STING (Study of Immunotherapy in Newly Diagnosed Glioblastoma): A Phase III randomized double-blind, controlled study of ICT-107 with maintenance temozolomide (TMZ) in newly diagnosed glioblastoma following resection and concomitant TMZ chemoradiotherapy

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Primary Objective* To determine the OS of subjects treated with ICT-107 and standard of care (RT and TMZ) vs. placebo control and standard of care (RT and TMZ) :Secondary Objectives* To determine the OS of subjects with unmethylated MGMT tumors...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Nervous system neoplasms malignant and unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON45749

Source
ToetsingOnline

Brief title
STING

Condition

- Nervous system neoplasms malignant and unspecified NEC
- Nervous system neoplasms malignant and unspecified NEC

Synonym

Glioblastoma brain tumor

Research involving
Human

Sponsors and support

Primary sponsor: ImmunoCellular Therapeutics Ltd.
Source(s) of monetary or material Support: ImmunoCellular

Intervention

Keyword: Glioblastoma, ICT-107, Immunotherapy

Outcome measures

Primary outcome

The primary efficacy endpoint is OS. The primary analysis will be conducted in the ITT Population and will use a stratified log-rank test, stratified by MGMT methylated status. An unstratified log-rank test will be used as supportive evidence of efficacy. An additional supportive analysis will be a stratified log-rank test including all 4 of the stratification factors used for randomization. These same analyses will be performed in the PP population.

Secondary outcome

The secondary endpoint of PFS will be analyzed in the ITT population using a stratified log-rank test, stratified by MGMT methylated status. In the absence of symptomatic clinical progression, radiographic progression will be based on central radiologic review. Methods similar to those used for OS will be used for PFS analysis.

Additional secondary endpoints are:

* OS in the subgroup of subjects with methylated MGMT gene

* OS in the subgroup of subjects with unmethylated MGMT gene

If the primary endpoint of OS is statistically significant, a hierarchical

closed testing procedure will be used to test key secondary endpoints, in the

following order:

1. OS in the subgroup of subjects with the methylated MGMT gene

2. OS in the subgroup of subjects with the unmethylated MGMT gene

3. PFS in overall population

Study description

Background summary

ICT-107 is a DC therapy designed to induce immunity capable of rejecting an established tumor, especially if the tumor is in a minimal residual state such as after complete surgical resection. The DCs that are contained within ICT-107 secrete their own IL-12, thereby providing their own *adjuvant.* In addition it has been shown that the antigens targeted by the peptides are expressed on glioblastoma cells and cancer stem cells. By targeting multiple antigens with MHC Class I peptides that induce the T-cell immune response most associated with clinical benefit, ICT-107 can prevent the emergence of antigen negative escape variants. Targeting cancer stem cells may delay or prevent tumor recurrence.
It is believed that this clinical study will present minimal risk to participants. This assessment is based on:
* Results from the Phase I and Phase II studies conducted with ICT-107 have shown a good safety profile combined with clinical potential. This suggests the potential for therapeutic efficacy of ICT-107 with minimal risk, justifying additional clinical studies in this population, which has a clear and unmet medical need.
* Safety data from ~50 clinical trials performed with various peptide pulsed DC from 1998 to the present reported in the literature with only Grade 1 and Grade 2 AEs.
* This Phase III study plans a schedule of frequent monitoring and laboratory testing to capture early signs of AEs or intolerability.
* The convening of an independent DMC for this Phase III trial.

Study objective

Primary Objective
* To determine the OS of subjects treated with ICT-107 and standard of care (RT and TMZ) vs. placebo control and standard of care (RT and TMZ) :
Secondary Objectives
* To determine the OS of subjects with unmethylated MGMT tumors treated with ICT-107 and standard of care vs. control and standard of care :
* To determine the OS of subjects with methylated MGMT tumors treated with ICT-107 and standard of care vs. control and standard of care.
* To evaluate progression-free survival (PFS) of subjects treated with ICT-107 and standard of care vs. control and standard of care
* To determine the overall safety of ICT-107 vs. control

Study design

This is a double blind Phase III study where eligible subjects are randomized into two treatment arms following the SOC primary treatment with chemoradiation: Arm 1 will receive ICT-107 in combination with the standard of care, temozolomide (TMZ), Arm 2 will receive TMZ with a blinded control consisting of autologous monocyte-enriched peripheral blood mononuclear cells (PBMC).

Intervention

Study Therapy Regimen:
All Administrations: Intradermally in axilla
Induction Phase: Induction will consist of administration of subject-specific study therapy once a week for 4 weeks.
Maintenance Phase: Maintenance will consist of administration of subject-specific therapy monthly for the 11 months after induction and once every 6 months thereafter until depletion of supply or confirmation of progressive disease (PD). Subject-specific study therapy and TMZ will be administered two weeks apart during Maintenance Cycle 1 to Maintenance Cycle 6. TMZ will be given Days 1-5 ± 2 days on a 28-day cycle. Study therapy will be given on Day 21 ± 2 days.
Standard of Care (SOC) Regimen:
Radiotherapy Regimen
Post Surgery SOC: 5 days per week, every week during the Post-Surgery Standard of Care Treatment Phase (Week -7 to Week -2) :
Administration: As per SOC and institutional procedures
Dose: 60 Gy in 30 fractions
TMZ Regimen
Post Surgery SOC: SOC, daily for 42 days (Week -7 to Week -2) :
Maintenance: SOC; 5 days per month for 6 months (Day 1 - Day 5 from Cycle 1 - Cycle 6)

Administration: As per institutional procedures; hard capsules provided as commercially available
Dose: Induction: 75 mg/m2/day
Maintenance Cycle 1: 150 mg/m2/day
Maintenance Cycle 2 to Cycle 6: 200 mg/m2/day

