



Codes ATC: L01XG01

Indication	Plasma cell myeloma Code ICD11: 2A83.1
INN	Bortezomib
Type de médicament	Chemical agent
Type de liste	Liste complémentaire
Formulations	Parenteral > General injections > unspecified: 3.5 mg in vial powder for injection
Historique des statuts LME	Ajouté pour la première fois en 2019 (TRS 1021)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.

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Recommandation du comité d'experts

The Committee acknowledged the treatment of MM to be complex and recognized the need to provide the best available care within the context of both non-transplant and transplant settings. The Committee recommended the addition of bortezomib, lenalidomide and thalidomide to the complementary list of the EML for the treatment of multiple myeloma patients in both non-transplant and transplant eligible/available settings, on the basis of good evidence showing large improvement in survival outcomes with acceptable safety for patients with newly diagnosed multiple myeloma. With regard to MM treatment in transplant-eligible populations, the Committee noted the additional evidence presented as part of the review process supporting standard regimens used in the induction phase before ASCT involving three-drug combinations: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone) and RVD (lenalidomide, bortezomib, dexamethasone); and of the benefit of lenalidomide maintenance therapy following ASCT. In the non-transplant setting, the Committee acknowledged that the proposed medicines are administered as part of treatment regimens involving companion cytotoxic agents and/or steroids (melphalan, cyclophosphamide, prednisone, dexamethasone). Accordingly, the Committee recommended the addition of melphalan to the complementary list of the EML for treatment of multiple myeloma, and that the current listings for cyclophosphamide, doxorubicin, prednisone and dexamethasone be extended to include multiple myeloma as an indication.

Contexte

The application requested the addition of bortezomib, lenalidomide and thalidomide to the EML for the treatment of newly diagnosed multiple myeloma patients in non-transplant settings. Treatments for multiple myeloma had not previously been

considered by the Expert Committee for addition to the EML. [Abbreviations: M = melphalan, P = prednisone, C = cyclophosphamide, D = dexamethasone, V = bortezomib, R = lenalidomide, T = thalidomide].

Pertinence pour la santé publique

Multiple myeloma (MM) is the second most common haematological malignancy and accounts for 2.1% of all cancer deaths in the United States (1, 2). In 2018, 159 985 new MM cases and 106 105 MM deaths were estimated worldwide (3). Globally, myeloma caused 2.1 million disability-adjusted life-years (DALYs) in 2016 (4). Globally, the incidence rate increased by 126% between 1990 and 2016 and is strongly related to age (4, 5). The largest increase has been observed in low- and middle-income countries (LMICs) (4). Based on the latest statistics in the United States, the median age of myeloma diagnosis across all races and both genders is 69 years (2). In high-income countries (HIC), autologous stem cell transplantation (ASCT) is routinely used for younger patients with a good general state of health. However, ASCT is not available in many LMICs (3). Lack of access to general and specialized health care leads to wide disparities in survival rates between HICs and LMICs. In the United Kingdom, for example, 47% of diagnosed MM patients are predicted to survive at least five years (32.5% at least 10 years) (5). In comparison, a five-year survival rate of only 7.6% was recently reported in Nigeria, as a result of constraints in access to ASCT, unavailability of medicines for MM and delayed diagnosis with more advanced presentations and related organ failures (6). Of patients diagnosed with MM in Nigeria, up to one-third qualify for renal dialysis as a result of MM-related end-stage nephropathy (7). In non-transplant settings (no transplant-accessibility or transplantineligibility), the introduction of immunomodulatory drugs and proteasome inhibitors has led to an improvement in the overall survival of patients. A retrospective analysis of 631 patients, who received an initial therapy of bortezomib, lenalidomide or thalidomide, reported a median OS of 7.3 years (95%CI 5.9 to not reached). In comparison, a median OS of 3.8 years (95%CI 3.1 to 4.6) was reported for 425 patients, whose initial therapy did not include these agents (8). The lack of availability ASCT services is more common in LMICs. Some regions of the world lack access to stem cell transplantation entirely; for example, in sub-Saharan Africa there is no facility to deliver ASCT care for MM patients outside of South Africa (4). This raises the issue of a public health urgency requiring diversified actions including ensuring access to effective medicines, and building capacity for transplant services. The application focused on the transplant-ineligible/inaccessible setting, more applicable in LMICs, proposing the inclusion in the EML of bortezomib, lenalidomide and thalidomide to address an unmet medical need.

