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Mapatumumab

Rec INN; USAN

Anti-TRAIL-R1 (DR4) Monoclonal Antibody
Apoptosis Inducer
Oncolytic

HGS-ETR1
TRAIL-R1 MAb
TRM-1

Agonistic fully human monoclonal antibody to tumor necrosis factor apoptosis-inducing ligand (TRAIL) receptor-1

Immunoglobulin G_1, anti-(human cytokine receptor DR4 [death receptor 4]) (human monoclonal TRM-1 heavy chain), disulfide with human monoclonal TRM-1 λ-chain, dimer

Immunoglobulin G_1, anti-(human TRAIL-R1) (human monoclonal TRM-1 heavy chain), disulfide with human monoclonal TRM-1 λ-chain, dimer

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Abstract

Deregulation of apoptosis (or programmed cell death) is a hallmark of cancer cells. Apoptosis is classically triggered by two upstream pathways, named the intrinsic and extrinsic pathways, the final result being activation of several cysteine proteases called caspases and induction of an apoptotic cell phenotype. The extrinsic pathway of apoptosis is triggered mainly by death receptors and their ligands, while the intrinsic pathway (also named the mitochondrial pathway) is activated by DNA damage and defective cell cycle and triggered by Bcl-2 family members. Inducing apoptosis in cancer cells represents a novel and promising area of discovery and research. Targeting elements from the extrinsic or intrinsic pathway may have either a direct proapoptotic effect or sensitize cancer cells to other cytotoxics. Several drugs are being developed to target death receptors, including monoclonal antibodies to the TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) receptors. Mapatumumab is a fully human monoclonal antibody to TRAIL-R1 currently undergoing phase II clinical development as a single agent and in combination with chemotherapies. Combination studies with other therapeutic options such as targeted therapies are either ongoing or planned. Preclinical and clinical studies with mapatumumab demonstrated an acceptable toxicity profile, as well as encouraging antitumor activity.

Introduction

Death receptors that activate the extrinsic pathway of apoptosis are members of the tumor necrosis factor receptor (TNFR) superfamily and include functional receptors characterized by a functional death domain (DD), and decoy receptors (DcR) that lack the functional domain. Studies revealed that certain members of this family (*e.g.*, TNF-α receptor, CD95/FasL/Apo-1L receptor and TRAIL/Apo-2L receptor) appear to be implicated in several biological functions, including cell metabolism, proliferation, cytokine production and apoptosis, while others (*e.g.*, TRAIL-R3, osteoprotegerin [OPG]) may be involved in cell proliferation and survival (1-3). Each receptor has a distinct ligand specificity (*e.g.*, TRAIL-R1 and -R2 will only bind TRAIL, but not Fas or TNF-α). The ligand-receptor interaction determines the recruitment of adaptor proteins, called Fas-associated death domain proteins (FADDs), to the intracytoplasmic domain of the receptor, which results in further recruitment of procaspase-8 and -10 and the formation of a death-inducing signaling complex (DISC) that induces autocleavage and activation of these two caspases (4-6). Caspase-8 and -10 activate downstream "executioner" caspases-3, -6 and -7, which cleave the cellular death substrates and lead to apoptosis. FLICE (FADD-like interleukin-1β-converting enzyme)-like inhibitory protein (c-FLIP) represents the principal negative regulator of TRAIL-induced apoptosis through binding and inhibiting DISC. Studies have demonstrated that both the recruitment of FADD and caspase activation are important for TRAIL-mediated apoptosis. Furthermore, deficiency or mutations in caspase-8 and -10 or FADD genes could contribute to resistance to TRAIL (6-10).

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The TRAIL receptor family includes five known members that interact with the TRAIL ligand. TRAIL-R1 (DR4) and -R2 (DR5) contain the DD, which is essential for the activation of the extrinsic apoptotic pathway upon TRAIL ligand binding. TRAIL-R3 (DcR1), TRAIL-R4 (DcR2) and circulating osteoprotegerin (OPG) lack a functional DD. These decoy receptors may play a role in negatively regulating apoptosis by competing with the TRAIL ligand, particularly in normal cells. The TRAIL ligand, a cytotoxic cytokine, is a bell-shaped homotrimer that induces apoptosis in tumor cells but not in normal cells. TRAIL possesses a free cysteine residue (Cys230) stabilized by a zinc ion, which is essential for the proapoptotic activity (8, 10-12). TRAIL binds to different receptors with different affinities, showing the highest affinity for TRAIL-R2 and the weakest affinity for OPG. TRAIL induces p53-independent cell death in several transformed cell lines, but not in normal cells (13).

