INTRODUCTION

The possibility to manage patients with multiple myeloma has improved dramatically in the past decade. The survival of patients has improved significantly with the incorporation of new therapeutic agents with novel mechanisms, and advances in diagnostic procedures and supportive care.\(^1\)\(^-\)\(^3\) The advances have come rapidly with several new drugs entering the market in the current decade. Combining medicines with different mechanisms of action present clinicians with viable approaches for achieving deeper responses and overcoming drug resistance.\(^4\) Translation of benefits from experimental settings to clinical practice is a crucial element for substantial improvements in survival. Access to and affordability of new treatments pose a major challenge, especially when it
comes to multidrug regimes, continuous therapy, and prolonged
disease courses. Also, a transition of research advances to clini-
cal practice requires knowledge, judgment, and experience with
patients.

The age-standardized incidence estimates of multiple myeloma
in 2018 for Norway was 10.1/100,000, being one of the highest in
Europe. A recent article focused on patients eligible to SCT showed
that younger patients with MM in Norway benefited from improved
treatment in routine clinical practice in years 2001-2009 compared
with earlier Nordic studies. The difference in survival parameters
was visible already when comparing the first and second parts of
the past decade. Among factors that contributed to the change, in-
creased use of the salvage SCT, bortezomib, and lenalidomide was
indicated.

This is the first analysis evaluating the Norwegian practice of
treatment and supportive care of patients with myeloma in different
clinical situations in the current decade. Using the annual physician
survey, changes in treatment pattern of multiple myeloma in Norway
between the years 2013 and 2019 are illustrated. Results show how
the treatment of newly diagnosed MM (NDMM) and relapse man-
agement, as well as supportive care, changed in recent years.

2 | MATERIALS AND METHODS

An electronic questionnaire was sent to members of the Norwegian
Society of Hematology (NSH) to evaluate the treatment situation
for MM on an annual basis. Only members of the NSH who were
treating patients at the time of each survey were asked to respond.
Doctors were reminded digitally until we had responses from a large
majority of the recipients. Persons not involved in patient treatment
or physicians not professionally active (eg, retired) were not asked
to participate. Responses were anonymous, but regions and hos-
pital category (university hospital/local hospital) were entered. No
honorarium was provided. No commercial support was received to
prepare survey questions. The first survey was sent in 2013 and the
last one in 2019.

Surveys were divided by demographics and investigated clinical
practice. Demographic characteristics included only region and the
type of healthcare institution of the participant. The clinical practice
part included questions about treatment selections for patients with
NDMM and patients with relapse, as well as diagnostic workup, use of
guideline disease criteria and bone-targeted treatment. Over the years,
more questions were added and lists of agents were updated with
newly registered agents. The first survey conducted in 2013 included
13 questions and the last one in 2019 contained 30 questions. Each
year, the survey was published to respondents via an online link. The
survey was conducted using the Survvs platform in the 2013-2017 and
the Oriola/Farenta platform in 2018 and 2019. Both platforms offered
similar functionalities.

Given that all study participants were physicians who gave their
responses anonymously and voluntarily and who did not receive any
incentive for taking part in the survey, the survey was not submitted
for ethics board review. Surveys did not use patient-related data at
any time.

Results are presented as percentage of respondents selecting an
option in every question in a year. For questions with a large num-
ber of options, for example, treatment regimen, the results were
presented on bubble charts. Treatment regimens were presented
in the order starting from most common triplets in 2019 and fol-
lowed by the most common doublets and monotherapies. In the
case of single-choice questions with a limited number of answers,
results were presented on stacked bar graphs and in the case of
multiple-choice questions on bar graphs. The abbreviation used to
describe drug combinations are similar to nomenclature commonly
present in clinical trials: bendamustine (B), bortezomib (V), carfil-
zomib (K), cyclophosphamide (C), daratumumab (Dara), elotuzumab
(Elo), dexamethasone (d), melphalan (M), ixazomib (I), panobinostat
(Pano), pomalidomide (Pom), lenalidomide (R), prednisone (P), and
thalidomide (T).

3 | RESULTS

3.1 | Survey response

The survey was sent to all members of the Norwegian Society of
Hematology, except the doctors we knew were retired or not work-
with myeloma. Depending on the year of the survey from 41
(2014) to 74 (2018), respondents completed the questionnaire. The
survey was sent to around 120 respondents each year. However,
from our knowledge of the transparent Norwegian hematology en-
vironment, we assume that no more than 80-90 doctors in Norway
treat myeloma. The biggest group were respondents from the
Southern and Eastern Norway consisting around 50% of respond-
ents each year, and the smallest group were respondents from the
Northern Norway consisting of less than 10% of all respondents. All
groups were well correlated to the regions’ number of inhabitants.
The majority of the respondents worked in a local clinical setting.
3.2 | Treatment of newly diagnosed multiple myeloma

3.2.1 | Transplantation-ineligible patient

Figure 1 presents treatment selection for a patient with NDMM who is not eligible for SCT. The patient has no comorbidities, no neuropathy, and no renal failure.

Comment: This group includes patients usually older than 65 years old and/or not fit enough to tolerate an intensive regimen of high-dose chemotherapy. Historically, these patients were treated with combination of melphalan, thalidomide, and prednisone (MPT) which efficacy has been shown to be superior over melphalan and prednisone (MP) at the end of the past decade. Usage of MPT regimen was declared by over half of respondents in 2013 and 2014. MP alone was not the standard of care in these patients; still, it was used by over 10% of respondents in 2013. A decline in the frequency of use of MPT started with increasing popularity of the combination of bortezomib, melphalan, and prednisone (VMP) driven by evidence from the VISTA study. The results of the FIRST study, published in 2014, changed clinical practice demonstrating the superiority of lenalidomide-dexamethasone (Rd) doublet over the MPT in terms of survival and tolerance parameters. Later, this treatment regimen became available for Norwegian patients with NDMM and the results of the survey conducted in 2016 showed that almost every fourth respondent declared use of the Rd regimen. In 2019, Rd was the only doublet declared to be used in this clinical setting (Figure 1).

The combination has become the starting point for creating many triplets used in various clinical situations. In 2015, SWOG 0777 was the first randomized study that showed an advantage of the lenalidomide, bortezomib, and dexamethasone (RVd) triplet over the Rd in patients without intent for immediate autologous SCT. The use of the RVd in the first-line setting developed quickly, and almost half of respondents declared its use in patients not eligible for transplant in 2019. Other Rd-based triplets have been studied, but were not included in clinical practice in the first-line treatment. Access to triplets with the newest anti-myeloma agents is limited due to its high cost.

