All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA228)

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Final Appraisal Report:

Thalidomide (Thalidomide Pharmion®▼) in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy

Celgene Ltd

Advice No: 0109 – February 2009

Recommendation of AWMSG

Thalidomide (Thalidomide Pharmion®▼) is recommended for use within NHS Wales in combination with melphalan and prednisone* as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

It should only be prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

AWMSG is of the opinion that Thalidomide (Thalidomide Pharmion®▼) is not suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday 25th February 2009

The recommendation of AWMSG is:

Thalidomide (Thalidomide Pharmion®▼) is recommended for use within NHS Wales in combination with melphalan and prednisone* as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

It should only be prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

AWMSG is of the opinion that Thalidomide (Thalidomide Pharmion®▼) is not suitable for shared care within NHS Wales.

> ***** *The licence and trials specify the use of prednisone. This is not available in the UK, where a direct substitution of prednisolone for prednisone is made as they are considered dose-equivalent* †.

† Sweetman S (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version, Thomson Micromedex, Greenwood Village, Colorado, USA. Available at: http://www.thomsonhc.com (cited: *27/01/2009)*

2.0 PRODUCT DETAILS

2.1 Licensed indication

Thalidomide (Thalidomide Pharmion®▼) is licensed for use in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma (MM), aged ≥ 65 years or ineligible for high dose chemotherapy[1].

Thalidomide Pharmion®▼ is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme[1] (see section 10.1).

2.2 Dosing

Thalidomide treatment must be initiated and monitored under the supervision of physicians with expertise in managing immunomodulatory or chemotherapeutic agents and a full understanding of the risks of thalidomide therapy and monitoring requirements.

The recommended dose of thalidomide is 200mg taken orally once daily, at bedtime. A maximum of 12 cycles of six weeks should be used. Patients should be monitored for: thromboembolic events; peripheral neuropathy; rash/skin reactions; bradycardia, syncope and somnolence. Thromboprophylaxis using low molecular weight heparins (LMWH) or warfarin should be administered for at least the first five months of treatment, especially in patients with additional thrombotic risk factors. Dose delay, reduction or discontinuation may be necessary to manage adverse effects. See the Summary of Product Characteristics (SPC) for full details[1].

2.3 Market authorisation date

A European marketing authorisation was granted April 2008[2].

2.4 UK Launch date

June 2008[3].

3.0 DECISION CONTEXT

MM is a plasma cell neoplasm that mainly affects older people – approximately 70% of patients are aged 65 years and over[4]. The clinical presentation is varied but may include symptoms of bone disease (typically unexplained persistent back pain), impaired renal function, anaemia, and hypercalcaemia. Despite advances in treatment, it remains incurable[2,4]. Median survival is six months without treatment and extends to three to six years with treatment[5].

The 2005 British Committee for Standards in Haematology (BCSH) guidelines indicate that initial treatment for newly diagnosed, symptomatic MM patients depends on their potential to benefit from high dose therapy and stem cell transplant (SCT)[4]. In those considered suitable for SCT, a VAD-type regimen (e.g. vincristine + doxorubicin + dexamethasone) has been the standard initial treatment. In older and less fit patients who are considered unsuitable for high dose therapy and SCT, melphalan or cyclophosphamide, with or without prednisolone, has been the standard recommended regimen[4]. There have, however, been significant clinical developments since the BCSH guidelines were issued. Thalidomide has been increasingly used at earlier stages of the disease and is now licensed for use in combination with melphalan and prednisone as first line treatment of patients with untreated MM aged ≥ 65 years or those who are ineligible for high dose chemotherapy[1].

Data from *in vitro* studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor-alpha (TNF-α) production, down-modulation of selected cell surface adhesion molecules involved in leukocyte migration and anti-angiogenic activity[1]. Thalidomide is a potent human teratogen and the conditions of the Thalidomide Pharmion Pregnancy Prevention Programme must be fulfilled for all male and female patients[1]. Given the typical age profile of patients with MM, the company submission considers that the risk of birth defects from thalidomide use is not substantial in the licensed indication[3].

Thalidomide does not meet the All Wales Medicines Strategy Group (AWMSG) criterion for ultra-orphan status, as it is indicated for a condition affecting more than 1 in 50,000 persons in the UK (i.e. 60 persons in Wales) at the time of submission.

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The main efficacy data are available from study Intergroupe Francophone du Myélome (IFM) 99-06, which was a phase III, open-label, randomised trial in previously untreated patients with MM, aged 65 to 75 years, or younger if ineligible for high dose therapy. The addition of thalidomide to melphalan plus prednisone significantly increased median overall survival (OS) by 18.4 months over a median 51.5 months of follow-up. This improvement in OS was achieved mainly as a result of a significant increase in progression-free survival (PFS). Two further company-supported studies, that used different thalidomide regimens, have also found significant improvements in PFS, but one of these did not find a significant difference in OS. It is suggested that this finding was due to the greater use of more active second line agents in the arm not receiving thalidomide.

The addition of thalidomide to melphalan plus prednisone significantly increases the incidence of serious adverse events and treatment discontinuations due to adverse events. Key amongst these are peripheral neuropathy and thromboembolic events. Study IFM 99-06 did not employ thromboprophylaxis, but this is routinely recommended in the thalidomide SPC. Thalidomide is a potent teratogen. Although most patients who meet the licensed indication are unlikely to be of child-bearing potential, all patients must comply with a detailed pregnancy prevention programme.

4.2 Review of the evidence on cost-effectiveness

A lifetime Markov model has been developed to conduct a cost utility analysis of the addition of thalidomide to melphalan and prednisone. Data from study IFM 99-06 has been extrapolated to provide risks of progression and death, and resource use is based largely on expert opinion.

In the base case analysis, the model estimates the incremental cost per quality adjusted life year (QALY) gained from the addition of thalidomide to melphalan and prednisone to be £17,002. A series of one way sensitivity analyses indicate that the model is relatively insensitive to the changes in parameter values that were explored. Probabilistic sensitivity analysis (PSA) estimates the mean incremental cost per QALY to be £17,483 (95% confidence interval [CI] £12,686 to £24,978), with a probability of being cost effective at a willingness to pay threshold of £20,000/QALY of around 82%. However, there are some issues with the parameter distributions employed in this analysis.

