Clinical trials for adults

Brentuximab vedotin or B-CAP in the treatment of older patients with newly diagnosed classical Hodgkin Lymphoma

– A GHSG-NLG Intergroup Phase II trial –

(Start June 2015)

Sponsor code: Uni-Koeln-1707
ClinicalTrials.gov ID: NCT02191930
Eudra-CT number: 2013-003990-89

Document History

Version	Reason(s) for change	Date
1.0	Initial document	16.02.2023

Responsible Persons and Organizations

Sponsor	University of Cologne, Albertus-Magnus-Platz, 50923 Cologne
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The reported trial was executed in accordance with the Declaration of Helsinki, the Guidelines for Good Clinical Practice (GCP) as well as applicable laws.

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1. Name of Sponsor / Company

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2. Name of Finished Product

- Adcetris

3. Name of Active Substance

- Brentuximab vedotin

4. Individual Study Table: Referring to Part of the Dossier

Not applicable

5. Title of Study

Brentuximab vedotin or B-CAP in the treatment of older patients with newly diagnosed classical Hodgkin Lymphoma - A GHSG-NLG Intergroup Phase II trial

5.1 Latest Protocol Version and included Amendments

- Version 6.0 (07.03.2018)
- Included amendments:
  - Amendment 1, date 01 Jul 2016
  - Amendment 2, date 14 Nov 2016
  - Amendment 3, date 04 Sep 2017

6. Investigators

All principal investigators are listed in Section 7.

7. Study centers

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8. Publication

Boris Boell, Alexander Fosså, Helen Goergen, Peter Kamper, Sirpa Leppa, Daniel Molin, Julia Meissner, Ellen Ritter, Jacob H. Christensen, Martin Hutchings, Michael Fuchs, Andreas Engert, Carsten Kobe, Peter Borchmann; B-CAP (brentuximab vedotin, cyclophosphamide, doxorubicin and predniso(lo)Ne) in Older Patients with Advanced-Stage Hodgkin Lymphoma: Results of a Phase II Intergroup Trial By the German Hodgkin Study Group (GHSG) and the Nordic Lymphoma Group (NLG). *Blood* 2018; 132 (Supplement 1): 926. doi: https://doi.org/10.1182/blood-2018-99-119363

9. Studied Period

Six years and 4 months: 02 November 2015 (first patient, first visit) – 17 March 2022 (last patient, last visit).

10. Phase of development

Phase II

11. Objectives

The aim of the B-CAP trial was to establish a well-known and tolerable CHOP regimen with the highly active brentuximab vedotin that might be a valuable option for the treatment of older HL patients. The primary objectives were to show efficacy of B-CAP in older patients with advanced-stage cHL, and to show efficacy of brentuximab vedotin monotherapy in older cHL patients not eligible to receive poly-chemotherapy.

Secondary objectives were to show the safety and feasibility of B-CAP and brentuximab vedotin monotherapy.

12.Methodology

The B-CAP trial was an open-label, multi-center, single-arm phase II study for patients with classical hodgkin lymphoma and 60 years or older, registered with clinicaltrials.gov (NCT02191930). The EudraCT number is 2013-003990-89.

12.1 B-CAP group

Based on experiences with feasible poly-chemotherapy regimens in older patients the ORR after treatment with six cycles of B-CAP is assumed to be 80%. In case of an ORR of 60% or less, B-CAP would not be considered effective enough to merit further investigation.

B-CAP was considered effective enough for further investigation if at least 33 patients showed an objective response (at least PR) in the CT-based restaging after six cycles.

Given these test parameters and a sample size of 45 patients, B-CAP will be considered effective enough for further investigation if at least 33 patients show an objective response (at least PR) in the CT-based restaging after six cycles.

12.2 Brentuximab vedotin monotherapy

In older frail patients not deemed eligible to receive poly-chemotherapy, an increase of the ORR from 5% with current approaches to 30% with brentuximab vedotin monotherapy is assumed. In case of an ORR of 5% or less, brentuximab vedotin would not be considered effective enough to merit further investigation.

Given these test parameters and a sample size of 16 patients, brentuximab vedotin monotherapy will be considered effective enough for further investigation if at least three patients show an objective response (at least PR) in the CT-based restaging after six cycles.

The trial was terminated with last patient, last visit six months after end of therapy of the last patient. The reported results are based on the final and follow up analysis (database lock: December 2022).

13.Number of patients (planned and analyzed)

It was planned to recruit 50 patients over a two-year period in the B-CAP group. After one patient has withdrawn consent and another patient died before interim staging, 48 patients were eligible for primary endpoint. The patients were enrolled between 02 November 2015 and 08 September 2017.

