthened the case for a link between prolonged alkylating agent exposure and SPM development in patients with MM, reporting 5-, 8-, and 10-year prevalences of myelodysplastic syndromes (MDS) or AML in MM patients treated with melphalan or (albeit less consistently) cyclophosphamide of 3%, 10%, and 20%, respectively [3]. More recently, detailed pathological analysis of myeloid neoplasms secondary to MM (mainly MDS or AML) has furnished support for the hypothesis that alkylating agents exert a mutagenic effect on the pathogenesis of hematologic SPMs, with evidence of complex cytogenetic abnormalities/unbalanced aberrations of chromosomes 5/7 being particularly associated with melphalan/cyclophosphamide combinations [4].

Over the past decade, the successive introduction of high-dose melphalan followed by autologous stem cell transplantation (ASCT) as standard initial therapy in younger patients, and of the first generations of 'novel' agents, such as the immunomodulatory drugs (IMiDs; thalidomide and lenalidomide) and the proteasome inhibitor bortezomib, has improved clinical outcomes and life expectancy in MM, with current expected median survival ranging from 5 to 8 years [5–8]. However, increased life expectancy has rekindled concerns about the long-term risk of solid or hematologic SPMs [9–11], particularly as the prognosis of many potential SPMs remains very poor in comparison with MM [12–15]. A recent Swedish, population-based study of 26,627 patients diagnosed with MM between 1958 and 2011 confirmed a statistically significant 2.3-fold (95% confidence interval [CI] 2.1–2.5) increased mortality risk in patients with SPMs versus a control group of MM patients without SPMs [16]. The finding in randomized, phase III trials that lenalidomide maintenance therapy is associated with an increased risk of SPMs (7%–8%) versus placebo/observation (2%–3%), in both elderly [17] and transplant-eligible patients [18, 19], has further added to these concerns [20–22].

This paper aims to disseminate the latest knowledge of SPM risk factors in patients with MM, and provides practical recommendations and guidance to assist physicians in the management of such patients. In particular, a Panel composed of members of the International Myeloma Working Group has considered the following questions:

1. What is the 'true' risk of SPM development in patients with MM?
2. What are the possible host- and disease-related risk factors for SPMs in patients with MM?
3. Do older and novel therapies increase the risk of SPM development in MM?

The Panel's recommendations in relation to each of these questions are summarized in Table 1, and are presented in detail in the Supplementary Appendix, available at *Annals of Oncology* online. These recommendations are based on the most relevant data published in the literature as full papers (identified through the PubMed database) or presented at meetings of the American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, or International Myeloma Workshops, up to June 2016.

what is the 'true' risk of SPM development in patients with MM?

Table 2 summarizes major population-based, cancer registry studies that investigated SPM incidence in patients with MM. These studies generally found no overall increase in SPM risk among patients with MM, but did identify an augmented incidence of MDS, AML and, to a lesser degree, non-Hodgkin lymphoma (NHL). In contrast, significant heterogeneity in the risk of different solid SPM subtypes was observed (Table 2).

It is difficult to draw firm conclusions about the 'true' risk of SPMs in MM, or to identify specific risk factors in a process that is likely multifactorial. First, the estimated overall risk reported is relatively small: the cumulative incidence of 1%–10% is comparable with the incidence of cancer per life-year in the general population [31]. Consequently, some reports—particularly of uncontrolled/retrospective and post-hoc studies—may underestimate SPMs, as they are not specifically tracked during follow-up. Conversely, over-reporting may occur if SPMs are expected to be found in specific arms or subgroups of trials, or when appropriate screening is used to prospectively detect early SPMs. In general, well-designed, registry-based, population studies, which include individual treatment and long follow-up, may be a more effective means of determining therapy-associated SPM risk than some randomized trials, which are limited by inclusion/exclusion criteria, lower power, and treatment crossover.

Table 1. Panel recommendations

Recommendation
What is the 'true' risk of SPM development in patients with MM?
• Well-designed, population-based studies suggest that the risk of SPMs in MM is low, and partially related to the lengthening survival of patients with MM.
• The risk of SPMs should be evaluated in individual patients, according to patient-, disease-, and treatment-related factors.
• Additional and systematic data gathering is needed to determine the incidence and types of SPMs in patients with MM currently treated both in clinical trials and in the real-world setting.
• Ongoing trial protocols should be amended to include enhanced monitoring and precise measurement of secondary cancers (including non-invasive neoplasms), and include SPMs as an 'a priori' well-defined endpoint. These measures should be integral to the design of any future prospective clinical trials.
• Prospective population-based studies gathering information on the baseline characteristics and treatment of individual patients should also report SPM data.
• SPM data collected in clinical trials and observational studies should include details of the time to development, clinical and biologic characteristics, prognosis, and natural history of SPMs observed.
• SPM incidence rates should be adjusted for person-years at risk (that is, rate per 100 person-years).
• Specific routine screening for SPMs, beyond that suggested for the general population, is not recommended. However, diagnostic measures that would aid the detection of suspected SPMs during daily clinical work-up should be considered, on a case-by-case basis, in long-term MM survivors. In particular, bone marrow examination with cytogenetic analyses (or FISH, if necessary) is recommended at baseline and in the event of unexplained blood count abnormalities in the real-life setting and in prospective observational and investigational studies.
• Every SPM case should be reviewed carefully to accurately assess the true impact of treatment on SPM development, and to prevent false inflation of reported SPM rates.
What are the possible host- and disease-related risk factors for SPMs in patients with MM?
• The pathogenesis of SPMs in MM is likely to be multifactorial.
• Biologic samples from all MM patients included in clinical trials and, when possible, encountered in clinical practice, should be collected and stored for genetic analysis. Ideally, samples should yield DNA for genomic analysis or, better still, RNA for gene expression profiling. Collection of germline and tumor-related material, and re-banking of biologic samples during the course of the disease, are also recommended.
• Next-generation sequencing genomic studies designed to identify genetic profiles associated with increased SPM risk should be planned.
Do older and novel therapies increase the risk of SPM development in MM?
• Based on the available evidence, the potential risk of SPMs in MM should not generally alter the current therapeutic decision-making process.
• Data regarding the use of ASCT in MM are reassuring, and the Panel recommends that first-line therapeutic approaches in eligible MM patients should always include ASCT conditioned with high-dose intravenous melphalan.
• For the current approved indication of lenalidomide in the treatment of relapsed MM, the benefits of therapy clearly outweigh any risk of SPMs.
• Similarly, in front-line therapy without concurrent oral melphalan, regimens such as lenalidomide plus dexamethasone (or alternatives such as cyclophosphamide or alkylating-free combinations) remain safe and effective options that should be considered for patients with MM, instead of oral melphalan in combination with lenalidomide.
• In the maintenance setting, prolonged administration of lenalidomide where there is antecedent melphalan exposure should generally be avoided, with the important exception of high-dose melphalan used as a conditioning regimen for ASCT.
• All patients initiating lenalidomide maintenance should undergo a baseline bone marrow examination with cytogenetics to ensure that there is no overt evidence of dysplasia or concerning cytogenetic abnormalities. There should also be a low threshold for careful bone marrow analysis with karyotyping for patients with unexplained cytopenias that persist despite lenalidomide withdrawal.
• In cases where the overall survival benefit of maintenance therapy with lenalidomide is still not well established, the risks versus any possible benefits of treatment should be considered carefully.
• The potential increased risk of SPMs should be adequately addressed through appropriate discussion with the patient, bearing in mind current knowledge and providing updated and balanced information about treatment-associated pitfalls and benefits, specifically in terms of OS, thus enabling the patient to make informed decisions regarding treatment selection on this basis.
• Physicians should remain well informed about the latest data on the risk of SPMs in MM.

ASCT, autologous stem cell transplantation; FISH, fluorescence in situ hybridization; MM, multiple myeloma; OS, overall survival; SPM, secondary primary malignancies.

