

## Safety and efficacy of obinutuzumab with CHOP or bendamustine in previously untreated follicular lymphoma

Andrew Grigg,<sup>1</sup> Martin J.S. Dyer,<sup>2</sup> Marcos González Díaz,<sup>3</sup> Martin Dreyling,<sup>4</sup> Simon Rule,<sup>5</sup> Guiyuan Lei,<sup>6</sup> Andrea Knapp,<sup>7</sup> Elisabeth Wassner-Fritsch<sup>7</sup> and Paula Marhton<sup>8</sup>

<sup>1</sup>Department of Clinical Haematology, Austin Hospital, Heidelberg, Australia; <sup>2</sup>Ernest and Helen Scott Haematological Research Institute, University of Leicester, UK; <sup>3</sup>Department of Hematology, University Hospital of Salamanca, Spain; <sup>4</sup>Department of Medicine III, LMU, Munich, Germany; <sup>5</sup>Department of Haematology, Derriford Hospital, Plymouth, UK; <sup>6</sup>Roche Products Ltd, Welwyn Garden City, UK; <sup>7</sup>F. Hoffmann-La Roche Ltd, Basel, Switzerland and <sup>8</sup>Department of Haematology, Princess Alexandra Hospital and University of Queensland School of Medicine, Brisbane, Australia

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Correspondence: [andrew.grigg@austin.org.au](mailto:andrew.grigg@austin.org.au)

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## Online supplementary appendix

### ***Prophylactic medication***

Premedication with oral acetaminophen and an antihistamine was given 30-60 min before each obinutuzumab infusion. Patients in the G-CHOP group began a 5-day course of prednisone on day 1 of cycle 1, prior to the obinutuzumab infusion. Premedication with prednisone or prednisolone (100 mg; or an alternative dose of dexamethasone/methylprednisone) was recommended for patients in the G-B group at least 1 hour prior to obinutuzumab infusion in cycle 1. Premedication with corticosteroids was recommended after the first infusion of obinutuzumab for G-B patients who experienced severe infusion-related reactions (IRRs) to the first dose of obinutuzumab. Any patient considered at risk of tumor-lysis syndrome due to high tumor burden and/or bulky disease ( $\geq 7$  cm) was also pre-medicated with allopurinol. For the G-CHOP group, antimicrobial prophylaxis for *Pneumocystis jirovecii* pneumonia and antiviral prophylaxis against herpes simplex and varicella zoster reactivation were at the discretion of the investigator. Granulocyte-colony stimulating factor (G-CSF) primary prophylaxis (starting in cycle 1 and continuing through subsequent cycles) was recommended as per American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines,<sup>1-3</sup> namely, in patients  $\geq 60$  years old and/or with comorbidities, and was strongly recommended in cycle 1 for all patients receiving G-CHOP.

***CHOP dose modifications in the event of neutropenia***

Neutrophils $<1.0 \times 10^9/L$ on treatment day	Delay cycle by 1-2 weeks; if the count has not recovered after 14 days, CHOP will be stopped
Grade 4 NCI-CTCAE version 3.0 neutropenia or any febrile neutropenia following any cycle of CHOP	All subsequent cycles of CHOP given with G-CSF support
Grade 4 NCI-CTCAE version 3.0 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 NCI-CTCAE version 3.0 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop CHOP and G

***Bendamustine dose modifications in the event of neutropenia***

Grade 4 NCI-CTCAE version 3.0 neutropenia	Delay dose for a maximum of 2 weeks  Administer G-CSF as required  First episode: if improvement to grade $\leq 2$ or baseline,* decrease B dose to 60 mg/m <sup>2</sup> for subsequent cycles with full dose of G  Second episode: discontinue bendamustine If improvement to grade $\leq 2$ or baseline,* then continue full-dose of G  Third episode: discontinue all study treatment
Grade 3 NCI-CTCAE version 3.0 neutropenia	Delay dose for a maximum of 2 weeks  Administer G-CSF as required  If improvement to grade $\leq 2$ or baseline,* then administer the previous dose  of B with the full dose of G

*\*If absolute neutrophil count  $< 1.5 \times 10^9/L$ . B: bendamustine; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; G: obinutuzumab; G-CSF: granulocyte-colony stimulating factor; NCI-CTAE: National Cancer Institute Common Terminology Criteria for Adverse Events.*

## **Assessments**

All AEs, irrespective of their relationship to study treatment, were collected until 6 months from the last date of drug administration of any component of induction or maintenance therapy during the last cycle. Treatment-related SAEs were collected without a post-treatment time limit.

CT scans were performed at screening, at cycle 3 day 1 for the G-B group or cycle 4 day 1 for the G-CHOP group, 28 days after the last immunochemotherapy dose, at 24, 48, and 72 weeks after the start of maintenance, and 28 days after the last maintenance dose (see below for schedule in follow-up). Positron emission tomography (PET) scans were not mandated and, therefore, not considered for the assessment of response.

Laboratory assessments, including blood counts, leukocyte immunotyping (including relative and absolute numbers of CD19+ subset), and serum biochemistry, were conducted at screening, during induction at cycle 1 days 1 and 8, day 1 of subsequent cycles, 28 days after the last immunochemotherapy dose, every 12 weeks until 96 weeks after the start of maintenance, 28 days after the last maintenance dose, every 12 weeks until 96 weeks after the start of follow-up (follow-up period described below), and every 6 months thereafter. B-cell depletion in peripheral blood was defined as a CD19+ B-cell count  $<0.07 \times 10^9/L$  and occurring after at least 1 dose of study drug had been administered. B-cell recovery was defined as when B-cells were no longer depleted (i.e.  $\geq 0.07 \times 10^9/L$ ) after the patient had completed study treatment. Total IgA, IgG, and IgM immunoglobulin electrophoresis was performed at screening, cycle 1 day 1, cycle 3 day 1 for G-B or cycle 4 day 1 for G-CHOP, and according to the same assessment schedule as blood testing thereafter.

For analysis of response or laboratory assessments, the follow-up period was defined as the time after the last G-CHOP/G-B treatment or the last maintenance dose of

obinutuzumab. During follow-up, CT scans were performed every 24 weeks up to 96 weeks, and every 6 months thereafter.

## References

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