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MONOGRAPH

# DALOTUZUMAB

Rec INN; USAN

*Humanized Anti-CD221 Monoclonal Antibody*
*Oncolytic*

A2CHM
F-50035
h7C10
MK-0646

Immunoglobulin $G_1$, anti-(human insulin-like growth factor 1 receptor) (human-mouse monoclonal heavy chain), disulfide with human-mouse monoclonal κ-chain, dimer

Immunoglobulin $G_1$, anti-(human insulin-like growth factor 1 receptor (EC.2.7.10.1 or CD221); humanized mouse monoclonal $\gamma_1$ heavy chain (220-219')-disulfide with humanized mouse monoclonal κ light chain, dimer (226-226'':229-229'')-bisdisulfide

EN: 375895


## SUMMARY

*There is abundant scientific evidence showing the key role of the insulin-like growth factor 1 receptor (IGF-I receptor, CD221) pathway in the malignant transformation of cells and in mediating resistance to various anticancer therapies. A rational approach in modulating this pathway is through blockade of growth factor signaling at the ligand–receptor interface. Dalotuzumab (MK-0646) is a recombinant humanized $IgG_1$ monoclonal antibody that binds specifically to CD221. It is currently in clinical development for the treatment of a wide variety of malignancies, such as cancers of the breast, alimentary tract and lung. Mechanisms of the anticancer activity of dalotuzumab are down-regulation of CD221 expression, as well as induction of antibody-dependent cell-mediated cytotoxicity. This article provides an overview of the research and development of dalotuzumab.*


## BACKGROUND

The importance of insulin-like growth factor 1 receptor (IGF-I receptor, CD221) in carcinogenesis was first established when it was demonstrated that 3T3-like fibroblasts lacking CD221 were refractory to malignant transformation by viral and cellular oncogenes (1). Upon binding of its cognate ligands (IGF-I and IGF-II), adaptor proteins are recruited that trigger various downstream signals, including the phosphoinositide 3-kinase (PI3K)/c-Akt/mTOR cascade that mediates prosurvival/antiapoptotic effects, chemo- and radioresistance (2). CD221 is overexpressed in a wide range of malignancies, including lung, breast, prostate and colon cancer (3). Conversely, ligand overexpression has been linked to carcinogenesis and may arise through genomic imprinting, such as in ovarian and colorectal cancer (4, 5), or through unique translocation abnormalities in certain tumor types, such as the *EWS-Fli1* translocation in Ewing's sarcoma and the t(X;18) translocation in synovial sarcomas (6, 7).

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## PRECLINICAL PHARMACOLOGY

A common approach to modulating growth factor receptor signaling is blockade of the ligand–receptor interaction using monoclonal antibody (mAb) technology. Dalotuzumab (MK-0646) is a humanized mAb that avidly binds to CD221 ($K_d$ = 0.9 nM), inhibiting IGF-I- and IGF-II-mediated cellular proliferation in vitro in conjunction with concentration-dependent CD221 downregulation (3). In tumor xenograft models, dalotuzumab was also demonstrated to potently inhibit tumor growth alone or in combination with other anticancer agents, such as cetuximab (3, 8). It specifically recognizes CD221 despite the close homology of CD221 to the insulin receptor. Because of its $IgG_1$ idiotypic backbone, its ability to elicit antibody-dependent cell cytotoxicity (ADCC) can contribute to its in vivo efficacy (3). In preclinical studies, antitumor activity was seen at concentrations above 3 μg/mL, with the targeted trough level of 3-25 μg/mL used to guide further clinical development based on antitumor activity seen in xenograft models

