A Randomized, Open-Label Phase 2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with relapsed, Recurrent, or Refractory Synovial Sarcoma.

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Primary:- To evaluate the progression free survival in patients who are treated with ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.Secondary:- To...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Synovial and bursal disorders
Study type	Observational invasive

Summary

ID

NL-OMON55480

Source
ToetsingOnline

Brief title
J1S-MC-JV02

Condition

- Synovial and bursal disorders

Synonym
malignant tumour that arises arount the tissues of the joints

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly

Intervention

Keyword: Ramucirumab, Synovial Sarcoma

Outcome measures

Primary outcome

To evaluate the progression free survival in patients who are treated with ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.

Secondary outcome

Safety and tolerability Serious adverse events, adverse events, laboratory assesments and vital signs

Efficacy evaluation by - Overall response rate, duration of response and complete response.

PK evaluation by - minimum and maximum concentration

Immunogenicity evaluation by - incidence of immunogenicity

Study description

Background summary

Synovial Sarcoma is the most common non-rhabdomyosarcoma STS in children and

adolescents and makes up 10% of all STSs (Soole et al. 2014). SS is found in both pediatrics and adults and is classified as a malignant mesenchymal tumor, characterized by local invasiveness and a propensity to metastasize (Ferrari et al. 2015). These tumors arise in close proximity to tendon sheaths, joint cavities, and bursae and often metastasize to the lungs or lymph nodes (Stanelle et al. 2013). Treatment strategies have been difficult to identify due to low incidence and unusual clinical behavior that does not follow typical patterns of local recurrence, metastasis, or response to treatment. For both adult and pediatric patients with SS, the current standard approach for local disease is surgical resection; radiation therapy and/or chemotherapy may be given before or after surgery. As a chemosensitive malignancy, SS tumors have shown response to ifosfamide-based chemotherapy (typically in combination with doxorubicin, and generally with multimodal therapy). However, there is no defined standard treatment regimen in the relapsed setting.
Despite initial treatment, approximately 25% to 40% of pediatric patients with SS who initially present with local tumors develop recurrent or refractory disease; in these patients the 5-year overall survival (OS) is just 30% to 42% after relapsing (Ferrari et al. 2015; Soole et al. 2014).

Ramucirumab is a human receptor-targeted monoclonal antibody (mAb) that specifically binds VEGF Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream signaling components, including p44/p42 mitogen-activated protein kinases. This neutralizes ligand-induced proliferation and migration of human endothelial cells and ultimately inhibits tumor growth and propagation.

Ramucirumab has not been approved in pediatrics; however, is being studied in the ongoing I4T-MC-JVDA (JVDA) trial. In adults, ramucirumab has improved outcomes, including OS, in multiple indications as both a monotherapy and combination with other agents. Ramucirumab is approved as monotherapy or in combination with paclitaxel in the United States (US), the European Union (EU), Japan, and other countries for the treatment of adult patients with advanced gastric cancer or gastroesophageal junction (GEJ) adenocarcinoma with disease progression on or after prior platinum and/or fluoropyrimidine chemotherapy. The approvals were based on the clinical efficacy and safety demonstrated in 2 global, randomized, doubleblind, and placebo-controlled Phase 3 studies, REGARD (Fuchs et al. 2014) and RAINBOW (Wilke et al. 2014).

Study objective

Primary:
- To evaluate the progression free survival in patients who are treated with ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.

Secondary:
- To evaluate the safety and tolerability of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.
- To evaluate the efficacy of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.
- To characterize the PK of ramucirumab when co-administered with gemcitabine and docetaxel in pediatric and young adult patients with SS.
- To assess the immunogenicity of ramucirumab when co-administered with gemcitabine and docetaxel in pediatric and young adult patients with SS.

Exploratory:
- To explore additional measures of the efficacy of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS.
- To explore the associations between biomarkers, disease state, and clinical outcomes

Study design

Study JV02, combined with Protocol J1S-MC-JAAA (hereinafter referred to as the CAMPFIRE Master Protocol), is a Phase 2, randomized investigation in pediatric patients and young adults diagnosed with relapsed, recurrent, or refractory SS not amendable to surgery evaluating
ramucirumab in combination with gemcitabine and docetaxel. Patients will be randomized at a ratio of 2:1 to receive either experimental or control therapy respectively.

The primary endpoint of the study (PFS) will be evaluated via a Bayesian analysis incorporating information regarding historical control outcomes as well as effect-size observed on Study JV01.

