

**NIHR Innovation Observatory
Evidence Briefing: April 2017****Denosumab for the prevention of skeletal
related events in patients with multiple
myeloma – first line**

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LAY SUMMARY

Multiple myeloma is a form of blood cancer that develops in the bone marrow and affects multiple organs and systems, such as bones, kidneys, blood and immune system. It is the 17th most common cancer in the UK. Treatment for this type of cancer includes chemotherapy, radiation and stem cell transplant. The cancer causes destruction of the bones, mainly the spine, pelvis or rib cage, which leads to significant pain and an increase in the risk of fractures. Multiple myeloma occurs mainly in older adults, with its peak between 85 to 89 years of age.

Denosumab is a novel drug used for the treatment of osteoporosis, prevention of skeletal-related events due to bone metastases, and giant cell tumour of the bone. It is also under development for rheumatoid arthritis, and prevention of bone metastases in breast cancer. Early results suggest the use of denosumab for the prevention of skeletal-related events in patients with multiple myeloma has the potential to be effective without some of the side-effects associated with other treatment options.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

- Multiple myeloma – first line, prevention of skeletal related events

TECHNOLOGY

DESCRIPTION

Denosumab [AMG 162; AMG-162; AMGN-0007; anti-OPGL MAb, Amgen; denosumab; Pralia; Prolia; Ranmark; Xgeva] is a fully-human IgG2 MAb against Receptor activator of nuclear factor kappa-B ligand (RANKL, osteoprotegerin ligand), developed by Amgen for the treatment of osteoporosis, skeletal-related events (SREs) due to bone metastases, and giant cell tumour of the bone. It is also under development for rheumatoid arthritis (RA) and prevention of bone metastases in breast cancer. RANKL is involved in bone resorption by osteoclasts.

INNOVATION and/or ADVANTAGES

If licenced for multiple myeloma denosumab will offer an alternative therapy to bisphosphonates for the prevention of skeletal related events (SRE). It is not associated with renal toxicity.

DEVELOPER

Amgen Ltd.

AVAILABILITY, LAUNCH or MARKETING

It is currently in Phase III trials.

Denosumab 60 mg every 6 months is currently licenced in the EU for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, as well as for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Denosumab 120 mg every 4 weeks is currently licenced in the EU for the prevention of skeletal-related events in adult patients with bone metastases associated with solid tumours, as well as for the treatment of giant cell tumour of the bone in adults or skeletally mature adolescents that is unresectable or where surgery is likely to result in severe morbidity.

PATIENT GROUP

BACKGROUND

Multiple myeloma is a form of blood cancer that develops in the bone marrow. Myeloma is a malignancy of the plasma cells which normally produce immunoglobulin; abnormal immunoglobulin, produced by myeloma cells, interferes with normal blood cell production. It is the 17th most common cancer in the UK, affecting multiple organs and systems, such as bones, kidneys, blood and immune system.¹ It is often found in multiple places in the body, hence the name multiple myeloma. Myeloma blood cancer treatment may include chemotherapy, radiation and stem cell transplant.²

Bone lesions from multiple myeloma are the primary cause of bone pain. The condition destroys the bones, primarily affecting the spine, pelvis and rib cage. Damage extends from the inner bone to the outside surface of the bones. As the damage progresses it weakens the bone, causing pain and

increasing the risk of fractures. Of those diagnosed with multiple myeloma 85% have some degree of bone loss. The cause of multiple myeloma has not yet been identified.²

CLINICAL NEED and BURDEN OF DISEASE

A total of 5501 people were diagnosed in the UK in 2014;³ diagnosis occurring more frequently in men and in people of African-Caribbean family origin.¹ In 2012, 39,000 cases were diagnosed across Europe.³ It is also the second most common form of blood cancer; although only represents 2% of all cancers.⁴ The lifetime risk of developing myeloma was around 1 in 115 for men and around 1 in 155 for women in the UK, with the majority of those affected being older adults (peak rate between 85 to 89 years of age). In 2014, there were around 2,900 myeloma deaths in the UK and is therefore the 15th most common cause of cancer death. Of those diagnosed with myeloma in England and Wales 33% survive their disease for ten or more years according to data from 2010/11.³

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance. Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours [TA265]. October 2012.
- NICE guideline. Myeloma and management [NG35]. February 2016.

NHS ENGLAND and POLICY GUIDANCE

No guidance is currently available.

