MEDICAL SCIENTIFIC ADVISORY GROUP (MSAG)
TO MYELOMA AUSTRALIA (MA)

MSAG Update

Bortezomib, Lenalidomide and Dexamethasone (VRd)

for initial treatment of multiple myeloma

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Bortezomib, Lenalidomide and Dexamethasone for initial treatment of multiple myeloma

As of the 1st of June 2020, the combination of bortezomib, lenalidomide and dexamethasone (VRd) for the upfront treatment of patients with MM was made available on the Australian Pharmaceutical Benefits Scheme. This decision was based on the positive outcomes of the SWOG S0777 study[1]. The initial report was updated in 2020 [2]. Importantly, this study enrolled patients *not specifically planned for front-line ASCT* (table 1); at a median follow up of 84 months, VRd was superior to Rd with respect to PFS (41m vs. 29m, HR 0.742, p=0.003) and OS (NR vs. 69m, HR 0.709, p = 0.0114). Undoubtedly, the availability of VRd for initial treatment of MM is an important milestone and will no doubt improve outcome for patients with MM.

Indeed, maximising first-line therapy remains the best opportunity to optimise long term patient outcomes. It would seem obvious then to use a three-drug combination, where feasible, to achieve the best response rate and consequently a long first remission. This is a clear objective in younger transplant-eligible patients who achieve high response rates with RVd and so move into the AuSCT phase in deeper remissions and consequently longer survival[3]. Nonetheless, even in younger transplant-eligible patients, considerations must be made to minimise toxicities such as peripheral neuropathy.

However, for the older patients, the price that is paid for combining three drugs is the potential for more side effects. Our challenge is to balance tolerance with efficacy. It is recognised that the likelihood of drug-toxicity will be dependent on the patient's pre-treatment frailty. The challenge for clinicians is to assess frailty accurately? Moreover, selecting patients for the 'right treatment' must go beyond just examining the characteristics of those entered on clinical trials. It is well recognized that although trial data is crucial for determining the efficacy of various therapies, the patients that enter such clinical trials do not always represent 'real world' patients and 'real world' outcomes. Indeed, in myeloma trials, the median age and performance status of patients on trials is typically less than in the 'real world'[4].

Of note, MSAG recognises that variations of published VRd schedules will be used by different institutions to minimise toxicity, however, we have not made firm recommendations about schedules that are outside what is published due to the lack of robust data. Notwithstanding, when selecting the appropriate VRd regimen (including variations of published regimens) for patients, the following needs to be considered by clinicians (also see Box below for details):

- The PBS will reimburse 32 doses of bortezomib (total 32) and we believe is important to utilize all the bortezomib if tolerable. In the transplant context, this may mean considering post-transplant consolidation.
- The published VRd studies[1, 3] utilize a twice-weekly intravenous bortezomib schedule. Vigilance is required to assess for the development of peripheral neuropathy.
- Alternatively, the use of VRd-lite schedule with weekly subcutaneous bortezomib to minimise the risk of peripheral neuropathy could be considered (level 2A evidence, grade B recommendation) but it is important to recognize that such regimens have not been subjected to Phase III comparisons to intravenous twice weekly treatment.
- Lenalidomide is available on the PBS as either (i) 8 x 21 day cycles [14 days of lenalidomide] or (ii) 6 x 28 day cycles [21 days of lenalidomide]. Either dosing schedule is acceptable and expected to achieve equivalent results.
- Lenalidomide at reduced doses (ie. 15mg) should be strongly considered in non-transplant eligible patients to increase tolerability
- As lenalidomide is known to negatively impact on stem cell yield, we suggest early stem cell collection after 2 and no more than 4 cycles of VRd. G-CSF plus cyclophosphamide or plerixafor may be required for stem cell mobilisation.

The principles of treatment of patients with "high risk myeloma" (as defined by R-ISS 3, cytogenetics or novel molecular methods including various gene expression profiles including the validated and EMA/FDA approved SKY92 MMprofiler) remains unchanged as per outlined in section 3.2.3 of the 2019 MSAG clinical practice guideline for myeloma.