3.2.2 | Duration of Rd therapy of newly diagnosed disease

In 2015, lenalidomide was adapted into clinical practice in treatment of NDMM in Norway based on the results of the FIRST study, and in 2016, the question about duration of treatment with Rd regimen was asked. Figure 2 shows answers collected in the years 2016-2019.

Comment: The FIRST study compared three regimens in transplant-ineligible patients NDMM: continuous Rd vs. 18 cycles of Rd vs a standard treatment option of the MPT triplet. The results supported Rd continuous as a standard of care for patients with transplant-ineligible NDMM significantly reducing the risk of progression or death compared with MPT and 18 cycles of Rd. It lead to an increase of use of

---

| Year | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 |
|------|------|------|------|------|------|------|------|
| N    | 56   | 41   | 55   | 61   | 63   | 74   | 59   |

| Treatment | 2016 | 2017 | 2018 | 2019 |
|-----------|------|------|------|------|
| RVd       | 18%  | 29%  | 15%  | 42%  |
| VMP       | 13%  | 15%  | 38%  | 48%  |
| VCD       | 5%   | 8%   | 3%   | 11%  |
| MTP       | 66%  | 76%  | 44%  | 8%   |
| Rd        | 23%  | 38%  | 41%  | 20%  |
| MP        | 2%   | 2%   | 2%   | 2%   |
| Vd        | 7%   | 8%   | 5%   | 3%   |
| Others    | 5%   | 2%   | 3%   | 2%   |

**FIGURE 1** Treatment selection for transplant-ineligible patients. Others include treatments selected with <5% of respondents in any year (MPR, RCd, VTd, VMPR, and Td)

**FIGURE 2** Duration of treatment with lenalidomide and dexamethasone regimen of a newly diagnosed non-transplant-eligible patient. Most commonly, respondents selecting treatment with fixed number of cycles indicated 18 cycles (18 months)
the Rd doublet in NDMM setting in Norway, with over half of respondents preferring continuous treatment in 2018, compared with 79% declaring treating until plateau phase in 2016. The use changed again in late 2018 after the restriction of Rd use in the setting for maximum of 18 cycles and only if a patient was ineligible to be treated with VMP. The prespecified final analysis of overall survival (OS) from the FIRST trial was published in 2018. OS was similar in the Rd continuous and 18 cycles Rd arms.\textsuperscript{16} It illustrates the potential discrepancy of response rate and progression-free survival (PFS) outcomes with longer-term outcomes such as OS. Nevertheless, the Norwegian Directorate of Health recommends stopping treatment with Rd after 18 cycles.\textsuperscript{17} The results also illustrate the waning of “plateau phase” as an indication for treatment stop.

3.2.3 | Treatment of transplant-ineligible patient with severe renal insufficiency

The simultaneous presence of comorbidities may complicate antimalignantoma treatment. Renal impairment (RI) is a common complication of

MM. Effective treatment of MM reduces serum light chain concentration and improve renal function.\textsuperscript{18} Patients with severe renal impairment, typically with serum creatinine clearance <30 mL/min/m$^2$, are often excluded from clinical trials, and therefore, study data may not necessarily guide treatment decisions for this population. Figure 3 presents the answers to the question asked every year from 2013 to 2019, about treatment selection for the transplant-ineligible patient with NDMM and severe renal insufficiency but without peripheral neuropathy.

Comment: Combinations with bortezomib remain the mainstay of management of MM with RI. Bortezomib-based regimens achieve high renal responses and dialysis independence rates.\textsuperscript{19-23} A significant improvement of renal function has been observed in the majority of patients treated with bortezomib-based regimens compared with immunomodulatory drugs (IMiDs).\textsuperscript{19} Over 70% of respondents indicated Vd regimen as the choice for patients with severe RI in the years 2013-2017. Addition of a third drug to Vd seems to improve renal outcomes.\textsuperscript{24} The popularity of triplets in the myeloma-related RI management increased in the last years, and IMiDs were the most common third drugs added to the Vd regimen.

| Year | 2015 | 2016 | 2017 | 2018 | 2019 |
|------|------|------|------|------|------|
| N    | 55   | 60   | 60   | 72   | 58   |

### FIGURE 3

Treatment selection for transplant-ineligible but fit patient with severe renal insufficiency and no peripheral neuropathy. Others include treatments selected with <5% of respondents in any year (BP, DaraVd, Kd, MCVP, MP, MRVP, MRBP, Rd, Pomd, Td, and VBP)

### FIGURE 4

Treatment selection for elderly frail patient with newly diagnosed multiple myeloma. The patient had no contraindications to any drug. Others include treatments selected with less than 5% of respondents in any year (BP, CP, RVd, VCd, and VTP)

| Year | 2015 | 2016 | 2017 | 2018 | 2019 |
|------|------|------|------|------|------|
| N    | 55   | 60   | 60   | 72   | 58   |
Treatment of elderly and frail patient

The treatment of multiple myeloma in advanced age and frailty needs special consideration. A question about the preferred regimen for an old and frail patient with NDMM was asked every year from 2015 to 2019. The regimens selected are presented on Figure 4.

Comment: Doublet regimens dominate the landscape of treatment of elderly frail patients. However, none or minimal improvement was achieved among older patients in registry data the later years.\(^3\),\(^25\),\(^26\) In the past, MP regimen was the reference treatment for elderly NDMM patients ineligible for high-dose therapy.\(^27\),\(^28\) The regimen was well established in Norway and preferred by almost two-thirds of respondents in 2015 (Figure 4), despite developing evidence of advantages of addition of bortezomib or thalidomide as third drugs.\(^10\),\(^29\),\(^30\) Instead, the Rd regimen emerged as a preferred option of upfront treatment in elderly patients after results of the FIRST trial\(^12\) followed by approval in Norway in 2015. Patients aged >75 years old constituted 35% of the total population of the FIRST study.\(^12\) In the last survey, 69% of survey participants indicated the regimen as preferred and alkylator-containing regimens were indicated by only 17% of respondents (Figure 4).

Induction regimen before stem cell transplantation

Around half of patients in Norway with NDMM receive SCT.\(^17\) Norwegian hematologists were asked to indicate the preferred induction regimen before SCT. Figure 5 illustrates responses collected in survey editions from 2016 to 2019 when the question was asked.