In the brentuximab vedotin single agent group 20 patients were planned to recruit. From 14 December 2015 to 22 October 2018 18 patients were eligible for the primary endpoint (1x disconfirmed diagnosis of Hodgkin Lymphoma; 1x less than two cycles of treatment received). 20 trial centers were needed for enrollment.

14.Diagnosis and main criteria for inclusion

14.1 Main inclusion criteria (B-CAP group):

- Classical Hodgkin Lymphoma
- Age 60 years or older
- ECOG performance status ≤ 2 or ≤ 3 if due to HL
- CIRS-G score of ≤ 6 and ≤ 3 per organ system (except score 4 for eye, ear, nose and throat)
- Advanced stages: Stage IIB with large mediastinal mass and/or extranodal lesions, stage III or IV disease
- Written informed consent

14.2 Main exclusion criteria (B-CAP group):

- Composite lymphoma or nodular lymphocyte- predominant Hodgkin lymphoma (NLPHL)
- Prior chemotherapy or radiation for HL except prephase
- Peripheral neuropathy greater than CTC Grade 1

14.3 Main inclusion criteria (Brentuximab vedotin monotherapy):

- Classical Hodgkin Lymphoma
- Age 60 years or older
- Stage IA to IVB
- CIRS-G score of ≥ 7 or 4 in one organ system (except score 4 for eye, ear, nose and throat) or
- Patients not eligible to curative poly-chemotherapy at the investigators judgment
- Written informed consent

14.4 Main exclusion criteria (Brentuximab vedotin monotherapy):

- Composite lymphoma or nodular lymphocyte- predominant Hodgkin lymphoma (NLPHL)
- Prior chemotherapy or radiation for HL except prephase as outlined in the protocol
- Peripheral neuropathy greater than CTC Grade 1

15.Test product, dose and mode of administration, batch number

Brentuximab vedotin is an antibody-drug conjugate composed of a CD30-directed monoclonal antibody that is covalently linked to the antimicrotubule agent monomethyl auristatin E (MMAE). It is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT).

For those patients who are eligible for poly-chemotherapy, the CHOP protocol was slightly modified by replacing vincristine with Brentuximab vedotin. Patients not eligible for B-CAP but for Brentuximab vedotin as single agent receive 1.8 mg/kg BV as single agent accordingly for up to 16 cycles.

Brentuximab vedotin was administered every three weeks as a 30-minute infusion. The recommended starting dose in patients was 1.8 mg/kg. Treatment consists of six cycles in the B-CAP group and 16 cycles in the brentuximab vedotin monotherapy group, respectively.

All substances of the B-CAP regimen are resale products. Therefore, additional production or labeling measures are not necessary.

The study medication is provided by Millennium Pharmaceuticals, Inc. It is labeled in conformity with the according national GCP regulation (in Germany: 'GCP-V') and dispatched by the supplier for use in this trial.

16.Duration of treatment

Individual patients received treatment up to 50 weeks.

17.Reference therapy, dose and mode of administration, batch number

Not applicable.

18.Criteria for evaluation: Efficacy, Safety

Primary endpoint of the study is the objective response rate (ORR), defined as the proportion of patients having CR, CRr or PR in the centrally reviewed restaging after six cycles of chemotherapy. Efficacy will be determined using the objective response rate (ORR), which is defined as the proportion of patients showing an objective tumor response (CR, CRr, PR) in the centrally reviewed CT-based restaging, which takes place after six or, if the patient received less than six cycles, after the last cycle of poly-chemo- or monotherapy, respectively.

Patients will be judged as non-responders in case of one of the following events:

- NC or PRO according to the CT-based restaging
- More than six cycles of chemotherapy (B-CAP group only)
- Other chemotherapy than foreseen in the trial protocol
- Tumor status after termination of study therapy is unknown

Secondary endpoints include the complete remission rate assessed after the end of treatment, progression-free survival (PFS) after three years, overall survival (OS), HL-specific survival (OSHL) and time to progression PFSHL after three years (defined as OS and PFS but deaths for known reasons other than HL or toxicity of treatment are censored and not considered as failures), the frequency of adverse events and the relative dose intensity of the novel brentuximab vedotin-containing B-CAP regimen or brentuximab vedotin.

19.Statistical methods

Based on experiences with feasible poly-chemotherapy regimens in older patients, the ORR after treatment with six cycles of B-CAP was assumed to be 80%. In case of an ORR of 60% or less, B-CAP would not have been considered effective enough to merit further investigation. The above determined benchmarks for sufficient

and insufficient efficacy of B-CAP were tested with an exact single-stage phase II design. Based on the exact binomial distribution, the null hypothesis (H0: ORR ≤ 60%) was tested against a one-sided alternative.