VRd for initial treatment

Transplant eligible patients:

For transplant eligible (TE) patients, the incorporation of ASCT upfront even in the era of VRd induction remains the standard of care with proven superiority over a non-transplant approach as per the **IFM2009 study** (4 year PFS 47m (with ASCT) vs. 35m, HR 0.69, p<0.001) [3]. Here, the VRd regimen comprised: bortezomib given as 1.3mg/m2 IV on days 1,4,8,11, lenalidomide 25mg po on days 1-14 and dexamethasone 20mg on days of and days after bortezomib. Stem cell mobilisation was performed after 3 cycles of VRd and was off high-dose cyclophosphamide (3g/m2) prior to ASCT, followed by 2 further cycles of consolidation VRd before lenalidomide maintenance. ORR post ASCT was 99% with a CR rate of 59%.

The efficacy of VRd as induction prior to ASCT was also tested in the phase III **PETHEMA** study which compared melphalan versus busulfan-melphalan conditioning ASCT in 458 patients post 6 cycles of VRd. Here the VRd schedule was given over a 28-day cycle with bortezomib on days 1,4,8,11, lenalidomide 25mg days 1-21 and dexamethasone in pulses of 40mg days 1-4, 9-12. Here stem cells were collected after 3 cycles. Post ASCT, ORR was 81% with CR rate of 44% and an MRD negativity (10-6) of 28.7%.

Peripheral neuropathy was not an uncommon issue with both the IFM2009 and PETHEMA schedules of VRD; grade≥3 peripheral neuropathy occurred in 12.9% of patients in the former, and all grade peripheral neuropathy occurred in 38% in the latter, and resulted in treatment discontinuation in 15% of patients.

In an attempt to improve tolerability, two groups explored different versions of dose attenuated VRd, so called VRd-Lite[5, 6]. The **Japanese study** tested VRd-Lite in an approach that incorporated upfront ASCT [5]. Here, four 28-day cycles of weekly bortezomib (1.3mg/m2 sc D 1,8,15,22) in combination with lenalidomide 25mg orally days 1-21 except on the days of bortezomib and dexamethasone 40mg weekly was given prior to ASCT. ORR was 83% (≥VGPR 48%) after 4 cycles prior to ASCT. Importantly, grade ≥3 peripheral neuropathy was only 3%. Similarly, **Mookerjee** et al.[7] reported a phase III study (abstract publication) of 143 patients, comparing two VRd-lite schedules in cycles of 28 days: Arm A (Bortezomib 1.3 mg/m2 sc on days 1, 8, 15 and 22 with lenalidomide 15mg po days 1-14) and Arm B (Bortezomib 1.3 mg/m2 sc on days 1, 8, 15 and 22 with lenalidomide 25mg po days 1-21). Patients only received 4 cycles of treatment, which induced similar ORR and depth of response between arm A and B (ORR/CR rates 78%/28% and 74%/30%, respectively.)

Of note, the use of a quadruplet regimen containing VRd and cyclophosphamide has also been studied. The phase II EVOLUTION study[8] compared VDCR (bortezomib, dexamethasone, cyclophosphamide and lenalidomide) with triplet regimens of VRd or VCd. No substantial advantage of was noted with VDCR over the triplet regimen but instead, it was associated with modest increase of haematologic toxicity. Thus, we do not recommend regimens that include cyclophosphamide at full dose and any such regimens should be used cautiously.

Lenalidomide but not bortezomib is known to negatively impact stem cell mobilisation.

Stem cell collections post VRd induction in all of the aforementioned studies were performed usually after 3 to 4 cycles of VRd, and were performed with G-CSF (granulocyte-colony stimulating factor) and either high dose cyclophosphamide[3] or plerixafor[5]. Anecdotal successes are known with 'double dose' G-CSF alone when stem cell collections are performed earlier, after 2 or 3 cycles of VRd, however, there has been no studies published on this to date.