## SAFETY

Despite the ubiquitous expression of CD221 in most normal tissues, treatment with CD221-directed mAbs in general is usually well tolerated and this is true for dalotuzumab as well. As described below, the maximum tolerated dose (MTD) has not been identified for dalotuzumab as a single agent. Commonly associated mechanism-based adverse events of agents in this class are hyperglycemia, fatigue and infusion reactions. Hyperglycemia is manageable using oral agents such as metformin. Since the insulin receptor is not targeted, the true mechanism for hyperglycemia is not completely understood, although putatively the pathogenesis of this insulin resistance may be akin to acromegalic states wherein rebound IGF-I levels (also seen with CD221 mAb therapy) are unable to counteract hyperglycemia in association with growth hormone excess. Hemato-

logical toxicities may be seen as a class effect of $IgG_1$ idiotypic CD221 antibodies and the postulated mechanism is cytolysis of CD221-expressing peripheral erythrocytes, leukocytes and platelets via ADCC (9). Indeed, grade 3 and 4 thrombocytopenia has been observed with dalotuzumab. Thrombocytopenia has been reported with other $IgG_1$ CD221-targeting mAbs as well, such as ganitumab (AMG-479), cixutumumab (IMC-A12) and R-1507 (10-12). Pneumonitis and transaminitis are also seen with dalotuzumab and may also be class effects. Because sensorineural hearing loss has been described in humans with *IGF1* or *IGF1R* gene mutations and hearing changes have occurred in healthy volunteers receiving CD221-directed mAbs, this is being investigated in ongoing trials of dalotuzumab.

There are no published data on the development of neutralizing human anti-human antibodies (HAHAs) in response to dalotuzumab, although this has been described in a few patients. Monitoring is ongoing in various studies, and thus far this does not seem to pose a significant issue.

## CLINICAL STUDIES

Detailed phase I studies exploring various dose schedules of dalotuzumab monotherapy administered as 1- to 2-h infusions have been conducted. For the weekly schedule of administration, mean trough concentrations exceeded the target of 25 μg/mL at doses above 5.0 mg/kg/week. Likewise, serum clearance was predictable and saturable, remaining relatively constant for doses of ≥ 10 mg/kg/week, with a limited volume of distribution and a mean terminal half-life of approximately 4 days. The MTD on a 28-day cycle was not identified and the prespecified terminal 20 mg/kg/week dose level was well tolerated. A homeostatic increase in the IGF-I level in serum was documented after the second week of therapy at doses of ≥ 10 mg/kg/week. Pre- and post-treatment tumor biopsies showed modulation of downstream signaling proteins, with statistically significant inhibition of eukaryotic translation initiation factor 4A/E (eIF-4A/E), phosphorylated eukaryotic translation initiation factor 4E-binding protein 1 (p4E-BP1), phosphorylated ribosomal protein S6 kinase, antigen KI-67 and phosphorylated mitogen-activated protein kinase (MAPK) after treatment, including dose-dependent downregulation of CD221 with dalotuzumab at ≥ 5 mg/kg/week (13).

For the biweekly schedule, part 1 of the study explored escalating loading doses followed by a fixed maintenance dose, whereas part 2 explored a previously established fixed loading dose followed by escalating maintenance doses. A target trough concentration > 25 μg/mL was achieved with loading doses of > 10 mg/kg and at maintenance doses of > 10 mg/kg every 2 weeks, at which clearance showed saturation kinetics (14). Similar to the previous study, serum IGF-I increased over time with dalotuzumab doses above 5 mg/kg. There was also a parallel increase in insulin-like growth factor-binding protein 3 (IGFBP-3). Surrogate tissue analysis using peripheral blood mononuclear cells and an enzyme immunoassay showed downregulation of CD221 expression within 5 h of drug infusion versus baseline values in approximately 90% of patients, with an average reduction of 19%. The MTD was not reached with loading doses up to 20 mg/kg and at a biweekly maintenance dose of 15 mg/kg. An infusion schedule once every 3 weeks is currently ongoing and appears to be tolerable at 30 mg/kg.

