An Open-label, Multi-center, Phase 2 Study of Denosumab in Subjects with Giant Cell Rich Tumors of Bone.

Published: 19-01-2018
Last updated: 04-01-2025

Primary:Subjects with salvageable giant cell rich tumors:- To evaluate subjects who do not require surgery during the study- To evaluate subjects who are able to undergo a less morbid surgical procedure compared with the planned surgical procedure...

Ethical review	Approved WMO
Status	Completed
Health condition type	Skeletal neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON47771

Source
ToetsingOnline

Brief title
Denosumab in patients with giant cell rich tumors of bone.

Condition

- Skeletal neoplasms benign

Synonym
giant cell rich tumors of bone

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Amgen

Intervention

Keyword: Aneurysmal bone cyst, Denosumab, Giant cell granuloma, Giant cell rich tumor of bone

Outcome measures

Primary outcome

Subjects with salvageable giant cell rich tumors:

- The proportion of subjects who do not require surgery during the study

- The proportion of subjects undergoing the planned versus performed type of

surgery during the study

Subjects with unsalvageable giant cell rich tumors (combined endpoint):

- Disease control:

o Radiological response assessed by combined RECIST, PET, inverse Choi when

available AND/OR

o No progression at 1 year (based on disease assessment)

- Stable pain score, defined as * 1 point increase on *worst pain* question in

BPI-SF

Secondary outcome

- Frequency of adverse events (AEs), as determined by Common Terminology

Criteria for Adverse Events (CTCAE) v. 4.03 criteria

- The proportion of subjects with disease recurrence after denosumab followed

by surgery during the study

- Symptomatic improvement in the European Organization for Research and

Treatment of Cancer, Quality of Life Questionnaire C30 (EORTC QLC-30) / BPI-SF,

including:

1) Change from baseline at 1 year, and

2) Time to improvement in pain and time to worsening of pain

- Time to surgery (for subjects with salvageable disease), time to recurrence

after surgery, progression free survival

Translational research:

- Translational studies. Systematic analysis of pathologic and molecular

markers on tumor material, including evaluation of pathological response for

subjects undergoing surgery

Study description

Background summary

The current mainstay of treatment of giant cell rich tumors of bone is surgery, like in aneurysmal bone cysts, giant cell granuloma, osteoblastoma, fibroblastoma and chondromyoid fibroma. Novel treatment modalities are needed in order to decrease the significant morbidity that is caused by surgical intervention and to avoid recurrent disease.

Denosumab has been approved for the treatment of classical giant cell tumors of bone, after the success of two phase 2 studies. Since the histological presence of osteoclastic giant cells and expression of RANK/RANKL is something GCTB and other giant cell rich tumors all have in common, we hypothesize that giant cell rich tumors will show the same reponse to denosumab as previously seen in GCTB. This study will investigate the effect of denosumab in subjects with giant cell rich tumors that have recurred after surgery or require morbid surgery.

Study objective

Primary:

Subjects with salvageable giant cell rich tumors:
- To evaluate subjects who do not require surgery during the study
- To evaluate subjects who are able to undergo a less morbid surgical procedure compared with the planned surgical procedure at baseline during the study

Subjects with unsalvageable giant cell rich tumors (combined objective):
- To evaluate disease control:
o Radiological response assessed by combined RECIST, PET, inverse Choi when available AND/OR
o No progression at 1 year (based on disease assessment)
- Stable pain score, defined as * 1 point increase on *worst pain* question in Brief Pain Inventory - short form (BPI-SF)

Secondary:

- To evaluate the safety and tolerability of denosumab in subjects with giant cell rich tumors
- To evaluate the proportion of recurrences after denosumab followed by surgery
- To evaluate symptomatic improvement after denosumab in subjects with giant cell rich tumors
- To evaluate time to surgery (for subjects with salvageable disease), time to recurrence after surgery, progression free survival

Translational:

- Translational studies. Systematic analysis of pathologic and molecular markers on tumor material, including evaluation of pathological response for subjects undergoing surgery

Study design

In this open-label, multi-center, phase 2 trial subjects with giant cell rich tumors that would require morbid surgery or with tumors that have recurred after previous surgery will be treated with denosumab.

Denosumab will be given in a dose of 120mg subcutaneous (SC) on day 1 of every 4 week cycle with a loading dose of 120mg SC on days 8 and 15 of only the first cycle.

Surgical resection may occur at any time during the study based on the clinical judgement of the Investigator. For subjects that undergo surgical tumor resection, denosumab treatment will be discontinued after surgery. In all other cases, denosumab treatment continues for a maximum of up to 3 years, or until confirmation of disease progression, the Investigator*s or sponsor*s recommendation of discontinuation, the subject*s decision to discontinue for any reason or administration of any of the prohibited therapies listed in the study protocol. For subjects that continue to show clinical benefit after 3 years of treatment with denosumab, ongoing treatment outside of study protocol is optional after discussion with Amgen.

