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Open-label, multicentre expansion cohort to evaluate imgatuzumab in pre-treated patients with *KRAS*-mutant advanced colorectal carcinoma ☆

Jean-Pierre Delord [a], Josep Tabernero [b], Rocío García-Carbonero [c], Andres Cervantes [d], Carlos Gomez-Roca [e,f], Yann Bergé [a], Jaume Capdevila [b], Luis Paz-Ares [c], Desamparados Roda [d], Paul Delmar [g], David Oppenheim [h], Sophia Soehrman Brossard [g], Farzin Farzaneh [h], Luigi Manenti [i], Alexandre Passioukov [i], Marion Gabriele Ott [g], Jean-Charles Soria [e,f,*]

[a] *Institut Claudius Regaud and Toulouse III University, Toulouse, France*
[b] *Vall d'Hebron University Hospital, VHIO, Universitat Autònoma de Barcelona, Barcelona, Spain*
[c] *Oncology Department, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS) [Universidad de Sevilla, CSIC, HUVR], Seville, Spain*
[d] *Department of Haematology and Medical Oncology, INCLIVA, University of Valencia, Spain*
[e] *Institut Gustave Roussy, Villejuif, France*
[f] *University Paris South, France*
[g] *F. Hoffmann-La Roche Ltd., Basel, Switzerland*
[h] *Department of Haematological Medicine, King's College, London, UK*
[i] *Roche Glycart AG, Schlieren, Switzerland*

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Abstract ***Aim:*** Imgatuzumab (GA201) is a novel anti-epidermal growth factor receptor (anti-EGFR) antibody glycoengineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). We investigated the efficacy of imgatuzumab in patients with EGFR-positive, *KRAS*-mutant advanced colorectal cancer.
Methods: Patients received single-agent imgatuzumab (1400 mg on day 1 and 8 followed by q2W) as third line therapy in an open-label, multicentre, non-randomised, expansion study. The primary end-point was tumour response. Pre- and on-treatment biopsies and blood samples were investigated for biomarkers related to imgatuzumab's believed mechanism of action (MoA).

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* *Corresponding author*: Address: SITEP, Institut Gustave Roussy and South Paris University, 114 Rue Edouard Vaillant, 94805 Villejuif, France. Tel.: +33 (0) 1 42 11 43 39; fax: +33 (0) 1 42 11 64 44.
E-mail addresses: Jean-Charles.Soria@igr.fr, Jean-Charles.Soria@gustaveroussy.fr (J.-C. Soria).

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Results: 25 patients were treated and the best overall response was stable disease occurring in 40% of patients at 8 weeks, 24% at 16 weeks and 8% (two patients) at 32 weeks. Median overall survival was 9.3 months (95% confidence interval (CI): 5.1–12.3). Treatment-related rash, hypomagnesaemia and infusion-related reactions were the most common adverse events. Comparison of pre- and post-treatment biopsies revealed that the number of tumour-infiltrating immune cells increased notably after one cycle of therapy (median compound immune reactive score of 1491 versus 898 cells/mm^3 at baseline), whereas the number of peripheral natural killer cells decreased. A potential association between baseline tumour immune infiltration and clinical efficacy was seen.

Conclusions: These data may suggest that the MoA of imgatuzumab involves ADCC-related immune effects in the tumour and is not limited to simple receptor blockade.

1. Introduction

The anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) cetuximab and panitumumab are established treatment options for metastatic colorectal cancer (CRC); however, these agents are ineffective in patients with *KRAS*-mutant tumours [1–4]. This suggests that simple inhibition of the EGFR signalling pathway may be insufficient when the oncogenic signal arises downstream of EGFR [5]. *KRAS* mutation affects ~40% of CRC cases [6] and these patients are notoriously difficult to treat, with a median progression-free survival (PFS) and overall survival (OS) of approximately 3 and 6 months, respectively [7,8].

Imgatuzumab (GA201) is a novel humanised mAb that is glycoengineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) on top of EGFR-signalling inhibition. In preclinical experiments using *KRAS*-mutant cell lines, imgatuzumab exhibited enhanced ADCC compared with non-glycoengineered antibody and cetuximab, and this translated into superior *in vivo* efficacy in murine xenograft models of *KRAS*-mutant human cancer [9]. Promising efficacy and a manageable safety profile were recently demonstrated in a phase I/II trial of single-agent imgatuzumab in heavily pre-treated patients with solid tumours, including some who had previously progressed on other anti-EGFR mAbs [10]. Pharmacodynamic observations in this study supported the engagement of immune effector cells in the mechanism of action (MoA) of imgatuzumab [10].

We therefore conducted an expansion cohort of the Phase I/II trial to investigate the tumour growth control rate of single-agent imgatuzumab in patients with metastatic EGFR-positive, *KRAS*-mutant CRC. Secondary objectives included assessment of the tolerability and adverse event (AE) profile and further analysis of the immunological effects of imgatuzumab.

2. Patients and methods

2.1. Patient selection

Eligible patients were aged ⩾18 years with histologically/cytologically confirmed metastatic EGFR-positive and *KRAS*-mutant (codons 12/13/61) CRC. Patients had radiologically measurable progressive disease (PD), an Eastern Cooperative Oncology Group (ECOG) performance status of ⩽1 and adequate haematology, blood chemistry, renal and liver function. Patients with >2 previous cytotoxic regimens for metastatic disease were excluded. All patients provided written informed consent and the study was approved by local Ethics Committees and conducted according to Good Clinical Practice guidelines.

2.2. Study design

This was an expansion cohort of an open-label, multicentre, non-randomised, dose-escalating, phase I/II study [10]. Based on the safety profile and efficacy demonstrated in part I, 1400 mg imgatuzumab (fixed dosing) was administered intravenously on days 1 and 8 followed by dosing every 2 weeks (q2W). Patients were premedicated with paracetamol, anti-histamine and corticosteroids for the first two infusions to minimise the risk of infusion-related reactions (IRRs; see Supplementary information).

2.3. Assessments

EGFR positivity and *KRAS* mutation status were confirmed centrally at screening (Supplementary information). Clinical assessments, haematology and biochemistry were performed at baseline/screening and throughout the treatment period. Laboratory values and AEs were graded according to NCI-CTC-AE v3.0 criteria [11]. Tumour assessment was performed at screening and every 8 weeks beginning at cycle 4 accord-