Systemic Anti Cancer Therapy Protocol

Denosumab (XGEVA)
Solid Tumours

PROTOCOL REF: MPHADENXST
(Version No: 1.0)

Approved for use in:

Recommended for the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases associated with breast cancer or other solid tumours, **but not including prostate cancer.**

Prostate cancer patients with renal impairment that precludes bisphosphonate use will be eligible for this treatment.

Dosage:

Drug	Dose	Route	Frequency
Denosumab	**120mg**	Subcutaneous Injection	Day 1 only of a 28-42 day cycle*

To continue treatment until the clinician or clinical team manging care consider it appropriate to stop (no longer deriving clinical benefit).

*License states that cycle length is 4 weeks however this can be increased to 6 weeks in the following cases:

- If given with concurrent 3 weekly chemotherapy.
- Persistent hypocalcaemia, despite normal vitamin D levels, with 4 weekly dosing.

Administration:

- Inspect vial prior to administration, do not use if cloudy or discoloured
- Formulation is 120mg vial of Denosumab in 1.7ml of solution, do not shake excessively.

- To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly.
- A 27 gauge needle is recommended for the administration of denosumab.
- Single subcutaneous injection into the thigh, abdomen or upper arm.
- **Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present.**
- Calcium and vitamin D doses may be increased, reduced or stopped based on clinical need.
- Patients with rare hereditary problems of fructose intolerance should not use denosumab.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients listed in the **SmPC**.

Severe, untreatred hypocalcaemia (symptoms as detailed in the 'Main Toxicities' section).

Unhealed lesions from dental or oral surgery- unless reviewed by Maxillofacial Surgeons and/or Dentist and decision made by clinical team managing care to continue with treatment.

Emetogenic risk:

Mild emetogenic potential.

Supportive treatments:

Adcal D3 1-2 tablets taken once a day (please note: patient can be obtaining supply via repeat prescription from the GP).

Dosing in renal and hepatic impairment:

Renal	Patients with creatinine clearance < 30 mL/min (Severe renal impairment) or on dialysis are at increased risk of developing hypocalcaemia. The risk of developing hypocalcaemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels recommended.

Hepatic	No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment.

Interactions:

No interaction studies have been performed.

In clinical trials, Denosumab has been administered in combination with standard anti-cancer treatment and in subjects previously receiving bisphosphonates. There were no clinically-relevant alterations in serum concentration and pharmacodynamics of denosumab by concomitant chemotherapy and/or hormone therapy or by previous intravenous bisphosphonate exposure.

Main toxicities:

Refer to SmPC for full list of adverse drug reactions

Very Common
Hypocalcaemia- can be severe and symptomatic. Symptoms of hypocalcaemia in clinical studies included; paraesthesias or muscle stiffness, twitching, spasms and muscle cramps. Symptoms of severe hypocalcaemia include; QT interval prolongation, tetany, seizures, altered mental status (including coma) **Musculoskeletal pain**- in clinical trials discontinuation due to this side-effect was uncommon. **Diarrhoea** **Dyspnoea**

Other ADRs	
Common	**Osteonecrosis of the Jaw (ONJ)** A condition in which the jawbone becomes necrotic, exposed, and does not heal within 8 weeks. The etiology of ONJ is not clear, but may be associated with inhibition of bone remodeling. Known risk factors for ONJ include invasive dental procedures (e.g., tooth extraction, dental implants, and oral surgery), poor oral hygiene, or other pre-existing dental disease. It is recommended that patients should have a dental examination prior to treatment. If any invasive dental procedures need to be undertaken, treatment should be delayed until any oral lesions have healed (recommended duration 6 weeks).