TRAIL and its receptors represent an attractive area of research and several studies have demonstrated that TRAIL and TRAIL receptors fulfill essential functions, including tumor and immune system surveillance and inflammatory response. Additionally, other studies indicate that TRAIL/TRAIL-R may have proangiogenic activity by promoting the survival and proliferation of endothelial cells (14, 15). However, the complex functions of TRAIL and its receptors have been only partially characterized to date (16, 17). TRAIL-R1 and -R2 expression on the surface of normal cells is low in contrast to cell lines from numerous cancers, such as ovarian, uterine, colon, brain, lung and breast cancer and lymphoma (18-23). Additionally, TRAIL-R1 and -R2 expression in tumor samples is higher compared to the adjacent normal tissue (23). Expression of TRAIL-R1 and -R2 is required for TRAIL-mediated apoptosis, although the magnitude of receptor expression does not seem to have a direct relation to induction of apoptosis (4, 21, 24-28).

There are multiple lines of evidence suggesting that the TRAIL pathway is a promising target for cancer treatment (24). TRAIL-R1 and -R2 have been shown to play a strategic role in cancer surveillance, as both receptors are overexpressed in tumor cells and stimulate apoptosis upon activation. Recent studies revealed that during colorectal carcinogenesis, the sensitivity to TRAIL-induced apoptosis is markedly increased and associated with progression from benign to malignant tumor (29). Moreover, in animal models, TRAIL exerts cytotoxic activity on cancerous cells with minimal toxicity in most normal tissues, with the exception of hepatocytes, neurons and keratinocytes (24, 30, 31). The selective sensitivity of tumor cells, but not most normal cells, to TRAIL is not completely understood, but could be related to the greater expression of the TRAIL receptor in tumor cells, or to the relatively larger number of decoy receptors in normal cells (32, 33). Additionally, the TRAIL-induced apoptotic signal is blocked in normal human cells at the level of caspase-8 recruitment, and this blockade can be eliminated by Ras-induced transformation involving activation of the mitogen-activated protein kinase (MAPK) pathway (34).

Inducing TRAIL receptor-mediated apoptosis may enhance the activity of agents targeting the intrinsic pathway of apoptosis, such as DNA-damaging agents. This finding may be of relevance for the treatment of tumors bearing *p53* mutations, since sensitivity to TRAIL is independent of *p53* status. It has been shown that the combination of TRAIL with chemotherapeutic agents is particularly effective in cancer cells with wild-type *p53*, presumably through induction of DR5 expression (35, 36). Additionally, it has been shown that chemotherapeutic agents can upregulate death receptors and enhance the antitumor activity of monoclonal antibodies targeting these receptors (37).

The TRAIL-R1 agonistic human monoclonal antibody HGS-ETR1 (mapatumumab) was generated through a collaboration between Human Genome Sciences and Cambridge Antibody Technology. Mapatumumab was chosen from a pool of more than 100 different anti-TRAIL receptor monoclonal antibodies due to its high receptor affinity (0.8 nM) and potent antitumor activity in preclinical models. Mapatumumab binds to the extracellular domain of TRAIL-R1, activates the receptor and triggers the extrinsic component of the apoptotic pathway. Binding of mapatumumab to TRAIL-R1 induces the formation of DISC, recruitment of caspase-8 and -10 and apoptosis, similar to the natural ligand TRAIL. Additionally, mapatumumab recognizes the TRAIL-R1 protein but does not bind to other extracellular receptors, therefore displaying highly specific effects (19, 38).

Preclinical Pharmacology

Over the last decade, TRAIL- and TRAIL-R1- and -R2-targeting monoclonal antibodies with agonist activity have been extensively studied in preclinical models either as single agents or in combination with cytotoxic or targeted therapies. Additionally, as cytotoxic drugs activate the intrinsic (or mitochondrial) pathway of apoptosis and TRAIL or TRAIL receptor monoclonal antibodies target the extrinsic pathway, the combination may have synergistic activity by targeting both the extrinsic and intrinsic apoptotic pathways.

