Trial Description

Title

High-dose chemotherapy and autologous stem cell transplantion or consolidating conventional chemotherapy in primary CNS lymphoma – randomized phase III trial - MATRix / IELSG43 -

Trial Acronym

MATRix / IELSG43

URL of the trial

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Brief Summary in Lay Language

In the multicentre Phase III trial two therapies will be compared: after intensified induction treatment with 4 cycles rituximab, methotrexate, cytarabine and thiotepa (MATRix) all patients with a PR or CR after the induction therapy will be randomized between first-line high-dose chemotherapy followed by a ASCT against conventional consolidating therapy with 2 cycles of R-DeVic (Rituximab, Dexamthason, Etoposide, Ifosfamide, Carboplatin).

Brief Summary in Scientific Language

Primary central nervous system lymphoma (PCNSL) is a highly aggressive disease with rising incidence over the past 30 years. Similar to other hematological diseases, the rationale for consolidation in PCNSL is the elimination of minimal residual disease. The efficacy of WBRT, which is the current standard for consolidation after HD-MTX-based systemic treatment, is being compared to HDT-ASCT in the ongoing IELSG-32 trial.
High-dose chemotherapy with carmustine or busulfan and thiotepa followed by autologous stem cell transplantation has been shown to be feasible and highly effective in newly diagnosed eligible patients, but also in the salvage situation. The question we aim to answer is whether HDT-ASCT is superior to conventional therapy as consolidation after intensified immunochemotherapy in newly diagnosed PCNSL.
In the framework of the substantial amendment 01 dated May 7th, 2018 the following changes have been made: Increase of sample size from 250 to 330; prolongation of recruitment period until August 31st, 2019;
adapted inclusion criterion for randomization -> reduction of number of stemcells that need to be harvested before randomization. The Czech Repubic has withdrawn its confirmation to participate in the trial.

Organizational Data

- DRKS-ID: **DRKS00005503**
- Date of Registration in DRKS: **2014/04/22**
- Date of Registration in Partner Registry or other Primary Registry: **2015/08/24**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **AM-2014010-ff , Ethik-Kommission bei der Landesärztekammer Baden-Württemberg**

Secondary IDs

- EudraCT-No.
  (for studies acc. to Drug Law): **2012-000620-17**
- Primary Registry-ID: **NCT02531841 (clinicaltrials.gov)**

Health condition or Problem studied

- ICD10: **C83.3 - Diffuse large B-cell lymphoma**

Interventions/Observational Groups

- Arm 1: **INDUCTION TREATMENT:**

  4 cycles MATRix (every 3 weeks), stem-cell harvest after 2nd cycle:
  -Rituximab 375 mg/m²/d i.v. (d0,5)
  -MTX 3.5 g/m² i.v. (d1)
  -Ara-C 2 x 2 g/m²/d i.v. (d2-3)
  -Thiotepa 30 mg/m² i.v. (d4)

  CONSOLIDATION
  2 cycles of R-DeVIC (every 3 weeks):
  -Rituximab 375 mg/m²/d i.v. (d0)
  -Dexamethasone 40 mg/d i.v. (d1-3)
  -Etoposide 100 mg/m²/d i.v. (d1-3)
  -Ifosfamide 1500 mg/m²/d i.v. (d1-3)
  -Carboplatin 300 mg/m² i.v. (d1)

  Generic and proprietary name:
  Rituximab - MabT hera®

- Arm 2: **INDUCTION TREATMENT:**

  4 cycles MATRix (every 3 weeks), stem-cell harvest after 2nd cycle:

  -Rituximab 375 mg/m²/d i.v. (d0,5)

  -MTX 3.5 g/m² i.v. (d1)

  -Ara-C 2 x 2 g/m²/d i.v. (d2-3)

  -Thiotepa 30 mg/m² i.v. (d4)

  CONSOLIDATION:

  High-dose chemotherapy (HDT):

  -BCNU* 400 mg/m² i.v. (d-6)

  -Thiotepa 2 x 5 mg/kg/d i.v. (d-5-(-4))

  -ASCT (d0)

  ***if not available at study site, Busulfan can be administered instead:**

  -Busulfan 3,2 mg/kg/d i.v. (d-8-(-7))

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control (effective treament of control group)**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **III**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **No**

Primary Outcome

Primary efficacy endpoint:
Progression-free survival (PFS) time from randomization until progression, relapse, or death from any cause.