Bénéfices

The application presented the findings of a rapid Cochrane network meta-analysis conducted to compare the efficacy and safety of bortezomib, lenalidomide and thalidomide versus the former standard treatment of melphalan and prednisone (still used in many LMICs) for transplant-ineligible MM patients. Twenty-six randomized controlled trials (11 403 participants) were eligible for inclusion in the NMA: (Myeloma XI (9), EMN01 (10), FIRST (11), ECOG E1A06 (12), MM-015 (13), HOVON 87 (14), Myeloma IX (15), GBRAM0002 (16), Kim 2007 (17), Ludwig 2009 (18), TMSG (19), HOVON 49 (20), IFM 99-06 (21), GISMM2001-A (22), MM03 (23), IFM 01/01 (24), NMSG #12 (25), Katsuka 2013 (26), UPFRONT (27), VISTA (28), GEM2005 (29), Mookerje 2017 (30), SWOG S0777 (31), E1A05 (32), GIMEMA-MM-03-05 (33), NCT01274403 (34)). Included participants were randomized to 21 different treatment regimens involving fixed or continuous therapy with combination regimens involving melphalan (M), prednisone (P), cyclophosphamide (C), dexamethasone (D), bortezomib (V), lenalidomide (R) and thalidomide (T). Overall survival was measured for all 21 treatment regimens and a total of 11 071 patients. The network was not fully connected and consisted of three subnetworks comprising 30 pairwise comparisons. Compared to MP, four regimens showed a significant, clinically meaningful improvement in overall survival: Continuous VRDc (bortezomib, lenalidomide, dexamethasone) (HR 0.49, 95%CI 0.26 to 0.92), continuous VTMPc (bortezomib, thalidomide, melphalan, prednisone) (HR 0.49, 95%CI 0.26 to 0.93), fixed RD (HR 0.63, 95%CI 0.40 to 0.99), and fixed TMP (thalidomide, melphalan, prednisone) (HR 0.75, 95%CI 0.58 to 0.97). The estimated differences in median OS compared to MP were 37.4 months for VRDc and VTMPc, 21.1 months for RD and 12.0 months for TMP. The confidence in estimates for overall survival could be rated for RD, TMP, VMP, and VRDc. The use of RD, TMP, and VRDc for first-line treatment of multiple myeloma patients likely results in a large increase in overall survival (moderate confidence in estimates). The use of VMP as initial myeloma therapy may result in a large increase in overall survival (low confidence in estimates). The clinical benefit of the treatments was assessed in the application according to the ESMO-MCBS v1.1 (35). The application graded the magnitude of clinical benefit as 4 (survival benefit compared to comparator >nine months (36)) for VRDc, VTMPc, RD, RDc, VMP, RCPc and TMP. The Committee noted that to date, the ESMO-MCBS v1.1 has been validated only for solid tumours and that a version validated for haematological malignancies is in development. (Unpublished data of ESMO-MCBS ratings for the proposed

medicines were shared with the Expert Committee). Progression-free survival (PFS) was measured for all 21 treatment regimens and a total of 10 389 patients. The network was not fully connected and consisted of four sub-networks comprising 29 pairwise comparisons. In general, continuous treatment regimens were superior to fixed MP, and 7 out of 11 compared bortezomib, lenalidomide or thalidomide combinations showed a significant improvement of PFS compared to MP. The confidence in estimates for PFS could be rated for RD, TMP, and VRDc, but could not be rated for VMP, because VMP was not connected to MP in the network. The use of RD, TMP, and VRDc for first-line treatment of MM patients likely results in a large increase in PFS (moderate confidence in estimates).

