Tisagenlecleucel in Adult Patients With Aggressive B-cell Non-Hodgkin Lymphoma (BELINDA)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03570892

Recruitment Status: Recruiting
First Posted: June 27, 2018
Last Update Posted: July 29, 2020

See Contacts and Locations

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)
**Study Description**

**Brief Summary:**
This is a randomized, open label, multicenter phase III trial comparing the efficacy, safety, and tolerability of tisagenlecleucel to Standard Of Care in adult patients with aggressive B-cell Non-Hodgkin Lymphoma after failure of rituximab and anthracycline containing frontline immunochemotherapy.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
</tr>
</thead>
</table>
| Non-Hodgkin Lymphoma | Drug: Tisagenlecleucel after optional bridging and lymphodepleting chemotherapy  
Drug: Platinum-based immunochemotherapy followed in responding patients with high dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT) | Phase 3 |

**Study Design**

- **Study Type**: Interventional (Clinical Trial)
- **Estimated Enrollment**: 318 participants
- **Allocation**: Randomized
- **Intervention Model**: Parallel Assignment
- **Intervention Model Description**: Randomized, Open-Label
- **Masking**: Single (Outcomes Assessor)
- **Primary Purpose**: Treatment
- **Official Title**: Tisagenlecleucel Versus Standard of Care in Adult Patients With Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphoma: A Randomized, Open Label, Phase III Trial (BELINDA)

- **Actual Study Start Date**: May 7, 2019
- **Estimated Primary Completion Date**: December 30, 2025
- **Estimated Study Completion Date**: March 31, 2026

**Resource links provided by the National Library of Medicine**

- **MedlinePlus related topics**: Lymphoma
- **Drug Information** available for: Tisagenlecleucel-T
- **Genetic and Rare Diseases Information Center resources**: B-cell Lymphoma
### Arms and Interventions

<table>
<thead>
<tr>
<th>Arm</th>
<th>Intervention/treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experimental: Tisagenlecleucel treatment strategy</strong></td>
<td>Drug: Tisagenlecleucel after optional bridging and lymphodepleting chemotherapy</td>
</tr>
<tr>
<td>Patients will receive investigator's choice of optional platinum-based immunochemotherapy followed by lymphodepleting chemotherapy and a single dose of tisagenlecleucel</td>
<td>Investigator's choice of optional platinum-based immunochemotherapy (ie. R-ICE, R-GemOx, R-GDP, R-DHAP) + Lymphodepleting chemotherapy (fludarabine with cyclophosphamide or bendamustine) + Tisagenlecleucel (a second generation CAR-T composed of a CD19 antigen-binding domain, a 4-1BB costimulatory domain and a CD3-ζ signaling domain)</td>
</tr>
<tr>
<td><strong>Active Comparator: Standard of care treatment strategy</strong></td>
<td>Drug: Platinum-based immunochemotherapy followed in responding patients with high dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT)</td>
</tr>
<tr>
<td>Patients will receive investigator's choice of platinum-based immunochemotherapy followed in responding patients by high dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT)</td>
<td>Investigator's choice of platinum-based immunochemotherapy (ie. R-ICE, R-GemOx, R-GDP, R-DHAP) + High dose chemotherapy (ie. BEAM) + autologous HSCT.</td>
</tr>
<tr>
<td><em>Ibrutinib or lenalidomide may be used in patients who are no longer eligible for autologous HSCT after 2 cycles of immunochemotherapy</em></td>
<td></td>
</tr>
</tbody>
</table>

### Outcome Measures

**Primary Outcome Measures**

Go to [Tisagenlecleucel in Adult Patients With Aggressive B-cell Non-Hodgkin Lymphoma](https://clinicaltrials.gov/ct2/show/NCT03570892)
1. Event-free survival (EFS) [ Time Frame: 5 years ]

Event-free survival (EFS) is defined as the time from the date of randomization to the date of the first documented disease progression or stable disease at or after the week 12 (+/- 1 week) assessment, as assessed by Blinded Independent Review Committee (BIRC) per Lugano criteria, or death due to any cause, at any time.

