Antibody dependent cellular cytotoxicity (ADCC) is the process of lysis of (tumor) target cells by immune effector cells. It requires the simultaneous binding of an antibody to a cell surface receptor on the target cell and via the Fc region of the antibody to the FcγRIIa receptor on immune effector cells such as NK cells or macrophages/monocytes. Binding of the antibody to target and immune effector cells results in the cross-linking of FcγRIIa with subsequent activation of FcγRIIa signaling and release of proteins mediating the killing of the target cells such as perforin and of proteases such as granzymes. ADCC has been established as an important mode of action of therapeutic antibodies such as rituximab/MabThera (targeting CD20), cetuximab/Erbilux (targeting EGFR) and trastuzumab/Herceptin (targeting HER2) which are approved for the treatment of various cancers. Translational research on rituximab and cetuximab has established that the response to therapeutic antibodies in patients can be influenced by the FcγRIIa-158V/F polymorphism. This polymorphism results in the expression of a high affinity FcγRIIa receptor (158 V) and a low affinity FcγRIIa receptor (158F) on immune effector cells and impacts the capability of antibodies to mediate ADCC [1–7]. We have recently developed a so-called GlycoMab technology that enhances the affinity of therapeutic antibodies for both the high and low affinity FcγRIIa receptors through the introduction of a bisecting N-acetyl-glucosamine residue in the carbohydrate chain of the Fc region of the antibodies. The introduction of this bisecting N-acetyl-glucosamine moiety in the carbohydrate chain results in a steric interference with core fucosylation of the carbohydrate. This process and other approaches resulting in the afucosylation of therapeutic antibodies are known as “antibody glycoengineering”. We and others have demonstrated that glycoengineering and lack of the core fucose residue results in an up to 50-fold enhanced affinity of human IgG1 antibodies for the human FcγRIIa receptors, and this subsequently results in an up to 100-fold enhanced ADCC induction (potency). Recently, we have demonstrated that glycoengineering and lack of the core fucose residue in an up to 50-fold enhanced affinity of human IgG1 antibodies for the human FcγRIIa receptors, and this subsequently results in an up to 100-fold enhanced ADCC induction (potency). It was designed to combine potent EGFR signaling inhibition with enhanced ADCC induction. In xenograft models GA201 demonstrated superior activity compared to cetuximab and panitumumab. Hence, GA201 has the potential to show clinical activity in patients with solid tumors. Phase I clinical testing in heavily pretreated patients with advanced solid tumors demonstrated a manageable toxicity profile. Evidence of anti-tumor activity was also seen, especially in patients with colorectal cancer, including a number of patients who had previously received cetuximab and/or panitumumab (1 CR, 2 PR). Interestingly, one of the partial responses was reported in a tumor-harboring a k-ras mutation.

GA201 (RG7160) is a second anti-EGFR GlycoMab monoclonal antibody that is currently being investigated in Phase II clinical trials. It was designed to combine potent EGFR signaling inhibition with enhanced ADCC induction. In xenograft models GA201 demonstrated superior activity compared to cetuximab and panitumumab. Hence, GA201 has the potential to show clinical activity in patients with solid tumors. Phase I clinical testing in heavily pretreated patients with advanced solid tumors demonstrated a manageable toxicity profile. Evidence of anti-tumor activity was also seen, especially in patients with colorectal cancer, including a number of patients who had previously received cetuximab and/or panitumumab (1 CR, 2 PR). Interestingly, one of the partial responses was reported in a tumor-harboring a k-ras mutation.

GA201 is currently undergoing Phase II clinical trials in CRC and NSCLC in combination with chemotherapy as well as a neo-adjuvant biomarker study in HNSCC [25].

**Conflict of Interest:** The author is employed by Roche Glycart AG.

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