# Clinical Trial Protocol
# Iranian Registry of Clinical Trials

01 Aug 2026

## Efficacy of the intrathecal injection of activated allogeneic natural killer cells in patients with High-grade gliomas; A multi-center phase II clinical trial

## Protocol summary

**Study aim**
Evaluation of efficacy of intrathecal injection of activated allogenic NK cells in patients with high grade glioma

**Design**
Phase II clinical trial, controlled, randomized, non-blinded

**Settings and conduct**
Eligible patients will be allocated randomly in two stratum (adults and pediatrics) into intervention and control group in ratio of 3 to 1 and then they will receive NK cells intrathecally in 3 times in one of the recruiting hospitals.

**Participants/Inclusion and exclusion criteria**
New diagnosed patients with grade 3 or 4 brain tumor, which are included in the one of the following conditions: Astrocytoma IDH-mutant, Oligodendroglioma IDH-mutant, Glioblastoma IDH-wild type, Diffuse midline glioma, Diffuse hemispheric glioma, Diffuse pediatric-type high-grade glioma IDH-wild type Age range of 3 to 60 years old both sex Lansky/Karnofsky performance score above 60 Obtained informed consent of patients or parents or legal attendance in cases of pediatrics Hemoglobin above 10 gr/dL of blood AGC above 500 per microliter of blood Platelet count above 50000 per microliter of blood INR below 2 and PTT less than 1.5 times of maximum normal value Plasma bilirubin level less than 1.5 times of maximum normal value Plasma hepatic transaminases (ALT and AST) level less than 3 times of maximum normal value Plasma creatinine level less than 1.5 times of maximum normal value

**Intervention groups**
Intervention group: Patients will receive 200 millions NK cells via intrathecal injection for 3 times. Injection will be administered in period between radiotherapy to chemotherapy or in periods between chemotherapy courses. Control group: Patients in control group will receive no cell and just conventional treatments will be administered for them.

**Main outcome variables**
Efficacy

## General information

**Reason for update**

**Acronym**

**IRCT registration information**
IRCT registration number: **IRCT20170122032121N7**
Registration date: **2023-07-22, 1402/04/31**
Registration timing: **registered_while_recruiting**

Last update: **2023-07-22, 1402/04/31**
Update count: **0**

**Registration date**
2023-07-22, 1402/04/31

**Registrant information**

**Name**
Marzieh Ebrahimi
**Name of organization / entity**
Royan Institute
**Country**
Iran (Islamic Republic of)
**Phone**
+98 23562516
**Email address**
mebrahimi@royaninstitute.org

**Recruitment status**
**Recruitment complete**

**Funding source**

**Expected recruitment start date**
2023-06-22, 1402/04/01

**Expected recruitment end date**
2024-06-21, 1403/04/01

**Actual recruitment start date**
empty

**Actual recruitment end date**
empty
**Trial completion date**
empty

**Scientific title**
Efficacy of the intrathecal injection of activated allogeneic natural killer cells in patients with High-grade gliomas; A multi-center phase II clinical trial

**Public title**
Efficacy of allogenic NK cells IT injection in patients with high grade brain glioma
**Purpose**
Treatment
**Inclusion/Exclusion criteria**
**Inclusion criteria:**
New diagnosed patients with grade 3 or 4 brain tumor, based on WHO classification, which are included in the one of the following conditions: • Astrocytoma, IDH-mutant • Oligodendroglioma, IDH-mutant • Glioblastoma, IDH-wild type • Diffuse midline glioma • Diffuse hemispheric glioma • Diffuse pediatric-type high-grade glioma, IDH-wild type Age range of 3 to 60 years old both sex Lansky/Karnofsky performance score above 60 Obtained informed consent of patients or parents or legal attendance in cases of pediatrics Hemoglobin above 10 gr/dL of blood Absolute granulocyte count (AGC) above 500 per microliter of blood Platelet count above 50000 per microliter of blood INR below 2 and PTT less than 1.5 times of maximum normal value Plasma bilirubin level less than 1.5 times of maximum normal value Plasma hepatic transaminases (ALT and AST) level less than 3 times of maximum normal value Plasma creatinine level less than 1.5 times of maximum normal value
**Exclusion criteria:**
Evidence of radio necrosis in MRI or MRS Intolerance of new treatment due to emergency condition History of other malignancies History of any immunodeficiency diseases or any immune compromising conditions Rupture of cerebral shunt or unable to perform a lumbar puncture Pregnancy History of uncontrolled chronic diseases such as: Diabetes, CHF, liver cirrhosis, CKD, etc.
**Age**
From **3 years** old to **60 years** old
**Gender**
Both