Comment: The induction treatment in transplant-eligible patients aims to maximize disease response before transplant. The treatment is usually administered for four cycles before transplantation. The landscape is dominated by triplet regimens.\(^31\)-\(^34\) The European Society of Medical Oncology (ESMO) recommends the use of bortezomib-based triplets in the 1st line of therapy in patients eligible for transplantation.\(^35\) When the question was asked for the first time in 2016, bortezomib was most often combined with dexamethasone and cyclophosphamide.
The VTd combination is characterized by a significantly higher percentage of patients achieving at least a very good partial response (≥VGPR) compared with the VCd regimen; its limitation is the higher incidence of grade 3 or 4 peripheral neuropathy compared with VCd. It may result in less frequent use of the regimen. In 2017, the landscape of induction therapy started to evolve and in subsequent years, showing a significant increase in use of the RVd regimen. Results of the IFM 2009 study, published in 2017, showed that RVd therapy followed by transplantation was associated with significantly longer median PFS than RVd therapy alone. OS at 4 years has not differed significantly between the two approaches so far. Recently, network meta-analysis of results of 21 clinical trial publications endorsed combining IMiDs and proteasome inhibitors (PIs) for frontline regimens in transplant-eligible MM patients. It also confirmed superiority of lenalidomide over thalidomide in this setting.

### 3.2.6 Induction regimen before stem cell transplantation for a patient with severe renal insufficiency

The question about the preferred induction regimen for the patient with renal insufficiency was asked in the last three years of series of the survey. Figure 6 illustrates responses collected in survey editions from 2017 to 2019.

**Comment**: Patients with severe renal insufficiency are frequently considered ineligible for SCT because of a high risk of treatment-related toxicity. However, in recent years, several studies reported that SCT could be effective and safe in patients with severe renal impairment or even end-stage renal disease which could be reversible in a fraction of patients. The accumulated evidence suggests that SCT should be considered in the early course of the disease. The results of the three surveys show the use of four bortezomib-based regimens without a clear preference for any of them, although with a trend for the RVd regimen (Figure 6). The literature does not support any standard of treatment in this clinical situation. A paper from the Mayo Clinic suggests that lenalidomide 15 mg is safe for any degree of renal impairment.

### 3.2.7 Maintenance therapy after stem cell transplantation

Questions about offering a maintenance therapy to a patient after SCT were asked in the context of standard (Figure 7A) and high-risk (Figure 7B) patients in surveys conducted from 2017 to 2019.

**Comment**: Maintenance therapy is recommended after a stem cell transplant. This aims to maintain remission and prevent relapse. Typically, monotherapy is provided to avoid adverse events and decline in quality of life. The most common drugs used as maintenance therapy include lenalidomide, thalidomide, and bortezomib. Sometimes corticosteroids are used along with them. The potential limitation of maintenance treatment includes treatment-related toxicity and treatment costs. In the case of standard risk, from 36% to 53% of respondents in different years declared not to recommend any maintenance treatment (Figure 7A). It changes in the case of high-risk patients when not recommending maintenance treatment is less common (Figure 7B). Lenalidomide remains the mainstay of maintenance treatment in standard-risk patients. It is in line with the
recommendation from the Norwegian Directorate of Health to start treatment with 10 mg/d lenalidomide 3 months after the SCT; however, in 2018 reimbursement was declined, leading to a lower number of respondents selecting this option in 2019. For high-risk patients, use of bortezomib and bortezomib-dexamethasone maintenance was more frequently declared compared with standard-risk patients. For high-risk patients, the recommendation about use of lenalidomide is weaker. Bortezomib maintenance has shown specific benefit for high-risk patients, including patients with 17p deletion, in the European HOVON-65/GMMG study. Although there are limited data on combination therapy for maintenance, some respondents were indicating such options (<5% of respondents in a year).

### 3.3 Treatment of relapse

#### 3.3.1 Stem cell transplantation as salvage therapy

Time from the first SCT to relapse is the most important prognostic indicator of survival after the subsequent SCT. Also, type of the second induction therapy may vary depending on time form the first SCT and relapse. In surveys conducted in 2018 and 2019, respondents were asked whether to perform a second transplant upon relapse considering time from first transplant (Figure S1A). Between 2016 and 2019, they selected whether to change induction therapy before salvage transplant (Figure S1B).

**Comment:** Frontline autologous SCT is a standard of care for treating NDMM in fit patients. SCT can also be used as salvage therapy in patients with the disease progression after an earlier transplant. Longer time to disease progression favored salvage SCT over other treatments. The majority of respondents indicated that salvage SCT is a standard treatment if a patient is eligible. However, in 2018, they significantly differed considering the time from the first transplant to relapse, to recommend a new SCT. Almost half of the respondents indicated relapse recurrence after 12 months as suitable for retreatment, but the year after, none choose this option. The majority indicated the period from the first SCT to relapse to have to be at least 18 months (Figure S1A). Most of the retrospective studies aiming at identifying predictors of outcome after salvage ASCT included only small numbers of patients and had a variable duration of follow-up. The new study of the European Society for Blood and Marrow Transplantation, analyzing the outcomes of a salvage third SCT confirmed that the longer the duration of remission after the second SCT, the better the outcome, with median OS of 37 months if the relapse-free interval was between 18 and 36 months, and 64 months if the relapse-free interval was ≥36 months. The findings could contribute to change of paradigm in Norway (Figure S1A). However, according to the current guidelines of the Norwegian Directorate of Health, salvage SCT can be performed when relapse occurred from at least 1 year after initial SCT. The Directorate of Health recommends to change induction therapy for the second SCT. Duration of the first remission affects the Norwegian hematologists’ choice between repeating or changing the induction regimen, however to a declining degree (Figure S1B). In the years 2016-2019, percentage of hematologists who would change the induction regimen at salvage SCT irrespective of time passed increased to 28% of physicians in 2019. Simultaneously, the proportion of those who would re-induce with the same regimen decreased. Both using the same re-induction as induction was, and changing it, have supportive evidence. The decision that change of regimen depended on the time from the first transplant was selected by 43%-55% of respondents over the years.

#### 3.3.2 Selection of re-induction regimen for salvage stem cell transplantation

A combination of bortezomib, cyclophosphamide, and dexamethasone (VCd) is among the most common induction regimens used in Norway.
in recent years (Figure 5). Hematologists were asked to select a re-induction regimen before salvage SCT after progression of the disease treated initially with VCD followed by autologous SCT (Figure S2). The question was asked in surveys conducted from 2017 to 2019.