For the treatment of transplant eligible patients, the MSAG recommend the following:

- ASCT as part of initial treatment remains the standard of care.
- As the current PBS reimbursement of VRd for TE patients is based on the SWOG SO777 study in which ASCT was not incorporated upfront, the number of funded-bortezomib doses (total 32) is more than what is utilised in any of the aforementioned studies that incorporate upfront ASCT. Drawing from the analogy that that a higher cumulative dose of bortezomib correlates with improved OS in transplant ineligible patients, it is not unreasonable for clinicians to adapt a VRd schedule with upfront ASCT in such as way so as to maximise the use of what is offered on PBS to optimise patients' outcome, provided that there is no unacceptable treatment emergent toxicity. That is, to utilise the remaining doses of bortezomib (with or without lenalidomide) in *consolidation* post ASCT either in a weekly[9] or every two weekly[10] schedule to further deepen response prior to embarking on maintenance lenalidomide monotherapy.
- Subcutaneous route of bortezomib administration is preferred to intravenous to minimise peripheral neuropathy. If a twice-weekly bortezomib schedule is used per the IFM 2009 or PETHEMA studies, vigilance is required for the development of peripheral neuropathy that may occur precipitously post ASCT. Prompt withhold of bortezomib and/or dose reduction is required in the event of grade 3 (CTCAE) peripheral neuropathy particularly upon burning/painful cessation to avoid irreversibility. Alternatively, a weekly schedule of bortezomib (IV or SC) may be adopted at the outset.

VRd for initial treatment

Recommendation for initial therapy for transplant eligible patients:

- The incorporation of ASCT upfront in the current era remains the standard of care (level 1A evidence, grade A recommendation).
  - Triplet combination bortezomib, lenalidomide and dexamethasone (table 1) is reimbursed by the PBS and is considered the current standard of care for induction therapy prior to ASCT (level 1B evidence, grade A recommendation)
    - As the total PBS-reimbursed doses of bortezomib (total 32) is more than what is utilised in published studies that incorporate upfront ASCT, it is not unreasonable for clinicians to adapt a VRd schedule in such as way in induction ± consolidation post ASCT, so as to maximise the use of what is offered on PBS, to optimise patients' outcome, provided that there is no unacceptable treatment emergent toxicity.
    - Subcutaneous route of bortezomib administration is preferred to intravenous to minimise peripheral neuropathy
    - When a twice weekly bortezomib schedule is used, vigilance is required for the development of peripheral neuropathy that may occur precipitously post ASCT.
    - Alternatively, the use of VRd-lite schedule with weekly bortezomib is acceptable to minimise the risk of peripheral neuropathy (level 2A evidence, grade B recommendation)
    - Lenalidomide is available on the PBS as either (i) 8 x 21 day cycles [14 days of lenalidomide] or (ii) 6 x 28 day cycles [21 days of lenalidomide]. Either dosing schedule is acceptable and expected to achieve equivalent results.
    - As lenalidomide is known to negatively impact on stem cell yield, suggest early stem cell collection after 2 and no more than 4 cycles of VRd. GCSF plus cyclophosphamide or plerixafor may be required for stem cell mobilisation.
  - In situations where either bortezomib or lenalidomide is contraindicated, for example, severe peripheral neuropathy or renal impairment, respectively, either can be replaced by cyclophosphamide for an alternative triplet induction regimen prior to ASCT (level 1B evidence, grade A recommendation), table 6A.
  - A quadruplet combination of VRd plus cyclophosphamide is not routinely recommended (level 1B evidence, grade A recommendation)

Transplant ineligible patients:

In general, we believe that VRd should be considered in patients deemed 'fit enough' to receive this regimen. Indeed, in the SWOG S0777 study, a long-term follow up report demonstrated that VRd was superior to Rd with respect of PFS and OS *irrespective of age* (≥65 years or less) or transplant intent. Of note, 31% of patients had no intent for upfront transplant and only 43% (38% in the VRd arm) of patients were age 65 years or older. Indeed, data is lacking regarding the clinical outcome and treatment emergent adverse events (TEAE) of the elderly group of patients over the age of 75 – who are generally considered transplant ineligible based on Australian practice. There is no doubt that VRd is highly efficacious for TIE patients, however, for elderly patients, treatment related toxicities and early treatment cessation is a concern with the twice-weekly schedule of bortezomib as used in SWOG S0777, as these independently correlate with increased mortality [11].