The *in vitro* activity of mapatumumab and related compounds administered either alone or in combination with chemotherapeutic agents is particularly encouraging, and to some extent mirrors the results seen with TRAIL (27). Mapatumumab induces apoptosis in multiple human and murine cancer cell lines, including carcinomas of the ovary, brain, colon, breast, uterus and lung, as well as chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML) and multiple myeloma (19, 21, 23, 27, 28). Moreover, cytotoxicity was observed in some cases despite low expression of TRAIL-R1 (21). Multiple cell lines with detectable expression of TRAIL-R1, including SW480 colon adenocarcinoma, NCI-H2122 non-small cell lung cancer (NSCLC), A-498 renal cell carcinoma, ST486 Burkitt's lymphoma, COLO 205 colon adenocarcinoma, SU.86.86 pancreatic ductal carcinoma, NCI-H460 NSCLC, SNU-398 hepatocellular carcinoma, TTn

esophageal squamous carcinoma, HCT 116 colon adenocarcinoma, JURL-MK1 CML, RL95-2 uterine endometrial carcinoma, ES-2 ovarian clear cell carcinoma, as well as the WM 793B melanoma cell line that lacks expression of TRAIL-R1, were studied to evaluate induction of cell killing and the mechanism of action when treated with mapatumumab. Mapatumumab titration demonstrated a concentration-dependent reduction in cell viability. Induction of apoptotic signaling was measured by caspase-3/7 activation. Mapatumumab did not induce caspase activity in the cell line with no TRAIL-R1 expression. In contrast, the other cell lines showed different sensitivity to mapatumumab which was not predicted by the level of TRAIL-R1 expression. Interestingly, the only cell line that lacks TRAIL-R1 expression but expresses high levels of TRAIL-R2 was not affected by treatment with mapatumumab, thus further supporting the specificity of mapatumumab for its receptor (19).

MacFarlane and colleagues showed that primary cells from patients with CLL and mantle cell lymphoma signal to apoptosis through TRAIL-R1, in contrast to other tumors which signal through TRAIL-R2. These results emphasize the importance of better characterization of tumors to determine whether cells signal via TRAIL-R1 or -R2 (39, 40). This information could be essential in the future, not only to predict response to treatment but also for patient population enrichment for clinical trials.

Several studies reported synergistic antitumor activity for mapatumumab in combination with different chemotherapeutic agents. *In vitro*, mapatumumab increases apoptosis when combined with cisplatin, camptothecin, topotecan and doxorubicin. Pukac and colleagues analyzed mapatumumab-sensitive cell lines (HCT 116 and NCI-H460) and insensitive cell lines (ES-2 and TTn) when treated either with control antibodies, various concentrations of mapatumumab or combinations of mapatumumab with camptothecin (HCT 116), cisplatin (NCI-H460), carboplatin (ES-2) or 5-fluorouracil (TTn). All cell lines treated with combination therapy demonstrated increased cell killing. Interestingly, the same results were seen even in the cell lines insensitive to mapatumumab (19, 21, 27, 41). When combined with the topoisomerase inhibitors camptothecin and topotecan, mapatumumab demonstrated a 75% decrease in cell viability in colorectal (SW480) and breast (MDA-MB-231) carcinomas, as well as in Burkitt's lymphoma (ST486) (27). In an *in vitro* study using 8 models of NSCLC, mapatumumab was shown to enhance the cytotoxicity of cisplatin and paclitaxel. The results also confirmed previous evidence indicating that while several cell lines express high levels of TRAIL-R1, their sensitivity to mapatumumab is different (42). In the TOV112D ovarian cancer cell line, addition of carboplatin or paclitaxel to mapatumumab resulted in increased cytotoxicity. Similar results were seen in SK-OV-3 ovarian cancer cell lines with the combination of mapatumumab and carboplatin, paclitaxel or gemcitabine (21).

