Phase II single-arm “window-of-opportunity” study of a combination of obinutuzumab (GA-101) and venetoclax (ABT-199) in relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

Protocol Number: AGMT_NHL-15B
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Protocol Synopsis:

Indication:	Early relapsed or refractory DLBCL
Study design:	This is a uncontrolled, open-label, single arm phase II pilot study
Planned sample size:	21 patients
Status:	2 patients ([1]AKH Wien, UK Innsbruck), as of March 2017
Recruitment:	18 months
Duration:	First patient in (FPI): Q1 2017 Last patient out (LPO): Q2 2020 (expected)
Study medication:	Obinutuzumab, Venetoclax

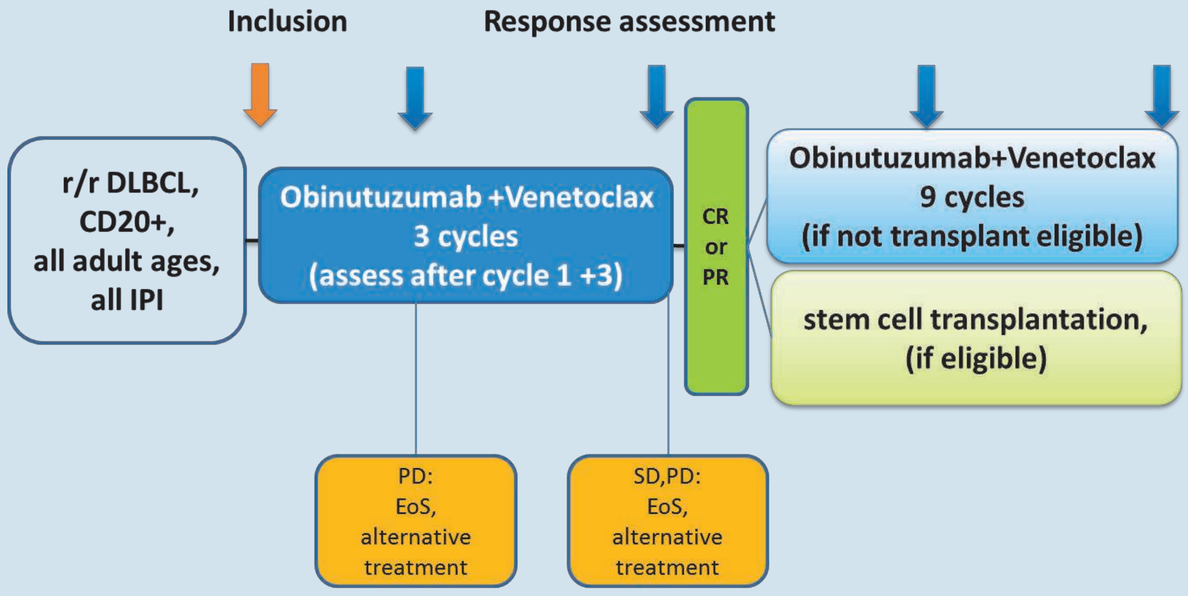
Primary objective:

- To evaluate clinical activity and tolerability of obinutuzumab in combination with venetoclax in patients with relapsed/refractory DLBCL .

Secondary objectives:

- Safety:
  Incidence of dose-limiting toxicities of the combination treatment.
- Response duration (from first documented response)
- Progression-free survival
- Overall survival
- Ability to proceed to further stem cell transplantation (assessed by number of eligible patients reaching transplant)
- Identification of genetically/biomarker defined subgroups regarding response and survival

Study Design:



Obinutuzumab will be given i.v. at a dose of 1000 mg on days 1, 8, 15 in cycle 1 and on day 1 of each following cycles. Venetoclax will be given at 800mg daily p.o. One cycle is 21 days.
This combination treatment will be repeated for up to 3 cycles.
Eligible patients will then proceed to stem cell transplantation.
A 9 cycles (27 weeks) maintenance phase with obinutuzumab and venetoclax will be given in patients ineligible for transplant.
The study will have a 6 patient run-in phase to determine safety and to adjust treatment. After 10 patients a futility analysis is planned.
A Data Safety Monitoring Board (DSMB) will review the safety data once the study is opened.

The first response assessment (including PET-CT) will be performed after the first cycle of obinutuzumab + venetoclax and patients with at least stable disease (SD) or better will be given another 2 cycles of therapy and then have assessment after a total of 3 cycles. Patients with complete or partial remission (CR, PR) after 3 cycles of therapy will either go on to transplant or receive 9 further cycles of the combination therapy (if transplant ineligible). In this case assessments will be performed after 6, 9 and 12 cycles.
Patients with progressive disease at any time-point or stable disease after 3 cycles will be taken off study.

Inclusion Criteria (selected):

- Patients ≥ 18 years of age
- Diffuse large B-cell lymphoma (DLBCL)
  with histologically confirmed relapse within 12 months after having achieved a PR or CR with initial R-anthracycline containing therapy,
  or
  with refractoriness to initial R-anthracycline containing therapy (not achieving at least a partial response)
- At least one bi-dimensionally measurable lesion on CT scan defined as > 1.5 cm in its longest dimension.
- ECOG Performance Status of 0, 1, or 2
- Adequate organ function

Exclusion Criteria (selected):

- DLBCL transformed from other malignancies or CD20 negative DLBCL
- Radiation, chemotherapy, or immunotherapy or any other anti-cancer therapy ≤ 4 weeks prior to Cycle 1 Day 1
- Ongoing corticosteroid use > 30 mg/day of prednisone or equivalent
- Acute or uncontrolled chronic infections
- Presence of positive test results for Hepatitis B, Hepatitis C and CMV
- Any sensory or motor peripheral neuropathy greater than or equal to Grade 2

An academic clinical trial
Sponsor: Arbeitsgemeinschaft medikamentöse Tumortherapie gemeinnützige GmbH, Clinical-Scientific Director: R. Greil