5.0 LIMITATIONS OF DECISION CONTEXT

- Myeloma has a higher incidence in Afro-Caribbean ethnic groups compared with Caucasians[4]; however, there appear to be little trial data in non-Caucasian ethnic groups.
- Patients with significant cardiac, renal, or hepatic dysfunction were excluded from the pivotal IFM 99-06 study[6].
- The company submission claims that 52% of patients aged <65 years are ineligible for high dose therapy and SCT[3]. However, there appear to be very few data in this group of patients (only five of the 447 patients in study IFM 99-06 were aged <65 years)[13]. Exploratory subgroup analyses suggest that response to thalidomide may be influenced by prognostic factors for MM, although those that have been conducted should be interpreted with caution.

6.0 CLINICAL EVIDENCE

The company submission[3] provides details of three company-supported, phase III trials of thalidomide added to melphalan and prednisone (MPT) against melphalan and prednisone (MP) as first-line treatment in patients with MM[6-10]. Interim results from a non-company-supported study[11,12] are also highlighted.

Recruitment of patients into all of these studies was stopped before all planned sample sizes had been reached due to interim results indicating a significant benefit of MPT over MP. Results of the longest follow up that is available for these studies, along with baseline characteristics, etc., are presented in Tables 1A and 1B in Appendix 1.

6.1 Clinical efficacy

6.1.1 Pivotal study IFM 99-06 in patients aged 65 to 75 years, or <65 years but ineligible for HDT

Patients in this open-label trial were randomised to initial treatment with 12 six-week cycles of MPT and MP as in Table 1A, Appendix 1. A third treatment arm of reduced intensity SCT using VAD followed by melphalan 100mg/m^2 was also included in this trial[6]. On the basis that the licensed indication for thalidomide includes patients aged 65 years or more or those who are unsuitable for SCT, and that reduced intensity SCT is not a standard recommended regimen, the company submission does not further consider this third treatment arm[3].

The addition of thalidomide to MP significantly improved the primary endpoint of median OS compared with MP alone. Recruitment was stopped early and the median follow-up at data cut off was 36.8 months for MPT, at which point per protocol analysis indicated that median OS was increased with MPT by 21.4 months (Hazard Ratio [HR] 0.56; p=0.001)[2,6]. Updated analyses, conducted on an intention-to-treat (ITT) basis, were provided at a median follow up 51.5 months. Median OS with MPT at that time point was 51.6 months versus 33.2 months with MP (difference of 18.4 months; HR 0.59; 95% CI 0.46 to 0.81; p=0.0006)[6]. Secondary endpoints also significantly favoured MPT, including median PFS (27.5 versus 17.8 months; HR 0.51; 95% CI 0.39 to 0.66; p<0.0001) and best response rates. There was no significant difference between MPT and MP in SAP[6] (see Table 1A, Appendix 1).

More patients who received MP than MPT completed the planned 12 cycles of treatment (36.7% versus 25.8%, respectively)[13]. In the MP group, the most common reason for discontinuation was first progression of the disease, whereas treatment toxicity was the most common reason in the MPT group[13] (see section 6.2). Median duration of thalidomide treatment was 11 months[6].

Points to note from study IFM 99-06

- The originally planned sample size was 500 patients. Due to the decision of the data safety monitoring board to stop recruitment into the trial, only 447 patients were randomised. The accrual and follow-up time, however, was longer than originally anticipated; which resulted in a greater number of events and preserved the power of the study[6].
- Patients with significant cardiac, liver or renal dysfunction, or peripheral neuropathy, were excluded from the study[6]. Many patients in clinical practice may present with such problems. Five of the 447 patients were aged <65 years and ineligible for high dose therapy and SCT[13].
- In those who responded to thalidomide treatment, no maintenance treatment with thalidomide beyond the planned 12 cycles was allowed[6].
- Second-line treatments may be expected to influence OS. Based on the updated analysis at a median follow-up of 51.5 months, 11% of patients randomised to MP did not receive any second-line treatment, compared with 23% in the MPT group[14]. Of those in the MP group who did receive second-line treatment, 83% received thalidomide, bortezomib or lenalidomide at some point during follow-up, at the discretion of investigators[14]. Median SAP was not statistically significantly different, indicating that OS was not affected by treatment received after progression[2].
- Exploratory sub-group analyses indicated that the OS data was consistent regardless of selected prognostic factors. The beneficial effect of the addition of thalidomide to MP was more pronounced in those patients with the least favourable prognostic factors, e.g. WHO performance status 2, β_2-microglobulin ≥ 2.5mg/L, Durie-Salmon stage III, and chromosomal aberration. The small number of patients with elevation of serum creatinine ≥ 20mg/L did not gain benefit from the addition of thalidomide to MP[2]. Nevertheless, all of these exploratory sub-group analyses should be interpreted with caution, as the trial was not designed to assess the influence of these factors[13].
- The recommended starting dose of thalidomide was 200mg daily, but initial dose and subsequent dose adjustments were based on tolerability, response and the investigator's judgment[13]. By the end of the first month, equal proportions of patients (44.4%) were receiving a dose of 200mg and 400mg daily[13]. It should be noted, however, that a greater percentage of patients who received the dose of 400mg daily required subsequent dose reductions compared to those who received a maximum daily dose of 200mg[2].

6.1.2 Study IFM 01-01 in patients aged ≥ 75 years and the GIMEMA study in patients aged 65-85 years or <65 and ineligible for transplant

Study IFM 01-01 was a double-blind study that employed a similar MP regimen as study IFM 99-06 above, but the dose of thalidomide in the MPT arm was lower at 100mg daily, and was given continuously for 18 months[7,8]. The primary endpoint of median OS (ITT analysis) was significantly improved with MPT compared with MP over the median of 24 months of follow-up (45.3 versus 27.7 months; p=0.033). Secondary endpoints of median PFS and best response at 12 months were also significantly in favour of MPT, and median SAP was not significantly different (see Table 1A, Appendix 1). This study is not fully published, which precludes a full critique.