Table 2. Key population-based registry studies evaluating the incidence of SPMs in patients with MM

Authors	Type of study	Study period	Patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	All SPMs SIR (95% CI)	Hematologic SPMs SIR (95% CI)	Solid tumor SPMs SIR (95% CI)
Dong et al. [23]	Population-based registry study	1958–1996	8656	475 (5.5)	83 (1.0)	392 (4.5)	2.9 y	NR	All HMs 2.19 (1.74–2.71); NHL 1.74 (1.12–2.57); AML 8.19 (5.70–11.4)	All STs 0.81 (0.70–0.90)
Mailankody et al. [24]	Population-based registry study	1986–2005	8740	577 (6.6)	69 (0.8)	508 (5.8)	45.3 mo MDS/AML	All SPMs 1.26 (1.16–1.36)	All HMs 2.04 (1.59–2.58); AML/MDS 11.51 (8.19–15.74)	All STs 1.19 (1.09–1.30); GI 1.30 (1.09–1.53); NMST 2.22 (1.74–2.80)
Youlden et al. [25]	Population-based registry study	1982–2001	2174	134 (0.6)	NR	NR	NR	Males 1.04 (0.84–1.27); females 0.89 (0.64–1.21)	NR	NR
Chakraborty et al. [26]	Selected population of MM patients with SPMs	1973–2008	3245 patients with MM as first of ≥ SPM	1657 (51.1)	214 (6.6)	1394 (43.0)	NR	All SPMs 0.99 (0.95–1.04)	All HMs 1.68 (1.46–1.92); all leukemias 3.07 (2.57–3.64); ALL 5.48 (NR); AML 7.01 (NR); CML 2.26 (NR)	All STs 0.94 (0.89–0.99); hypopharynx 0.0 (NR); esophagus 0.35 (NR); breast 0.76 (0.63–0.90); prostate 0.75 (NR); small intestine 2.03; skin, excluding basal/squamous carcinomas 1.43 (1.09–1.85); kidney 1.51 (1.13–1.98); KS 3.3 (1.06–7.69)
Razavi et al. [27]	Population-based registry study	1973–2008	36,491	2026, including 56 miscellaneous (5.5)	263 (0.7)	1707 (4.7)	5.2 y	All SPMs: 0.98 (0.94–1.02)	All HMs 1.63 (1.45–1.84); AML 6.51 (5.42–7.83); NHL 1.28 (1.04–1.57)	All STs 0.92 (0.88–0.97); esophagus 0.49 (0.28–0.87); lung 0.88 (0.78–0.99); breast 0.81 (0.69–0.94); prostate 0.69 (0.61–0.77); melanoma 1.36 (1.07–1.74); urinary bladder 1.22 (1.03–1.44); kidney/renal pelvis 1.30 (1.01–1.66); thyroid 1.63 (1.05–2.52)
Tzeng et al. [28]	Population-based registry study	1997–2009	3970	71 (1.8)	35 (0.9)	36 (0.9)	1.9 y	NR	All HMs 13.0 (7.79–21.6); NHL 7.72 (3.83–15.6); AML 23.9 (10.5–54.5)	All STs 0.57 (0.40–0.79); lung 0.28 (0.09–0.87)

continued

continued

Authors	Type of study	Study period	Patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	All SPMs SIR (95% CI)	Hematologic SPMs SIR (95% CI)	Solid tumor SPMs SIR (95% CI)
Rifkin et al. [29]	US MM Registry study	2009–2012	1493 enrolled, 1443 treated	74 (5.1); invasive 51 (3.5); NMST 26 (1.8)	14 (1.0)	37 (2.6)	NR	Incidence per 100/person-y in 977 patients +L: invasive: 0.85 (0.61–1.19); incidence per 100/person-y in 466 patients −L: invasive: 1.16 (0.72–1.86)	Incidence per 100/person-y in 977 patients +L: invasive HMs: 0.17 (0.08–0.36); incidence per 100/person-years in 466 patients −L: invasive HMs: 0.47 (0.22–0.99)	Incidence per 100/person-y in 977 patients +L: invasive STs: 0.67 (0.46–0.98); NMST 0.50 (0.32–0.77); incidence per 100/person-y in 466 patients −L: invasive STs: 0.68 (0.36–1.26); NMST 0.41 (0.18–0.91)
Engelhardt et al. [30]	Freiburg University Registry study	1997–2011	744	49 (6.6)	17 (2.3)	32 (4.3)	NR	NR	NR	NR

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CML, chronic myeloid leukemia; GI, gastrointestinal; HM: hematologic malignancy; KS, Kaposi's sarcoma; +L, exposure to lenalidomide; −L, no exposure to lenalidomide; MDS, myelodysplastic syndromes; MM, multiple myeloma; mo, months; NHL, non-Hodgkin lymphomas; NMST, non-melanoma skin tumors; *n*, number; NR, not reported; SIR, standardized incidence rate; SPM, secondary primary malignancy; ST, solid tumor; y, years.

Pre-existing or concomitant neoplasms could represent additional confounding factors [32–36]. On the other hand, some studies suggest that SPM risk may be elevated as a 'natural' consequence of the increased survival achieved with current treatments, rather than as a direct result of the therapies themselves [9–11].

Finally, a correct diagnosis of 'true' SPM is mandatory. An ad-hoc independent committee recently reviewed SPMs occurring in the UK MRC Myeloma XI study according to pre-determined criteria [37]. Of 88 reported cases, only 67 (76%) were confirmed as trial-related SPMs; the remaining cases were rejected because of: evidence that the second malignancy pre-existed prior to trial enrollment (57%); no evidence of malignancy found on further investigation (24%); reported non-malignant skin conditions (14%); and spontaneous resolution of cytopenias upon cessation of treatment (5%).

what are the possible host- and disease-related risk factors for SPMs in patients with MM?

SPM development is likely multicausal. In addition to specific treatments, possible risk factors may be classified as either host- or disease-related.

host-related risk factors

age and sex. Among potential host-related factors, older age and male sex have most commonly been associated with increased SPM incidence in patients with MM [18, 26, 38, 39]. Nevertheless, there are inconsistencies in the published data. Updated results from the Surveillance, Epidemiology, and End Results (SEER) program, for example, showed that the risk of AML development in patients with MM was increased 5-fold in those aged <65 years of age versus patients aged >75 years [27]. Meanwhile, women with MM were found to be at significantly increased risk of leukemia versus men [27].

ethnicity. Several SEER-based analyses demonstrate an impact of ethnicity on the risk of SPM development in patients with MM [26, 40]. In an analysis of 2021 patients with MM and SPMs (diagnosed between 1973 and 2008), Hispanic whites had a significantly decreased observed/expected (O/E) risk of developing solid tumors, particularly lung/bronchus and prostate SPMs. Non-Hispanic whites showed an increased O/E risk of developing skin melanomas, NHL, and, more consistently, AML, while the risk of developing SPMs of the kidney/renal pelvis and AML was increased among African Americans. The O/E risk of AML as a SPM was also found to be significantly increased among Asian-Pacific Islanders [40].

genetics. Genetic alterations and their interaction with environmental factors and/or therapy may contribute to familial and individual predisposition to MM and, possibly, to different SPMs [41–43]. Genotype studies have shown that germline mutations in the *CDKN2A* gene may predispose to both MM and other cancers [41]. Furthermore, the G/G phenotype of single nucleotide polymorphism (SNP) rs1617640 in the erythropoietin promoter gene has been found to be more common in individuals with MM who develop MDS versus those who do not [44], thus confirming a potential role for susceptibility genes in the development of SPMs. Other genetic polymorphisms have been found to be associated with an increased risk of MM [45], while conversely appearing to protect against specific solid SPMs [27, 46]. Genome-wide association studies and gene expression microarray analysis of patients with or without SPMs have identified several other candidate SNPs that are associated with acute leukemia after other neoplasms [47, 48]. Studies investigating baseline whole bone marrow gene-expression profiling, proteomic analyses, and SNPs are currently ongoing, with the aim of identifying patients who may have a marked propensity to develop SPMs [43].

prior cancer. Studies have shown that prior or synchronously different malignancies (PSMs) are more common than SPMs in MM, occurring in 3%–24% of patients and thus representing a possible confounding factor when a diagnosis of SPM is suspected [33, 35, 36, 49–51]. While these tumors are often early stage or good-prognosis neoplasms, the largest group (up to 90%) of invasive PSMs comprises prostate, gastric, colorectal, and breast cancers, while fewer hematologic malignancies (10%–27%) have been reported.