OTHER GUIDANCE

No guidance is currently available.

CURRENT TREATMENT OPTIONS

Due to non-specific symptoms, diagnosis is often delayed, leading to significant early morbidity and mortality. Effective new treatment developments have increased survival rates and improved quality of life, however, myeloma is still incurable and its management complex and challenging. Treatment increasingly involves expensive drugs and frequent hospital visits.¹

Guidelines recommend the use of bisphosphonates for the treatment of multiple myeloma bone diseases. These drugs help prevent myeloma bone disease from getting worse, decrease bone pain, and reduce the likelihood of fracture. The majority of multiple myeloma patients take these drugs, which are used at a higher dose than the bisphosphonates used to treat osteoporosis in people who do not have cancer. These higher doses of bisphosphonates are also used to treat hypercalcemia (elevated calcium levels in the blood), another common problem in myeloma.²

Intravenous bisphosphonates are associated with serious side effects, including reduced kidney function (renal impairment) and osteonecrosis of the jaw (ONJ), a painful condition in which the jawbone is exposed. To reduce the risk of side effects, creatinine levels are monitored by blood tests. Blood tests are done before each dose of bisphosphonate therapy.² The most commonly used intravenous bisphosphonates (e.g. zoledronic acid) are contraindicated in patients with severe renal

impairment (CrCl <30 ml/min) and increased infusion time/dose modification is required for patients with CrCl <60 ml/min.

EFFICACY and SAFETY

Trial	AMGEN-20050134 NCT1345019
Sponsor	Amgen, Daiichi Sankyo Inc
Status	Primary analysis reported.
Source	ClinicalTrials.gov
Location	United States, Canada, Europe, Asia
Design	Interventional, randomised, double-blind, multicentre study of denosumab compared with zoledronic acid (Phase 3)
Participants	N=1700; Newly diagnosed with multiple myeloma with radiographic evidence of at least one bone lesion at baseline. Participants had adequate organ function (incl. creatinine clearance \geq 30 mL/min), planned to receive or was receiving first-line primary anti-myeloma therapy.
Schedule	Denosumab 120 mg subcutaneous every 4 weeks plus IV placebo Or Zoledronic acid 4 mg IV over 15 minutes (adjusted for renal function) every 4 weeks plus subcutaneous placebo.
Follow-up	2- year planned follow-up for overall survival once the study meets its primary endpoint.
Primary outcome	Time to the first on-study skeletal related event (SRE) (non-inferiority test) [Time Frame: Approximately 50 months] Until approximately 676 subjects have experienced at least one on-study SRE (anticipated to be approximately 50 months). SRE was defined as: pathological fracture, surgery to bone, radiation to bone or spinal cord compression.
Secondary outcomes	- Time to the first on-study skeletal-related event (superiority) - Time to the first-and-subsequent on-study skeletal-related event (superiority) - Overall survival
Key results	This study met its primary endpoint of non-inferiority for time to first on-study skeletal-related event between denosumab and ZA (HR 0.98, p=0.01). During the primary blinded treatment period (median follow-up = 17.4 months), the time to first on-study SRE (primary endpoint) was similar between denosumab- and ZA-treated patients: 43.8 percent and 44.6 percent, respectively. Superiority was not demonstrated for time to first on-study skeletal-related event or time to first-and-subsequent skeletal-related events (secondary endpoints). Overall survival was similar in both treatment arms: HR (95% CI) = 0.90 (0.70, 1.16); P = 0.41.
Adverse effects	Overall adverse event rate was similar between treatment arms. Significantly lower incidence of adverse events related to renal toxicity associated with denosumab therapy compared with zoledronic acid. There were 35 (4.1%) and 24 (2.8%) positively adjudicated events of osteonecrosis of the jaw in the denosumab and zoledronic acid arms, respectively.
Expected reporting date	Primary analysis reported in March 2017 at the International Myeloma Workshop (citation given above) . Estimated study completion March 2019.