Comment: The majority of respondents decided to change the re-induction regimen vs. the initial one, every year when the question was asked in surveys. In 2017, over one-fourth of respondents indicated to re-use the same regimen, and in the next years, the preference to continue with the same induction regimens decreased to 16%. The most popular regimen was RVd (Figure S1), which used emerged in this setting in parallel with its popularity in the frontline induction (Figure 5). Carfilzomib-based induction regimens (KCd and Kd) were selected by 14% of respondents in 2017 and by 7% in 2019. These combinations have been studied in the frontline setting.

3.3.3 | Selection of treatment for a patient relapsing after transplant but ineligible for salvage stem cell transplantation

Treatment of relapse after frontline transplant is one of the most common challenges of therapy of RRMM. Bortezomib-based regimens, like VCD and VTD, were the most common induction regimens used in Norway in recent years (Figure 5). Starting from 2014, Norwegian hematologists were declaring treatment regimens for management of relapse after transplant in the case when salvage SCT is not an option (Figure 8).

Comment: Most of the patients with MM will ultimately relapse. Nowadays, the landscape of treatment of RRMM rapidly evolves and includes combinations of classical, novel, and the newest agents.

3.3.4 | Selection of treatment for a patient relapsing after bortezomib, melphalan, and prednisone used in the first line

Bortezomib, melphalan, and prednisone (VMP) was an established standard of the frontline treatment in transplant-ineligible patients (Figure 1). To assess the choice of treatment after relapse, hematologists were declaring treatment regimens for management of relapse after VMP in the first line in surveys conducted from 2014 to 2019 (Figure 9).

Comment: Similar to relapse after transplant, IMiD-based regimens were recommended for treatment disease progression after VMP in the first line. The Norwegian Directorate of Health recommends using non–bortezomib-containing regimens, like Rd, Kd, Td, and Daratre. However, access to the newest combinations, including carfilzomib and daratumumab, is limited. With time, the landscape evolved; Rd regimen substituted Td in the treatment path, followed by the addition of bortezomib to Rd starting from 2017 (Figure 9). Alkylator-based triplets were used in this setting in the first half of the current decade, consisting of more than 20% of choices in 2014 and 2015.

3.3.5 | Selection of treatment for a patient relapsing after lenalidomide and dexamethasone used in the first line

With the increasing use of the Rd regimen in the first-line therapy (Figures 1 and 3) new question about management of relapse was added to surveys conducted from 2017 to 2019 (Figure 10).
Comment: The ESMO guidelines recommend to treat the first relapse after IMiD-based regimen with Vd or Kd doublets or bortezomib-based triplets as DaraVd, PanoVd, EloVd, or VCd. The Norwegian Directorate of Health lists similar non-IMiD-containing combinations in this setting. In 2017, one-third of respondents preferred Vd regimen and the same number indicated VMP triplet, which was not mentioned in the above guidelines. The use of both declined simultaneously in the next years below 20%. The presence of the newest generation of antimyeloma agents is visible in the landscape of treatment of relapse after Rd regimen (Figure 10). Daratumumab combined with bortezomib and dexamethasone (DaraVd), which was in 2019 the most common choice of treatment of relapse after Rd regimen, demonstrated significant efficacy in patients with RRMM and provided the greatest benefit to patients treated at first relapse of the bortezomib-containing regimens. Pomalidomide is the best studied drug in patients relapsing or refractory to lenalidomide. By design, the drug is indicated to treat relapses after previous use of lenalidomide, both in early relapse and advanced disease settings. Finally, carfilzomib used in combination with dexamethasone (Kd) extended OS of patients with RRMM over the standard of care, Vd regimen. Nowadays, many of the newest drugs and combinations are not reimbursed in Norway.

3.3.6 | Retreatment or switch after relapse

From 2015 to 2019, Norwegian hematologists were asked about their preferences toward retreatment with the same regimen or switch at relapse, in the non-transplant setting (Figure S3). Comment: The Norwegian Directorate of Health stated that the evidence for retreatment is weaker in the non-transplant setting than in the case of planned salvage SCT (Figure S1B). If the disease relapses after a short time, for example, <12 months, or a patient is still on treatment, it likely indicates an aggressive or refractory disease justifying the switch of drugs. In the review focused on treatment sequencing and retreatment approaches in the era of new drugs, Mohty et al state that if relapse occurs after a long treatment-free period (>12 months), the retreatment approach can be considered. The period from the beginning of treatment to the disease progression of 18-36 months was regarded as including a treatment-free period. Proportions of respondents who consider switch and retreatment or other options oscillated in years 2016-2019 around 50%, after higher prevalence toward retreatment in 2015 (Figure S3A). In the setting of a very long time from the start of treatment to relapse (>36 months), most of the respondents preferred to retreat a patient, and the willingness to change treatment is slowly increasing from 2016 to 2019 (Figure S3B). The findings highlight in both figures the trend toward always switching treatment at relapse, which is in line with the trend for continuous treatment in all treatment lines.

3.4 | Practicalities of myeloma care in Norway

3.4.1 | Treatment of multiple myeloma without CRAB symptoms

The acronym CRAB summarizes the typical clinical manifestations of MM: hypercalcemia, renal insufficiency, anemia, and bone lesions, and was until 2014 the defining features of active myeloma. Gradually it was realized that observation was detrimental to a fraction of the patients without CRAB findings. Thus, in 2014, the definition of active myeloma was expanded to include hypercalcemia, renal insufficiency, anemia, and bone lesions.
In contrast, the Cochrane did not support superiority of any specific bisphosphonate for any outcome.84

In clinical trials, the bisphosphonates have been given for around 2 years. The Norwegian Directorate of Health recommends continuing the treatment with zoledronate for 2 years.17 The attitude toward a fixed time of treatment is low among Norwegian hematologists and was decreasing over time. Today's practice is dominated by preferences for treatment the initial two years and restarting of therapy at disease progression together with the next line of antimyeloma treatment or if new bone lesions occur (Figure S5C). The current practice is confirmed in the guidelines.85–88 The European Myeloma Network indicates that zoledronate should be given continuously.83

The incidence of vitamin D deficiency in patients with MM is high.89,90 The Mayo Clinic recommended maintaining adequate vitamin D and calcium intake in patients treated with bisphosphonates.91 Each year, the percentage of Norwegian hematologists recommending supplementation of calcium and vitamin D was increasing (Figure S5D).

Dentists have great importance for myeloma bone disease management. Patients treated with the bisphosphonates are at an increased risk of developing medication-related osteonecrosis of the jaw. Thus, there are several factors to consider when deciding about bisphosphonates use, for example, undergoing all necessary dental procedures before the treatment, review of dental symptoms, and dental hygiene.88 Dental referral became the standard of care in Norway in recent years (Figure S5).