Thus, the choice for clinicians with respect to TIE will be between a modified VRd regimen (eg. VRd-lite) or lenalidomide-dexamethasone alone. It is important to note that for transplant ineligible patients, there have been no studies comparing VRd-lite to lenalidomide and dexamethasone (Rd). Data from the randomised controlled phase III FIRST study remains robust, with Rd inducing high-quality responses with ≥VGPR of 77%, 86%, and 92% of the patients who were treated for >18 months, ≥3 years, and at publication data cutoff, respectively[12]. Median PFS and OS for patients treated with Rd was 26 months and 59 months, respectively.

O'Donnell et al.[6] explored VRd-lite for transplant ineligible patients. Here, 50 patients with a median age of 73 years (65-92) were given nine 35 day cycles of induction bortezomib 1.3mg/m2 subcutaneously on days 1,8,15,22 with low-dose lenalidomide 15mg po days 1-21 and dexamethasone 20mg on the days of and after bortezomib, followed by six 28-day cycles of consolidation consisting of bortezomib 1.3mg/m2 every 2 weeks and lenalidomide 15mg days 1-21 without dexamethasone. After a median follow up of 30 months, best ORR was 86% with ≥VGPR 66% and median PFS was 35.1m. Grade 3 peripheral neuropathy only occurred in 1 patient.

In the treatment of transplant ineligible patients, the MSAG recommend the following. For elderly patients, minimization of treatment related toxicities will improve duration on treatment and correlate with improved survival [11]. As such, robust **frailty assessment** is required for choosing the appropriate induction regimen. The International Myeloma Working Group (IMWG) frailty score[13] is widely accepted, but is cumbersome and may not be conveniently assessed in the clinics. Alternatively, a simplified frailty scale based on ECOG performance status, charlson comorbidity index and age (table 2A+2B) as described by Facon et al[14], can be used to select appropriate induction regimen that balances between tolerability and efficacy.

VRd for initial treatment

If triplet VRd is chosen, the VRd-Lite regimen is deemed less toxic, noting that this has not been tested in phase III randomised studies against Rd. If a patient is deemed fit for the twice weeky bortezomib containing VRd schedule per the SWOG S0777 study, perhaps upfront ASCT ought to be considered. For frail patients, Rd remains one of the standard of care as is doublet Vd, particularly for patients with moderate to severe renal impairment.

Of note, In Australia, there are two national studies that are still accruing for initial treatment of transplant-ineligible patients:

1. The AMaRC 19-02/ALLG-MM22, FRAIL-M study (anzctr.org.au; ACTRN12619001199101) testing VRd-lite vs. Vd vs. Rd, and
2. The AMaRC 18-02, IRIL study (anzctr.org.au; ACTRN12619000362190) testing the addition of isatuximab to patients who have not achieved CR by 9 cycles of Rd (patients need to be enrolled prior to completion of cycle 4 of Rd).

Where ever possible, patients ought to be enrolled in a clinical study if available.

Recommendation for initial therapy for transplant ineligible patients:

- In elderly patients, minimization of treatment related toxicities will improve duration on treatment and correlate with improved survival.
    - frailty assessment is recommended in choosing the appropriate induction regimen (Table 2A+2B)
- The current accepted standard of care for initial treatment of TIE patients with MM include:
    - Enrolment into a clinical study if one is available.
    - Continuous lenalidomide and dexamethasone (Rd) (Level 1B evidence, grade A recommendation)
    - VRd:
        - If a patient is deemed fit for the twice weekly bortezomib containing VRd schedule per the SWOG S0777 study, upfront ASCT ought to be considered
        - VRd-lite with weekly subcutaneous bortezomib appears to have comparable efficacy with reduced toxicity but have only been tested in phase II studies and have not been compared to Rd.
    - For frail elderly patients with renal impairment, doublet bortezomib and dexamethasone could be considered (level 1B evidence, grade B recommendation)

VRd for initial treatment

Table 1: Bortezomib, Lenalidomide and Dexamethasone Schedules incorporating upfront ASCT