Progression-free survival PFS:
Response Assessment III at the end of study treatment (EOT) visit and every imaging diagnostic assessments during follow-up period:
during year 1-2: every 3 month

from year 3-5: every 6 month
or imaging in case of clinical suspicion of disease progression or relapse

Secondary Outcome

Secondary endpoints:
Efficacy:
- Complete response (CR)
- Response duration
- Overall survival (OS)
- Quality of life (QOL): EORTC QLQ-C30.
CR will be determined on day 60 after randomization.
Response duration is defined as time from CR, CRu or PR until relapse or PD.
OS is defined as time from randomization until death of any cause.

For overall survival (OS), Quality of life (QLQ), (serious)adverse events (S)AEs, toxicity and neurotoxicity timepoints of evaluation are defined as every assessment during follow up period in accordance with the protocol.
year 1-2: every 3 month
year 3-5: every 6 month.

Response duration observation times for patients where the event of interest was not observed, will be censored at the time last seen alive without the respective event.

Safety:
- (Serious) adverse events
- Toxicity
- Neurotoxicity (MMSE, EORTC QLQ-BN20, neuropsychological test battery)

Test Battery:
ECOG Performance Status,
Mini-mental Status Examination (MMSE),
EORTC QLQ-C30,
EORTC QLQ-BN20,
Brief Repeatable Battery of Neuropsychological Tesrs

Countries of recruitment

- DE **Germany**
- IT **Italy**
- CH **Switzerland**
- DK **Denmark**
- NO **Norway**

Locations of Recruitment

- University Medical Center **Universitätsklinikum Freiburg Medizinische Klinik I Hugstetter Str. 55 79106 , Freiburg im Breisgau**
- Medical Center **Klinikum Stuttgart, Stuttgart Cancer Center Tumorzentrum Eva-Mayr-Stihl Interdisziplinäre internistische Onkologie,Haematologie und Palliativmedizin Kriegsbergstr.60 70174 , Stuttgart**
- Medical Center **Klinikum Bremen-Mitte gGmbH Medizinische Klinik I St.Jürgen.Str. 1 28177 Bremen, Bremen**
- University Medical Center **Universitätsklinikum Münster, Med. Klinik A, Albert-Schweizer-Campus 1, Geb. D3, 48149 Münster, Münster**
- University Medical Center **Universitätsklinikum Essen Klinik für Hämatologie Hufelandstraße 55 45122, Essen**
- University Medical Center **Universitätsmedizin Greifswald Klinik und Poliklinik für Innere Medizin C Hämatologie, Onkologie und Transplantationszentrum Sauerbruchstraße 17475, Greifswald**
- University Medical Center **Universitätsklinikum Halle (Saale) Klinik für Innere Medizin IV Hämatologie/ Onkologie Ernst-Grube-Straße 40 06120, Halle Saale**
- University Medical Center **Universitätsklinikum Jena Klinik und Poliklinik für Innere Medizin II Hämatologie und internistische Onkologie Erlanger Allee 101 07740 Jena, Jena**
- University Medical Center **Universitätsklinik Schleswig-Holstein II. Medizinische Klinik und Poliklinik Chemnitzstr. 33 24116, Kiel**
- Medical Center **Stiftungsklinikum Mittelrhein GmbH Zentrum für Innere Medizin Johannes-Müller-Str. 7 56068, Koblenz**
- University Medical Center **Universitätsmedizin der Johannes Gutenberg-Universität III. Med. Klinik Langenbeckstr. 1 55101, Mainz**
- Medical Center **Pius-Hospital Abteilung für Internistische Onkologie Georgstraße 12 26121, Oldenburg**
- Medical Center **Klinikum der Stadt Villingen-Schwenningen GmbH Klinik für Innere Medizin II Vöhrenbacher Str. 23 78050, Villingen-Schwenningen**
- University Medical Center **Klinik für Onkologie, Hämatologie und Stammzelltransplantation (Med. Klinik V), Pauwelsstr. 30, 52074, Aachen**
- Medical Center **Klinikum Oldenburg gGmbH Abt. Onkologie/Hämatologie, Rahel-Straus-Str. 10 26133 , Oldenburg**
- Medical Center **Städtisches Klinikum Braunschweig gGmbH Medizinische Klinik III Hämatologie und Onkologie; Celler Straße 38 38114, Braunschweig**
- University Medical Center **Universitätsklinikum Erlangen Medizinische Klinik 5 Hämatologie und Internistische Onkologie Ulmenweg 18 91054, Erlangen**
- University Medical Center **Klinikum der Johann-Wolfgang-Goethe-Universität Medizinische Klinik II Hämatologie und Onkologie Theodor-Stern-Kai 7 60590 Frankfurt/Main, Frankfurt a.M.**
- University Medical Center **Universitätsklinikum Göttingen Abteilung Hämatologie/Onkologie, Neurochirurgie Robert-Koch-Str. 40 37075, Göttingen**
- University Medical Center **Universitätskrankenhaus Hamburg-Eppendorf Medizinische Klinik II Onkologisches Zentrum Martinistr. 52 20246, Hamburg**
- Medical Center **Medizinische Hochschule Hannover Klinik für Hämatologie, Hämostaseologie, Onkologie und Stammzelltransplantation Carl-Neuberg-Str. 1 30625, Hannover**