3.4.3 | Diagnostic workout

Every year, Norwegian hematologists were asked to indicate the diagnostic workup they perform as standard practice during diagnosis MM (Figure 11).

Comment: The International Myeloma Working Group defined minimal requirements for the diagnosis and monitoring of patients with MM in 2013.92 At diagnosis, the absolute minimum is bone marrow aspiration or bone biopsy, which were declared as a standard by the majority of Norwegian hematologists at the time of publication of the recommendations (Figure 11). With time, most of the Norwegian hematologists participating in the surveys selected diagnostic workout elements considered by the IMWG as necessary (Figure 11). Computed tomography substituted X-ray survey due to its higher sensitivity for myeloma specific bone lesions. FISH cytogenetics initially available at biobanks became routinely available and frequently used at the end of the current decade. Karyotypic abnormalities were studied in multiple myeloma by every fifth hematologist in 2019. In Norway, several tests providing information about organ function and aggressiveness of the disease were commonly used (eg, albumin, blood count, glutamyltransferase, alkaline phosphatase, lactate dehydrogenase). In addition, Norwegian hematologists frequently test cardiovascular biomarkers, including troponin and pro-B-type natriuretic peptide.

3.4.2 | Bone health in patients with multiple myeloma

MM results in osteolytic bone disease. Every year, starting from 2014 hematologists declared their preferences in bone health care in patients with MM answering five questions (Figure S5).

Comment: The current Norwegian guidelines recommend bisphosphonates as prophylactic treatment with and without presence of skeletal lesions.16 In the past, the preventive treatment was not standard and physicians declared use of bisphosphonates mainly in patients with lytic lesions (Figure S5A). The European Myeloma Network recommends treating symptomatic patients without bone disease assessed by conventional radiography, but the advantage is not as clear for patients without bone involvement on MRI or PET/CT.83

The use of pamidronate has a long tradition in Norway.16 The study published in 2010 showed that zoledronate resulted in less skeletal-related events and increased OS compared to treatment with clodronic acid.79 Since pamidronate did not have similar evidence, zoledronate penetrated clinical practice and was the preferred bisphosphonate choice by almost 100% of respondents in 2019 (Figure S5B). The Norwegian Directorate of Health recommends the use of zoledronate based on evidence of OS advantage.17

the presence of at least one of the disease biomarkers denoted by the acronym SLiM (S—Sixty/Percentage of clonal plasma cells in bone marrow biopsy at least 60%, Li—Light chains/Ratio of clonal to non-clonal free light chains in serum > 100, M—Magnetic resonance imaging/Presence of at least two focal infiltrates in bone marrow magnetic resonance imaging), which jointly with CRAB defines active disease with plasma cell myeloma (SLiM CRAB).80 Figure S14 shows how new criteria were adopted into clinical practice of MM care in Norway. In addition, it assessed willingness to start the treatment in the case of high-risk cytogenetics and immunoparesis (suppression of uninvolved immunoglobulins) without other defining features.

Comment: The new criteria for the diagnosis of multiple myeloma allow for treatment of patients who are likely to progress to symptomatic disease. These patients are expected to benefit from therapy.80 In 2014, at the time of publication of the updated criteria, 71% of respondents declared not to treat any patient with these myeloma defining events (Figure S14). In each following year, increase in adoption of the SLiM criteria to clinical practice was visible. In 2019, the best adopted myeloma-related event was > 60% of clonal plasma cells on bone marrow examination and > 1 focal lesion on MRI. A minority of respondents declared beginning treatment based on high-risk cytogenetics or immunoparesis, which did not change significantly over the years (Figure S4). Cytogenetic abnormalities are incorporated in to a new staging system,81 and immunoparesis can be associated with shorter PFS82; however, they are not validated as diagnostic criteria.
levels mainly to discover light-chain amyloidosis. Awareness of the importance of biomarkers of asymptomatic heart failure was increasing in the last years (Figure 11).

3.5 Regional differences in care. The use of lenalidomide, bortezomib, and dexamethasone in different clinical setting across regions of Norway in 2019

To investigate regional differences in care, the use of a new and common regimen (RVd) was evaluated divided by regions. Table S1 shows percentages of respondents indicating the RVd regimen as treatment of choice in different clinical situation in 2019.

Comment: The basis of the use of the RVd regimen in the frontline setting was established in 2015, and it developed quickly in the next years (Figures 1, 5, 6, 8, and Figures S1 and S2). Besides strong clinical evidence, the regimen could be relatively easy adopted into clinical practice since it requires combining standard Rd regimen with the well-established drug bortezomib. In comparison with highly effective combinations of lenalidomide with the newest PIs, carfilzomib and ixazomib and monoclonal antibodies, the RVd regimen was used more by Norwegian hematologists, because the other triplets were not reimbursed. The main reason was a relatively low cost of the combination and possibility of use in different clinical situations. Finally, the use of lenalidomide in Norway increased most significantly during the studied period. It can be explained by multipurpose use of lenalidomide, its utilization in all lines of therapy, as a foundation for different regimens, in a broad group of patients undergoing transplantation or not. Experience with the drug in one area can encourage its use in others. New evidence quickly catalyzes change of practice, for example, similar to other European countries, where VCd regimen is a standard of induction before SCT, the RVd combination was increasingly being used, even if not yet approved.

Norway is the country in Western Europe with least access to myeloma drugs, and the case with lenalidomide illustrates how reimbursement policy affects treatment. Maintenance treatment is used very little now, similar to the lenalidomide-based triplets in the second line. Instead, the use of combinations with generic drugs is common, especially with RVd in the first line for the young and in relapse, VCd in relapse. But for now, doublet and monotherapy treatment dominate the Norwegian treatment algorithm, reducing the potential benefit of Norwegian patients. In later lines, bendamustine is also used to provide triplet treatment, combined with pomalidomide or carfilzomib. But this is not evidence-based and only an alternative because the proven triplets are not reimbursed.