Patients with PSMs frequently have a history of chemo-/radiotherapy, and/or hormone therapy, which confers a poor prognosis. In these patients, MM potentially occurs as a SPM. Interestingly, in a large Swedish study, MM patients with PSMs at diagnosis were not at increased risk of developing a subsequent SPM versus those without PSMs (odds ratio 1.19; 95% CI 0.97–1.46) [52]. These findings suggest that patients with MM and a PSM should not be denied the best available therapy because of fears of SPM development.

additional individual factors. Many additional socioeconomic, occupational, lifestyle, and environmental factors could potentially play a role in the development of SPMs. The potential involvement of such factors in the context of competing risks may be difficult to differentiate, especially if their real impact on the development of SPMs is small; consequently, no firm data have yet been produced in the setting of MM [10, 11, 53].

disease-related risk factors

That MM by itself (independent of MM therapy) may be a risk factor for SPM development was first hypothesized nearly 40 years ago [54]. Since then, adverse cytogenetics, advanced disease stage, and some MM subtypes have been associated with increased SPM incidence. Interestingly, the risk of developing MDS/AML appears significantly increased in individuals with monoclonal gammopathy of undetermined significance (MGUS) versus the general population. For example, in a large, Swedish, population-based study, the risk of MDS/AML was increased 8-fold in the subset of 2293 patients with IgG or IgA MGUS versus age- and sex-matched individuals from the general population [24]. Risk levels were increased in patients with M-component concentrations >1.5 g/dl versus those with lower levels, suggesting that the risk of MDS/AML development in MGUS patients with more extensive/advanced disease is similar to that in patients with symptomatic MM. As in MM, an excess risk of non-melanoma skin cancer was also seen in patients with MGUS.

A Mayo Clinic study systematically screened 17,315 individuals for the presence of MGUS [55]. Of the 605 patients found to have MGUS, seven were subsequently diagnosed with MDS, and

two with AML. Compared with non-MGUS controls, patients with MGUS had a 2.4-fold significantly increased risk of developing MDS; the risk of AML was slightly, but not significantly, increased, while no cases of acute lymphoblastic leukemia (ALL) were observed. In a subanalysis, MDS occurred in patients with all Ig isotypes (including IgM), while AML was observed only in patients with IgA/IgG. Such results were unchanged when 'early' MDS/AML patients, diagnosed within 1 year following diagnosis of MGUS, were excluded.

Despite differences in study design and number of MGUS patients included, the Swedish and Mayo Clinic findings both suggest a possible intrinsic causal role for plasma cell disorders, and a consequent inherent increased risk of MDS/AML that is independent of MM therapy. Recently, however, International Staging System stage and history of smoldering myeloma or MGUS were found to have no impact on SPM occurrence in a large, US disease registry study [29]. Interestingly, plasma cell cytogenetic abnormalities were linked with an increased SPM incidence in symptomatic MM (hazard ratio [HR] = 1.64, $P < 0.05$), when modeled from study enrollment in the Total Therapy (TT) trials [56]. Furthermore, three of the patients who ultimately developed MDS/AML in the lenalidomide arm in the MM-015 trial were among 11 patients with plasma cell complex cytogenetics at baseline [57]. In contrast, predominantly favorable cytogenetics have been reported in patients who develop SPMs, suggesting that less aggressive MM and long disease latency may favor the manifestation of additional malignancies [30].

Tumor-induced immunodeficiency, deregulated release of cytokines, chronic inflammation, and common tumor cell precursors may also play an important role in increasing the susceptibility of MM patients to SPM development [58]. Immunologic defects may include quantitative and functional abnormalities in T-cell and B-cell compartments, natural killer and dendritic cell populations, and neutrophils, as well as abnormal cytokine production, modified membrane antigen/receptor expression, and impaired phagocytosis. Multiple relapses and salvage therapies, using older and newer drugs in sequence, may also result in cumulative immunosuppression/dysfunction, further compromising immune surveillance against tumor cells. This could play a particularly significant role in increasing the risk of various skin cancers, including melanoma. Modified sex hormone levels could explain the decreased risk of some hormone-related solid SPMs, including breast and prostate cancer, observed in MM. Less frequent screening after MM diagnosis, however, is another possible explanation for the reported reduced risk of these solid SPMs [27].

do older and novel therapies increase SPM risk in MM?

Early studies identified that prolonged exposure to melphalan increases the risk of hematologic SPM development (in particular, MDS/AML) in patients with MM, likely as a result of a direct mutagenic effect inducing DNA damage [1–4]. The MM treatment paradigm has evolved significantly over the past few years, and numerous studies have continued to investigate treatment-related risk factors for SPMs. The characteristics and findings of the key retrospective studies and prospective first-line phase III randomized trials that have gathered information on the impact of various anti-myeloma treatments on SPM incidence in patients with MM are summarized in Tables 3 and 4, respectively.

radiotherapy

Radiation dose and extended fields are supposed, but not well proven, factors favoring SPM development in patients with MM. Indeed, several solid SPMs have been described in MM patients following combination chemo-radiotherapy [10, 24, 49, 56]. However, compared with other malignancies in which locoregional radiation treatments may induce SPMs in surrounding tissues (including bone marrow), information about the exact role of radiotherapy and risk of SPMs in MM is currently limited. Recent US Connect MM registry data did not support a relationship between radiotherapy and SPM incidence [29]; this could be due to the lower radiotherapy dose usually administered to patients with MM.

ASCT

Data suggest that secondary MDS/AML risk is increased following ASCT in patients with lymphoma (14.5% cumulative incidence up to 15 years) [72]. This risk is increased further by older age, male sex, obesity, and pre-transplant treatment with alkylating agents [13, 38]. In contrast to lymphoma patients, however, studies have found no significant increase in SPM incidence following ASCT in patients with MM [24, 27, 38, 73]. In particular, a recent retrospective study in the USA found a similar incidence of new cancers in a large auto-transplantation cohort to that in age-, race-, and gender-adjusted comparison subjects [38].

SPM rates in patients with MM post-ASCT may be attributable to 'conventional', alkylating agent-incorporating therapy prior to transplantation, rather than to the myeloablative therapy itself. For example, while investigating the possible role of high-dose melphalan in augmenting the risk of secondary MDS/AML in MM patients, Govindarajan et al. [61] observed seven MDS cases in 117 patients who had received extended courses of chemotherapy prior to tandem ASCT, whereas no cases were observed among 71 patients who received limited chemotherapy before ASCT [61]. The authors concluded that preceding treatments, and not conditioning with high-dose melphalan, were the likely cause of MDS post-ASCT.

The low risk of SPM development after ASCT in MM versus lymphoma patients may be partially explained by the earlier use of transplants in MM, the attention paid to avoiding pre-transplant stem-cell-damaging agents, and the cessation of total body irradiation during conditioning [74].

novel agents

IMiDs: thalidomide and lenalidomide. Initial population studies found no relationship between SPM incidence in MM and treatment with novel agents, including thalidomide and lenalidomide [24, 27, 60]. However, these studies were limited by a short follow-up period, lack of focus on SPMs, and the non-uniform use of novel agents during their first few years of availability. Several major studies have since indicated that lenalidomide may increase SPM risk, particularly in the maintenance setting [75]. These studies include three large, phase III, randomized trials

Table 3. Key retrospective studies that evaluated SPM incidence in patients with MM

Authors	Type of study	Study period (median follow-up)	Patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	Additional information
Cuzick et al. [3]	Retrospective study based on clinical trials (MRC)	1964–1975	648	12 (1.9)	12 (1.9) MDS, AML	NR	82 mo	Actuarial prevalence 3%, 10%, and 20% at 5, 8, and 10 y, respectively
Finnish Leukemia Group [15]	Retrospective study based on clinical trials	1979–1985 (16 y)	432	40 (9.3)	17 (3.9) AML, NHL	23 (5.3)	37 mo ST; 56 mo AML	O/E ratio 45.6 for AML, $P < 0.001$; 4.29 for NHL, $P =$ ns; 0.75 for STs, $P =$ ns
Munker et al. [35]	Retrospective, single-center study	1995–2010	197	5 (2.5)	1 (0.5)	4 (2.0)	NR	IR of SPMs or subsequent cancers: 2%, 4.8%, and 11.9% at 3, 5, and 10 y, respectively. 34 additional malignancies were diagnosed before MM diagnosis was made
Przepiorka et al. [59]	Retrospective, single-center study, ASCT	1996–2005	82	10 (12.2)	10 (12.2) MDS	NR	50 mo	5-y cumulative incidence 18%
Barlogie et al. [32]	Retrospective, single-center study, ASCT	1989–2007	2418	26 (1.1)	26 (1.1) MDS, AML	NR	NR	72 patients with transient MDS-associated cytogenetic abnormalities
Grudeva-Popova [33]	Retrospective, single-center study	1990–2010	332	5 (1.5)	NR	NR	6.6 y	Most additional cancers were present before the diagnosis of MM. Higher incidence of SPMs associated with longer survival
Hasskarl et al. [49]	Retrospective, single-center study	1997–2008	589	18 (3.1)	6 (1.0) MDS, AML, NHL	12 (2.0) 50% lung and prostate cancers	35 mo	IR 7.8%, 10.3%, and 11.6%, at 2, 5, and 10 y, respectively
Usmani et al. [56]	Retrospective, single-center study with multiple protocols	1998–2009	1148	73 (6.4)	36 (3.1) MDS, AML, NHL, ALL	37 (3.2) Prostate, NMST, breast, thyroid, bladder, colon, renal, lung	NR	HR = 0.63–1.30 (95% CI 0.18–2.67), without significant differences according to type of SPM (HMs or STs) or time of evaluation (enrollment versus maintenance)

