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HEALTH TECHNOLOGY BRIEFING
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Tanezumab for cancer pain due to bone metastasis

NIHRIO ID	5480	NICE ID	10189
Developer/Company	Pfizer Limited, Eli Lilly &Co	UKPS ID	651713

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Tanezumab is in clinical development for the treatment of adults with cancer pain due to bone metastasis. Pain is an uncomfortable, unpleasant physical feeling. It usually happens when subjects have an injury or illness. Pain is common in cancer patients, particularly in the advanced stage of disease when the prevalence is estimated to be more than 70%, contributing to poor physical and emotional well-being. Most cancer pain is caused by the tumour pressing on bones, nerves or other organs in the body. Cancer can spread into the bone and cause pain by damaging the bone tissue. Cancer pain due to bone metastasis can be difficult to manage and current treatment with opioids have a risk for of addiction, misuse or dependence.

Tanezumab is an investigational humanized monoclonal antibody, that works by selectively targeting, binding to and inhibiting nerve growth factor (NGF), a known mediator of pain signalling, which is known to be elevated in chronic pain states. By tightly binding NGF, tanezumab prevents interaction between NGF and its receptors, thereby disrupting ongoing pain signalling. As an NGF-inhibitor, tanezumab has a novel mechanism that acts in a different manner compared to opioids and analgesics', including nonsteroidal anti-inflammatory drugs. Tanezumab is not centrally-acting and has no evidence of addiction. If licensed, tanezumab will offer an additional treatment option for patients with cancer pain due to bone metastasis.

PROPOSED INDICATION

Treatment of adults with cancer pain due to bone metastasis.[1]

TECHNOLOGY

DESCRIPTION

Tanezumab (PF-04383119, RN624) is a humanised monoclonal antibody directed against nerve growth factor (NGF), a modulator of nociceptor function, with potential analgesic activity. Tanezumab binds to NGF and prevents NGF binding to its high affinity, membrane-bound, catalytic receptor tropomyosin-related kinase A (TrkA), which is present on sympathetic and sensory neurons; reduced stimulation of TrkA by NGF inhibits the pain-transmission activities of these neurons. NGF, a neurotrophin, is critical to the growth and maintenance of sympathetic and sensory neurons. In addition, NGF may induce mast cells to release inflammatory proteins and may induce the upregulation of substance P and other pain-related peptides in sympathetic and sensory neurons. Upon neurotrophin binding, TrkA phosphorylates itself and members of the MAPK pathway, mediating the multiple neuronal effects of NGF.[2]

Tanezumab is currently in clinical development for the treatment of cancer pain due to bone metastasis. In the phase III clinical trial (NCT02609828), participants receive tanezumab 20 mg subcutaneously at 8-week intervals over a period of 24 weeks, followed by 24 weeks safety follow-up.[1,a]

INNOVATION AND/OR ADVANTAGES

Tanezumab is a potential first-in-class, non-opioid treatment being evaluated for cancer pain due to bone metastases. Tanezumab has a novel mechanism that acts in a different manner than opioids and other analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs), and in studies to date tanezumab has not demonstrated a risk of addiction, misuse or dependence.[3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Tanezumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Tanezumab has completed phase II and III clinical trials for the treatment of several chronic pain conditions in osteoarthritis knee, osteoarthritis hip and lower back pain, and is currently in phase III development in palliative care pain associated with bone metastasis.[4]

PATIENT GROUP

DISEASE BACKGROUND

Cancer pain due to bone metastasis, means cancer has spread into the bone and caused pain by damaging the bone tissue. The cancer can affect one specific area of bone or several areas.[5] The pain may be a dull, persistent ache that does not go away. It can happen during the day as well as at night.[6]

[a] Information provided by Pfizer

When there is damage to any part of the body, the nervous system sends a message along nerves to the brain. When the brain receives these messages, the patient feels pain. This includes pain caused by cancer.[7]

Cancer pain has different causes and most cancer pain is caused by the tumour pressing on bones, nerves or other organs in the body. Sometimes pain is due to cancer treatment. There are different types of cancer pain such as nerve pain, bone pain, soft tissue pain, phantom pain, and referred pain. It is extremely important the doctor to find out the type and the cause of pain. Then they can treat in the right way. Different types of pain need different treatment.[5]

CLINICAL NEED AND BURDEN OF DISEASE

Not everyone with cancer will have pain. Around half of the people who have treatment for cancer have some pain. When cancer has come back or spread, up to 9 out of 10 people (90%) have pain.[8] Applying this to the number of cases with metastatic cancers (stage 4) registered in England in 2017,[9] this would equate to 60,606 cases that may experience cancer pain.

The World Health Organization (WHO) estimates that 25% of all cancer patients die with unrelieved pain.[10] The relative incidence of bone metastasis by type of tumour, in patients with advanced metastatic disease, is: 65-75% in breast cancer; 65-75% in prostate; 60% in thyroid cancer; 30-40% in lung; 40% in bladder; 20-25% in renal cell carcinoma and 14-45% in melanoma.[11] Applying these estimates to the number of stage 4 of these cancers registered in England in 2017,[9] this would be equivalent to the following number of people with bone metastases:

- 1542 – 1779 breast cancer;
- 5519 – 6368 prostate cancer;
- 5464 – 7285 lung cancer;
- 586 – bladder cancer;
- 367 – 459 renal cancer;
- 49 – 156 melanoma.