The *Gruppo Italiano Malattie Ematologiche dell'Adulto* (GIMEMA) study[9,10] was an open-label trial that employed a different treatment regimen to the IFM 99-06 and IFM 01-01 studies. The MP component of treatment in both arms was given at a different dose and for a maximum of six four-week cycles, and the MPT arm involved thalidomide dosed at 100mg daily on a continuous basis until relapse. The primary endpoints were response rates and median PFS, both of which significantly favoured MPT over MP. The secondary endpoint of time to progression (TTP) also favoured MPT over MP (see Table 1A, Appendix 1). In contrast however, to the two studies above, there was no statistically significant difference between MP and MPT in terms of median OS (a secondary endpoint in this study). Median SAP was statistically significantly greater in the MP arm than in the MPT arm and the study authors note that second-line treatments were given more frequently in the MP arm than in the MPT arm (56.7% versus 48.5%, respectively), and that bortezomib and thalidomide were used more frequently in the MP arm than in the MPT arm (41.5% versus 22.2%, respectively). Further analyses indicated that second line bortezomib or thalidomide-based regimens significantly improved SAP in patients who received initial treatment with MP (HR 0.25; 95% CI 0.12 to 0.51; p=0.0002), but not in those who had already been exposed to thalidomide in the MPT regimen (HR 0.75; 95% CI 0.42 to 1.35; p=0.34)[10]. The authors, therefore, suggest that the lack of difference in OS could be due to the greater use of more active second-line treatments in the MP group than in the MPT group[10]. As these salvage treatment analyses do not appear to have been pre-specified, they should be interpreted with caution.

Points to note from the GIMEMA study

- A higher proportion of early deaths from adverse events was reported in the first nine months of treatment in the MPT group compared with the MP group[9].
- Thromboprophylaxis with enoxaparin 40mg daily was instituted following protocol amendment but only after 65 patients had already been randomised to MPT. The incidence of grade 3–4 adverse events was significantly reduced with the introduction of prophylaxis, although this was not a randomised comparison[9].
- Abnormal cardiac function, chronic respiratory disease, and abnormal liver or renal function were not criteria for exclusion in this trial.

6.1.3 Supporting trial

The HOVON study was an open-label study that uses a different MP regimen over a maximum of eight four-week cycles[11,12]. Thalidomide was dosed at 200mg daily, followed by 50mg daily as maintenance therapy until disease progression. Preliminary data from a conference abstract indicate that there was significant difference in the primary endpoint of event-free survival in favour of MPT (p<0.001) but the magnitude of that difference is not stated. The co-primary endpoint of best overall response was also improved with MPT, driven by a difference in very good partial response rates, rather than complete response or partial response rates (see Table 1B, Appendix 1). There is reportedly no significant difference in OS or PFS[11,12]. Notably, however, the follow up period for these results is not stated and it is not possible to interpret these results on the basis of the limited data that is presented.

6.2 Safety

The licensed indication and recommended dose of thalidomide is based primarily on study IFM 99-06[1,13]. As the other studies discussed in section 6.1 used a different thalidomide regimen[7-12], and do not report a different adverse event profile, the safety information presented here is based mainly on that observed in study IFM 99-06.

In study IFM 99-06, at a median follow-up of 36.8 months for MPT, 98.4% of the MPT group experienced at least one adverse event of any grade compared with 79.8% of

the MP group[13]. Four specific groups of adverse events were of particular interest: neuropathy (occurred at any grade in 55.6% of the MPT group compared with 4.1% of the MP group); deep vein thrombosis/pulmonary embolism (DVT/PE, 12.9% versus 7.3%, respectively); cardiac events (12.1% versus 5.7%, respectively) and rash/skin reactions (10.5% versus 3.6%, respectively)[13]. Grade 3-4 adverse events that occurred statistically significantly more frequently with MPT than MP were: neutropenia (48% versus 26%, number needed to harm [NNH] 4); DVT/PE (12% versus 4%, NNH 12); peripheral neuropathy (6% versus 0%, NNH 16); somnolence/fatigue/dizziness (8% versus 0%, NNH 12); and constipation (10% versus 0%, NNH 10)[6]. The study authors report that the increased incidence of neutropenia did not lead to an increase in the incidence of severe infection[6].

Serious treatment-related adverse events occurred more frequently in the MPT group than in the MP group (34.7% versus 19.7%, NNH 15). Adverse events leading to treatment discontinuation also occurred more frequently in the MPT group (42.7% versus 7.8%, NNH 2), the most common being peripheral neuropathy (8.9% versus 0%)[13]. Around 52% of patients who received MPT had an initial dose of thalidomide $\leq$200mg/day, and 48% >200mg/day. Overall, 38% of patients required a reduction in thalidomide dose, of which 60% were receiving a dose >200mg/day[6].

Thromboprophylaxis was not routinely used in study IFM 99-06[6], and was only instituted in the GIMEMA study following a protocol amendment after 65 patients had already been randomised to MTP[9]. Introduction of prophylaxis with daily enoxaparin in the GIMEMA study significantly reduced the rate of thromboembolism from 20% to 3% ($p=0.005$)[9] although this was not a randomised comparison and so should be interpreted with caution. However, the SPC for thalidomide recommends that thromboprophylaxis using LMWH or warfarin should be administered for at least the first 5 months of treatment, especially in patients with additional thrombotic risk factors[1]. The SPC also details the recommended dose modification required in response to the development of different degrees of peripheral neuropathy[1].

Thalidomide is a potent human teratogen and must only be used according to the Thalidomide Pharmion Pregnancy Prevention Programme[1] (see section 10.1).

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

The 2005 BCSH guidelines indicate that, in those in whom high dose therapy and SCT is planned, a VAD-type regimen is recommended[4]. However, in older and less fit patients who are considered unsuitable for high dose therapy and SCT, melphalan or cyclophosphamide, with or without prednisolone, are the standard recommended regimens[4]. There have been several developments in the treatment of MM since the 2005 BCSH guidelines were issued. The licensed indication for thalidomide is for use in combination with melphalan and prednisone as first line treatment of patients with untreated MM, aged $\geq$ 65 years or ineligible for high dose chemotherapy[1]. MP would, therefore, be an appropriate comparator.