This design allows for a reduced proportion of patients to be randomized to control therapy while maintaining power in light of sample-size limitations associated with the underlying rarity of the disease. Details of the Bayesian analysis are provided in the SAP,

Study burden and risks

As of 31 December 2020, ramucirumab or ramucirumab/placebo has been administered either as a single agent (monotherapy) or in combination with various anti-tumor agents to approximately 10637 patients with different cancers in Phase 1/1b, Phase 2, and Phase 3 clinical trials in the ramucirumab development program. An estimated 6501 patients have received ramucirumab: 1452 patients received single-agent ramucirumab and 5049 patients received

ramucirumab in combination with other anti-cancer agents. A single dose of ramucirumab has also been administered subcutaneously or intravenously to approximately 28 healthy participants.

This Risk Profile is based on safety data from clinical trials in which patients were either treated with ramucirumab as a single agent (monotherapy) or in combination with other anti-cancer agents.

Risks and discomforts associated with ramucirumab are described below by cancer type in the following categories

- Gastric Cancer
- Single-agent Ramucirumab
Very Common Side Effects (>=10% of study population)
• Stomach pain
• High blood pressure
• Loose stools

Common Side Effects (>=1% to <10% of patients)
• Headache
• Low levels of important chemicals, such as potassium and sodium, in the blood
• Low neutrophil (a kind of white blood cell) count
• Blocking of the arteries by a blood clot
• Blockage of bowel
• Nosebleed
• Rash
• Protein in the urine

Uncommon Side Effects (<1% of patients)
• Tears (perforations) in the walls of the stomach or intestines

-Hepatocellular Carcinoma
-Single Agent Ramucirumab
Very Common Side Effects (>=10% of study population)
• Feeling tired/lack of energy/weakness
• Accumulation of fluid, causing swelling in tissues in body areas such as the legs
• High blood pressure
• Stomach pain
• Decrease or loss of appetite
• Loss of sleep
• Fever
• Nausea
• Belly swelling due to fluid build-up
• Vomiting
• Protein in the urine
• Headache

• Nosebleed
• Back pain
• Low platelet count,
• Abnormally low level of protein (albumin) in the blood.

Common Side Effects (>=1% to <10% of patients)
• Decreased brain function in patients with liver damage/failure
• Decline in kidney function in patients with liver failure,
• Low neutrophil (a kind of white blood cell) count.
• Reactions related to infusion of ramucirumab: symptoms may include shaking, back pain or spasms, chest pain and/or tightness, feeling cold, red skin, trouble breathing, rash, fever, headache, body aches, stomach pain, nausea, vomiting, blurry vision, alterations in heart rate and blood pressure, low blood pressure, and tingling or burning in the hands or feet.

Other Data Associated with Ramucirumab across Trials

Abnormal or slow/poor healing of wounds

Ramucirumab may increase the risk of abnormal or slow/poor healing of wounds. You should not receive ramucirumab for at least 4 weeks before you undergo planned surgery and your doctor will decide when to re-start treatment based on clinical judgment of adequate wound healing. If a patient develops abnormal or slow/poor healing of wounds during therapy, ramucirumab should be discontinued until the wound is fully healed.

Risk of liver failure and other significant liver injury

Patients with scarring of the liver with moderate to severe impairment of liver function are at a higher risk of developing liver failure. Signs of liver failure include high levels of liver enzymes in the blood, belly swelling due to fluid build-up, changes in brain function, and decline in kidney function. These events have the potential to be life-threatening or fatal.

Abnormal tube-like connections or passageways inside the body called fistulas
Ramucirumab may increase the risk of developing abnormal tube-like connections or passageways inside the body between a hollow or tubular organ and the body surface, or between two hollow or tubular organs. Ramucirumab treatment should be discontinued in patients who develop abnormal tube-like connections or passageways inside the body.
Changes in brain function and structure

Thyroid dysfunction
Ramucirumab may affect the function of thyroid, resulting in decreased production of certain important hormones.

Adverse reactions from spontaneous reporting
Common side effects
• Abnormal growth of blood vessels, usually on the surface of the skin. This may appear as a red, raised lesion and may grow larger and/or bleed (hemangioma).
• Altered voice, such as hoarseness.
• Abnormally low activity of the thyroid gland

Rare side effects
Abnormal blood clotting in small blood vessels in various organs of the body, most commonly in the kidney, and leading to decreased blood flow and possible damage to organs (thrombotic microangiopathy). Red blood cells (which carry oxygen) and platelets (which help the blood to clot) may be destroyed. Symptoms of thrombotic microangiopathy include bruising/bleeding, tiredness, shortness of breath, decreased urine output, swollen legs, headache, confusion, and symptoms of stroke. Protein in the urine and high blood pressure may occur.