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Authors	Type of study	Study period (median follow-up)	Patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	Additional information
Fenk et al. [60]	Retrospective, single-center study, ASCT	1994–2009	313	18 (5.8)	9 (2.8) MDS, AML, HL	9 (2.8) Breast, lung, others	56 mo	Cumulative incidence 19.7%; IR 0.7%, 5.8%, and 15.7% at 2, 5, and 10 y, respectively
Srivastava et al. [36]	Retrospective, single-center study (LD, ASCT 50%)	2003–2011 (4.2 y)	286	21 (6.6)	2 (0.7) AML	19 (6.6; 10 [3.5], excluding NMST) melanoma, breast, others	44 mo	21 (9) SPMs/1120 person-y of follow-up from MM diagnosis
Govindarajan et al. [61]	Retrospective, single-center study, ASCT	NR	188	7 (3.7)	7 (3.7) MDS	NR	63 mo	Prolonged CT before ASCT correlated with evidence of SPMs
Ormerod et al. [62]	Retrospective, single-center study, ASCT	1990–2010 (2995 d)	279	10 (3.6)	2 (0.7) MDS, ALL	8 (different types)	360 d	9 SPMs in patients +L
Rollison et al. [63]	Retrospective cohort study with nested case-control analysis (+L versus −L)	2004–2012 (40 mo)	1653	51 (3.1)	14 (0.8) 8 +L versus 6 −L	37 (2.2) 9 +L versus 28 −L; 14 different types	NR	IR of SPM 0.55 per 100 person-y with +L and 1.27 per 100 person-y with −L; HR = 0.44 (95% CI 0.24–0.80); HMs HR = 0.90 (95% CI 0.31–2.63); STs HR = 0.55 (95% CI 0.15–0.69)
Dimopoulos et al. [64]	Retrospective, pooled analysis of 11 clinical trials in RRMM treated with lenalidomide	2002–2008	3846	52 (1.3)	8 (0.2) MDS, NHL, AML	44 (1.1)		Overall IR of SPMs, including non-invasive skin cancers: 3.62; IR of invasive (both HMs and STs) SPMs: 2.08 (95% CI 1.60–2.60)
Dimopoulos et al. [64]	Retrospective, pooled analysis of 2 phase III randomized trials (LD versus placebo-dex)	2003–2008	703	23 (3.3)	2 (0.3) MDS (in +L)	17 (2.4) in +L (11 NMST); 4 (0.6) in −L (2 NMST)	1–45 mo	Overall IR of SPMs: 3.98 (95% CI 2.51–6.31) in +L versus 1.38 (95% CI 0.44–4.27) in −L; IR of NMST: 2.40 (95% CI 1.33–4.33) in +L versus 0.91 (95% CI 0.23–3.66) in −L; IRs of invasive SPMs: 1.71 (95% CI 0.86–3.43) in +L versus 0.91 (95% CI 0.23–3.66) in −L

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Authors	Type of study	Study period (median follow-up)	Patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	Additional information
Mahindra et al. [38]	Retrospective analysis in patients receiving ASCT	1990–2010	4161	163 (3.9)	O/E ratio 5.19 (99% CI 1.67–12.04; $P = 0.0004$) for AML	O/E ratio 3.58 (99% CI 1.82–6.29; $P < 0.0001$) for melanoma	NR	Crude IR 1.2 per 100 person-y; cumulative incidences of 2.6% (95% CI 2.09– 3.17), 4.2% (95% CI 3.49–5.00), and 6.1% (95% CI 5.08–7.24) at 3, 5, and 7 y, respectively

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; CI, confidence interval; CT, chemotherapy; d, days; HL, Hodgkin lymphoma; HM, hematologic malignancy; HR, hazard ratio; IR, incidence rate; +L, exposure to lenalidomide, −L no exposure to lenalidomide; LD, lenalidomide plus dexamethasone; MDS, myelodysplastic syndromes; MM, multiple myeloma; mo, months; MRC, Medical Research Council; NHL, non-Hodgkin lymphomas; NMST, non-melanoma skin tumors; NR, not reported; ns, not significant; O/E ratio, observed-to-expected ratio; RRMM, relapsed/refractory multiple myeloma; SPM, secondary primary malignancy; ST, solid tumor; y, years.

(IFM 2005-002, CALGB 100104, MM-015), all of which reported a significantly increased incidence of SPMs in newly diagnosed patients with MM who received lenalidomide maintenance versus similar patients who did not receive lenalidomide maintenance after either ASCT [18, 19, 76] or induction therapy [17, 77]. A recent update to CALGB 100104 confirmed that lenalidomide maintenance post-ASCT is associated with an increased risk of SPMs versus placebo [78]; however, a post-hoc survey of this study raised the possibility that the entire patient population may have had an inherent risk for other malignancies, due, at least in part, to risk factors such as age, prior tumors, prior therapies, and family history [50]. Interestingly, secondary ALL after lenalidomide treatment has been reported only rarely [18, 79].

A 2014 meta-analysis of seven randomized, controlled, phase III clinical trials that included lenalidomide as first-line therapy reported increased hematologic SPM incidence in newly diagnosed MM patients: 32/2620 (1.2%) versus 3/598 (0.5%) in patients treated (+L) or not treated (−L) with lenalidomide [39]. The cumulative incidence at 5 years was 3.1% (95% CI 1.9–4.3%) in the +L group versus 1.4% (95% CI 0.0–3.6%) in the −L group. In +L patients, SPM incidence increased linearly over time, and was significantly higher than in −L patients (HR = 3.8, 95% CI 1.15–12.62, $P = 0.029$). Co-exposure to lenalidomide and oral melphalan appeared to be the main driver of increased hematologic SPM risk (5-year cumulative incidence 3.9%), while lenalidomide plus cyclophosphamide (not estimable), lenalidomide alone (1.3%), and melphalan alone (1.4%) had no impact. The hematologic SPM risk associated with the combination of oral melphalan plus lenalidomide was also significantly increased (HR = 4.86, 95% CI 2.79–8.46, $P < 0.0001$) versus high-dose intravenous melphalan and lenalidomide (HR = 2.21, 95% CI 0.49–10.02, $P = 0.304$). The distribution of solid SPMs was similar in the +L and −L groups, with the exception of urinary tract tumors, which were more common in the +L group, probably as a consequence of the renal excretion of lenalidomide. Importantly, the risk of SPM-related mortality in the +L group (2.4%) was significantly lower than the risk of death due to either MM (26.5%) or treatment-related adverse events (9.8%) [39].

A still-unpublished meta-analysis of three randomized trials including a total of 1188 patients with newly diagnosed MM who received lenalidomide maintenance, placebo, or no maintenance following ASCT [18, 19, 65], was presented at the June 2016 Annual Meeting of the American Society of Clinical Oncology [80]. Lenalidomide maintenance was associated with an increased HR of 2.03 (95% CI 1.14–3.61, $P = 0.015$) for hematologic SPMs and 1.71 (95% CI 1.04–2.79, $P = 0.032$) for solid tumors. However, the survival benefit of lenalidomide maintenance (a 26% reduction in mortality risk, with an estimated 2.5-year increase in median survival) largely outweighed the increased risk of SPM development across all subgroups and response categories.