- University Medical Center **Medizinische Universitätsklinik Heidelberg Medizinische Klinik V Im Neuenheimer Feld 410 69120, Heidelberg**
- University Medical Center **Universitätsklinikum des Saarlandes Homburg Innere Medizin I Kirrberger Straße 66424 Homburg/ Saar, Homburg**
- University Medical Center **Universitätsklinikum Köln Innere Medizin 1 Kerpener Str. 62 50937 Köln, Koeln**
- University Medical Center **Klinikum der Universität München - Großhadern Medizinische Klinik und Poliklinik III Hämatologie/Onkologie Marchioninistr. 15 81377 München, Muenchen-Grosshadern**
- University Medical Center **Klinikum rechts der Isar TU München III. Med. Klinik und Poliklinik Hämatologie u. Internistische Onkologie Ismaninger Straße 22 81675, Muenchen**
- University Medical Center <style fontName='DejaVu Sans' isBold='true'>Universitätsklinikum Regensburg Klinik & Poliklinik für Innere Medizin III Hämatologie & Onkologie Franz-Josef-Strauss-Allee 11 93053, Regensburg</style>
- University Medical Center **Universitätsklinikum Tübingen Medizinische Klinik II Otfried-Müller-Str. 10 72076 Tuebingen, Tuebingen**
- University Medical Center **Universitätsklinikum Ulm Klinik für Innere Medizin III Hämatologie, Onkologie, Rheumatologie und Infektionskrankheiten Albert-Einstein-Allee 23 89081, Ulm**
- Medical Center **Asklepios Klinik Altona Hämatologie, internistische Onkologie und Palliativmedizin Paul-Ehrlich-Straße 1 22763 Hamburg, Hamburg-Altona**
- University Medical Center **Klinik für Hämatologie und Onkologie, Leipziger Str. 44, 39120, Magdeburg**
- Medical Center **Klinikum Augsburg, I. Medizinische Klinik, Stenglinstr. 2, 86156 , Augsburg**
- Medical Center **Klinikum Chemnitz gGmbH, Klinik für Innere Medizin III Hämatologie, Onkologie, Stammzellentransplantation, Bürgerstraße 2, 09113, Chemnitz**
- University Medical Center **Klinik für Innere Medizin III Hämatologie, Onkologie, Stammzellentransplantation, Moorenstraße 5, 40225, Duesseldorf**
- Medical Center **Carl Gustav Carus Universitätsklinikum Dresden, Medizinische Klinik I und Poliklinik, Fetscherstr. 74. 01307, Dresden**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2014/07/18**
- Target Sample Size: **330**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **70 Years**

Additional Inclusion Criteria

INCLUSION CRITERIA

1.Immunocompetent patients with newly-diagnosed primary central nervous system B-cell lymphoma

Exclusion criteria

EXCLUSION CRITERIA

1.Congenital or acquired immunodeficiency

2.Systemic lymphoma manifestation (outside the CNS)

3.Isolated ocular lymphoma without manifestation in the brain parenchyma or spinal cord

4.Previous or concurrent malignancies with the exception of surgically cured carcinoma in-situ of the cervix, carcinoma of the skin or other kinds of cancer

14. Taking any medications likely to cause interactions with the study medication
15. Known or persistent abuse of medication, drugs or alcohol
16. Patient without legal capacity and who is unable to understand the nature, significance and consequences of the study and without designated legal representative
17. Persons who are in a relationship of dependency/employment to the sponsor and/ or investigator
18. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
19. Concurrent (or planned) pregnancy or lactation
20. Fertile patients refusing to use safe contraceptive methods during the study.

Addresses

- **Primary Sponsor**

  Klinik für Haematologie, Onkologie und Palliativmedizin, Stuttgart Cancer Center / Tumorzentrum Eva Mayr-StihlKlinikum Stuttgart
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Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

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  E-mail: **[---]***
  URL: **www.bmbf.de**
- **Commercial (pharmaceutical industry, medical engineering industry, etc.)**

  Riemser Pharma GmbHvertreten durch die Geschäftsführung und/ oder Prokuristen
  An der Wiek 7
  17493 Greifswald-Insel Riems
  Germany

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

Status

- Recruitment Status: **Recruiting complete, follow-up continuing**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*