The growing number of available therapies has heightened the need to identify optimum treatments for myeloma in different clinical situations. Among them, the impact of initial treatment is of special importance. Updated diagnostic criteria have allowed to start treatment before organ damage, which potentially would enable patients to live longer with the disease or to limit its burden. The majority of Norwegian hematologists adapted new criteria to their practice within a few years after the publication. Response to the first-line treatment is among the most important factors associated with longer PFS and OS. The landscape of the first-line treatment evolved to enable better survival outcomes. Norwegian hematologists limited the use of thalidomide and alkylators in the first-line treatment of transplant-ineligible patients; however, the VMP regimen remains a treatment of choice in the reimbursement policy. Lenalidomide and bortezomib became the major first-line treatments, in most patients with NDMM in different clinical situations. The use of maintenance treatment after SCT was increasing rapidly, until 2018, when the lack of reimbursement limited it. Worth to note is that the use of maintenance remains high in the group of patients with high-risk cytogenetics. The use of lenalidomide in Norway increased most significantly during the studied period. It can be explained by multipurpose use of lenalidomide, its utilization in all lines of therapy, as a foundation for different regimens, in a broad group of patients undergoing transplantation or not. Experience with the drug in one area can encourage its use in others. New evidence quickly catalyzes change of practice, for example, similar to other European countries, where VCd regimen is a standard of induction before SCT, the RVd combination was increasingly being used, even if not yet approved.

Norway is the country in Western Europe with least access to myeloma drugs, and the case with lenalidomide illustrates how reimbursement policy affects treatment. Maintenance treatment is used very little now, similar to the lenalidomide-based triplets in the second line. Instead, the use of combinations with generic drugs is common, especially with RVd in the first line for the young and in relapse, VCd in relapse. But for now, doublet and monotherapy treatment dominate the Norwegian treatment algorithm, reducing the potential benefit of Norwegian patients. In later lines, bendamustine is also used to provide triplet treatment, combined with pomalidomide or carfilzomib. But this is not evidence-based and only an alternative because the proven triplets are not reimbursed.

The landscape of relapse treatment changed in parallel with the initial treatment. Independently of the nature of relapse, previous treatment, and transplantation plan, lenalidomide is the foundation of treatment of the first relapse in Norway. Although many lenalidomide-based triplets were introduced into the clinical practice of RRMM treatment, the only lenalidomide-based treatment well-established combination in Norwegian is RVd. The evidence from the frontline setting influenced the second line easily since the use of most triplets was not deemed acceptable for payers. It can be assumed that many patients in Norway are sequentially retreated with lenalidomide since the drug is commonly used in the first line and there is a strong attitude to retreat patients with the same regimen after relapse based on duration of a treatment-free period. However, this is probably
changing as physicians are moving toward continuous treatment. Typically, switch of treatment after relapse on Rd therapy is managed by the use of bortezomib-based first-line alternative regimens, as VMP, VCd, and Vd; however, in recent years, there is a tendency to use the newest generation of antimyeloma agents, like daratumumab, pomalidomide, and carfilzomib. The study did not assess practice of treatment of late relapses in RRMM.

Introduction of new antimyeloma agents, thalidomide, lenalidomide, and bortezomib is gradually transforming MM from an acute condition to a potentially manageable chronic disease. In the United States, the median OS is expected to continue rising to 72 months in 2022. It represents 67% improvement from 2008 and 140% improvement from 2001.\(^5\) Also in Norway the median OS has increased the latest years.\(^6\) This is the first report documenting the evolution of treatment regimens and therapeutic approaches, signifying changing habits, and has been performed in a large majority of Norwegian myeloma physicians. The future will show the long-term outcome of the translation of advances in clinical science to practice in Norway.

The presented data reflect the opinion and choices of Norwegian hematologists treating patients with MM in their daily practice. It can be assumed that in Norway, there are around 80 professionally active physicians with experience in the treatment of MM. Thus, surveys involved a majority of practitioners over the years. Using the survey results, clinicians can compare their practices against those of a general panel of doctors. All of them face similar clinical situations and can evaluate their practice. It must be stressed that the fact that the majority of physicians agree does not mean they are correct. Only medical research can validate the opinions, and the opinions also change, which is very well reflected in the study results. The value of the study is to illustrate the rate of adaptation of advances in medicine and updates in guidelines into clinical practice.

ACKNOWLEDGMENTS
The author thanks Marcin Balcerzak of Oriola for providing analysis and medical writing support. The surveys conducted in 2017-2019 were supported by Celgene with funding limited to data collection and analysis. Medical writing service for this article was supported by Celgene. The author also thanks all Norwegian myeloma doctors participating in the survey.

ORCID
Fredrik Schjesvold https://orcid.org/0000-0003-1096-0569

REFERENCES
1. Thorsteinsdottir S, Dickman PW, Landgren O, et al. Dramatically improved survival in multiple myeloma patients in the recent decade: results from a Swedish population-based study. Haematologica. 2018;103:e412-e415.
2. Kristinsson SY, Anderson WF, Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. Leukemia. 2014;28:1346-1348.
3. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv. 2017;1:282-287.
4. Offidani M, Corvatta L, Gentili S. Triplet vs. doublet drug regimens for managing multiple myeloma. Expert Opin Pharmacother. 2018;19:137-149.
5. European Cancer Information System. European Cancer Information System: Estimates of cancer incidence and mortality in 2018, for all countries [Internet]. European Union; 2019.
6. Tangen J-M, Tjennfjord GE, Gulbrandsen N, et al. Improved outcome in patients following autologous stem cell transplantation for multiple myeloma in southern Norway 2001-2010: a retrospective, population based analysis. BMC Cancer. 2018;18:801.
7. Lenhoff S, Hjorth M, Turesson I, et al.; Nordic Myeloma Study Group. Intensive therapy for multiple myeloma in patients younger than 60 years. Long-term results focusing on the effect of the degree of response on survival and relapse pattern after transplantation. Haematologica. 2006;91:1228-1233.
8. Lenhoff S, Hjorth M, Westin J, et al. Impact of age on survival after intensive therapy for multiple myeloma: a population-based study by the Nordic Myeloma Study Group. Br J Haematol. 2006;133:389-396.
9. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and prednisone chemotherapy plus thalidomide and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 2006;367:825-831.
10. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007;370:1209-1218.
11. 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.
12. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2004;371:906-917.
13. Durie BG, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017;389:519-527.
14. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med. 2019;380:2104-2115.
15. Dytfeldt D, Jasielec J, Griffith KA, et al. Carfilzomib, lenalidomide, and low-dose dexamethasone in elderly patients with newly diagnosed multiple myeloma. Haematologica. 2014;99:e162-e164.
16. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018;131:301-310.
17. Norwegian Directorate of Health. National Action Program with Guidelines for Diagnosis, Treatment and Follow-up of Malignant Blood Disorders, 2019 [Internet]. Oslo: Norwegian Directorate of Health; 2019.
18. Dimopoulos MA, Sonneveld P, Leung N, et al. International myeloma working group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol. 2016;34:1544-1557.
19. Dimopoulos MA, Roussou M, Gkotzamanidou M, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia. 2013;27:423-429.
20. Dimopoulos MA, Richardson PG, Schlag R, et al. VMP (bortezomib, melphalan, and prednisone) is active and well tolerated in newly diagnosed patients with multiple myeloma with moderately
impaired renal function, and results in reversal of renal impairment: cohort analysis of the phase III VISTA study. *J Clin Oncol*. 2009;27:6086-6093.