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Various health and social care professionals such as general practice, nurse, physiotherapist, occupational therapist, pharmacist, specialist palliative care team, and others may be involved in managing cancer pain.[12] There are many different ways of treating cancer pain. Doctors and nurses will assess the pain to make sure the patients get the right treatment.[13]

Cancer that spreads to the bones often causes pain. Also, cancer in the bones can make them weak and more likely to break. This type of break is called a pathological fracture. Doctors can treat bones affected by cancer by using special cement to strengthen them. This is called cementoplasty. There are two techniques:[14]

- percutaneous cementoplasty
- vertebroplasty and kyphoplasty

Additionally, NICE clinical knowledge summaries on managing cancer bone pain suggests the following:[15]

- Consider whether there is a treatable underlying cause and discuss with an oncologist if this is suspected (for example, regarding radiotherapy for bone metastases).
- Seek urgent advice from an orthopaedic surgeon if there is evidence or suspicion of an actual or imminent fracture.
- For symptomatic relief:
  - Apply hot or cold packs.
  - Use standard analgesia in a stepwise approach
  - If incident pain occurs on movement, encourage the person to take a dose of their breakthrough analgesia 20–30 minutes before anticipated movement.
- If pain is difficult to manage, seek advice from a specialist (such as a palliative care specialist or an anaesthetist with an interest in chronic pain).

CURRENT TREATMENT OPTIONS

There are many different types of painkillers. The type needed depends on the type of pain that the patient has. Patients might need one or more type to help relieve the pain.[16]

Opioids
The type to be delivered depends on what kind of pain patients have and how much pain they are in. Opioids for mild to moderate pain include codeine. Opioids for severe pain include morphine, diamorphine, fentanyl and alfentanil, buprenorphine, hydromorphone, methadone, and tramadol.[16]

Non opioid drugs
Patients might take non opioid painkillers for mild to moderate pain. Patients can also take them alongside stronger painkiller for more severe pain. There are different types and include paracetamol and anti-inflammatory drugs, there are also called non-steroidal anti-inflammatory drugs (NSAIDs).[16]

Other drugs for pain control
Patients might have other drugs to take alongside painkillers. These are sometimes called co-analgesics or advent analgesics. There are different types of drugs including steroids, bisphosphonates, anti-depressants, drugs to prevent fits (anti-convulsants), local anaesthetics, and monoclonal antibodies.[16]

The ESMO guidelines recommend that treatment of bone pain should always take into consideration the use of analgesic drugs. In addition, external beam radiotherapy (EBRT), radioisotopes and targeted therapy given in association with analgesics have an important role in bone pain management.[17]

RT is highly effective in the management of metastatic bone pain. Numerous randomised, prospective trials show improvements in pain relief in 60-80% of patients after RT with complete responses (no pain and no increase in analgesic requirements) in up to 30%. The ESMO guidelines recommend that all patients with painful bone metastases should be offered EBRT.[17]

The ESMO guidelines also make the following lower grade recommendations based on less robust evidence; radioisotope therapy with strontium, samarium or rhenium can be effective in some cases but may cause bone marrow toxicity. Bisphosphonates may be considered as part of the therapeutic regimen for the treatment of patients with bone metastases in patients with a good prognosis, and especially when pain is not localised or RT is not readily accessible. Denosumab is indicated as an alternative to bisphosphonates for the treatment of patients with metastatic bone disease from solid tumours and myeloma, and is effective in delaying bone pain recurrence.[17]

PLACE OF TECHNOLOGY

If licensed, tanezumab will offer an additional treatment option for adults with cancer pain due to bone metastasis.

CLINICAL TRIAL INFORMATION

Trial	NCT02609828, A4091061, EudraCT 2013-002223-42; A phase 3 randomized, double-blind, placebo-controlled, multicenter study of the analgesic efficacy and safety of the subcutaneous administration of tanezumab (PF-04383119) in subjects with cancer pain predominantly due to bone metastasis receiving background opioid therapy **Phase III** **Location(s):** EU (including the UK) and other countries
Trial design	Randomised, placebo-controlled, multicentre, parallel assignment, quadruple-blind
Population	N=155 (planned); ≥ 18 years; subjects with cancer diagnosed as having metastasised to bone or multiple myeloma; average pain score ≥ 5 at screening for the index bone metastasis cancer pain site; patient's Global Assessment of Cancer Pain of "fair", "poor" or "very poor" at screening.
Intervention(s)	Tanezumab 20 mg subcutaneously dosed at 8 week intervals
Comparator(s)	Placebo matched to active treatment subcutaneously dosed at 8 week intervals.
Outcome(s)	Change from baseline in daily average pain intensity in index bone metastasis cancer pain site [Time frame: 8 weeks] See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of tanezumab is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Neuropathic pain in adults: pharmacological management in non-specialist settings (CG173). Last updated July 2019.
- NICE clinical guideline. Palliative care for adults: strong opioids for pain relief (CG140). Last updated August 2016.
- NICE clinical guideline. Metastatic spinal cord compression in adults: risk assessment, diagnosis and management (CG75). November 2008.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013 NHS Standard Contract for Specialised Pain. D08/S/a.

- NHS England. Clinical Com: Ziconotide (intrathecal delivery) for chronic cancer pain. 16011/P. July 2016.

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO). Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. July 2018.[17]
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ADDITIONAL INFORMATION

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