**Phase**
2
**Groups that have been masked**
*No information*
**Sample size**
Target sample size: **40**
**Randomization (investigator's opinion)**
Randomized
**Randomization description**
In this trial, patients will be stratified in 2 level: first level patient under 18 y/o and second level above 18 y/o. For random allocation in each stratum, permuted-block randomization method will be used. Ratio of patients in intervention group to patients in control group would be 3 to 1 and for randomization 5 foursome blocks in each stratum would be selected. Each block contains one patient in control group and 3 patients in intervention group. Required blocks will be designed and randomly selected using Sealed Envelope software and the patients would be placed in houses of each block in order of date of recruitment.
**Blinding (investigator's opinion)**
Not blinded
**Blinding description**
**Placebo**
Not used
**Assignment**
Parallel
**Other design features**

## Secondary Ids

empty

## Ethics committees

**1**

**Ethics committee**
**Name of ethics committee**
Royan institute ethics committee
**Street address**
Royan ethics committee, Royan alley, Hafez street, Banihashem square, Banihashem street, Resalat highway, Tehran, Iran
**City**
Tehran
**Province**
Tehran
**Postal code**
1665659911
**Approval date**
2023-02-28, 1401/12/09
**Ethics committee reference number**
IR.ACECR.ROYAN.REC.1402.001

## Health conditions studied

**1**

**Description of health condition studied**
High grade brain glioma
**ICD-10 code**
C71
**ICD-10 code description**
Malignant neoplasm of brain

## Primary outcomes

**1**

**Description**
Response rate comparison between control and intervention groups
**Timepoint**
1 to 2 weeks after last injection with the follow up of 3, 6, and 12 months after last injection

**Method of measurement**
Using iRANO (Immunotherapy Response Assessment in Neuro-Oncology) checklist and using MRI and MRS

## Secondary outcomes

### 1

**Description**
Safety
**Timepoint**
After each injection to next injection and 2 weeks after last injection
**Method of measurement**
Using CTCAEs (Common Terminology Criteria for Adverse Events) checklist

### 2

**Description**
Overall survival and progression-free survival
**Timepoint**
After the end of the study
**Method of measurement**
using Kaplan-Meier method

### 3

**Description**
Analysis of CSF including: hematology, biochemistry, culture, cytokine level and immunophenotype of cells
**Timepoint**
Before each injection, CSF sample will be taken from patients for analysis
**Method of measurement**
using microscope and slides, spectrophotometer, enzyme assay, ELISA and Flowcytometry

## Intervention groups

### 1

**Description**
Intervention group: Patients in intervention group will receive 200 millions NK cells via intrathecal injection (LP or resorvor) for 3 times. In cases who have ongoing surgery or have been operated recently and have been planned for radiotherapy after surgery, if the patient condition would be suitable for IT injection, the first injection will be administered one or two weeks after the end of radiotherapy. The other doses would be injected in the period between courses of chemotherapy (one week after the end of last chemotherapy course). In cases who have passed surgery and radiotherapy and in the cases who are not eligible for surgery and radiotherapy (such as diffuse midline glioma cases) all three injections will be administered in the period between chemotherapy courses. CSF will be taken before each injection for intended assessments. The therapist physicians would be suggested to not prescribe corticosteroids or prescribe low dose of them from 3 days before to one week after NK cell injection to avoid their suppressing effects on NK cells. But this is not mandatory because of the risk of brain edema. Also therapist physicians would be suggested to prescribe immune checkpoint inhibitors if there is indication (PD-L1 expression or MSI) for prescription to intensify the cytotoxic effect of NK cells.
**Category**
Treatment - Other

### 2

**Description**
Control group: patients in control group will not receive any cells and just conventional treatments (surgery, radiotherapy and chemotherapy) will be ordered for them. Because of the risk of the adverse events, IT injection of the placebo will not be done for patients in control group. But if the study results 6 months after last injection of last patient would reveal that there is significant superiority in the intervention group, patients in the control group can be benefited with NK cell therapy for free. Patients in control group will be Followed-up till one year after recruitment for comparison with intervention group.
**Category**
Other

## Recruitment centers

### 1

**Recruitment center**
**Name of recruitment center**
Rasoul Akram hospital
**Full name of responsible person**
Dr. Mohammad Faranoush
**Street address**
Pediatric oncology ward, floor 4, Rasoul Akram hospital, Niayesh street, Shahr Ara street, Sattar Khan vicinity, Tehran, Iran
**City**
Tehran
**Province**
Tehran
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1445613131
**Phone**
+98 21 6652 5328
**Email**
faranoush47@gmail.com

### 2

**Recruitment center**
**Name of recruitment center**
Children's medical center hospital
**Full name of responsible person**
Dr. Zohreh Habibi
**Street address**
Children’s Medical Center, No 63, Gharib Ave, Keshavarz Blv, and Tehran, Iran
**City**