Bortezomib (Velcade®▼) is also licensed for use in combination with melphalan and prednisone for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant[15]. Theoretically, bortezomib may therefore be a comparator for thalidomide in its licensed indication. WMP-sought expert opinion however indicates that bortezomib is not widely used in Wales in this indication.

7.2 Comparative effectiveness

- Thalidomide is licensed as first-line treatment in MM patients who are aged ≥65 years or are unsuitable for high dose therapy and SCT, primarily on the basis of the IFM 99-06 trial[1]. This trial demonstrated significant improvements in OS, PFS and response rates with the addition of thalidomide to MP. Very few patients in this trial were aged <65 years and unsuitable for high dose therapy.
- The recommended dose of thalidomide is 200mg/day, given at night time to reduce the impact of the adverse event of somnolence[1]. Dose adjustment may be required in response to the development of adverse events[1]. In study IFM 99-06, 38% of patients required reduction of their thalidomide dose, of which 60% were receiving an initial dose >200mg/day.
- The IFM 01-01 study in patients aged ≥75 years used a thalidomide dose of 100mg/day, but given on a continuous basis for up to 18 months[7,8]. The limited available data from this study indicates a significant improvement in OS with MPT compared with MP, and the company submission asserts that thalidomide at 100mg/day in patients aged 75 years or older should be the reference treatment[3]. However, the SPC states that no dose adjustment is required in elderly patients[1].
- The GIMEMA study in patients aged 65-85 years found significant improvements in the primary endpoints of response rates and PFS, and in the secondary endpoint of TTP with the addition of thalidomide 100mg/day to melphalan and prednisone[9,10]. There was no significant difference observed for the secondary endpoint of OS. The use of more active second-line treatments in the MP group than in the MPT group has been proposed as the reason for this finding[10]. The non-company-supported HOVON study is also reported to have found no significant difference in PFS and OS with the addition of thalidomide to MP, but the limited data that are currently available are not sufficient to fully interpret these findings.
- The addition of thalidomide to MP significantly increases the incidence of serious adverse events and treatment discontinuations due to adverse events[6,13]. Key amongst these are thromboembolism and peripheral neuropathy[1,6]. Careful monitoring for these events is required, and patients must be made aware of the relevant signs and symptoms[1].
- Thromboprophylaxis with LMWH or warfarin is recommended for all patients for at least the first five months of thalidomide therapy[1]. Although no randomised comparisons are available, there is some evidence from the GIMEMA study that thromboprophylaxis significantly reduces the incidence of thromboembolism in patients receiving thalidomide[9]. Caution is required in patients with a previous history of thromboembolic events and those taking other agents that increase the risk of thromboembolism (e.g. erythropoietic agents, hormone replacement therapy, combined oral contraceptives)[1]. Peripheral neuropathy should be managed by dose reduction or discontinuation as recommended in the SPC[1].

- Patients with significant cardiac, renal, or hepatic dysfunction were excluded from the IFM 99-06 study[6]. The BCSH guidelines stated that thalidomide may be used without dose modification in patients with renal failure, with a caveat that further data are required before a firm recommendation can be made[4]. The SPC notes that thalidomide has not formally been studied in patients with impaired renal or hepatic function and states that no specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions[1].
- Due to the teratogenic potential of thalidomide, a detailed pregnancy prevention programme has been instituted and must be adhered to[1] (see section 10.1). Given the typical age profile of patients with MM, the company submission considers that the risk of birth defects from thalidomide use is not substantial in its licensed indication[3].
- There is significant overlap in the licensed indications for thalidomide and bortezomib in untreated patients with MM[1,15]. There are no direct comparative efficacy and safety data but, like thalidomide, bortezomib is associated with a significant risk of neuropathy[15]. Bortezomib is administered as an intravenous bolus injection[15] and the oral dosage form of thalidomide may be preferred. WMP-sought expert opinion indicates that bortezomib is not widely used in Wales in this indication.
- There are no quality of life data specific to thalidomide presented in the company submission.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by thalidomide over the relevant comparator(s) justify any additional costs and, if so, whether the total budgetary impact of supporting the use of is thalidomide is acceptable.

8.2 Description and critique of the company's submission

The company submission describes a cost utility analysis of thalidomide added to MP compared with MP alone in patients meeting the licensed indication for thalidomide. A lifetime Markov model has been developed in which all patients start in a pre-progression state without adverse events, and remain there until they experience a serious adverse event or disease progression. Once patients experience a serious adverse event, it is assumed that they are no longer at risk of additional adverse events. History of adverse events does not affect progression rates or death, and patients can only die after experiencing disease progression.

Data from the pivotal IFM 99-06 study has been used to provide the risks of progression and death following progression. PFS with each of MP and MPT has been used as a proxy for TTP. As patient-level data were not available, extrapolation of PFS has been undertaken by reading data points from the respective Kaplan-Meier curves. SAP has been extrapolated in the same way, but once patients experience progression, their risk of death is assumed to be the same, regardless of treatment received. There are significant uncertainties in the approach used to model adverse events, which are incorporated as a weighted "average" overall adverse event in the model. Resource use in the model is largely based on expert opinion. In the base case analysis that was originally submitted by the company, disutility due to adverse events and thromboprophylaxis, which is routinely recommended for patients treated with thalidomide, were not incorporated. These have been incorporated in revised analyses that have been provided in response to the draft ASAR that was sent to the

company. Probabilistic analysis has been conducted, although the variation and uncertainty in the parameter point estimates are not based on actual observed data.

The economic model has not been validated as it was provided to WMP late in the appraisal process. The results, however, presented in the model for the base-case analysis agree with the data presented in the company submission.

8.3 Population

The population considered in the model is based on the population of the IFM 99-06 study[3]. These patients were aged 65 to 75 years, or younger and ineligible for high dose therapy[6]. Only five of the 447 patients who were randomised in this study were aged <65 years[13]. Importantly, patients with significant cardiac, renal, or hepatic dysfunction, or peripheral neuropathy, were excluded from this study (see Table 1A, Appendix 1). Many patients in practice may present with such problems.