For assessment of histopathological response and for translational research purposes a tumor sample will be requested either during study or at the end of

treatment visit (surgical sample only for the subject group that has undergone surgery).

During the time the study is still open, re-treatment may be allowed for subjects who demonstrated a response to denosumab and are currently not receiving denosumab treatment (e.g., in the case of recurrent disease while subject is in the safety follow-up phase or subjects that have completed the study and have later experienced disease progression). The re-treatment decision including the use of the loading dose and discontinuation of therapy will be handled on a case-by-case basis; prior authorization from the Sponsor is required. Subjects must meet all inclusion/exclusion criteria prior to being considered for re-treatment, with the exception of the exclusion criterium of previous denosumab treatment. The same subject number will be assigned to avoid bias.

Intervention

Denosumab will be given in a dose of 120mg subcutaneously (SC) on day 1 of every 4 week cycle with a loading dose of 120mg SC on days 8 and 15 of the first cycle. Maximum treatment period is 3 years. For subjects that continue to show clinical benefit after 3 years of treatment with denosumab, ongoing treatment outside of study protocol is optional after discussion with Amgen.

Study burden and risks

Burden subjects
- Vena puncture: possible discomfort / pain
- Hospital visits: 30-45 minutes per visit every 4 weeks (for blood withdrawal, physical exam, administration of medication)
- Completing 2 questionnaires per visit, 5 minutes per questionnaire. During first 6 months of study once every 4 weeks, after that once every 12 weeks

Risks / side-effects
- Side-effects study medication: common side effects (>10%) bone pain, hypocalcemia / phosphatemia, shortness of breath. Rare serious side effects are: osteonecrosis of the jaw, atypical femoral fractures, severe hypocalcemia. These may lead to hospital admission, and in severe cases to prolonged disability.
- In cases with operable tumors the planned surgical procedure will be postponed in order to evaluate the effect of denosumab. This is justified since these are slow growing lesions which are frequently monitored and that can possibly regress as a result of denosumab.
- In cases of inoperable tumors there is no standard treatment procedure outside of this study

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The population will consist of patients with the following tumor types:;- Pathologically proven giant cell rich tumor ;* ABC;* GCG;* Other giant cell rich lesions (primary bone, non-malignant, pathology and radiology to be reviewed during multidisciplinary meeting LUMC);- Patients with surgically unsalvageable disease (e.g., sacral, spinal giant cell rich tumors, or multiple lesions including pulmonary metastases) OR patients whose planned surgery includes joint resection, limb amputation, hemipelvectomy or surgical procedure resulting in severe morbidity;- Measurable evidence of active disease within 1 year before study enrollment;- Albumin-adjusted serum calcium level * 2.0 mmol/L (8.0 mg/dL);- Aged 18 years and up and skeletally mature ;- ECOG performance status 0, 1 or 2;- Written signed informed consent

Exclusion criteria

- Known or suspected current diagnosis of classic GCTB;- Known or suspected current diagnosis of underlying malignancy including but not limited to high-grade sarcoma, osteosarcoma, fibrosarcoma, malignant giant cell sarcoma;- Known or suspected current diagnosis of brown cell tumor of hyperparathyroidism, Paget*s disease or cherubism;- Known or suspected current diagnosis of primary soft tissue tumor with invasion of the bone ;- Known diagnosis of other malignancy within the past 5 years (patients with definitively treated basal cell carcinoma and cervical carcinoma in situ are permitted);- Previous treatment with denosumab (with the exception of patients eligible for re-treatment with denosumab after completing this study);- Prior history or current evidence of osteonecrosis/osteomyelitis of the jaw;- Active dental or jaw condition which requires oral surgery, including tooth extraction;- Non-healed dental/oral surgery;- Planned invasive dental procedure for the course of the study;- Known hypersensitivity to denosumab;- Known hypersensitivity to products to be administered during the study (calcium and/or vitamin D) ;- Currently receiving other specific treatment for giant cell rich tumors of bone (e.g., radiation, chemotherapy or embolization);- Concurrent bisphosphonate treatment;- Major surgery less than 4 weeks prior to start of treatment;- Treatment with other investigational device or drug 30 days prior to study enrollment ;- Unstable systemic disease including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, or myocardial infarction within 6 months before study enrollment;- Patient is pregnant or breast feeding, or planning to become pregnant within 5 months after the EOT visit;- Patient or partner of patient of child bearing potential is not willing to use a highly effective method of contraception during treatment and for 5 months after the EOT visit;- Patient has any kind of disorder that compromises the ability of the patient to give written informed consent and/or to comply with study procedures

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	18-06-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xgeva
Generic name:	Denosumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-01-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	04-06-2018
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	10-04-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-005244-42-NL
CCMO	NL61206.058.17

Study results

Date completed:	19-03-2020
Results posted:	26-11-2020
Actual enrolment:	2

First publication
16-06-2020