Torts

regimens in 3318 patients, however the studies were not comparable in NMA. Serious adverse events (SAEs) were reported in eight studies for 14 treatment regimens in 7306 patients. The relative risk (RR) for at least one SAE was similar across treatment regimens. The confidence in estimates could only be rated for VMP. There was moderate confidence in the estimates that VMP likely increases occurrence of SAEs (RR 1.28, 95%CI 1.06 to 1.54). Infections were reported in 15 studies for 17 treatment regimens in 7470 patients. The RR for infections tended to be slightly higher for patients receiving lenalidomide-based therapies compared to patients receiving thalidomidebased therapies. The RR for infections was also significantly higher in patients receiving continuous therapies compared to fixed MP. Polyneuropathies were reported in 18 studies for 19 treatment regimens in 8978 patients. The RR for polyneuropathies was the highest in patients receiving bortezomib-based therapies compared to MP (RR 88.22, (95%CI 5.36 to 1451.11) to 441.08 (95%CI 7.74 to 25 145.52)). The RR for polyneuropathy appeared to be smaller for patients receiving lenalidomide-based therapies, compared to patients receiving thalidomide-based therapies. Thromboembolism was analysed from 13 studies for 13 treatment regimens in 4 277 patients. The RR for thromboembolism was higher for patients receiving continuous therapy compared to fixed duration MP (RR 3.91, (95%CI 0.41 to 37.12) to 13.09 (95%CI 1.03 to 167.25)). Patients receiving a thalidomidebased therapy had a greater risk for thromboembolism compared to patients receiving bortezomib- or lenalidomide-based therapies, or MP. Withdrawals due to adverse events were reported in 16 studies for 19 treatment regimens in 7 052 patients. The RR to discontinue assigned therapy was greater for patients receiving double or triple drug combinations compared to MP alone (RR 1.06, (95%CI 0.63 to 1.81) to 8.92 (95%CI 3.82 to 20.84)). Study withdrawal was similar across bortezomib-, lenalidomide-, and thalidomide-based regimens. There was no difference between double versus triple drug combinations, or between fixed duration versus continuous therapy. The confidence in estimates for withdrawals due to AEs was rated for RD, TMP, VMP, and VRDc. Compared to MP, use of RD, TMP, and VRDc results in a large increase in withdrawals due to AEs (high confidence in estimates). Use of VMP probably results in little or no difference in withdrawals due to AEs (moderate confidence in estimates).

Preuves supplémentaires

The Committee also considered additional evidence, not presented in the application, for the treatment of MM in the ASCT-eligible/accessible settings. The standard treatment for ASCT-eligible MM patients involves induction therapy followed by high-dose melphalan and ASCT with lenalidomide maintenance. A meta-analysis of four studies (1572 patients) compared bortezomibbased induction therapy prior to ASCT with non-bortezomib-based induction therapy. The studies compared bortezomib-dexamethasone with vincristinedoxorubicin- dexamethasone (IFM 2005-01 trial); bortezomib-doxorubicindexamethasone with vincristine-doxorubicin-dexamethasone (HOVON-65); and bortezomib-thalidomide-dexamethasone with thalidomide-dexamethasone (PETHEMA GEM05MENOS65 and GIMEMA MM-BO2005). The bortezomibbased therapies were associated with longer PFS (+7.3 months; HR 0.75), longer OS (+5% at 3 years, HR 0.80) and greater activity (complete response rates: +14%, OR 2.05), compared to non-bortezomib-based therapies. Peripheral neuropathy was reported more frequently in bortezomib treated patients compared to non-bortezomib treated patients: 19% vs 7% (all Grade), and 3.3% vs 2% (\geq Grade 3) (37). A randomized controlled trial involving 525 patients with newlydiagnosed MM evaluated the efficacy and safety of the addition of bortezomib to lenalidomide and dexamethasone (SWOG S0777). Findings were consistent with the thalidomide-containing regimens: the addition of bortezomib to lenalidomide-dexamethasone was associated with gains in both PFS (+13 months, HR 0.71) and OS (+11 months, HR 0.71). Adverse events of Grade 3 or higher, and treatment discontinuations were also more common in the bortezomib-treated group (38). The Committee also considered the role of lenalidomide after ASCT, as maintenance up to relapse and maximal tolerance. A meta-analysis of three RCTs (CALGB/Alliance 100104 study, IFM 2005-02 Trial and the Italian GIMEMA RV-MM-PI-209) involving 1208 patients evaluated the effect of lenalidomide maintenance after ASCT in newly diagnosed MM. Lenalidomide maintenance demonstrated a significant gain in both