	All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling. If invasive dental work is required while on denosumab then treatment will be withheld for 6 weeks or until dentist or oral surgeon confirms that is safe to resume treatment. Patients who experience ONJ should be managed in collaboration with a dentist or oral surgeon. Treatment with denosumab should be interrupted until the condition resolves and the contributing risk factors are mitigated where possible. Alternatively, the decision to resume treatment can be made by clinical team managing their care in conjunction with the dentist/oral surgeon and the patient. **Hypophosphataemia** Refer to CCC Hypophosphataemia guidelines for replacement.
Uncommon **Frequency unknown**	**Atypical femoral fracture** Risk increased with longer duration of treatment. May occur with little or no trauma. Patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture. **Skin toxicity/rash** Lichenoid drug eruptions **Osteonecrosis of the external auditory canal** Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D15	Cycle 2	Prior to cycle 3	Cycle 3	Cycle 4	Ongoing
Informed Consent	X							
Clinical Assessment	X				X			Every 3 to 6 months as clinically indicated
SACT Pre-assessment	X							Can be done on same day of 1st SACT assessment
SACT Assessment (to include PS and toxicities)		X		X		X	X	Every cycle
U&E & serum creatinine (Renal profile)	X			X		X	X	Every Cycle
Bone Profile	X		X	X		X	X	Every Cycle
Magnesium								If clinically indicated (hypocalcaemia and concurrent chemotherapy that affects Magnesium e.g. platinum)
CrCl (Cockcroft and Gault)	X			X		X	X	Every cycle
CT scan	X							Every 3-6 months and/or as clinically indicated
ECG								If clinically indicated (suspected Hypocalcaemia-induced QT prolongation)
Blood pressure measurement	X							Repeat if clinically indicated
Respiratory Rate								If clinically indicated
Weight recorded	X	X		X		X	X	Every cycle
Blood glucose								If clinically indicated

Dose Modifications and Toxicity Management:

Proceed Rules in Hub clinic:

Prior to cycle 1 day 1- confirm patient has completed baseline dental check.

Proceed on day 1 of cycle 1 and subsequent cycles if-

Adjusted Calcium ≥ Lower Limit Normal (LLN*)	CrCl (creatinine clearance calculated using Cockcroft and Gault equation) ≥ 30ml/min

Delay 1 week**on day 1 if-

If given concurrent with other SACT then consider deferring until next cycle is due.

Adjusted Calcium < Lower Limit Normal (LLN*)	CrCl (creatinine clearance calculated using Cockcroft and Gault equation) < 30ml/min

*Please refer to adjusted calcium range specific to the biochemistry laboratory that has processed the sample.

** Unless decision made by clinical team to continue with treatment with appropriate intervention (monitoring and/or increased supplementation).

When assessing blood results it is important to check for trends in adjusted calcium and creatinine clearance. If the trend denotes a decline in-:

- Adjusted calcium- then provided patient is adherent with supplementation then to consult with medical team or appropriate non-medical prescriber with regards to increasing supplementation dose.
- Serum creatinine ≥ 15% then consult with the appropriate clinical team (refer to 'Dosing in Renal and Hepatic impairment' section.

Following any deferral- confirm patient adherence with calcium and vitamin D supplementation.

If patient deferred for 2 consecutive weeks despite patient adherence with supplementation- please check vitamin D level. It is important to ensure all patients receiving denosumab treatment are vitamin D replete. Contact clinical team if vitamin D level is low.

Denosumab Given via Clatterbridge in the Community (CIC) Team

If patient has had stable bone and renal function for 6 consecutive treatments then blood check will be repeated on the day of treatment, starting with the 6th cycle, and checked within 72 hours for the subsequent cycles that will be administered in 4 weeks' time. Patients who fall into the exclusion criteria outlined the 'Denosumab Risk Assessment- CIC Administration' will have their bloods taken 72 hours prior to each treatment and checked ahead of administration.

References:

Amgen Denosumab Health Care Professional Letter. Denosumab 120mg (XGEVA®▼): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia (July 2014).

NICE TA265 – Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (October 2012). Accessed on 27th January 2020 via https://www.nice.org.uk/guidance/ta265/chapter/1-Guidance

Prevention of Skeletal-Related Events in Patients with Bone Metastases, CCC Clinical Procedure, v1.

Society for Endocrinology. Emergency Management of Acute Hypocalcaemia in Adult Patients (September 2016). Accessed on 27th of January 2020 via www.endocrinology.org

Summary of Product Characteristics (SmPC) for Denosumab (Last updated 22nd November 2019). Accessed on 27th of January 2020 via https://www.medicines.org.uk/emc/product/4675/smpc