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**Province**
Tehran

**Postal code**
1419733151

**Phone**
+98 21 6692 9234

**Email**
mahdizadehmd@yahoo.com

**3**

**Recruitment center**

**Name of recruitment center**
Loghman e Hakim hospital

**Full name of responsible person**
Dr. Guive Sharifi

**Street address**
Loghman e Hakim hospital - Makhsoos street, Lashgar crossroad, Tehran

**City**
Tehran

**Province**
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1333635445

**Phone**
+98 21 5541 9005

**Email**
gsharifi@gmail.com

## Sponsors / Funding sources

**1**

**Sponsor**

**Name of organization / entity**
Kian immune cell company

**Full name of responsible person**
Hassan Salehi Moghadam

**Street address**
Kian immune cell company, first floor, Royan RITAC center, Number 6, Keshvari alley, Banihashem square, Banihashem street, Resalat highway, Tehran, Iran

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**Province**
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**Postal code**
1665813339

**Phone**
+98 21 2233 8248

**Email**
kiacell.immune@gmail.com

**Web page address**
https://kiacell-immune.com

**Grant name**

**Grant code / Reference number**

**Is the source of funding the same sponsor organization/entity?**
Yes

**Title of funding source**
Kian immune cell company

**Proportion provided by this source**
90

**Public or private sector**
Private

**Domestic or foreign origin**
Domestic

**Category of foreign source of funding**
*empty*

**Country of origin**

**Type of organization providing the funding**
Other

**2**

**Sponsor**

**Name of organization / entity**
Royan institute

**Full name of responsible person**
Marzieh Ebrahimi

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Royan institute, Hafez street, Banihashem square, Banihashem street, Resalat highway, Tehran, Iran

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**Grant name**

**Grant code / Reference number**

**Is the source of funding the same sponsor organization/entity?**
Yes

**Title of funding source**
Royan institute

**Proportion provided by this source**
10

**Public or private sector**
Public

**Domestic or foreign origin**
Domestic

**Category of foreign source of funding**
*empty*

**Country of origin**

**Type of organization providing the funding**
Academic

## Person responsible for general inquiries

**Contact**

**Name of organization / entity**
Royan institute & Kian immune cell company

**Full name of responsible person**
Hamid Mahdizadeh

**Position**
Research assistant

**Latest degree**
Medical doctor
**Other areas of specialty/work**
Immunology
**Street address**
Kian immune cell company, first floor, Royan RITAC center, Number 6, Keshvari alley, Banihashem square, Banihashem street, Resalat highway, Tehran, Iran
**City**
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## Person responsible for scientific inquiries

**Contact**
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Royan institute & Kian immune cell company
**Full name of responsible person**
Hamid Mahdizadeh
**Position**
Research asisstant
**Latest degree**
Medical doctor
**Other areas of specialty/work**
Immunology
**Street address**
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## Person responsible for updating data

**Contact**
**Name of organization / entity**
Royan institute & Kian immune cell company
**Full name of responsible person**
Hamid Mahdizadeh
**Position**
Research assistant
**Latest degree**
Medical doctor
**Other areas of specialty/work**
Immunology
**Street address**
Kian immune cell company, first floor, Royan RITAC center, Number 6, Keshvari alley, Banihashem square, Banihashem street, Resalat highway, Tehran, Iran
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**Email**
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## Sharing plan

**Deidentified Individual Participant Data Set (IPD)**
Yes - There is a plan to make this available
**Study Protocol**
Yes - There is a plan to make this available
**Statistical Analysis Plan**
Yes - There is a plan to make this available
**Informed Consent Form**
Yes - There is a plan to make this available
**Clinical Study Report**
Yes - There is a plan to make this available
**Analytic Code**
Undecided - It is not yet known if there will be a plan to make this available
**Data Dictionary**
Not applicable
**Title and more details about the data/document**
After concealment of personal information of participants, data of eligibility, CRFs and measured outcomes can be shared in case of request
**When the data will become available and for how long**
After publishing results in a scientific journal with no deadline
**To whom data/document is available**
Just to academic PIs
**Under which criteria data/document could be used**
Any usage of data should be consulted and approved by the PIs
**From where data/document is obtainable**
Applicant should send an e-mail to Dr.Mahdizadeh and propose their detailed requirements of the study data
**What processes are involved for a request to access data/document**
After sending an e-mail to Dr.Mahdizadeh, he will assess the authenticity of the applicant in almost 2 weeks. Then he will plan a meeting (visual or attendance) for the applicant with Dr.Ebrahimi in next month. The applicant can obtain approval of data sharing in this meeting and the data will be sent in next 14 days
**Comments**