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. A lifetime time horizon has been used[3], which is appropriate for this incurable condition. A Markov cycle length of six weeks has been used, to coincide with the treatment cycle length in study IFM 99-06[3].

8.5 Comparator

MP is the comparator in the model[3]. This has been a standard treatment in this population for many years. The company submission implies that bortezomib is not a relevant comparator, as it is licensed as monotherapy in patients who have progressive multiple myeloma and who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation[3]. Whilst that is one of its licensed indications, bortezomib is also licensed for use in combination with melphalan and prednisone for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant[15]. Theoretically, bortezomib may therefore be a comparator for thalidomide in its licensed indication, but it appears not to be used widely in Wales (see section 7.1).

8.6 Clinical inputs

8.6.1 Efficacy data

Efficacy data for the model is derived from that in IFM 99-06. TTP was not reported in study IFM 99-06, and so PFS has been used as a proxy for TTP. Patient-level data was not available from the IFM 99-06 study; therefore, PFS has been extrapolated for MPT and MP by fitting exponential and Weibull distributions respectively, to data points taken from their Kaplan-Meier curves. These were reported to be the best parametric fits for the data. There was no significant difference in SAP amongst the three treatment arms in study IFM 99-06[6].

It is assumed in the model that the risk of death following disease progression is the same across treatments. SAP, therefore has been extrapolated using combined ITT data from all three treatment arms and an exponential distribution that was reported to fit these data best. One way sensitivity analyses have explored the resultant HRs within the range +/- 20%. It is assumed that all deaths are due to disease and there are no deaths due to treatment adverse events or from other causes.

8.6.2 Adverse events

More patients in the MPT group experienced serious adverse events and treatment discontinuations due to adverse events compared with the MP group[4] (see section 6.2). It is assumed that the impact on survival of treatment interruptions and discontinuations, etc., is implicitly reflected in TTP[3]. The impact of adverse events of

treatment, however, is considered in terms of overall costs of treatment and utility weights (see sections 8.6.3 and 8.7.2). Therefore, the risk of adverse events per cycle has been estimated and applied to patients whilst on treatment. PFS has been used to define the point of treatment cessation, which results in longer treatment duration than the average reported in the trial[3].

An important point to note is that IFM 99-06 did not employ routine thromboprophylaxis. The revised base case model considers the costs of thromboprophylaxis, based on the first five months of thalidomide treatment with the low molecular weight heparin dalteparin (£2.82/day), but conservatively assumes no reduction in the risk of thromboembolic events. A "best case" scenario has been conducted, in which it is assumed that thromboprophylaxis is provided for the first five months of thalidomide treatment with the relatively inexpensive warfarin 5mg/day (£0.05/day) and is assumed to result in an 88% reduction in thromboembolic events, as was observed with the use of enoxaparin in the GIMEMA study[9]. A "worst case" scenario has also been conducted, in which thromboprophylaxis is assumed to be provided for the entire duration of thalidomide treatment with the more expensive factor X inhibitor fondaparinux (£6.66/day), but with no reduction in the risk of thromboembolic events.

8.6.3 Utility weights

There are no health-related quality of life or utility value data available from the thalidomide trials conducted in untreated MM patients aged ≥65 years, discussed in section 6.1. Utility values therefore that were assumed in a cost utility analysis of intensive chemotherapy alone compared to intensive chemotherapy followed by myeloablative chemotherapy with autologous SCT in newly diagnosed patients aged ≤65 years[16] have been assumed in this model for the states of progressive disease, stable disease and response to treatment. A utility weight of 0.64 is assumed for patients who experience progression, and it is assumed that patients who respond to treatment have the same utility value as aged-matched members of the general population, based on EQ-5D-derived values. A utility value of 0.77 is assumed for those patients who have not progressed by the end of two years[3], based on the same analysis[16]. The extent to which these utility values are representative of those values for patients in the economic analysis, who are older and/or considered unsuitable for SCT, is uncertain.

The quality of life impact associated with adverse events of treatment has been considered in the revised base case analysis. Relative reductions have been applied to the above utility values for patients experiencing a range of adverse events based on the relative reductions from baseline found in the literature for different populations and diseases. The duration of the different adverse events, the durations of their management and their relative frequencies have been used to derive a weighted "average" utility decrement for patients experiencing an adverse event.

Very few details of the literature search that was conducted to derive these relative reductions in utility values associated with the various adverse events are provided, and it would appear that this approach could be associated with some uncertainty that may act to favour MPT. Supplementary one-way sensitivity analyses explore the impact of increasing the duration of the decrement in utilities up to eight-fold on the model outputs. A "best case" scenario, in which the relative decrement in utility due to adverse events and the duration of that decrement are both reduced by 50%, has been modelled. A "worst case" scenario, in which the relative decrement in utility is assumed to be double that in the base case, and the duration is assumed to be eight times longer, has also been modelled.

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

In the base case analysis drug costs are based on the doses used in the IFM 99-06 study. The mean dose of thalidomide was 238.1mg/day. The cost/mg has been estimated from published sources (e.g. the British National Formulary [BNF][17]), and the cost per cycle for each of thalidomide, melphalan and prednisolone has been estimated assuming a patient weight of 70.8kg. It should be noted that the modelled treatment duration is marginally longer than the actual treatment duration observed in the IFM 99-06 study.

The assumed costs of thromboprophylaxis in the base case and sensitivity analyses are discussed in section 8.6.2.

8.7.2 Adverse event costs

As with the approach to the utility values associated with adverse events, the cost of an "average" adverse event has been estimated. Two Welsh haematologists are reported to have provided estimates of resource use, and the frequency and setting, for the treatment of the serious adverse events observed in the IFM 99-06 study[3]; however, these data are not provided and so the precision of the estimates of resource use by these haematologists is unclear. Published unit cost data have been used to cost in-patient and out-patient care, and primary and community care, where appropriate[3]. BNF costs have been used for drug treatments, etc.