Several other studies have also suggested that, in patients with either newly diagnosed or relapsed/refractory MM, SPM risk may be increased with lenalidomide plus oral melphalan, but not with lenalidomide plus cyclophosphamide [81, 82] or dexamethasone [36, 64–66, 83–86]. As no increase in SPM incidence has been reported with lenalidomide in combination with dexamethasone, even on prolonged administration [66, 84–86], a

Table 4. Key first-line phase III trials that evaluated SPM incidence in MM patients

Authors	Type of study	Study period (median follow-up)	Enrolled patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	Additional information
Bergsagel et al. [2]	Comparison of different alkylating agent-based regimens	1973–1977	364	14 (3.8) AML	14 (3.8)	NR	NR	Actuarial risk of AML rapidly increased to 17.4% at 50 mo
Attal et al. [18]	Lenalidomide consolidation followed by lenalidomide versus placebo as maintenance after ASCT	2006–2008	614 (6 did not receive randomized treatment) (306 +L versus 302 −L)	All SPMs: 32 (10.4) +L versus 12 (4.0) −L; invasive SPMs: 23 (7.5) +L versus 9 (3.0) –L	13 (4.2) +L versus 5 (1.7) −L	10 (3.3) +L versus 4 (1.3) −L	NR	IR per 100 person-y: 3.1 +L versus 1.2 −L ($P = 0.002$)
McCarthy et al. [19]	Lenalidomide versus placebo as maintenance after ASCT	2005–2009	460 (231 +L versus 229 −L)	18 (7.8) +L versus 6 (2.6) −L	8 (3.5) +L versus 1 (0.4) −L	10 (4.3) +L versus 5 (2.2) −L	HMs: 28 mo +L versus 30 mo −L; STs: 15 mo +L versus 21 mo −L	Overall, cumulative risk of SPMs was greater in +L than in placebo group ($P = 0.0008$)
Palumbo et al. [17]	MPR-R versus MPR versus MP in patients not eligible for ASCT	2007–2008	459 (152 MPR-R versus 153 MPR versus 154 MPT)	12 (7.9) MPR-R versus 9 (5.9) MPR versus 4 (2.6) MPT	7 (4.6) MPR-R versus 5 (3.3) MPR versus 1 (0.7) MPT	5 (3.3) MPR-R versus 4 (2.6) MPR versus 3 (1.9) MPT	NR	IR/100 person-y: 1.4% for MPR-R versus 2.1% for MPR versus 0.7% for MP
Palumbo et al. [65]	RD followed by ASCT versus MPR, then lenalidomide maintenance versus no maintenance	2007–2009 (51.2 mo)	402 (273 randomized to consolidation: 141 ASCT versus 132 MPR; 251 randomized to L maintenance versus no maintenance: 57 ASCT +L versus 59 ASCT −L, and 59 MPR +L versus 56 MPR −L)	11 (2.7)	1 (0.2)	10 (2.5) 1 during induction; 5 in +L versus 4 in −L maintenance arm	NR	

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Authors	Type of study	Study period (median follow-up)	Enrolled patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	Additional information
Benboubker et al. [66]	RD until progression versus RD 18 cycles versus MPT in patients not eligible for ASCT	2008–2011 (37 mo)	1613 (535 RD, 541 RD 18 cycles, 547 MPT)	All SPMs (including NMST): 37 (7) RD until progression versus 44 (8.1) RD 18 cycles versus 47 (8.7) MPT; Invasive SPMs: 17 (3.2) RD until progression versus 30 (5.6) RD 18 cycles versus 27 (5.0) MPT	2 (0.4) RD until progression versus 2 (0.4) RD 18 cycles versus 12 (2.2) MPT (all MDS/AML)	15 (2.8) RD until progression versus 29 (5.4) RD 18 cycles versus 15 (2.8) MPT	NR	IR/100 person-y (CI): ALL SPMs: RD until progression 2.76 (2–3.81) versus RD 18 cycles 3.33 (2.48–4.48) versus MPT 3.68 (2.76–4.89): HMs: RD until progression 0.14 (0.04–058) versus RD 18 cycles 0.14 (0.04–058) versus MPT 0.91 (0.52–1.61); STs: RD until progression: 1.09 (0.66–1.81) versus RD 18 cycles 2.15 (1.49–3.09) versus MPT 1.15 (0.69–1.90); NMST: RD until progression 1.62 (1.07–2.46) versus RD 18 cycles 1.25 (1.78–2.02) versus MPT 1.62 (1.05–2.48). Overall, IR of incidence of hematologic SPMs was significantly lower with RD (0.4%) versus MPT (2.2%).

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Authors	Type of study	Study period (median follow-up)	Enrolled patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	Additional information
Jones et al. [37]	CRD versus CTD (induction); bortezomib versus no consolidation; lenalidomide- based maintenance versus no maintenance[a]	2010–2015	2745	69 (2.5)	8 (0.3) MDS, AML, CML, HD	61 (2.2) including NMST	All SPMs: 15.6 mo (range 1.2–42.5); HMs: 18.2 mo (5.9–42.5)	Cumulative incidence (95% CI) of all SPMs: 0.65% (0.35–0.97), 1.84% (1.26–2.41), and 3.41% (2.49–4.43) at 1, 2, and 3 years, respectively
Stewart et al. [67]	MPT-T versus MPR-R	2008–2011 (40.7 mo)	306 (298 received randomized treatment: 148 MPT-T versus 150 MPR-R)	All SPMs: 32 (10.7); 18 MPT-T (12.2) versus 14 MPR-R (9.3) excluding NMST: all SPMs: 22 (7.4); 14 MPT-T (9.5) versus 8 MPR-R (5.3)	14 (4.7) 10 MPT-T (6.7) versus 4 (2.6) MPR-R	18, including 9 NMST (6); invasive: 8 (2.7): 4 (2.7) MPT-T versus 4 (2.7) MPR-R	NR	IR/100 person-y: total 4.06; MPT-T 4.56, versus MPR-R 3.56, excluding NMST: total 2.74; MPT-T 3.47 versus MPR-R 2.01
Zweegman et al. [68]	MPT-T versus MPR-R	2009–2012	560 (280 MPT-T versus 280 MPR-R)	Invasive, excluding NMST: 38 (6.8)	9 (1.6) AML/MDS: 3 (0.5) MPT-T versus 6 (1.1) MPR-R	29 (5.2): 18 (3.2) MPT-T versus 11 (2.0) MPR-R	NR	IR/100 person-y: 3.3 (MPT-T) versus 2.4 (MPR-R), $P = 0.33$
Palumbo et al. [69]	VMPT-VT versus VMP	2006–2009 (54 mo)	511 (254 VMPT-VT versus 257 VMP)	0.9% VMPT-VT versus 1.5% VMP	NR	NR	NR	
San Miguel et al. [70]	VMP versus MP	2004–2006 (60.1 mo)	682 enrolled; 655 analyzed for SPMs (327 VMP versus 328 MP)	19 (5.8) VMP versus 13 (4.0) MP	3 (0.9) VMP versus 3 (0.9) MP	16 (4.9) VMP versus 10 (3.0) MP	HMs: 18–48 mo in the VMP arm, 1–35 mo in the MP arm; STs: 1–56 mo (22.7 median VMP and 30.3 MP)	Similar exposure-adjusted incidence rates: 0.017 VMP versus 0.013 MP per person-y

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Authors	Type of study	Study period (median follow-up)	Enrolled patients (*n*)	All SPMs *n* (%)	Hematologic SPMs *n* (%)	Solid tumor SPMs *n* (%)	Time from MM diagnosis to SPM development (median)	Additional information
Brioli et al. [71]	VTD versus TD followed by ASCT	2006–2008 (73 mo)	299 (148 VTD versus 151 TD)	25 (8.3); 5% VTD versus 11% TD	7 (2.3%); 1.3% VTD versus 3.2% TD	18 (6.0%); 3.8% VTD versus 7.8% TD	36 mo	IR for total population 1% at 1 y and 9.9% at 6 y

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ASCT, autologous stem cell transplantation; CI, confidence interval; CML, chronic myeloid leukemia; CRD, cyclophosphamide, lenalidomide, and dexamethasone; CTD, cyclophosphamide, thalidomide, and dexamethasone; HD, Hodgkin's disease, HM: hematologic malignancy; IMWG, International Myeloma Working Group; IR, incidence rate; +L lenalidomide exposure; −L no lenalidomide exposure; MDS, myelodysplastic syndromes; MM, multiple myeloma; mo, months; MP, melphalan + prednisone; MPR, MP + lenalidomide (revlimid); MPR-R, MPR followed by lenalidomide maintenance; MPT, melphalan + prednisone + thalidomide; MPT-T, MPT followed by thalidomide maintenance; NMST, non-melanoma skin tumors; NR, not reported; RD, lenalidomide + dexamethasone; SPM, secondary primary malignancy; ST, solid tumor; TD, thalidomide + prednisone; VGPR, very good partial response according to IMWG criteria; VMP, bortezomib + melphalan + prednisone; VMPT-VT, bortezomib + melphalan + prednisone + thalidomide followed by bortezomib + thalidomide maintenance; VTD, bortezomib + thalidomide + prednisone; y, years.