Study burden and risks

There may be side effects associated with the study therapy and procedures for the study. Some potential side effects
are: fatigue, convulsions and nausea. Other potential side effects seen in the previous study include headache,
muscle weakness, changes in blood cell counts, infection, decreased appetite, difficulty sleeping, and skin rash.
With the injection, there is the chance of an allergic reaction. With the Immune System Testing there may be pain or
swelling. The potential side effects of the Td vaccine include mild pain, redness, or swelling where the injection is
given, mild fever, headache, and feeling tired. Rarely, a high fever (over 102°F or 39°C), severe pain, redness, and
swelling where the injection was given or fainting can occur. Severe allergic reaction can also occur, but it is very rare.
For the routine laboratory tests- blood drawing does not usually have any risks, but in rare cases it can cause pain,
bleeding, burning, dizziness, fainting, or a bruise or an infection at the site where the needle was inserted to take the
blood
Apheresis- The patient may experience temporary discomfort, including pain, irritation, swelling, or bruising at the
place where the needle was inserted into the vein to collect the blood. Apheresis can also occasionally cause
nausea, vomiting, fainting, seizures, blood loss, infection, skin rash, flushing, hives, numbness and tingling, swelling
of feet and ankles, or cramps in hands or feet. Patient may also feel cold during the procedure.
Magnetic Resonance Imaging (MRI)- can be loud and is carried out in a small space so may not be suitable for
subjects with claustrophobia.
Radiation and chemotherapy
During this study patient will receive standard treatment with radiation therapy and chemotherapy (temozolomide).
There may be risks associated with these treatments.
Immune System Testing
For the immune system test, the study doctor or nurse will inject the tetanus diphtheria (Td) vaccine just under the
skin. The potential side effects of the Td vaccine include mild pain, redness, or swelling where the injection is given,

mild fever, headache, and feeling tired. Rarely, a high fever (over 102°F or 39°C), severe pain, redness, and swelling
where the injection was given, or fainting can occur. Severe allergic reaction can also occur, but it is very rare.
Risks can be minimized for injection reactions by pre-medicating with anti-histamine. MRI patient can wear ear
defenders.
The clinical experience to date provides strong evidence for potential clinical benefit with an acceptable risk profile. Taken together, available information suggests that the benefit/risk ratio for ICT-107 therapy is acceptable for further development.

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

Screening Inclusion Criteria:
Subjects may sign informed consent and submit a sampale for HLA typing prior to surgical resection of tumor. Upon receipt of an eligible HLA type resulting (HLA-A2+), tissue should be submitted for determination of MGMT methylation status by the central laboratory, and a post surgical MRI should be submitted for central radiological assessment. These submissions can occur concurrently. Upon receipt of an eligible determination of MRI radiological assessment, a full review of the Inclusion and Exclusion criteria should be completed to determine subject eligibility for enrollment and randomization.;Main study inclusion criteria:
1. Subjects or Legal Authorized Representative (LAR) (varies by region) must understand and sign the study specific informed consent
2. Subjects must be in primary remission
3. Subjects should have non-measureable disease as defined by iRANO for post surgical resection as confirmed by central radiological assessment of MRI with residual tumor * 1 cm x 1 cm on the x and y axes, i.e. tumors > 1cm2 will be excluded.
4. Subjects must be HLA-A2 positive by central lab.
5. Subjects must have adequate renal, hepatic and bone marrow function based on screening laboratory assessments. Baseline hematologic studies and Chemistry and coagulation profiles must meet the following criteria:
a. Hemoglobin (Hgb) > 8 g / dl
b. Absolute Neutrophil Count (ANC) > 1500 / mm3
c. Platelet count > 100.000 / mm3
d. Blood Urea Nitrogen (BUN) < 30 mg / dl
e. Creatinine < 2 mg / dl
f. Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) , 2 x upper limit of normal (ULN)
g. Prothrombin Time (PT) and activated partial thromboplastin time (PTT) * 1.6 x ULN unless therapeutically warranted
6. Subjects must use effective contraceptive methods during the study and for three months following the last dose of study product, if of reproductive age and still retain fertillity potential.
7. Confirmed Initial Diagnosis of glioblastoma, including documentation of unmutated iso-citrate dehydrogenase (IDH)
8. Tissue available for MGMT methylation analysis by central laboratory
9. * 18 years of age
10. WHO performance score 0-2
11. Subjects must understand and sign the informed consent.

Exclusion criteria

1. Subjects receiving investigational study drug for any indication or immunological-based treatment for any reason (Filgrastim may be used for prevention of severe neutropenia).
2. Subjects with glioblastoma mutated IDH by Immunohistochemistry (IHC).

3. Subjects with concurrent conditions that would jeopardize the safety of the subjects or compliance with the protocol.
4. Subjects with a history of chronic or acute hepatitis B, C or HIV infection.
5. Subjects require or are likely to require more than a 2-weeks course of corticosteroids for intercurrent illness. Subjects must have completed the course of corticosteriods at the time of apheresis to meet eligibility.
6. Subjects have any acute infection that requires specific intravenous (IV) therapy. Acute IV therapy must have completed within seven days prior to study enrollment.
7. Subjects with active malignancy diagnosed in the past 3 years (excepting in situ tumors).
8. Subjects known to be pregnant or nursing.
9. See section 8.12.1 for excluded therapies.
10. Patients with hypersensitivity towards a known constituent of the study therapy, TMZ or dacarbazine
11.Patients treated with a live vaccination within the past 4 weeks.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO Date:	07-04-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-11-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-04-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2015-00266685--NL
ClinicalTrials.gov	NCT02546102
CCMO	NL56619.000.16