Secondary Outcome Measures:

1. EFS as assessed by local investigator [ Time Frame: 5 years ]

EFS as assessed by local investigator

2. Overall Survival (OS) [ Time Frame: 5 years ]

Overall survival (OS) is defined as the time from date of randomization to date of death due to any cause

3. Overall Response Rate (ORR) [ Time Frame: 5 years ]

Overall Response Rate (ORR) as per the Lugano criteria as per BIRC review and local investigator assessment

4. Duration of Response (DOR) [ Time Frame: 5 years ]

Duration of response: time from the date of first documented response of CR or PR to the date of first documented progression (SD or PD at or after the week 12 assessment will be considered progression) or death due to aggressive B-cell NHL. DOR will be summarized by BIRC and local response

5. Time to Response (TTR) [ Time Frame: 5 years ]

Time from the date of randomization to the date of a patient's first achieved a response of CR or PR on or after the Week 12 assessment

6. SF-36v2 [ Time Frame: 5 years ]

Time to definitive deterioration in SF-36v2

7. FACT-Lym [ Time Frame: 5 years ]

Time to definitive deterioration in FACT-Lym
8. EQ-VAS [Time Frame: 5 years]
   Time to definitive deterioration in EQ-VAS

9. Tisagenlecleucel transgene concentrations [Time Frame: 5 years]
   qPCR will be used to measure tisagenlecleucel transgene concentrations in peripheral blood and bone marrow

10. Tisagenlecleucel immunogenicity (humoral and cellular) [Time Frame: 5 years]
    Pre-existing and treatment related immunogenicity (humoral and cellular) of tisagenlecleucel will be characterized.

11. Presence of replication competent lentivirus (RCL) [Time Frame: 5 years]
    The presence of RCL will be assessed by VSV-qPCR in patients receiving tisagenlecleucel

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Eligibility Criteria

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Histologically confirmed, aggressive B-cell NHL at relapse/progression or PR after front line therapy. Aggressive B-cell NHL is heretofore defined by the following list of subtypes (Swerdlow et al 2016):

[Further details provided]
a. DLBCL, NOS,
b. FL grade 3B,
c. Primary mediastinal large B cell lymphoma (PMBCL),
d. T cell rich/histiocyte rich large B cell lymphoma (T/HRBCL),
e. DLBCL associated with chronic inflammation,
f. Intravascular large B-cell lymphoma,
g. ALK+ large B-cell lymphoma,
h. B-cell lymphoma, unclassifiable, (with features intermediate between DLBCL and classical Hodgkin's Lymphoma (HL)),
i. High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements,
j. High-grade B-cell lymphoma, NOS
k. HHV8+ DLBCL, NOS
l. DLBCL transforming from follicular lymphoma
m. DLBCL transforming from marginal zone lymphoma
n. DLBCL, leg type

2. Relapse or progression within 365 days from last dose of anti CD20 antibody and anthracycline containing first line immunochemotherapy or refractory (have not achieved a CR).

3. Patient is considered eligible for autologous HSCT as per local investigator assessment. Note: Intention to transplant and type of high dose chemotherapy (HDCT) regimen will be documented at the time of study entry.

4. Disease that is both active on PET scan (defined as 5-Deauville scorepoint-scale of 4 or 5) and measurable on CT scan, defined as::
   a. Nodal lesions >15 mm in the long axis, regardless of the length of the short axis, and/or
   b. Extranodal lesions (outside lymph node or nodal mass, but including liver and spleen) >10 mm in long AND short axis

5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

6. Adequate organ function:
   Renal function defined as:
   a. Serum creatinine of $\leq 1.5 \times$ upper limit of normal (ULN), OR estimated glomerular filtration rate (eGFR) $\geq 60$ mL/min/1.73 m2
   Hepatic function defined as:
   b. Alanine Transaminase (ALT) and Aspartate Transaminase (AST) $\leq 5 \times$ ULN
   c. Total bilirubin $\leq 1.5 \times$ ULN with the exception of patients with Gilbert syndrome who may
be included if their total bilirubin is ≤3.0 × ULN and direct bilirubin ≤1.5 × ULN

Hematologic Function (regardless of transfusions) defined as:

d. Absolute neutrophil count (ANC) >1000/mm3

e. Absolute lymphocyte count (ALC) >300/mm3 OR Absolute number of CD3+ T cells >150/mm3 (only for patients with non-historical apheresis)

f. Platelets ≥50000/mm3

g. Hemoglobin >8.0 g/dl

Adequate pulmonary function defined as:

h. No or mild dyspnea (≤ Grade 1)

i. Oxygen saturation measured by pulse oximetry > 90% on room air

j. Forced expiratory volume in 1 s (FEV1) ≥ 50% and/or carbon monoxide diffusion test (DLCO) ≥50% of predicted level

7. Must have a leukapheresis material of non-mobilized cells available for manufacturing.

Exclusion Criteria:

1. Prior treatment with anti-CD19 therapy, T cell therapy, or any prior gene therapy product

2. Treatment with any systemic lymphoma-directed second line anticancer therapy prior to randomization. Only steroids and local irradiation are permitted for disease control

3. Patients with active central nervous system (CNS) involvement by disease under study are excluded, except if the CNS involvement has been effectively treated and local treatment was >4 weeks before randomization

4. Prior allogeneic HSCT

5. Clinically significant active infection

6. Any of the following cardiovascular conditions:

   ○ Unstable angina, myocardial infarction, coronary artery bypass graft (CABG), or stroke within 6 months prior to screening,

   ○ Left ventricle ejection fraction (LVEF) <45% as determined by echocardiogram (ECHO) or magnetic resonance angiography (MRA) or multigated acquisition (MUGA) at the screening assessment.