Trial	05-1166 20050134 AMGEN-20050134 FHCRC-2082.00 MDACC: 2005-0831 NCT00259740 NCT00337363 TrialTroveID-039743
Sponsor	Amgen, Daiichi Sankyo, National Institutes of Health/National Cancer Institute
Status	Completed
Source of Information	Trialtrove
Location	Australia, North America, United States
Design	Interventional Study Design, Non-Randomized, Safety/Efficacy, Single Group, Open Label, Single-arm Two-cohort Proof of Concept
Participants	N= 96. Aged > or = 18 years. Patients with relapsed or plateau-phase multiple myeloma (>0.5 g/dL) as determined by special blood tests ECOG 0 or 1.
Schedule	Denosumab: 120mg administered subcutaneously on study days 1, 8, 15 and every 28 days thereafter. Each dose will be administered in two separate injections of 60mg (1.0mL) each. Patients undergo blood collection periodically during study for pharmacologic and biomarker correlative studies. All patients enrolled into the study will get drug denosumab, and supplements of calcium and vitamin D as part of the study. ASH 2007: Patients were given subcutaneous injections of denosumab 120mg monthly with additional loading doses on days 8 and 15 of month 1. Patients were instructed to take calcium 500mg and Vit D 400 IU daily.
Follow-up	After completion of study treatment, patients are followed every 3 months for up to 5 years.
Primary Outcomes	To estimate the objective response rate in patients with relapsed or plateau-phase multiple myeloma.
Secondary Outcomes	Overall response rate and the CR rate in these patients. Overall safety profile of denosumab, in terms of adverse events, antibody formation, and survival in these patients. Time to disease progression. Duration of response. First occurrence of a skeletal-related event. Progression-free survival, the effect of denosumab on bone turnover markers, myeloma-associated biomarkers, and myeloma cells by immunohistochemistry. Measure serum through levels of denosumab in these patients. Effect of denosumab on patient reported outcomes.
Key Results	No subjects in either cohort met the protocol-defined objective response criteria of complete response (CR) or partial response (PR), but denosumab effectively inhibited the RANKL pathway regardless of previous exposure to bisphosphonates, as evidenced by suppressed levels of bone turnover marker, serum C-terminal telopeptide of type 1 collagen (sCTX). Eleven (21%) subjects who relapsed within 3 months before study entry maintained stable disease for up to 16.5 months. Nineteen (46%) subjects with plateau-phase myeloma maintained stable disease for up to 18.3 months.

Adverse effects (AEs)	The AE profile for denosumab and its dosing schedule in these populations was consistent with that for advanced cancer patients receiving systemic therapy. Additional controlled clinical studies of denosumab in subjects with both relapsed and plateau-phase MM are warranted.
Expected reporting date	-

Trial	15-571 NCT02833610 TrialTroveID-282410
Sponsor	Amgen, Massachusetts General Hospital
Status	Open
Source of Information	TrialTrove
Location	United States
Design	Interventional Study Design, Safety/Efficacy, Single Group, Open Label, Treatment, Single-arm
Participants	Patients with symptomatic multiple myeloma renal insufficiency. N=55
Schedule	Arms: Experimental: Denosumab injection patients will be administered Denosumab Q4W at a pre-determined dose for 12 cycles. Denosumab Q4W is administered by subcutaneous injection.
Follow-up	Not reported.
Primary Outcomes	Possible treatment for the consequences of multiple myeloma with renal insufficiency. Safety and tolerability of denosumab in MM participants, by studying drug interactions with different parts of the body. Percent change of sCTX Levels.
Secondary Outcomes	Percent change in bone mineral density. Percent change in uNTX levels. Subject incidence of hypocalcemia. Subject incidence of occurrence of documented SRE at 12 months. Subject incidence of AEs. Percent Change in Bone Turnover Markers.
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Estimated Study Completion Date October 2023

ESTIMATED COST and IMPACT

COST

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

- Reduced mortality/increased length of survival
 Reduced symptoms or disability

- Other: improved patient convenience, wider societal benefits. No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- Increased use of existing services Decreased use of existing services
- Re-organisation of existing services Need for new services
- Other None identified

IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs Reduced drug treatment costs
- Other increase in costs Other reduction in costs
- Other None identified

OTHER ISSUES

- Clinical uncertainty or other research question identified None identified

REFERENCES

- 1 NICE. Myeloma: Diagnosis and Management. NICE Guideline. 2016.
- 2 The Multiple Myeloma Research Foundation. Multiple Myeloma.
- 3 Cancer Research UK. Myeloma incidence statistics. [cited; Available from: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence>
- 4 Myeloma UK. Facts and Figures. [cited; Available from: <https://www.myeloma.org.uk/information/facts-and-figures/>