21. Malani AK, Gupta V, Rangineni R. Bortezomib and dexamethasone in previously untreated multiple myeloma associated with renal failure and reversal of renal failure. *Acta Haematol*. 2006;116:255-258.

22. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Reversibility of renal impairment in patients with multiple myeloma treated with bortezomib-based regimens: identification of predictive factors. *Clin Lymphoma Myeloma*. 2009;9:302-306.

23. Ponisch W, Moll B, Bourgeois M, et al. Bendamustine and prednisone in combination with bortezomib (BPV) in the treatment of patients with relapsed or refractory multiple myeloma and light chain-induced renal failure. *J Cancer Res Clin Oncol*. 2013;139:1937-1946.

24. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. *Am J Hematol*. 2016;91:499-502.

25. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. *Blood*. 2008;111:2521-2526.

26. Ludwig H, Bolejaka V, Crowley J, et al. Survival and years of life lost in different age cohorts of patients with multiple myeloma. *J Clin Oncol*. 2010;28:1599-1605.

27. Alexanian R, Haut A, Khan AU, et al. Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. *JAMA*. 1969;208:1680-1685.

28. Facon T, Mary JY, Pegourie B, et al. Dexamethasone-based regimens. *Blood Cancer J*. 2018;8:1-15.

29. Harousseau JL, Palumbo A, Richardson PG, et al. Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. *Blood*. 2010;116:3743-3750.

30. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. *J Clin Oncol*. 2010;28:3160-3166.

31. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol*. 2012;30:2946-2955.

32. Mai EK, Bertsch U, Durig J, et al. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAD) in newly diagnosed myeloma. *Leukemia*. 2015;29:1721-1729.

33. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia*. 2009;23:1337-1341.

34. Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood*. 2012;120:1589-1596.

35. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:i52-i61.

36. Cavo M, Pantani L, Pezzi A, et al. Bortezomib-thalidomide-dexamethasone (VTD) is superior to bortezomib-cyclophosphamide-dexamethasone (VCD) as induction therapy prior to autologous stem cell transplantation in multiple myeloma. *Leukemia*. 2015;29:2429-2431.

37. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. *N Engl J Med*. 2017;376:1311-1320.

38. Sekine L, Ziegelmann PK, Manica D, et al. Frontline treatment for transplant-eligible multiple myeloma: a 6474 patients network meta-analysis. *Hematol Oncol*. 2019;37:62-74.

39. St Bernard R, Chodirker L, Masih-Khan E, et al. Efficacy, toxicity and mortality of autologous SCT in multiple myeloma patients with dialysis-dependent renal failure. *Bone Marrow Transplant*. 2015;50:95-99.

40. El Fakih R, Fox P, Popat U, et al. Autologous hematopoietic stem cell transplantation in dialysis-dependent myeloma patients. *Clin Lymphoma Myeloma Leuk*. 2015;15:472-476.

41. Waszczyk-Gajda A, Lewandowski D, Drozd-Sokolowska J, et al. Autologous peripheral blood stem cell transplantation in dialysis-dependent multiple myeloma patients-DAUTOS Study of the Polish Myeloma Study Group. *Eur J Haematol*. 2018;101:475-485.

42. Parikh GC, Amjad AI, Saliba RM, et al. Autologous hematopoietic stem cell transplantation may reverse renal failure in patients with multiple myeloma. *Blood Marrow Transplant*. 2009;15:812-816.

43. Augueul-Meurnier K, Chretien ML, Stoppa AM, et al. Extending autologous transplantation as first line therapy in multiple myeloma patients with severe renal impairment: a retrospective study by the SFGM-TC. *Bone Marrow Transplant*. 2018;53:749-755.

44. Mikhail J, Manola J, Dueck AC, et al. Lenalidomide and dexamethasone in patients with relapsed multiple myeloma and impaired renal function: PrE1003, a PrECOG study. *Blood Cancer J*. 2018;8:86.

45. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol*. 2017;4:e431-e442.

46. McCarthy PL, Ozwars K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770-1781.

47. 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.

48. Morgan GJ, Gregory WM, Davies FE, et al.; National Cancer Research Institute Haematological Oncology Clinical Studies Group. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. *Blood*. 2012;119:7-15.

49. Mateos MV, Oriol A, Martinez-Lopez J, et al. GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? *Blood*. 2014;124:1887-1893.

50. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. *Leukemia*. 2014;28:690-693.

51. Cook G, Ashcroft AJ, Cairns DA, et al.; National Cancer Research Institute Haematological Oncology Clinical Studies Group. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2016;3:e340-e351. https://doi.org/10.1016/S2352-3026(16)30049-7.

52. Grov达尔 M, Nahi H, Gahrton G, et al. Autologous stem cell transplantation versus novel drugs or conventional chemotherapy for patients with relapsed multiple myeloma after previous ASCT. *Bone Marrow Transplant*. 2015;50:808-812.

53. Atanackovic D, Schilling G. Second autologous transplant as salvage therapy in multiple myeloma. *Br J Haematol*. 2013;163:565-572.