Mapatumumab was also tested as a single agent and in combination with bortezomib in primary and cultured cells of lymphoid origin. Mapatumumab inhibited cell proliferation and induced apoptosis in a concentration- and time-dependent manner. However, similar to in solid tumor models, the different level of sensitivity of lymphoma cell lines to mapatumumab did not correlate with the level of surface receptor exposure. In some cell lines, treatment with mapatumumab had synergistic activity with bortezomib and doxorubicin; however, the synergistic activity was not seen in all cell lines (41).

In NSCLC cell lines, combination therapy with TRAIL and bortezomib also gave synergistic activity. Furthermore, treatment with bortezomib was associated with enhanced surface expression of TRAIL-R1 and -R2 (43).

Several *in vivo* studies confirmed the promising activity observed with mapatumumab *in vitro*. In one study, animals with COLO 205 human colon cancer xenografts received mapatumumab at 10 mg/kg every other day starting 5 days after xenograft implantation. In the control arm, animals were treated with immunoglobulin G (IgG). Mapatumumab completely inhibited the growth of xenografts, in contrast to the animals treated with IgG. In animals with well-established tumors of around 250 mm^3, treatment with mapatumumab inhibited tumor growth by 50-70% compared to animals treated with IgG (19). Similarly, robust antitumor activity was seen against xenografts from a variety of human tumors, including lung and colon carcinomas (23, 27).

Pukac and colleagues tested the antitumor activity of mapatumumab in NSCLC (NCI-H2122), colon (COLO 205) and renal tumor (A-498) xenograft models in athymic nude mice. Animals with a tumor volume of approximately 100 mm^3 received mapatumumab at a dose of 2.5 or 10 mg/kg every 2 or 7 days. Significant tumor regression was observed after only one injection of mapatumumab, with a tumor volume reduction of 50% on day 10 and of 97% (for the 10 mg/kg dose) by day 25. Interestingly, no tumor regrowth was seen for 20 days after the last dose of mapatumumab. The authors hypothesized that these findings may be due to a residual effect of mapatumumab, but also to a possible loss of tumor cell number, tumor burden and tumor vasculature during tumor regression (19).

In NCI-H460 NSCLC tumor xenografts, administration of mapatumumab in combination with cisplatin resulted in 60-70% inhibition at the end of a 22-day study compared with 30% inhibition for the cisplatin group (42). Similarly, the combination of mapatumumab with topotecan was demonstrated to be 3-fold more effective than topotecan alone at inhibiting *de novo* tumor growth in an SW480 colon carcinoma xenograft model and a similar synergistic effect was seen with combination of mapatumumab and 5-FU (27). Pukac *et al.* tested the antitumor activity of mapatumumab in combination with 5-FU, irinotecan and topotecan in three colon cancer xenograft models. Enhanced efficacy was seen in the combination arm when compared with animals treated with the drugs alone. Moreover, concurrent administration of mapatumumab and chemotherapy was not necessary for attaining maximal efficacy (19).

Pharmacokinetics and Metabolism

In the study by Pukac *et al.*, the pharmacokinetic characteristics of mapatumumab were also evaluated in mice. Mapatumumab was shown to have a long half-life (6.9-8.7 days; similar to endogenous immunoglobulin) and a large volume of distribution, suggesting broad tissue penetration (19).

Clinical Studies

Two open-label phase I studies were performed with mapatumumab in patients with solid tumors in the U.S. and Canada (44, 45).