8.7.3 Other resource use and costs

Routine tests and monitoring for the underlying disease are based on disease status: patients during relapse and/or on treatment; patients in remission/plateau and on maintenance therapy; and patients in remission/plateau and off therapy. Mean estimated resource use is based on the company-sought opinion of two Welsh haematologists. Published unit costs have been applied and/or assumed[3].

8.8 Discounting

Costs and outcomes are discounted at 3.5% per annum[3], which is the preferred discount rate. Discount rates of 0%, 6% and 3.5% have been explored in one way sensitivity analyses[3].

8.9 Results

8.9.1 Base-case analysis

In the revised base case analysis, the model predicts that the addition of thalidomide to melphalan and prednisolone treatment would result in a gain of 1.15 years of life, or 0.91 QALYs when adjusted for health-related quality of life, at an additional cost of £15,413. The estimated incremental cost per QALY gained is £17,002.

This analysis may be considered conservative as it incorporates the assumed costs of thomboprophylaxis, but no clinical benefit in terms of reducing the risk of thromboembolic events.

8.10 Sensitivity analysis

8.10.1 One way sensitivity analyses

A series of one way sensitivity analyses have been performed. In general, the model was relatively insensitive to the changes in parameter values that were explored. Reducing the time horizon from lifelong to the length of follow-up in the IFM 99-06 study increased the incremental cost effectiveness ratio (ICER) to £41,903; however, a lifelong time horizon (as in the base case analysis) would be more appropriate for this disease. When the HR for progression that was extrapolated from the IFM 99-06 data was varied by +/-20%, the ICER ranged from £12,930 to £23,599. There was no real

change in the model outputs when monitoring and adverse event costs were varied by +/-100%. Varying utility scores (excluding adverse event disutility) by +/-10% resulted in an ICER ranging from £15,456 to £18,891.

Supplementary sensitivity analyses exploring the impact of the assumed duration and magnitude of decrements applied to utility values due to adverse event indicate that the model is stable – there was little change in the model outputs when the duration of the utility decrements was eight times longer, or when the decrement was double that assumed in the base case analyses. There was also little change in the model outputs when the best and worst case scenarios of thromboprophylaxis, described in section 8.6.2, were run in the model.

8.10.2 Probabilistic sensitivity analysis (PSA)

The PSA was performed by sampling from distributions around the parameters of risk of progression, risk of death following progression, utility scores and management costs. Data on the distribution around the point estimates of these parameters were not available, and so the distributions are defined by the ranges explored in the one way sensitivity analyses above. This in itself is subject to some uncertainty.

The revised PSA estimated a mean ICER of £17,483 (95% CI £12,686 to £24,978). At willingness to pay thresholds of £20,000 and £30,000 the probabilities that the addition of thalidomide to MP is cost effective are estimated by this model to be around 82% and 100%, respectively[3].

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by the Welsh Medicines Partnership (WMP) have not identified any published evidence on the cost-effectiveness of thalidomide in the first-line treatment of patients with MM.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

UK prevalence and incidence data are extrapolated over time to the Welsh population to provide estimates of patient numbers over five years. Market research data have been used to determine the proportions of patients aged less than 65 years who are eligible for treatment with thalidomide, and all new cases in patients aged 65 years and older are assumed to be eligible for treatment

9.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over a five year period[3].

9.3 Data sources

9.3.1 Incident and prevalent cases

Data from the GLOBOCAN project is used to determine the number of patients with MM and malignant plasma cell neoplasms in the UK in 2002[18]. These have been extrapolated to the Welsh population, which results in an estimated prevalence in Wales in 2002 of 139 patients. It is assumed that 94.5% of these patients have MM alone, based on hospital episode statistics. Cancer research UK data has been used to estimate the average annual increase in incidence between 1995-2005 (1.7%)[19], which has been applied to the 2002 estimate of prevalent MM cases to produce an estimate for 2009 of 148 patients.

Based on Cancer Research UK data, the incidence of MM in 2005 has been estimated as 221 patients (94.5% of the 234 cases recorded)[19]. Applying the 1.7% increase in incidence to this figure, the incident case for 2009-13 have been estimated (237, rising to 253). Based on market research data (not provided), it is assumed that 67% of prevalent cases are aged ≥65 years or ineligible for high dose therapy and SCT. Of those aged <65 years, 52% are estimated to be ineligible for high dose therapy and SCT[3].

Assuming that 10% of prevalent cases in 2009 have not been treated, and that 75% of these will be eligible to receive thalidomide within a year, in 2009 the number of eligible patients is estimated as 207. There are estimated to be 213 patients eligible in 2013.

9.3.2 Projected rate of adoption and market share

The base case budget impact analysis assumes that no thalidomide is currently being used in the licensed population and that uptake will be 60% in 2009, rising by 2.5% each year to 70% in year 2013. All other patients are assumed to be treated with MP. A further analysis however is provided, which uses 2008 market research data and suggests that 54% of all eligible patients are currently already receiving thalidomide.

9.3.3 Costs and resource use

The undiscounted total costs from the revised base case cost utility analysis are reported to have been used in the base case budget impact analysis[3]. These include the costs of MPT and MP and costs of monitoring, adverse events, thromboprophylaxis with dalteparin for the first five months of treatment, etc.

9.4 Results

If all the eligible patients were to receive MP only, the cost to NHS Wales is estimated to be £113,500 in 2009, rising to £294,400 in 2013. The additional budget impact of adding thalidomide to MP is estimated to be £1.74 million in 2009, rising to £2.30 million in 2013[3]. This estimate is based on the revised base case cost utility analysis, including the costs of thromboprophylaxis.

Market research data are reported to indicate that 54% of eligible patients already receive thalidomide as a first line treatment. The overall budget impact remains the same, but the additional budget impact compared with current thalidomide use is estimated as £174,000 in 2009, rising to £521,000 in 2013[3].

9.5 Sensitivity analysis

No further sensitivity analysis was conducted for the budget impact analysis.

9.6 Comparator costs

Assuming an adult body mass of 70.8kg and a mean daily dose of 238mg (as per the economic model) one cycle of treatment with thalidomide would cost £2,132.04[3].

Bortezomib (Velcade®) is also licensed for use in combination with melphalan and prednisone for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant[15]. Theoretically, bortezomib may be a comparator for thalidomide in its licensed indication, although it would appear not to be used widely in Wales (see section 7.1).