In the phase I dose-finding monotherapy trials, enrollment was restricted to patients with either histologically confirmed CD221-expressing (≥ 10% as determined by immunohistochemistry) tumors or in tumor types with known postulated reliance on the CD221 signaling pathway, e.g., colorectal cancer and carcinoma of the breast and prostate (13, 14). Early signs of clinical activity, either objective tumor responses or prolonged disease stabilization, were observed in patients with sarcoma and colorectal cancer.

Results were recently reported from a phase II study investigating the role of dalotuzumab monotherapy in subjects with well-differentiated metastatic neuroendocrine tumors. While dalotuzumab was well tolerated, no antitumor activity was seen in the 25 patients treated (15).

Modest single-agent activity comes as no surprise due to the complicated nature of intracellular signaling in most malignancies, with multiple interconnected pathways that crosstalk, thus evading the "one-target, one-drug" paradigmatic success exemplified by imatinib. Preclinical models have demonstrated the role of CD221 in mediating resistance to therapies targeting estrogen, receptor tyrosine-protein kinase erbB-2 (HER2) or epidermal growth factor receptor (EGFR), and thus combination of these agents with dalotuzumab is rational (16-18). Another approach is through longitudinal dual blockade of CD221 and the mTOR pathway. This is a feasible strategy due to known CD221-dependent feedback activation of c-Akt signaling, leading to treatment resistance upon exposure to rapamycin analogues (19). Conversely, inhibition of CD221 activation abolished treatment resistance. The focus of further clinical development is on the evidence-based combination of dalotuzumab and other anticancer therapies.

Dalotuzumab is being actively explored in combination with anti-EGFR therapies in a variety of settings, with or without the addition of cytotoxic chemotherapy. A placebo-controlled phase II/III study investigating weekly versus biweekly dalotuzumab in combination with cetuximab and irinotecan for patients with metastatic wild-type *KRAS* colorectal cancer is ongoing (20). The rationale is based on preclinical models revealing a synergistic effect with cetuximab therapy (3). In patients with advanced chemotherapy-naïve pancreatic cancer, a three-arm randomized phase II study is ongoing comparing dalotuzumab/gemcitabine combination and dalotuzumab/gemcitabine/erlotinib hydrochloride combination therapy to combined gemcitabine/erlotinib treatment. This study is based on promising clinical activity seen during the phase I study of this combination, with sustained partial responses of > 32 weeks in 3 of 6 patients with partial response. Of note, during the phase I development of this combination, the MTD was not reached with dalotuzumab 10 mg/kg/week in combination with standard weekly gemcitabine dosing. However, the addition of the oral EGFR inhibitor erlotinib was associated with increased toxicity, requiring erlotinib dose modification in half of the patients treated, despite the fact that a low erlotinib dose of 100 mg/day was initially given. Dose-limiting toxicities (DLTs) of febrile neutropenia and hepatic transaminitis were seen with 10 mg/kg/week dalotuzumab. The recommended dose of dalotuzumab, currently used in the ongoing phase II study, is 5 mg/kg/week with the triple regimen (21).

On the other hand, the combination of erlotinib at its FDA-approved dose of 150 mg daily with dalotuzumab 10 mg/kg/week was shown