   ○ New York Heart Association (NYHA) functional class III or IV (Chavey et al 2001), within the past 12 months.

   ○ Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade atrioventricular (AV) block (e.g., bifascicular block, Mobitz type II) and third degree AV block unless adequately controlled by pacemaker implantation.

   ○ Resting QTcF ≥450 msec (male) or ≥460 msec (female) at screening or inability to
determine the QTcF interval

- Risk factors for Torsades de Pointes (TdP), including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia, or any of the following:
  - Long QT syndrome, family history of idiopathic sudden death or congenital long QT syndrome
  - Concomitant medication(s) with a "Known Risk of Torsades de Pointes" per crediblemeds.org that cannot be discontinued or replaced by safe alternative medication.

7. Patients with active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré Syndrome (GBS), Amyotrophic Lateral Sclerosis (ALS)) and clinically significant active cerebrovascular disorders (e.g. cerebral edema, posterior reversible encephalopathy syndrome (PRES))

Other protocol-defined inclusion and exclusion criteria may apply.

Contacts and Locations

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number):
NCT03570892

Contacts

Contact: Novartis Pharmaceuticals 1-888-669-6682 novatis.email@novartis.com
Contact: Novartis Pharmaceuticals +41613241111

Locations

Hide 59 study locations

United States, California

Moores UC San Diego Cancer Center
La Jolla, California, United States, 92093

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Contact: Viktoriya Duda  858-822-5364  vduda@ucsd.edu
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Principal Investigator: Herbert Eradat

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Principal Investigator: Michael R. Bishop

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Principal Investigator: Joseph P McGuirk
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United States, Texas

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Contact: Katherine Annandale    713-792-2860    kannanda@mdanderson.org
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San Antonio, Texas, United States, 78229
Contact: George DeLeon    210-575-3817    George.deleon@mhshealth.com
Principal Investigator: Paul Shaughnessy

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University of Wisconsin Carbone Cancer Center
Madison, Wisconsin, United States, 53792-6164
Contact 608-265-3794
Principal Investigator: Vaishalee Kenkre

Australia, New South Wales

Novartis Investigative Site

Recruiting
Darlinghurst, New South Wales, Australia, 2010

**Australia, Victoria**

Novartis Investigative Site  
Melbourne, Victoria, Australia, 3000

**Australia, Western Australia**

Novartis Investigative Site  
Murdoch, Western Australia, Australia, 6150

**Austria**

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Novartis Investigative Site  
Salzburg, Austria, 5020  
Novartis Investigative Site  
Vienna, Austria, A-1090

**Brazil**

Novartis Investigative Site  
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Novartis Investigative Site  
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Nantes Cedex 1, France, 44093  
Novartis Investigative Site  
Paris, France, 75010  
Novartis Investigative Site  
Pierre Benite Cedex, France, 69495  
Novartis Investigative Site  
Toulouse, France, 31059

**Germany**

Novartis Investigative Site  
Regensburg, Bavaria, Germany, 93053

Tisagenlecleucel in Adult Patients With Aggressive B-cell Non-Hodgkin... https://clinicaltrials.gov/ct2/show/NCT03570892
Novartis Investigative Site
Berlin, Germany, 13353
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Hamburg, Germany, 20246
Novartis Investigative Site
Koeln, Germany, 50937
Novartis Investigative Site
Leipzig, Germany, 04103
Novartis Investigative Site
Muenchen, Germany, 81377
Novartis Investigative Site
Ulm, Germany, 89081

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Hong Kong, Hong Kong

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Singapore, Singapore, 169608  

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Madrid, Spain, 28009  
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Madrid, Spain, 28041  

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Sponsors and Collaborators  
Novartis Pharmaceuticals  

Investigators  
Study Director: Novartis Pharmaceuticals  

More Information  
Go to

Responsible Party: Novartis Pharmaceuticals  
ClinicalTrials.gov Identifier: [NCT03570892](https://clinicaltrials.gov/ct2/show/NCT03570892)  
Other Study ID Numbers: CCTL019H2301  
2016-002966-29 (EudraCT Number)
Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: Yes

Plan Description: Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent expert panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

This trial data is currently available according to the process described on www.clinicalstudydatarequest.com.