[a]Age-adjusted CRD versus CTD as induction; consolidation with bortezomib versus no consolidation (before ASCT in younger patients) if response < VGPR; lenalidomide-based maintenance versus no maintenance.

possible 'protective' effect of this drug might be considered. Different melphalan dose [67] and/or lenalidomide dosing schedules (3 weeks on, 1 week off versus continued treatment) could explain the lack of increased SPM incidence in some studies of lenalidomide maintenance therapy.

The actions of lenalidomide are complex, and the mechanism(s) by which it might favor SPM development remain undefined. Lenalidomide's immunosuppressive activity, and its effects on the tumor microenvironment, may favor the escape/growth of abnormal clones that could result in SPM development. Alternatively, treatment-related MDS/AML might be caused by a possible damaging stem-cell effect of lenalidomide. Cereblon, a molecular target for the anti-MM activity of lenalidomide, is a component of the E3 ubiquitin-ligase complex that is essential for nucleotide excision repair [87]. Inhibition of cereblon/DDB1 complex by lenalidomide impairs repair mechanisms after melphalan-induced DNA damage, and could therefore facilitate the development of SPMs [87].

The TT2 trial showed a trend for increased solid SPM risk from the initiation of maintenance therapy in the TT plus thalidomide maintenance versus the TT without thalidomide arm [56]. This suggests an IMiD class effect, rather than a lenalidomide-specific effect, associated with alkylator exposure. However, the absence of a randomized comparison and the number and variety of drugs used in the TT trials make it difficult to determine whether the thalidomide-associated increased SPM risk in TT2 is of similar magnitude to that seen with lenalidomide.

bortezomib. Studies conducted to date indicate that bortezomib is associated with a low risk of SPM development. For example, after 54 months' follow-up, SPM incidence in elderly patients with MM who were treated with VMPT-VT (a four-drug combination comprising bortezomib, melphalan, prednisone, and thalidomide, followed by maintenance treatment with bortezomib plus thalidomide) was 0.9% versus 1.5% in similar patients treated with VMP (bortezomib, melphalan, and prednisone) [69]. In the phase III VISTA trial in patients with previously untreated MM, incidences of hematologic and solid tumor SPMs after 60.1 months' follow-up did not differ significantly between VMP-treated patients (1% and 5%, respectively) versus those treated with melphalan plus prednisone (1% and 3%, respectively), and were consistent with background rates [70].

Mature data on the incidence of SPMs were recently available for 299 patients enrolled in the phase III, multicenter, GIMEMA 26866138-MMY-3006 clinical trial that compared bortezomib, thalidomide, and dexamethasone (VTD) versus thalidomide plus dexamethasone (TD) as induction before, and consolidation after, a double ASCT [71]. The proportion of patients who developed SPMs was lower in the VTD (5%) than in the TD arm (11%, $P = 0.068$). Among those patients who developed SPMs, solid (75% versus 71%) and hematologic (25% versus 29%) SPM rates were similar in the two arms. In the overall population, SPM incidence was significantly reduced at 6 years among patients randomized to VTD versus TD (6% versus 13%; $P = 0.037$). These data suggest that bortezomib is associated with a low risk of SPM development, and that this particular drug may even decrease the risk of SPMs due to thalidomide when used in combination. A large, single-institution, registry

analysis of host-, myeloma-, and treatment-specific risks for SPMs in 744 consecutive MM patients recently confirmed that cumulative incidence rates for SPMs were decreased in bortezomib-treated patients [30].

other novel agents. Consolidated data examining the SPM risk associated with the novel proteasome inhibitors carfilzomib and ixazomib, the third-generation IMiD pomalidomide, the histone-deacetylase inhibitor panobinostat, and the monoclonal antibodies elotuzumab (anti-SLAMF7) and daratumumab (anti-CD38) are not yet available. However, none of the studies published or presented to date reported an increased SPM risk in patients treated with these drugs [88–101]. In particular, when specifically investigated in relapsed/refractory MM treated in randomized trials including a control arm with lenalidomide plus dexamethasone, the incidence of SPMs was: 2.8% with a combination of carfilzomib, lenalidomide, and dexamethasone (versus 3.3% in the control arm) [91]; 5% with ixazomib, lenalidomide, and dexamethasone (versus 4% in the control arm) [92]; 2.8% with daratumumab, lenalidomide, and dexamethasone (versus 3.6% in the control arm) [101]; and 6.9% with elotuzumab plus lenalidomide, and dexamethasone (versus 4.1% in the control arm) [97]. In the latter study, SPM incidence after adjustment for exposure to study therapy was 3.5% versus 2.8% per 100 person-years in the elotuzumab versus the control arm.

summary

SPMs represent a relatively small, but clinically relevant, issue that must be considered and managed within the current treatment paradigms available to patients with MM. For individual patients in whom a secondary hematologic or solid tumor is diagnosed, the clinical and psychological consequences may, indeed, be devastating. These two parallel perspectives ('on average' versus 'individual patients') should be weighed carefully by any physician. Our goal should be to significantly reduce the impact of SPMs on patients with MM by clarifying the biologic mechanisms involved, identifying associated risk factors, improving understanding of clinical behavior, and applying appropriate preventive strategies.

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references

1. Kyle RA, Pierre RV, Bayrd ED. Multiple myeloma and acute myelomonocytic leukemia. N Engl J Med 1970; 283: 1121–1125.
2. Bergsagel DE, Bailey AJ, Langley GR et al. The chemotherapy on plasma-cell myeloma and the incidence of acute leukemia. N Engl J Med 1979; 301: 743–748.
3. Cuzick J, Erskine S, Edelman D, Galton DA. A comparison of the incidence of the myelodysplastic syndrome and acute myeloid leukaemia following melphalan and cyclophosphamide treatment for myelomatosis. A report to the Medical Research Council's working party on leukaemia in adults. Br J Cancer 1987; 55: 523–529.
4. Reddi DM, Lu CM, Fedoriw G et al. Myeloid neoplasms secondary to plasma cell myeloma: an intrinsic predisposition or therapy-related phenomenon? A clinicopathologic study of 41 cases and correlation of cytogenetic features with treatment regimens. Am J Clin Pathol 2012; 138: 855–866.
5. Kumar SK, Dispenzieri A, Lacy MQ et al. continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia 2014; 28: 1122–1128.
6. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011; 364: 1046–1060.
7. Pulte D, Gondos A, Brenner H. Improvement in survival of older adults with multiple myeloma: results of an updated period analysis of SEER data. Oncologist 2011; 16: 1600–1603.
8. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. J Clin Oncol 2010; 28: 830–834.
9. Pratt G. Lenalidomide and second malignancies in myeloma patients. Lancet Oncol 2014; 15: 253–254.
10. Thomas A, Mailankody S, Korde N et al. Second malignancies after multiple myeloma: from 1960s to 2010s. Blood 2012; 119: 2731–2737.
11. Yang J, Terebelo HR, Zonder JA. Secondary primary malignancies in multiple myeloma: an old NEMESIS revisited. Adv Hematol 2012; 2012: 801495.