PFS and OS: PFS in patients receiving lenalidomide was 29.3 months longer (HR 0.48, 95%CI 0.41 to 0.55). The 7-year survival rate was 62% with lenalidomide maintenance and 50% with placebo or observation (HR 0.75, 95%CI 0.63 to 0.90). The use of lenalidomide resulted in more major adverse events than placebo. In particular, an increased risk of secondary malignancies was observed, 6.1% vs 2.8% with placebo/ no maintenance (39). The long-term follow-up data of CALGB (Alliance) 100104 study showed a meaningful and significant OS gain in patients receiving lenalidomide maintenance. After three interim analyses, the study was unblinded at a median follow-up of 18 months, at which point 86 (67%) of 128 patients without progressive disease in the placebo group chose to cross over to the lenalidomide group. The analysis of survival on the intention-to-treat population demonstrated an increase in 3-year OS of 8%, with 88% (95%CI 84 to 93) among patients in the lenalidomide group and 80% (95%CI 74 to 86) among patients in the placebo group (HR 0.62, 95%CI 0.40 to 0.95) (40). The Myeloma XI study more recently provided results consistent with the previous clinical trials of lenalidomide maintenance, confirming a gain in median PFS (39 months vs 20 months; HR 0.46, 95%CI 0.41 to 0.53; $p < 0.0001$) but not in OS (78.6% vs 75.8%; $p = 0.15$). The analysis was published at 31 months of median follow up (41). Notably, mature data for OS in ASCT-eligible settings require long-term follow up. For this reason, PFS and myeloma response rates have been agreed as valuable surrogate endpoints for OS and PFS is used as primary endpoint to assess the benefit of anti-myeloma medicines (42).