The recommended starting dose of bortezomib is 1.3 mg/m^2 body surface area (BSA) twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle[15]. Assuming an adult BSA of 1.8m^2, and wastage of unused vial contents, one cycle of treatment with bortezomib would require four vials, at a cost of £3,049.52[17].

The costs presented here do not imply therapeutic equivalence.

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- Thalidomide may not be suitable for a shared-care agreement. Treatment, monitoring, and supervision should be retained under specialist care[1].
- Thalidomide is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the Thalidomide Pharmion Pregnancy Prevention Programme are met[1]. These stipulate that all women of childbearing potential must:
    - Receive counselling regarding the potential teratogenic effects of thalidomide and understand the need to avoid pregnancy.
    - Use an effective method of contraception for four weeks before therapy, during therapy, during dose interruptions and four weeks after therapy has finished, unless the woman commits to absolute and continued abstinence confirmed on a monthly basis.
    - Have a medically supervised negative pregnancy test once she has been established on contraception for 4 weeks, at 4 weekly intervals during therapy and 4 weeks after the end of therapy.

In addition, male patients with partners who are pregnant or who are of childbearing potential must use a condom when engaging in sexual activity.

Pharmacies must be registered with Celgene Ltd before they can dispense the drug[3].

Full details are provided in the SPC[1].

10.2 Related advice

- National Institute for Clinical Excellence issued a manual on improving outcomes in haematological cancers in October 2003[21].
- National Institute for Health and Clinical Excellence issued referral guidelines for suspected cancer in June 2005[22]
- National Institute for Health and Clinical Excellence proposed technology appraisal: Bortezomib and thalidomide for the first-line treatment of multiple myeloma. Scoping workshop scheduled November 2008.

10.3 Previous AWMSG/NICE advice

- National Institute for Health and Clinical Excellence. Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under certain circumstances (see guidance); October 2007[23].
- All Wales Medicines Strategy Group. Lenalidomide (Revlimid®) - not recommended for use within NHS Wales for the treatment of multiple myeloma; July 2008[24].

10.4 Ongoing Studies

- The company submission indicates that a publication of study IFM 01-01 is being prepared and that there are no new or updated analyses[3]. Actual date of publication is not provided.
- A further non-company-supported, double-blind, randomised study of thalidomide in untreated patients with MM has been completed by the Nordic Myeloma Study Group[25]. Few results appear to have been made available.

10.5 Patient organisation information

Patient organisation submissions by Leukaemia CARE and Myeloma UK were provided to AWMSG members.

GLOSSARY

Incidence:
The rate at which new cases occur in a population during a specified period[26].

Prevalence:
The proportion of a population that are cases at a point in time[26].

MM classification systems:
Proper staging of multiple myeloma helps in determining prognosis and developing a treatment plan. In the **Durie-Salmon system**, the clinical stage of multiple myeloma (stage I, II, or III) is based on several measurements, including levels of M protein, the number of bone lesions, haemoglobin values, and serum calcium levels. The stages are further divided according to renal function as determined by serum creatinine levels (<2.0 mg/dL or ≥2.0 mg/dL)[21].

The Durie-Salmon system has been superseded by the **International Staging System (ISS)**, which is based on serum β_2 microglobulin and serum albumin concentrations[4].

Stage	Durie-Salmon system[21]	ISS[4]
I	All of the following: -Haemoglobin value >10 g/dL -Serum calcium value normal or <12 mg/dL -Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only -Low M-component production rate -IgG value <5 g/dL; IgA value <3 g/dL -Bence Jones protein <4 g/24 h	Serum β_2 microglobulin <3.5 mg/l and serum albumin >35 g/l [Median survival 62 months, irrespective of type of therapy]
II	Neither stage I nor stage III	Neither stage I nor stage III [Median survival 45 months, irrespective of type of therapy]
III	One or more of the following: -Haemoglobin value <8.5 g/dL -Serum calcium value >12 mg/dL -Advanced lytic bone lesions (scale 3) -High M-component production rate -IgG value >7 g/dL; IgA value >5 g/dL -Bence Jones protein >12 g/24 h	Serum β_2 microglobulin >5.5 mg/l [Median survival 29 months, irrespective of type of therapy]

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Appendix 1. Additional Clinical Information

Table 1A. Phase III trials of thalidomide + melphalan and prednisolone in the first-line treatment of multiple myeloma

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcome (MPT versus MP)
Pivotal study IFM 99-06 in patients aged 65 to 75 years						
2,6 (IFM 99-06)	Randomised, open-label, phase III trial Conducted in France, Belgium and Switzerland	321 randomised (3:2) to melphalan + prednisolone or melphalan + prednisolone + thalidomide (total study population at data cut-off 447, including third arm of reduced intensity SCT, not discussed here)	Treatment-naive Aged 65 to 75 years, or < 65 years if ineligible for HDT Stage II or III MM based on Durie-Salmon criteria, or stage I if high risk of progression WHO PS 0-2 (or greater if unrelated to MM), adequate renal, liver and cardiac function, no peripheral neuropathy, no HIV or hepatitis B or C infection.	Mean age: 69.6 years (41% ≥70 years) Males: 53% Caucasian: 99.3% Durie-salmon stage II/III: 91% ISS stage I: 32% ISS stage II: 37% ISS stage III: 31%	12 six-week cycles of: Melphalan 0.25mg/kg + prednisone 2mg/kg given orally on days 1 to 4 of each cycle (MP, n=196) versus MP + thalidomide 200mg daily, titrated up to 400mg daily (MPT, n=125) [No thromboprophylaxis given]	Recruitment stopped early by DSMB as interim analyses indicated significant advantage with thalidomide. Results from additional follow up to 51.5 months: **Primary endpoint (ITT analysis):** Median OS: 51.6 versus 33.2 months; HR 0.59 (95% CI 0.46 to 0.81); p=0.0006 **Secondary endpoints (ITT analysis):** Median PFS at 51.5 months: 27.5 versus 17.8 months; HR 0.51 (95% CI 0.39 to 0.66); p<0.0001 Best response at 12 months: CR: 13% versus 2.0%; p=0.0008 At least PR: 76% versus 35%; p<0.0001 At least VGPR: 47% versus 7%; p<0.0001 Median SAP: 13.4 versus 11.4 months; p=NS
Study IFM 01-01 in patients aged ≥75 years						
7,8 (IFM 01-01)	Randomised, double-blind, placebo-controlled trial Conducted in France and Belgium	232 randomised	Treatment-naive Aged ≥ 75 years Other details lacking	Median age 78.5 years (36% ≥80 years) Males: 45% Durie-salmon stage III: 68% ISS stage II: 43% ISS stage III: 32% WHO PS 2-4: 35%	12 six-week cycles of: Melphalan 0.2mg/kg + prednisone 2mg/kg (MP) + placebo given orally on days 1 to 4 of each cycle (n=116) versus MP plus thalidomide 100mg daily continuously for 18 months (MPT, n=113) [No thromboprophylaxis given]	Recruitment stopped early by DSMB as interim analyses indicated significant advantage with thalidomide. Median follow-up at data cut off 24 months. **Primary endpoint (ITT analysis):** Median OS: 45.3 versus 27.7 months; p=0.033 **Secondary endpoints (ITT analysis):** Median PFS: 24.1 versus 19 months; p=0.001 Best response at 12 months: CR: 7% versus 1%; p=0.0001 At least PR: 61% versus 31%; p=0.0001 At least VGPR: 23% versus 8%; p=0.0001 Median SAP: 9.3 versus 9.2 months; p=NS