REGIMEN	SCHEDULE	OUTCOME	COMMENTS
VRD – FULL DOSE			
IFM 2009[3] (phase III RCT comparing VRd with or without ASCT as part of upfront treatment)	**Induction:** 21-day VRd cycle: Bor 1.3mg/m^2 IV D1,4,8,11 Len 25mg po D1-14 Dex 20mg D1,2,4,5,8,9,11,12 • Three 21-day VRd cycles then • cyclophosphamide 3g/m^2 stem cell mobilisation, then • Mel200 ASCT then • two 21-day VRd consolidation cycles then R maintenance. **R maintenance:** Twelve 28-day cycle. Len 10mg (15mg if tolerated from cycle 4) po D1-28	Superior PFS with the ASCT approach; 4yr PFS 47m vs. 35m (HR 0.69), p<0.001 59% ORR post ASCT 99%; CR rate 59% Grade ≥3 peripheral neuropathy 12.9% 11% in the transplant group stopped treatment due to adverse events.	MSAG recommends: - Sc bortezomib is preferential to IV route of administration to minimise peripheral neuropathy -Caution of peripheral neuropathy with the twice weekly bortezomib schedule.
PETHEMA [15] (phase III RCT comparing Mel vs. BulMel condition for ASCT in patients post VRd induction.	**Induction:** 28-day VRd cycle: Bor 1.3mg/m^2 IV D1,4,8,11 Len 25mg po D1-21 Dex 40mg days 1-4, 9-12. • Three 28-day VRd cycles then • stem cell mobilisation (86% patients collected off G-CSF alone, 12% plerixafor and 2% cyclophosphamide. • 2 VRd consolidation cycles then • Lenalidomide maintenance. **Lenalidomide maintenance:** Twelve 28-day cycle. Len 10mg (15mg if tolerated from cycle 4) po D1-28	Post ASCT: ORR 91% CR rate of 44% MRD negative rate (10^{-6}) 42% Any grade peripheral neuropathy (PN) 38% PN (14.6%) was the most common treatment emergent adverse event (TEAE) leading to bortezomib dose reduction during induction. 18% of patients had at least one AE leading to dose reduction of bortezomib	

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VRd for initial treatment

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REGIMEN	SCHEDULE	OUTCOME	COMMENTS
VRD-LITE			
Okazuka et al. [5] (phase II study of VRd-Lite induction prior to ASCT)	**Induction:** 28-day VRd cycles: Bor 1.3mg/m^2 sc D 1,8,15,22 Len 15mg po D1-21 (omit on days of Bor) Dex 40mg D1,8,15,22 • Four 28-day cycles of VRd then • GCSF + plerixafor or cyclophosphamide stem cell mobilisation then • MEL200 ASCT.	N=48 (TE patients) After 4 cycles induction ORR 83%, ≥VGPR 48% Gde 3 PN 2%.	In TE patients, VRd-Lite has never been compared to VRd. However, phase II studies have shown good efficacy with low level of PN.
Mookerjee et al. [7]	**Induction:** 28-day VRd cycles: Bortezomib 1.3 mg/m2 SC on days 1, 8, 15 and 22 Len (arm A or b) A: 15mg/day from day 1 to 14 B: 25 mg/day from day 1 to 21 **(no mention of subsequent treatment post 4 induction cycles)**	No difference in ORR and PFS between arm A+B, after 4 cycles. Arm A: ORR 78%, ≥CR 28% Arm B: ORR 74%, ≥CR 30%,	

Table 2: Bortezomib, Lenalidomide and Dexamethasone Schedules NOT incorporating upfront ASCT