12. Gertz MA, Terpos E, Dispenzieri A et al. Therapy-related myelodysplastic syndrome/acute leukemia after multiple myeloma in the era of novel agents. Leuk Lymphoma 2015; 56: 1723–1726.
13. Pedersen-Bjergaard J, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. Blood 2000; 95: 3273–3279.
14. Pemmaraju N, Shah D, Kantarjian H et al. Characteristics and outcomes of patients with multiple myeloma who develop therapy-related myelodysplastic syndrome, chronic myelomonocytic leukemia, or acute myeloid leukemia. Clin Lymphoma Myeloma Leuk 2015; 15: 110–114.
15. A Finnish Leukaemia Group study. Acute leukaemia and other secondary neoplasms in patients treated with conventional chemotherapy for multiple myeloma. Eur J Haematol 2000; 65: 123–127.
16. Jonsdottir G, Lund SH, Björkholm M et al. Survival in multiple myeloma patients who develop second malignancies: a population-based cohort study. Haematologica 2016; 101: e145–e148.
17. Palumbo A, Hajek R, Delforge M et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012; 366: 1759–1769.
18. Attal M, Lauwers-Cances V, Marit G et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012; 366: 1782–1791.
19. McCarthy PL, Owzar K, Hofmeister CC et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012; 366: 1770–1781.
20. Areethamsirikul N, Reece DE. The risk of secondary primary malignancies after therapy for multiple myeloma. Leuk Lymphoma 2015; 56: 3012–3021.
21. Dasanu CA, Mewawalla P, Grabska J. Multiple myeloma and its therapies: to what extent do they contribute to the increased incidence of second malignant neoplasms? Curr Med Res Opin 2012; 28: 1129–1140.
22. Landgren O, Mailankody S. Update on second primary malignancies in multiple myeloma: a focused review. Leukemia 2014; 28: 1423–1426.
23. Dong C, Hemminki K. Second primary neoplasms among 53 159 haematolymphoproliferative malignancy patients in Sweden, 1958-1996: a search for common mechanisms. Br J Cancer 2001; 85: 997–1005.
24. Mailankody S, Pfeiffer RM, Kristinsson SY et al. Risk of acute myeloid leukemia and myelodysplastic syndromes after multiple myeloma and its precursor disease (MGUS). Blood 2011; 118: 4086–4092.
25. Youlden DR, Baade PD. The relative risk of second primary cancers in Queensland, Australia: a retrospective cohort study. BMC Cancer 2011; 11: 83.
26. Chakraborty S, Hauke RJ, Bonthu N, Tarantolo SR. Increased incidence of a second lymphoproliferative malignancy in patients with multiple myeloma—a SEER based study. Anticancer Res 2012; 32: 4507–4515.
27. Razavi P, Rand KA, Cozen W et al. Patterns of second primary malignancy risk in multiple myeloma patients before and after the introduction of novel therapeutics. Blood Cancer J 2013; 3: e121.
28. Tzeng HE, Lin CL, Tsai CH et al. Time trend of multiple myeloma and associated secondary primary malignancies in Asian patients: a Taiwan population-based study. PLoS One 2013; 8: e68041.
29. Rifkin RM, Abonour R, Shah JJ et al. Connect MM®—the multiple myeloma (MM) disease registry: incidence of second primary malignancies (SPM). Leuk Lymphoma 2016; 9: 2228–2231.
30. Engelhardt M, Ihorst G, Landgren O et al. Large registry analysis to accurately define second malignancy rates and risks in a well-characterized cohort of 744 consecutive multiple myeloma patients followed-up for 25 years. Haematologica 2015; 100: 1340–1349.
31. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, based on November 2012 SEER data submission. https://seer.cancer.gov/archive/csr/1975_2008/ (23 November 2016, date last accessed).
32. Barlogie B, Tricot G, Haessler J et al. Cytogenetically defined myelodysplasia after melphalan-based autotransplantation for multiple myeloma linked to poor hematopoietic stem-cell mobilization: the Arkansas experience in more than 3,000 patients treated since 1989. Blood 2008; 111: 94–100.
33. Grudeva-Popova J, Nenova I, Spasova M et al. Multiple myeloma in association with second malignancy. J BUON 2013; 18: 448–452.
34. Matarraz S, Paiva B, Diez-Campelo M et al. Immunophenotypic alterations of bone marrow myeloid cell compartments in multiple myeloma patients predict for myelodysplasia-associated cytogenetic alterations. Leukemia 2014; 28: 1747–1750.
35. Munker R, Shi R, Lin D et al. Multiple myeloma and other malignancies: a pilot study from the Houston VA. Clin Lymphoma Myeloma Leuk 2014; 14: 102–106.
36. Srivastava G, Rana V, Lacy MQ et al. Long-term outcome with lenalidomide and dexamethasone therapy for newly diagnosed multiple myeloma. Leukemia 2013; 27: 2062–2066.
37. Jones J, Cairns D, Sigsworth R et al. Guidelines for the correct determination of second primary malignancies in myeloma trials. Clin Lymphoma Myeloma Leuk (IMW Meeting Abstracts). 2015; 15(Suppl 3): e175–e176. Abstract PO-164.
38. Mahindra A, Raval G, Mehta P et al. New cancers after autotransplantations for multiple myeloma. Biol Blood Marrow Transplant 2015; 21: 738–745.
39. Palumbo A, Bringhen S, Kumar SK et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol 2014; 15: 333–342.
40. Ailawadhi S, Swaika A, Razavi P et al. Variable risk of second primary malignancy in multiple myeloma patients of different ethnic subgroups. Blood Cancer J 2014; 4: e243.
41. Lynch HT, Ferrara K, Barlogie B et al. Familial myeloma. N Engl J Med 2008; 359: 152–157.
42. Morgan GJ, Johnson DC, Weinhold N et al. Inherited genetic susceptibility to multiple myeloma. Leukemia 2014; 28: 518–524.
43. Usmani SZ. Second primary malignancies and myeloma therapy: fad or fact? Oncotarget 2012; 3: 915–916.
44. Landgren O, Ma W, Kyle RA et al. Polymorphism of the erythropoietin gene promotor and the development of myelodysplastic syndromes subsequent to multiple myeloma. Leukemia 2012; 26: 844–845.
45. Zintzaras E, Giannouli S, Rodopoulou P, Voulgarelis M. The role of MTHFR gene in multiple myeloma. J Hum Genet 2008; 53: 499–507.
46. Li XL, Xu JH. MTHFR polymorphism and the risk of prostate cancer: a meta-analysis of case-control studies. Prostate Cancer Prostatic Dis 2012; 15: 244–249.
47. Ellis NA, Huo D, Yildiz O et al. MDM2 SNP309 and TP53 Arg72Pro interact to alter therapy-related acute myeloid leukemia susceptibility. Blood 2008; 112: 741–749.
48. Knight JA, Skol AD, Shinde A et al. Genome-wide association study to identify novel loci associated with therapy-related myeloid leukemia susceptibility. Blood 2009; 113: 5575–5582.
49. Hasskarl J, Ihorst G, De Pasquale D et al. Association of multiple myeloma with different neoplasms: systematic analysis in consecutive patients with myeloma. Leuk Lymphoma 2011; 52: 247–259.
50. Holstein SA, Owzar K, Richardson PG et al. Analysis of second primary malignancies (SPMs) in CALGB (Alliance)/ECOG/BMT CTN 100104. Clin Lymphoma Myeloma Leuk (IMW Meeting Abstracts). 2015; 15(Suppl 3): e61–e62. Abstract BP-027.
51. Nishimura N, Terui Y, Inoue N et al. Multiple myeloma as a second primary malignancy; one fourth of patients had prior history of other malignances. Clin Lymphoma Myeloma Leuk (IMW Meeting Abstracts) 2015; 15(suppl. 3): e113. Abstract PO-058.
52. Jónsdóttir G, Lund SH, Bjorkholm M et al. A prior cancer diagnosis is not a risk factor for the development of subsequent cancers in multiple myeloma patients. Haematologica (EHA Meeting Abstracts) 2015; 100(s1): Abstract P655.
53. Engelhardt M, Wasch R, Landgren O, Kleber M. Multiple myeloma and second malignancies. Clin Lymphoma Myeloma Leuk 2014; 14: 98–101.
54. Law IP, Blom J. Second malignancies in patients with multiple myeloma. Oncology 1977; 34: 20–24.
55. Roeker LE, Larson DR, Kyle RA et al. Risk of acute leukemia and myelodysplastic syndromes in patients with monoclonal gammopathy of undetermined significance (MGUS): a population-based study of 17 315 patients. Leukemia 2013; 27: 1391–1393.
56. Usmani SZ, Sexton R, Hoering A et al. Second malignancies in total therapy 2 and 3 for newly diagnosed multiple myeloma: influence of thalidomide and lenalidomide during maintenance. Blood 2012; 120: 1597–1600.
57. Palumbo AP, Delforge M, Catalano J et al. Incidence of second primary malignancy (SPM) in melphalan-prednisone-lenalidomide combination followed by lenalidomide maintenance (MPR-R) in newly diagnosed multiple myeloma patients (pts) age 65 or older. J Clin Oncol (ASCO Meeting Abstracts) 2011; 29(Suppl 15): Abstract 8007.