54. Olin RL, Vogl DT, Porter DL, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. *Bone Marrow Transplant*. 2009;43:417-422.
55. Michaelis LC, Saad A, Zhong X, et al. Salvage second hematopoietic cell transplantation in myeloma. Biol Blood Marrow Transplant. 2013;19:760-766.
56. Garderet L, Iacobelli S, Koster L, et al. Outcome of a salvage third autologous stem cell transplantation in multiple myeloma. Biol Blood Marrow Transplant. 2018;24:1372-1378.
57. Paccagnella A, Chiarion-Sileni V, Soesman M, et al. Second and third responses to the same induction regimen in relapsing patients with multiple myeloma. Cancer. 1991;68:975-980.
58. Gay F, Cerrato C, Rota Scalabrini D, et al. Carfilzomib–lenalidomide–dexamethasone (KRd) induction-autologous transplant (ASCt)-Krd consolidation Vs Krd 12 cycles Vs carfilzomib–cyclophosphamide–dexamethasone (KCd) induction-ASCt-KCd consolidation: analysis of the randomized forte trial in newly diagnosed multiple myeloma (NDMM). Blood. 2018;132:121.
59. Gay FM, Rota Scalabrini D, Belotti A, et al. A randomized study of carfilzomib–lenalidomide–dexamethasone versus carfilzomib–cyclophosphamide–dexamethasone induction in newly diagnosed myeloma patients eligible for transplant: high efficacy in high- and standard-risk patients. Blood. 2017;130:4541.
60. Moreau P, San Miguel J, Ludwig H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;6:v1133-v1137. https://doi.org/10.1093/annonc/mdt297
61. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357:2133-2142.
62. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357:2123-2132.
63. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015;372:142-152.
64. Dimopoulos MA, San-Miguel J, Belch A, et al. Daratumumab plus lenalidomide and dexamethasone versus lenalidomide and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of POLLUX. Haematologica. 2018;103:2088-2096.
65. Dimopoulos MA, Lonial S, Betts KA, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: Extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial. Cancer. 2018;124:4032-4043.
66. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, lenalidomide, and dexamethasone for multiple myeloma. New Engl J Med. 2016;374(17):1621-1634. https://doi.org/10.1056/NEJMo1516282
67. Richardson PG, Oriol A, Bekiac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20:781-794.
68. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17:27-38.
69. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375:754-766.
70. San-Miguel JF, Hungria VT, Yoon SS, et al. Overall survival of patients with relapsed multiple myeloma treated with panobinostat or placebo plus bortezomib and dexamethasone (the PANORAMA 1 trial): a randomised, placebo-controlled, phase 3 trial. Lancet Haematol. 2016;3:e506-e515.
71. Jakubowiak A, Offidani M, Pegourié B, et al. Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. Blood. 2016;127:2833-2840.
72. Fu W, Delasalle K, Wang J, et al. Bortezomib-cyclophosphamide-dexamethasone for relapsing multiple myeloma. Am J Clin Oncol. 2012;35:562-565.
73. Dimopoulos MA, Bekiac M, Benboubker L, et al. Phase II study of bortezomib-dexamethasone alone or with added cyclophosphamide or lenalidomide for sub-optimal response as second-line treatment for patients with multiple myeloma. Haematologica. 2013;98:1264-1272.
74. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018;103:2079-2087.
75. Miguel JS, 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.
76. Mohty B, El-Chiekh J, Yakoub-Agha I, Avet-Loiseau H, Moreau P, Mohty M. Treatment strategies in relapsed and refractory multiple myeloma: a focus on drug sequencing and ‘treatment’ approaches in the era of novel agents. Leukemia. 2012;26:73-85.
77. International Myeloma Working Group. Criteria for the classification of monoclonal gammapathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003;121:749-757.
78. Talamo G, Faroouq U, Zangari M, et al. Beyond the CRAB symptoms: a study of presenting clinical manifestations of multiple myeloma. Clin Lymphoma Myeloma Leuk. 2010;10:464-468.
79. Howell D, Smith A, Appleton S, et al. Multiple myeloma: routes to diagnosis, clinical characteristics and survival - findings from a UK population-based study. Br J Haematol. 2017;177:67-71.
80. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15:e538-e548.
81. Palumbo A, Avet-Loiseau H, Oliva S, et al. Multiple myeloma: routes to diagnosis, clinical characteristics and survival - findings from a UK population-based study. Br J Haematol. 2015;133:2863-2869.
82. Sorri R, Clausen TW, Salomo M, et al. Immunoparesis in newly diagnosed Multiple myeloma patients: effects on overall survival and progression free survival in the Danish population. PLoS One. 2017;12:e0188988.
83. Terpos E, Kleber M, Engelhardt M, et al. European Myeloma Network guidelines for the management of multiple myeloma-related complications. Haematologica. 2015;100:1254-1266.
84. Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Bisphosphonates in multiple myeloma: an updated network meta-analysis. Cochr Database Syst Rev. 2017;12:CD003188.
85. Anderson K, Ismaila N, Flynn PJ, et al. Role of bone-modifying agents in multiple myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2018;36:812-818.
86. Lee OL, Horvath N, Lee C, et al. Bisphosphonate guidelines for treatment and prevention of myeloma bone disease. Intern Med J. 2017;47:938-951.
87. Durie BG. Use of bisphosphonates in multiple myeloma: IMWG statement for the use of bisphosphonates in multiple myeloma. Mayo Clin Proc. 2007;82:516-517; author reply 517-518.
88. Lacy MQ, Dispenzieri A, Gertz MA, et al. Mayo clinic consensus statement for the use of bisphosphonates in multiple myeloma. Mayo Clin Proc. 2006;81:1047-1053.
49. Badros A, Goloubeva O, Terpos E, Milliron T, Baer MR, Streiten E. Prevalence and significance of vitamin D deficiency in multiple myeloma patients. Br J Haematol. 2008;142:492-494.
50. Lauter B, Schmidt-Wolf IG. Prevalence, supplementation, and impact of vitamin D deficiency in multiple myeloma patients. Cancer Invest. 2015;33:505-509.
51. Calcium and Vitamin D Supplementation in Myeloma. Mayo Consensus. [Internet] Mayo Clinic College of Medicine, Mayo Clinic Comprehensive Cancer Center, Version 1, reviewed in September 2012. Available online:https://static1.squarespace.com/static/5b44f08ac25893a25099b3a/t/5b806e810ebbe8b9b8c6b367/1535143554065/VitD+replacement+MM.pdf. Accessed June 23, 2020.
52. Ludwig H, Miguel JS, Dimopoulos MA, et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia. 2014;28:981-992.
53. Wang Y, Bao L, Chu B, et al. Progressive elevation of NT-ProBNP during chemotherapy is related to asymptomatic cardiovascular events in patients with multiple myeloma. Clin Lymphoma Myeloma Leuk. 2019;19(3):167-176.e1.
54. 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.
55. Drawid AKS, Kiely D, Hussein MA, Kaman M, Gilra N, Durie BGM. Impact of novel therapies on multiple myeloma survivale current and future outcomes. Clin Lymphoma Myeloma Leuk. 2015;15:e63.
56. Langseth Ø, Myklebust TÅ, Johannesen TB, Hjertner Ø, Waage A. Incidence and survival of multiple myeloma: a population-based study on 10 961 patients diagnosed 1982-2017. Blood. 2019;134:4380. https://doi.org/10.1182/blood-2019-129816

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Schjesvold F. Evolution of diagnostic workup and treatment for multiple myeloma 2013-2019. Eur J Haematol. 2020;105:434-448. https://doi.org/10.1111/ejh.13464