REGIMEN	SCHEDULE	OUTCOME	COMMENTS
VRD – FULL DOSE			
SWOG SO777[1, 2] (phase III RCT)	**Induction:** Eight 21-day VRd cycle: Bor 1.3mg/m2 IV D1,4,8,11 Len 25mg po D1-14 Dex 20mg D1,2,4,5,8,9,11,12 followed by **Rd maintenance**: 28-day cycle. Len 25mg po D1-21 Dex 40mg po D1,8,15,22 Until disease progression.	Superior PFS + OS with VRD vs. Rd in a group of mainly transplant eligible patients. Med PFS 41m vs. 29 m, HR 0.74, p = 0.003 Med OS NR vs. 69m, HR=0.7, p = 0.011	MSAG recommends: - subcutaneous bortezomib is preferential to intravenous route of administration to minimise peripheral neuropathy -caution of peripheral neuropathy with the twice weekly bortezomib schedule. -If a patient is deemed suitable for the schedule as outlined in this SWOG-SO777 study, consider incorporating upfront ASCT.
VRD-LITE			
O'Donnell et al.[6] (Phase II) Transplant-ineligible patients	**Induction:** Nine 35-day cycles of: Bor 1.3mg/m^2 sc D 1,8,15,22 Len 15mg po D1-21 Dex 20mg D1,2,8,9,16,16,22,23 Followed by **consolidation:** Six 28-day cycles of: Bor 1.3mg/m^2 D1,15 Len 15mg po D1-21	N=50 (TIE patients) ORR 86%, ≥VGPR 66% Med PFS 35.1m after med follow up of 30m. Grade 3 peripheral neuropathy in 1 patient.	

Table 2A: Simplified Frailty Scale.

Category	Score
Age	
≤75 years	0
76-80 years	1
>80 years	2
Charlson Comorbidity Index	
≤1	0
>1	1
ECOG performance status	
0	0
1	1
≥2	2
Sum of scores	
Nonfrail	0 – I
Frail	≥2

ECOG Eastern Cooperative Oncology Group,
IMWG International Myeloma Working Group

Table 2B: Charlson comorbidity index[16]

CCI Weight	Comorbid conditions
0	No comorbid conditions
1	Heart attack (myocardial infarction) Peripheral arterial disease Other diagnosed heart problems Stroke Asthma Ulcer disease Insulin-dependent diabetes Arthritis
2	Renal disease/kidney stones Diagnosed cancer
3	Cirrhosis

1. Durie, B.G., 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**(10068): p. 519-527.
2. Durie, B.G.M., et al., *Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT).* Blood Cancer J, 2020. **10**(5): p. 53.
3. Attal, M., et al., *Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma.* N Engl J Med, 2017. **376**(14): p. 1311-1320.
4. Bergin, K., et al., *Myeloma in the Real World: What Is Really Happening?* Clin Lymphoma Myeloma Leuk, 2017. **17**(3): p. 133-144 e1.
5. Okazuka, K., et al., *The efficacy and safety of modified bortezomib-lenalidomide-dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma.* Eur J Haematol, 2020. **104**(2): p. 110-115.
6. O'Donnell, E.K., et al., *A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma.* Br J Haematol, 2018. **182**(2): p. 222-230.
7. Mookerjee, A., et al., *Bortezomib, Lenalidomide and Low-Dose Dexamethasone (VRD) Versus Lenalidomide and Low-Dose Dexamethasone (Ld) for Newly-Diagnosed Multiple Myeloma- a Randomized Phase III Study.* Blood, 2017. **130**: p. 906.
8. Kumar, S., et al., *Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma.* Blood, 2012. **119**(19): p. 4375-82.
9. Cohen, O.C., et al., *Bortezomib consolidation post-ASCT as frontline therapy for multiple myeloma deepens disease response and MRD-negative rate whilst maintaining QOL and response to re-treatment at relapse.* Br J Haematol, 2019. **185**(5): p. 948-951.
10. Sivaraj, D., et al., *Outcomes of Maintenance Therapy with Bortezomib after Autologous Stem Cell Transplantation for Patients with Multiple Myeloma.* Biol Blood Marrow Transplant, 2017. **23**(2): p. 262-268.
11. Bringhen, S., et al., *Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials.* Haematologica, 2013. **98**(6): p. 980-7.
12. Facon, T., et al., *Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma.* Blood, 2018. **131**(3): p. 301-310.
13. Palumbo, A., et al., *Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report.* Blood, 2015. **125**(13): p. 2068-74.
14. Facon, T., et al., *A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial.* Leukemia, 2020. **34**(1): p. 224-233.
15. Rosinol, L., et al., *Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplant in multiple myeloma.* Blood, 2019. **134**(16): p. 1337-1345.
16. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.