In older frail patients not deemed eligible to receive poly-chemotherapy, an increase of the ORR from 5% with current approaches to 30% with brentuximab vedotin monotherapy was assumed. In case of an ORR of 5% or less, brentuximab vedotin would not have been considered effective enough to merit further investigation.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, as well as safety observations and measurements, for both treatment groups. Each group was analyzed separately without adjustment for multiple testing. Descriptive analyses for gender subgroups were performed.

The following statistical analysis plans are in effect for the B-CAP trial:

- Statistical analysis plan for the final analysis V 1.0, 08 June 2018
- Statistical analysis plan for the follow up analysis, V 2.0, 01 December 2022

20. Summary – Conclusions

20.1 Feasibility Results (B-CAP group)

Patients received a median number of 6 cycles of B-CAP (min. 4 to max. 6 cycles). Treatment duration was 3.6 months (min. 1 to max. 4.1 months).

20.2 Feasibility Results (Brentuximab vedotin monotherapy)

Patients received a median number of 6 cycles of Brentuximab vedotin (min. 3 to max. 16 cycles). Treatment duration was 3.8 months (min. 1 to max. 10.7 months).

20.3 Efficacy Results (B-CAP group)

48 of 49 patients were eligible for the primary endpoint. One Patient dropped out as result of a toxicity after one cycle of B-CAP. The CT-based ORR was 98% (one-sided 95% CI 90.5%) with 21 patients having CR, 26 patients having PR, and one patient having progressive disease in the restaging after completion of B-CAP therapy. All patients with CT-based CR and 10/26 patients with PR had a negative PET (Deauville < 4), resulting in a complete metabolic CR rate of 65%. After a median follow up time of 35 months, the 3 year PFS estimate was 64.3% (95%-CI: 50.1-78.5%) with B-CAP. The 3 year OS estimates was 89.3% (95%-CI: 80.5-98.2%).

20.4 Efficacy Results (Brentuximab vedotin monotherapy)

18 of 20 patients were eligible for the primary endpoint (1x disconfirmed diagnosis of Hodgkin Lymphoma, 1x less than 2 cycles of treatment). The CT-based ORR was 67% (one-sided 95% CI 39.2%) with four patients having CR, seven patients having PR, and four patients having progressive disease in the restaging after completion of Brentuximab vedotin monotherapy. Two patients missed restaging after chemotherapy and

one had no change in tumor growth. All patients with CT-based CR and 3/6 patients with PR had a negative PET (Deauville < 4), resulting in a metabolic CR rate of 50%. After a median follow up time of 19 months, the 3 year PFS estimate was 29.5% (95%-CI: 7.8-51.1%) with B-CAP. The 3 year OS estimate was 59.1% (95%-CI: 35.2-83.0%).

20.5 Safety Results (B-CAP group)

20.5.1 Non-serious adverse events (B-CAP group)

Among 5/49 (10.2%) patients a total of 11 adverse events occurred. The most common adverse events were gastrointestinal disorders, musculoskeletal and connective tissue disorders and nervous system disorders. 21 (43%) of 49 patients had grade 4 leukopenia. Severe (grade 3 or 4) infections occurred in 15 (31 %) patients.

20.5.2 Non-serious adverse events (Brentuximab vedotin monotherapy)

Among 5/19 (26.3%) patients a total of 11 adverse events occurred. The most common adverse events were musculoskeletal and connective tissue disorders, metabolism and nutrition disorders and general disorders and administration site conditions. 2 (11%) of 19 patients had grade 3 leukopenia. Severe (grade 3 or 4) infections occurred in 4 (22 %) patients.

20.5.3 Serious adverse events (B-CAP group)

Among 28/49 (57.1%) patients a total of 38 serious adverse events occurred. The most common serious adverse events were blood and lymphatic system disorders, infections and infestations and general disorders and administration site conditions.

20.5.4 Serious adverse events (Brentuximab vedotin monotherapy)

Among 13/19 (68.4%) patients a total of 25 serious adverse events occurred. The most common serious adverse events were infections and infestations, general disorders and administration site conditions and gastrointestinal disorders.

20.6 Conclusion

With a complete metabolic CR rate of 65%, the primary endpoint of the study was met. B-CAP is feasible and effective in patients older than 60 years with advanced-stage cHL and should be subject of further research.

21.Date of report

Version 1.0 / 16 February 2022

22.References

Not applicable.