Table 1A. Continued

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcome (MPT versus MP)
GIMEMA trial in patients aged 65 to 85 years						
9,10	Randomised, open-label, phase III trial Conducted in Italy	331 patients randomised	Treatment-naive Aged 65 to 85 years, or < 65 years if ineligible for HDT Stage II or III MM based on Durie-Salmon criteria No peripheral neuropathy Abnormal cardiac function, chronic respiratory disease, and abnormal liver or renal functions were not criteria for exclusion.	Median age 72 years (25% >75 years) Durie-salmon stage III: 58% WHO PS 3-4: 6%	Six four-week cycles of: Melphalan 4mg/m^2 + prednisolone 40mg/m^2 given orally on days 1 to 7 of each cycle (MP, n=164) versus MP plus thalidomide 100mg daily, followed by thalidomide 100mg daily maintenance treatment until relapse (MPT, n=167) [Thromboprophylaxis with s.c enoxaparin 40mg daily given only after protocol amendment when 65 patients had been randomised to MPT]	Trial stopped early by DSMB due to interim analyses indicating significant advantage with thalidomide treatment. Updated results presented for all randomised patients. Median follow-up 38.4 months for MPT and 37.7 months for MP **Primary endpoints (ITT analysis):** CR: 15.6% versus 3.7%; p=0.0002 VGPR: 29.3% versus 11.0%; p<0.0001 PR: 68.9% versus 47.6%; p<0.0001 Median PFS: 21.8 versus 14.5 months; HR 0.63 (95% CI 0.48 to 0.81); p=0.0004 **Secondary endpoints (ITT analysis):** Median TTP: 24.7 versus 15.0 months; HR 0.57 (95% CI 0.44 to 0.75); p<0.0001 Median SAP: 11.5 versus 24.3 months; HR 1.56 (95% CI 1.09 to 2.24); p=0.01 Median OS: 45.0 versus 47.6 months; HR 1.04 (95% CI 0.76 to 1.44); p=0.79 NS

CR = complete response (absence of the original monoclonal protein in serum and urine by immunofixation, < 5% of plasma cells in a bone-marrow aspirate, and the disappearance of soft-tissue plasmacytomas[6]); DSMB = data safety monitoring board; Durie-Salmon criteria (see Glossary); HDT= high dose therapy; HR = hazard ratio; ISS = International Staging System (see Glossary); ITT = intention-to-treat; MM = multiple myeloma; NS= not statistically significant; OS = overall survival; PFS = progression-free survival; PR = partial response (reduction in the size of soft-tissue plasmacytomas, more than a 50% reduction in the concentration of serum monoclonal protein, and more than a 75% reduction in 24-h urinary light chain excretion[6]); SAP = survival after progression; s.c = sub-cutaneous; TTP = time to progression; VGPR = very good partial response (>90% decrease in monoclonal protein in serum and urine[6]); WHO PS = WHO performance status

Table 1B. Supporting Trial

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcome (MPT versus MP)
HOVON 49 study in patients aged >65 years (abstract only)						
11,12	Randomised, open-label, phase III trial	344 patients randomised to melphalan + prednisolone or melphalan + prednisolone + thalidomide Data on first 320 patients presented here	Treatment-naive Aged >65 years Stage Ib, II or III MM based on Durie-Salmon criteria WHO PS 0-3 adequate renal, liver and cardiac function, no peripheral neuropathy	Median age: 72 years Other details lacking	8 four-week cycles of: Melphalan 0.25mg/kg + prednisone 1mg/kg given orally on days 1 to 5 of each cycle (MP, n=149) versus Thalidomide 200mg daily + MP, followed by thalidomide 50mg daily maintenance if good response and plateau reached (MPT, n=152) [Not stated if thromboprophylaxis given]	Trial recruitment stopped early due to other studies indicating significant advantage with thalidomide treatment. Median follow-up at data cut off not stated. **Primary endpoint:** Event-free survival: significant difference in favour of MPT reported ($p<0.001$) but magnitude not stated. Best response: 63% versus 47%; $p<0.001$ CR: 1% versus 1% VGPR: 28% versus 8% PR: 34% versus 38% **Secondary endpoints:** OS and PFS: no significant difference

CR = complete response; DSMB = data safety monitoring board; Durie-Salmon criteria (see Glossary); HR = hazard ratio; ISS = International Staging System (see Glossary); ITT = intention-to-treat; MM = multiple myeloma; NS= not statistically significant; OS = overall survival; PFS = progression-free survival; PR = partial response; SAP = survival after progression; s.c = sub-cutaneous; TTP = time to progression; VGPR = very good partial response; WHO PS = WHO performance status