Posterior reversible encephalopathy syndrome (PRES), a rare, but serious, brain disorder has been reported in patients treated with ramucirumab. Signs and symptoms of PRES may include headache, seizures, visual changes, and changes in mental function, with or without high blood pressure. These symptoms usually stop or improve within days, but some patients can experience continuing changes in mental function or death. Ramucirumab should be permanently discontinued in patients who experience PRES.

The use of the drugs in the same class as ramucirumab may increase the risk of developing an enlargement and weakening of a blood vessel wall (aneurysm), a tear in a blood vessel wall (dissection), or a rupture of a blood vessel. Patients with a history of high blood pressure or aneurysm may be at a higher risk of developing these events.

Risks in Pregnant or Nursing Women and Women of Child Bearing Potential
For women of child bearing potential or women who become pregnant during treatment with ramucirumab, there may be risks to the unborn child and for maintaining pregnancy. Ramucirumab may affect the growth of new blood vessels and may potentially have undesirable effects during pregnancy and development after birth. Women should consider the use of birth control to avoid getting pregnant while receiving ramucirumab and for at least 3 months after the last dose of ramucirumab.
There are no available data on ramucirumab use in pregnant women. Pregnant women should avoid the use of ramucirumab and only use if the potential benefit to the mother justifies the potential risk to the unborn child.
Studies have not been conducted to assess ramucirumab*s impact on milk production, its presence in breast milk, or its effects on the breast-fed child. If breastfeeding, it is recommended to discontinue nursing or

discontinue ramucirumab.

Risks in Children
Ramucirumab is under evaluation for use in children (aged <12 years) or adolescents (aged 12 to <18 years). Despite limited clinical data, no new safety concerns were observed from 1 small completed study in children and young adult patients. The safety and efficacy have not yet been established in this group of patients. Based on an animal study with ramucirumab, changes in the growth plates of bones are a possible risk in children. If changes in the growth plates of bones occur, future effects on bone growth may be possible.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

- Patients with either relapsed, recurrent, or refractory SS., - Patients must be 36 months to <=29 years of age at the time of study enrolment., - Patients must have received at least one prior line of systemic treatment, have measurable disease by RECIST 1.1, and must not be eligible for surgical resection at time of enrolment., - Patients who have a Lansky (<16 years of age; Lansky et al. 1987) or Karnofsky (>=16 years of age; Karnofsky et al. 1948) performance score, of at least 50., - Patient with adequate hematologic, coagulation, liver, cardiac and renal function, and adequate blood pressure (BP) control as per protocol.

Exclusion criteria

- Patients who have had allogeneic bone marrow or solid organ transplant are excluded., - Patients who have active infections requiring therapy., - Patients who have a history of fistula, gastrointestinal (GI) ulcer or perforation, or intra-abdominal abscess within 3 months of study enrolment are not eligible., - Patients with a bowel obstruction, extensive intestinal resection or history or presence of inflammatory enteropathy or other GI pathology as per protocol. , - Patients with a history of hepatorenal syndrome., - Patients with evidence of active bleeding or a history of significant (>= Grade 3) bleeding event, deep vein thrombosis requiring medical, intervention (including pulmonary embolism), hemoptysis or other signs of pulmonary haemorrhage, or esophageal varices within 3 months of enrollment are not eligible., - Patients with a bleeding diathesis or vasculitis are not eligible., - Patients with a history of central nervous system (CNS) arterial/venous thromboembolic events (VTEs) including transient ischemic attack (TIA) or cerebrovascular accident (CVA) within 6 months of study enrolment are not eligible., - Patients with myocardial infarction or unstable angina within the prior 6 months., - Patients with significant vascular disease or peripheral vascular disease., - Patients with a history of hypertensive crisis or hypertensive encephalopathy within 6 months of study enrolment are not eligible., - Patients who have non-healing wound, unhealed or incompletely healed fracture, or a compound (open) bone fracture at the time of, enrolment are not eligible., - Patients previously treated and progressed on combination gemcitabine or docetaxel. (Patients who received combination as maintenance therapy, without progression, would be eligible.), - Patients with a known hypersensitivity to gemcitabine, docetaxel or agents formulated with Polysorbate 80., - Patients who have previously received any exposure to ramucirumab are not eligible., - Patients with clinical or radiologic findings consistent with interstitial pneumonia or pulmonary fibrosis.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	1
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cyramza
Generic name:	Ramucirumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Docetaxel
Generic name:	Docetaxel
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemcitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	13-01-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-04-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2018-004243-23-NL
CCMO	NL69238.041.19

Study results

Results posted: 19-09-2023

Summary results
Trial never started

First publication
18-08-2023