to be well tolerated in a phase I study in patients with advanced non-small cell lung cancer (NSCLC) and is currently the dose schedule being studied in the phase II setting (22). Nonetheless, a recent string of negative studies involving figitumumab (CP-751871), an $IgG_2$ anti-CD221 mAb, have sown some trepidation in this field. The interim results of a randomized phase III study (ADVIGO 1018) of erlotinib with or without figitumumab led to early termination of the study in March 2010, when futility analysis revealed that the addition of figitumumab was unlikely to confer an overall survival advantage in patients with advanced NSCLC when used in combination with erlotinib compared to erlotinib alone (23). In light of this, the outcome of ongoing combination studies of erlotinib with other CD221-targeting agents is much awaited. A disappointing and more ominous report, however, pertained to the phase III trial of figitumumab with carboplatin and paclitaxel (ADVIGO 1016) in patients with advanced nonadenocarcinoma. The trial was permanently discontinued in March 2010 following a halt in new patient enrollment in September 2009, when the preplanned analysis revealed an imbalance of fatalities, with higher survival rates in the control cohort receiving chemotherapy alone, even after excluding deaths from disease progression. Serious adverse events in the figitumumab group included dehydration, anorexia, fatigue, hyperglycemia, fatal infections and cardiac events (including deaths). Subsequent analyses suggested that low pretreatment body mass index, creatinine clearance and baseline IGF-I levels were factors predictive of early death for patients receiving figitumumab (increased risk of adverse events included higher hemorrhagic or hemoptysis rates), whereas survival favored patients receiving figitumumab if they had high baseline IGF-I levels, in part due to a lower incidence of toxicity (24). Stratification based on this biomarker may thus be hypothesized as a strategy in the future development of anti-CD221 mAbs to select a target population. In this context, a Cancer Therapy Evaluation Program (CTEP)-approved randomized phase II study of gemcitabine and carboplatin with or without dalotuzumab in this patient population was not activated, while gathering more safety data in other ongoing trials of dalotuzumab in combination with chemotherapy for nonsquamous NSCLC (randomized phase II study of cisplatin and pemetrexed disodium with or without dalotuzumab) and extensive-stage SCLC (single-arm phase II trial of cisplatin, etoposide and dalotuzumab).

Nonetheless, clinical activity for dalotuzumab therapy was recently demonstrated. In a phase I study combining the mTOR inhibitor ridaforolimus (deforolimus, AP-23573) with dalotuzumab, the MTD of this combination was initially determined as ridaforolimus 40 mg/day for 5 days/week and dalotuzumab 10 mg/kg/week. In the expansion stage, further DLTs (stomatitis and fatigue) were observed for a total of 4 of 15 evaluable patients receiving the MTD. The recommended phase II dose is currently set at ridaforolimus 30 mg in combination with dalotuzumab 10 mg/kg/week, which was better tolerated, with DLT of stomatitis observed in only 1 of 19 evaluable patients treated. Hyperglycemia was common but medically manageable. Robust antitumor efficacy and prolonged disease stabilization were observed in 10 of 23 treated individuals with breast cancer, 6 of whom had tumors expressing the estrogen receptor (ER) and high levels of antigen KI-67, of 11 patients with this $ER^+$/high KI-67 tumor profile. Conversely, none of the five participants with $ER^+$/low KI-67 breast cancer exhibited clinical benefit from therapy. Pre- and post-treatment tumor biopsies showed partial downregulation of phosphorylated ribosomal protein S6 (pS6) activity with ridaforolimus monotherapy, converting to complete inhibition upon combination therapy with dalotuzumab (25). Thus, a randomized phase II study is being planned comparing the ridaforolimus/dalotuzumab combination to exemestane in patients with metastatic $ER^+/HER2^-$ breast cancer, with stratification to enrich for tumors with a high proliferation index.

## CONCLUSIONS

Because dalotuzumab is an $IgG_1$ mAb specific for CD221 with modest single-agent antitumor efficacy, a cogent developmental track is exploring rational combination with other anticancer agents. Indeed, early trial results demonstrate encouraging clinical activity when the mAb is combined with mTOR inhibitors. Toxicities, while manageable, constitute an important issue in combination studies, as they may potentially overlap with those of other anticancer agents (e.g., fatigue and cytopenia). Attention to the use of concomitant medications that may exacerbate mechanism-based adverse events (e.g., hyperglycemia with the use of corticosteroids) is also required. Identification and validation of predictive biomarkers are crucial to maximize dalotuzumab's benefit and enhance the personalized approach in the prescription of this agent.

## SOURCE

Merck & Co., Inc. (US); being developed under license from Pierre Fabre Médicament (FR).

## DISCLOSURES

The author states no conflicts of interest.

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