58. Dasanu CA. Immune alterations in untreated and treated multiple myeloma. J Oncol Pharm Pract 2012; 18: 257–263.
59. Przepiorka D, Buadi F, McClune B et al. Myelodysplastic syndrome after autologous peripheral blood stem cell transplantation for multiple myeloma. Bone Marrow Transplant 2007; 40: 759–764.
60. Fenk R, Neubauer F, Bruns I et al. Secondary primary malignancies in patients with multiple myeloma treated with high-dose chemotherapy and autologous blood stem cell transplantation. Br J Haematol 2012; 156: 683–686.
61. Govindarajan R, Jagannath S, Flick JT et al. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. Br J Haematol 1996; 95: 349–353.
62. Ormerod A, Fausel CA, Abonour R, Kiel PJ. Observations of second primary malignancy in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk 2012; 12: 113–117.
63. Rollison DE, Komrokji R, Lee JH et al. Subsequent primary malignancies among multiple myeloma patients treated with or without lenalidomide. Leuk Lymphoma 2016 Jul 18 [epub ahead of print]; 1–9.
64. Dimopoulos MA, Richardson PG, Brandenburg N et al. A review of second primary malignancy in patients with relapsed or refractory multiple myeloma treated with lenalidomide. Blood 2012; 119: 2764–2767.
65. Palumbo A, Cavallo F, Gay F et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 2014; 371: 895–905.
66. Benboubker L, Dimopoulos MA, Dispenzieri A et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014; 371: 906–917.
67. Stewart AK, Jacobus S, Fonseca R et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. Blood 2015; 126: 1294–1301.
68. Zweegman S, van der Holt B, Mellqvist U-H et al. Randomized phase III trial in non-transplant eligible patients with newly diagnosed symptomatic multiple myeloma comparing melphalan-prednisone-thalidomide followed by thalidomide maintenance (MPT-T) versus melphalan-prednisone-lenalidomide followed by maintenance with lenalidomide (MPR-R); A joint study of the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) and the Nordic Myeloma Study Group (NMSG). Blood (ASH Meeting Abstracts) 2014; 124: Abstract 179.
69. Palumbo A, Bringhen S, Larocca A et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. J Clin Oncol 2014; 32: 634–640.
70. San Miguel JF, Schlag R, Khuageva NK et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously untreated multiple myeloma. J Clin Oncol 2013; 31: 448–455.
71. Brioli A, Pezzi A, Derudas D et al. Bortezomib (BOR)-thalidomide-dexamethasone (VTD) and high-dose melphalan (HDM) as first line treatment for multiple myeloma (MM) is associated with a lower rate of second primary malignancies (SPMs) compared to TD plus HDM. Blood (ASH Meeting Abstracts) 2014; 124: Abstract 1182.
72. Miller JS, Arthur DC, Litz CE et al. Myelodysplastic syndrome after autologous bone marrow transplantation: an additional late complication of curative cancer therapy. Blood 1994; 83: 3780–3786.
73. Forrest DL, Nevill TJ, Naiman SC et al. Second malignancy following high-dose therapy and autologous stem cell transplantation: incidence and risk factor analysis. Bone Marrow Transplant 2003; 32: 915–923.
74. Moreau P, Facon T, Attal M et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Blood 2002; 99: 731–735.
75. Wang Y, Yang F, Shen Y et al. Maintenance therapy with immunomodulatory drugs in multiple myeloma: a meta-analysis and systematic review. J Natl Cancer Inst 2016; 108(3): pii: djv342. doi: 10.1093/jnci/djv342.
76. Attal M, Lauwers-Cances V, Marit G et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma: follow-up analysis of the IFM 2005-02 trial. Blood (ASH Meeting Abstracts) 2013; 122: Abstract 406.
77. Delforge M, Dimopoulos M, Adam Z et al. Long-term safety of continuous lenalidomide therapy in newly diagnosed multiple myeloma (NDMM) patients: MM-015 update. Clin Lymphoma Myeloma Leuk (IMW Meeting Abstracts) 2013; 13(Suppl 1): Abstract O-17.
78. Holstein SA, Owzar K, Richardson PG et al. Updated analysis of CALGB/ECOG/BMT CTN 100104: Lenalidomide (Len) vs. placebo (PBO) maintenance therapy after single autologous stem cell transplant (ASCT) for multiple myeloma (MM). J Clin Oncol (ASCO Meeting Abstracts) 2015; 33(Suppl 15): Abstract 8523.
79. Tan M, Fong R, Lo M, Young R. Lenalidomide and secondary acute lymphoblastic leukemia: a case series. Hematol Oncol 2015 July 31 [epub ahead of print], doi: 2010.1002/hon.2248.
80. Attal M, Palumbo A, Holstein SA et al. Lenalidomide (LEN) maintenance (MNTC) after high-dose melphalan and autologous stem cell transplant (ASCT) in multiple myeloma (MM): a meta-analysis (MA) of overall survival (OS). J Clin Oncol (ASCO Meeting Abstracts) 2016; 34(Suppl): Abstract 8001.
81. Gay F, Oliva S, Petrucci MT et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol 2015; 16: 1617–1629.
82. Jones JR, Cairns DA, Sigsworth R et al. Myeloma XI trial for newly diagnosed multiple myeloma (NDMM); A report of Second Primary Malignancy (SPM) rates and the importance of review of reported cases. Blood (ASH Meeting Abstracts) 2015; 126: Abstract 1847.
83. Rossi A, Mark T, Jayabalan D et al. BiRd (clarithromycin, lenalidomide, dexamethasone): an update on long-term lenalidomide therapy in previously untreated patients with multiple myeloma. Blood 2013; 121: 1982–1985.
84. Hulin C, Belch A, Shustik C et al. Updated outcomes and impact of age with lenalidomide and low-dose dexamethasone or melphalan, prednisone, and thalidomide in the randomized, phase III FIRST trial. J Clin Oncol 2016 Jun 20 [epub ahead of print]; pii: JCO667295.
85. Du X, Jin J, Cai Z et al. Long-term use of lenalidomide and low-dose dexamethasone in Chinese patients with relapsed/refractory multiple myeloma: MM-024 Extended Access Program. BMC Cancer 2016 Jan 28;16: 46. doi: 10.1186/s12885-016-2069-8. PMID: 26821931.
86. Lu J, Lee JH, Huang SY et al. The FIRST trial: analysis of the Asian subgroup of transplant ineligible patients with newly diagnosed multiple myeloma treated with continuous lenalidomide and low-dose dexamethasone. Haematologica (EHA Meeting Abstracts) 2016; 548: 101(s1): Abstract E1325.
87. Zhu YX, Braggio E, Shi CX et al. Identification of cereblon-binding proteins and relationship with response and survival after IMiDs in multiple myeloma. Blood 2014; 124: 536–545.
88. Bringhen S, Petrucci MT, Larocca A et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood. 2014; 124: 63–69.
89. Siegel D, Martin T, Nooka A et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 2013; 98: 1753–1761.
90. Sonneveld P, Asselbergs E, Zweegman S et al. Phase 2 study of carfilzomib, thalidomide, and dexamethasone as induction/consolidation therapy for newly diagnosed multiple myeloma. Blood 2015; 125: 449–456.
91. Stewart AK, Rajkumar SV, Dimopoulos MA et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015; 372: 142–152.
92. Moreau P, Masszi T, Grzasko N et al. Oral ixazomib, lenalidomide, and lexamethasone for multiple myeloma. N Engl J Med 2016; 374: 1621–1634.
93. Richardson PG, Siegel DS, Vij R et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood 2014; 123: 1826–1832.
94. San Miguel J, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol 2013; 14: 1055–1066.
95. Usmani SZ, Zhang Q, Stratton K et al. Phase II study of pomalidomide in high-risk relapsed and refractory multiple myeloma. Leukemia 2014; 28: 2413–2415.
96. San Miguel JF, Hungria VT, Yoon SS et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol 2014; 15: 1195–1206.

97. Lonial S, Dimopoulos M, Palumbo A et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015; 373: 621–631.
98. Lokhorst HM, Plesner T, Laubach JP et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015; 373: 1207–1219.
99. Lonial S, Weiss BM, Usmani SZ et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016; 387: 1551–1560.
100. Palumbo A, Chanan-Khan A, Weisel K et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375: 754–766.
101. Dimopoulos MA, Oriol A, Nahi H et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375: 1319–1331.