Rapport coût/efficacité

The application summarized the findings of a scoping review undertaken for economic evidence that addressed treatment regimens based on bortezomib, thalidomide or lenalidomide as first-line therapy in MM. The scoping review identified two cost-analyses (43, 44), one cost-impact analysis (45) and one retrospective study of claims data (46). Also identified was a health technology assessment report by the National Institute for Health and Care Excellence (NICE) (47). Reported incremental cost-effective ratios in the NICE technology appraisal ranged from £ 2234 per quality adjusted life year (QALY) to over £ 300 000, compared to MP depending on the intervention (47). A United States cost-analysis found the monthly on-treatment costs (drug cost, medical costs and AE management costs) were lowest for MP alone and highest for MPT. The total cost over 20 years for treatment with VMP and MPT were almost or over twice as high than with MP alone. Compared to VMP, MP was more effective with regard to costs per life-year and cost per QALY, while compared to MPT, VMP was cost-saving (44). A cost-impact model addressed the total costs associated with first-line treatment of newly diagnosed MM who were ineligible for stem cell transplant in France, Germany, Italy, Spain and the United Kingdom, modelled over five years. Three scenarios were evaluated and compared. A baseline-scenario represented the 2017 uptake of lenalidomide in the assessed countries. The market shares in this scenario were 64% for bortezomib, 25% for thalidomide and 11% for lenalidomide. The second scenario involved a steady increase of the uptake of lenalidomide to 50% of the market in year five. The third scenario evaluated a 20% increased uptake of the triple regimen carfilzomib, lenalidomide, and dexamethasone as a second-line of treatment. Direct drug costs were averaged from the listing prices across the five countries. The assumed annual treatment costs for the baseline scenario ranged between € 40 692 and € 40 781 per patient per year, while the total costs for an increased uptake of lenalidomide ranged between € 41 559 and € 44 139 per patient per year. The difference between both situations rose relatively steady from 2.13% of the total cost of the baseline scenario in year one to 8.23% of the baseline scenario in year five. Across all three scenarios the total treatment cost in the fifth year of treatment were lowest for the baseline scenario. For the increased uptake of lenalidomide in first-line therapy, the annual costs per patient in year five were € 44 139. For the 20% uptake of the triplet regimen as second-line treatment, the total increase in year five in total cost per patient and year was € 52 528 (45). A retrospective study based on United States claims data from 2006 to 2013 assessed patient monthly direct costs and cost patterns over quarterly time periods for patients with newly diagnosed MM treated with either bortezomib or lenalidomide based regimens. Costs were evaluated for 444 patients with newly diagnosed MM treated first-line with lenalidomide and 737 with bortezomib, for which data from treatment initiation until next treatment was available. For patients with first-line treatment with lenalidomide, the monthly treatment cost decreased steadily from US\$ 15 090 in the first to the third month since start of treatment to US\$ 5266 in month 19 or longer. In patients treated with firstline bortezomib the monthly costs fell from US\$ 16 126 in the first three months of treatment to US\$ 4833 in the 19th month or longer. Multivariable regression unadjusted for factors such as age, sex, number of prescriptions before index date for the beginning of first-line treatment, previous cancer history, etc. showed mean total cost of US\$ 7534 (standard deviation (SD) 3207) for patients treated first-line with lenalidomide, compared to US\$ 10 763 (SD 3938) in patients receiving first-line bortezomib. Monthly pharmacy costs included in the total monthly cost in the unadjusted analysis were US\$ 4101 (SD 1931) and US\$ 4855 (SD 2431) for lenalidomide and bortezomib, respectively (46).

Directives de l'OMS

None available.

Disponibilité

Bortezomib, lenalidomide and thalidomide have worldwide regulatory approval for use in the treatment of MM. Originator and generic brands of all three medicines are available.

Autres considérations

Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it supported the inclusion of these medicines on the EML. The technical unit noted that use of these medicines is either as part of preautologous stem cell transplantation treatment in fit patients, or as an alternative treatment in transplant-ineligible patients, although the difference in transplant eligible and ineligible patients was not addressed in the application.

1. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. *Semin Oncol.* 2016;43(6):676–81.
2. Cancer Stat Facts: Myeloma. Bethesda: National Cancer Institute; 2018. Available from: <https://seer.cancer.gov/statfacts/html/mulmy.html>, accessed 29 September 2019.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424.
4. Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP et al. Global Burden of Multiple Myeloma: A Systematic Analysis of the Global Burden of Disease Study 2016. *JAMA oncology.* 2018; 4(9):1221–1227.
5. Myeloma statistics 2018. London: Cancer Research UK; 2018. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma>, accessed 29 September 2019.
6. Nwabuko OC, Igbigbi EE, Chukwuonye, II, Nnoli MA. Multiple myeloma in Niger Delta, Nigeria: complications and the outcome of palliative interventions. *Cancer Manag Res.* 2017;9:189–96.
7. Madu AJ, Ocheni S, Nwagha TA, Ibegbulam OG, Anike US. Multiple myeloma in Nigeria: an insight to the clinical, laboratory features, and outcomes. *Niger J Clin Pract.* 2014;17(2):212–7.
8. Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia.* 2014;28(5):1122–8.
9. Pawlyn C, Davies F, Cairns D, Striha A, Best P, Sigsworth R et al. Continuous treatment with lenalidomide improves outcomes in newly diagnosed myeloma patients not eligible for autologous stem cell transplant: results of the myeloma xi trial. *Blood Conference: 59th annual meeting of the american society of hematology, ASH 2017 United States.* 2017;130(Supplement 1).
10. Magarotto V, Brinchen S, Offidani M, Benevolo G, Patriarca F, Mina R et al. Triplet vs doublet lenalidomide-containing regimens for the treatment of elderly patients with newly diagnosed multiple myeloma. *Blood.* 2016;127(9):1102–8.
11. Bahlis N, Corso A, Mugge L, Shen Z, Desjardins P, Stoppa A et al. Benefit of continuous treatment for responders with newly diagnosed multiple myeloma in the randomized FIRST trial. *Leukemia.* 2017;31(11):2435–42.
12. Stewart AK, Jacobus S, Fonseca R, Weiss M, Callander NS, Chanan-Khan AA et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. *Blood.* 2015;126(11):1294–301.
13. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. [Erratum appears in *N Engl J Med.* 2012 Jul 19;367(3):285]. *N Engl J Med.* 2012;366(19):1759–69.
14. Zweegman S, Holt B, Mellqvist U, Salomo M, Bos G, Levin M et al. Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. *Blood.* 2016;127(9):1109–16.
15. Morgan G, Davies F, Gregory W, Russell N, Bell S, Szubert A et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. *Blood.* 2011;118(5):1231–8.
16. Hungria V, Crusoe E, Maiolino A, Bittencourt R, Fantl D, Maciel J, et al. Phase 3 trial of three thalidomide-containing regimens in patients with newly diagnosed multiple myeloma not transplant-eligible. *Ann Hematol.* 2016;95(2):271–8.
17. Kim Y, Lee J, Sohn S, Shin H, Lee S, Shim H et al. Efficacy and safety of thalidomide and dexamethasone combination with or without cyclophosphamide in patients with newly diagnosed multiple myeloma. *Haematologica.* 2007;92(Suppl 1):411–2.
18. Ludwig H, Hajek R, Tothova E, Drach J, Adam Z, Labar B et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood.* 2009;113(15):3435–42.
19. Beksac M, Haznedar R, Firatli-Tuglular T, Ozdogu H, Aydogdu I, Konuk N et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: results of a randomized trial from the Turkish Myeloma Study Group. *Eur J Haematol.* 2011; 86(1):16–22.
20. Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H 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(19):3160–6.
21. Facon T, Mary J, Hulin C, Benboubker L, Attal M, Pegourie B 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(9594):1209–18.
22. Palumbo A, Brinchen S, Caravita T, Merla E, Capparella V, Callea V et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. *Lancet.* 2006;367(9513):825–31.
23. Sacchi S, Marcheselli R, Lazzaro A, Morabito F, Fragasso A, Di Renzo N et al. A randomized trial with melphalan and prednisone versus melphalan and prednisone plus thalidomide in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplantation. *Leuk Lymphoma.* 2011;52(10):1942–8.
24. Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol.* 2009; 27(22):3664–70.
25. Waage A, Gimsing P, Fayers P, Abildgaard N, Ahlberg L, Björkstrand B et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. *Blood.* 2010;116(9):1405–12.
26. Katsuo Y, Kato Y, Omoto E, Sasaki O, Kimura H, Meguro K et al. Phase II trial of bortezomib based regimen for transplant-ineligible multiple myeloma-tomato study. *Clinical lymphoma, myeloma and leukemia.* 2013;13:S148.
27. Niesvizky R, Flinn I, Rifkin R, Gabrail N, Charu V, Clowney B et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. *J Clin Oncol.* 2015;33(33):3921–9.

28. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med*. 2008;359(9):906–17.
29. Mateos MV, Oriol A, Martinez-Lopez J, Gutierrez N, Teruel AI, de Paz R et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol*. 2010;11(10):934–41.
30. Mookerjee A, Gupta R, Jasrotia S, Sahoo R, Kumar R, Thulkar S 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(Supplement 1).
31. Durie GM, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP 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):519–527.
32. Jacobus SJ, Rajkumar SV, Weiss M, Stewart AK, Stadtmauer EA, Callander NS et al. Randomized phase III trial of consolidation therapy with bortezomib-lenalidomide-Dexamethasone (VRd) vs bortezomib-dexamethasone (Vd) for patients with multiple myeloma who have completed a dexamethasone based induction regimen. *Blood Cancer J*. 2016;6(7):e448.
33. Palumbo A, Brinchen S, Larocca A, Rossi D, Di Raimondo F, Magarotto V 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(7):634–40.
34. A Randomized Study With Oral Melphalan + Prednisone (MP) Versus Melphalan, + Prednisone + Thalidomide (MPT) for Newly Diagnosed Elderly Patients With Multiple Myeloma [Internet]. Bethesda: National Library of Medicine (ClinicalTrials.gov); 2011. Available from <https://clinicaltrials.gov/ct2/show/NCT01274403>, accessed 29 September 2019.
35. ESMO-Magnitude of Clinical Benefit Scale. The ESMO-MCBS Score Card [website]. Lugano: European Society for Medical Oncology. (<https://www.esmo.org/score/cards>, accessed 29 September 2019).
36. ESMO Magnitude of Clinical Benefit Scale v1.1. Form 2a: for therapies that are not likely to be curative with primary endpoint of OS 2018. Lugano: European Society for Medical Oncology. Available from <https://www.esmo.org/content/download/117388/2059152/file/ESMO-MCBS-Version-1-1-Evaluation-Form-2a-OS-24-Months.pdf>, accessed 29 September 2019.
37. Sonneveld P, Goldschmidt H, Rosinol L, Blade J, Lahuerta JJ, Cavo M et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. *J Clin Oncol*. 2013;31(26):3279–87.
38. Durie BG, Hoering A, Abidi MH, Rajkumar SV, Epstein J, Kahanic SP 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):519–27.
39. McCarthy PL, Holstein SA, Petrucci MT, Richardson PG, Hulin C, Tosi P et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. *J Clin Oncol*. 2017;35(29):3279–89.
40. Holstein SA, Jung SH, Richardson PG, Hofmeister CC, Hurd DD, Hassoun H 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(9):e431–e42.
41. Jackson GH, Davies FE, Pawlyn C, Cairns DA, Striha A, Collett C et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2019;20(1):57–73.
42. Committee for Medicinal Products for Human Use (CHMP). Guideline on the use of minimal residual disease as a clinical endpoint in multiple myeloma studies (EMA/CHMP/459559/2018). Amsterdam: European Medicines Agency; 2018. Available from https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies_en.pdf, accessed 29 September 2019.
43. Picot J, Cooper K, Bryant J, Clegg AJ. The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation. *Health Technol Assess*. 2011;15(41):1–204.
44. Garrison LP, Jr., Wang ST, Huang H, Ba-Mancini A, Shi H, Chen K et al. The cost-effectiveness of initial treatment of multiple myeloma in the U.S. with bortezomib plus melphalan and prednisone versus thalidomide plus melphalan and prednisone or lenalidomide plus melphalan and prednisone with continuous lenalidomide maintenance treatment. *Oncologist*. 2013;18(1):27–36.
45. Schey S, Montero LFC, Stengel-Tosetti C, Gibson CJ, Dhanasiri S. The Cost Impact of Lenalidomide for Newly Diagnosed Multiple Myeloma in the EU5. *Oncol Ther*. 2017;5(1):31–40.
46. Arikian SR, Milentijevic D, Binder G, Gibson CJ, Hu XH, Nagarwala Y et al. Patterns of total cost and economic consequences of progression for patients with newly diagnosed multiple myeloma. *Curr Med Res Opin*. 2015;31(6):1105–15.
47. Bortezomib and thalidomide for the first-line treatment of multiple myeloma. Technology appraisal guidance [TA228]. London: National Institute for Health and Care Excellence; 2011. Available from <https://www.nice.org.uk/guidance/ta228>, accessed 29 September 2019.