In the 2-site U.S. study of mapatumumab in patients with refractory advanced solid tumors (44), the protocol allowed single treatments, and in the absence of tumor response at doses of 0.01-0.1 mg/kg subsequent treatments every 28 days at doses of 0.3-10 mg/kg. After safety confirmation at 10 mg/kg every 28 days, patients received 10 mg/kg every 14 days. Forty-nine patients (31 males and 18 females) with a median age of 56 years received a total of 158 courses of mapatumumab, with a median number of cycles of 2 (range = 1-20). The main tumor types were colorectal cancer (15 patients), NSCLC (5 patients), sarcoma (6 patients), prostate and renal cancer (4 patients each), ovarian and thyroid cancer and cholangiocarcinoma (2 patients each). At the first dose level, 1 patient with pre-existing grade 1 neuropathy experienced an increase in symptoms up to grade 3, prompting cohort expansion, with no further dose-limiting toxicity (DLT). At the next three dose levels (0.03. 0.1 and 0.3 mg/kg), only grade 1 side effects were noted. The majority of patients treated at 10 mg/kg had mild to moderate (grade 1 or 2) elevation in AST or ALT, with no elevation in bilirubin. Transaminase elevation was seen mainly in patients with pre-existing transaminitis and liver metastasis. At 10 mg/kg every 14 days, 2 patients experienced grade 3 elevation in liver function tests after 2 doses. Although both patients had baseline transaminase abnormalities and metastatic liver involvement, toxicities were considered dose-limiting and possibly drug-related. The possible relationship of this side effect to the study drug is supported by preclinical evidence indicating that normal hepatocytes express TRAIL-R1 and that mapatumumab binds to hepatocytes. Other toxicities included mild to moderate fever, myalgias, fatigue and nausea. No hematotoxicity was observed, except for a mild decrease in lymphocytes in 4 of 11 patients treated at the highest dose level. Mapatumumab did not induce hypersensitivity reactions and no anti-mapatumumab antibodies were detected. Although no objective responses were obtained, 2 patients had persistent stable disease for more than 8 months (appendix carcinoma and sarcoma).

Pharmacokinetic evaluation above 1 mg/kg demonstrated trough plasma concentrations exceeding 1 μg/ml, which represents the effective concentration for killing 90% of cells *in vitro*. Mapatumumab plasma concentrations in studies in xenograft-bearing mice were equivalent to plasma concentrations attained at the 10 mg/kg dose in the clinical study. The half-life was established at around 18 h, which supports treatment every 2-3 weeks. The pharmacokinetics appeared to be linear up to 3 mg/kg and less than proportional at higher doses. The steady-state volume of distribution was 63-131% greater than the volume of distribution in the central compartment, which indicated that mapatumumab is distributed to tissues (44).

TRAIL-R1 expression in 19 tumor samples was also assessed. Surprisingly, 13 tumors (68%) showed at least 10% of cells staining positive for TRAIL-R1, while the other 6 (32%) were negative. Specific staining for TRAIL was heterogeneous (44).

The second phase I study was performed in Canada (45). Twenty-four patients were enrolled and received treatment with mapatumumab every 28 days. In the first four cohorts (0.01, 0.03, 0.3, 3.0 mg/kg) the drug was well tolerated, with no DLT. Only 1 episode of grade 3 thrombocytopenia and 1 episode of hypertension were reported. No objective responses were seen, although 8 patients had stable disease for 2-14 months.

Pharmacokinetic analysis revealed linear behavior for doses up to 0.3 mg/kg, but a less than proportional increase at doses of 3 and 10 mg/kg (45).

Based on preclinical evidence revealing synergistic activity when combining mapatumumab and chemotherapy, two phase Ib studies are ongoing to evaluate the safety and tolerability of mapatumumab in combination with paclitaxel and carboplatin and with gemcitabine and cisplatin, respectively (46-48).

Twenty-eight patients were enrolled in a phase Ib study combining mapatumumab and carboplatin/paclitaxel (46). Mapatumumab was administered at doses of 3, 10 or 20 mg/kg, carboplatin at AUC6 and paclitaxel at 200 mg/m^2 every 21 days. DLTs included neutropenic fever and hypersensitivity reactions. Other side effects included fatigue, myalgia, transaminitis, anorexia and arthralgia. Pharmacokinetic analysis did not reveal any drug-drug interaction between mapatumumab and the two cytotoxics. Four of the 28 patients enrolled achieved a partial response (PR), including 3 patients with NSCLC and 1 patient with adenocarcinoma of unknown primary (47).

Another study combining mapatumumab with cisplatin and gemcitabine was performed in Europe (48). Patients (n=32) with solid malignancies received gemcitabine 1250 mg/m^2 i.v. on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 every 21 days. Mapatumumab was administered i.v. every 21 days at doses of 1, 3, 10 and 20 mg/m^2. The most common side effects were nausea and vomiting, liver function abnormalities, hematological toxicity and ototoxicity. Five patients experienced grade 3 transient transaminase elevation that was considered to be related to gemcitabine. Additionally, 1 patient had grade 4 fatigue and another experienced grade 4 thrombocytopenia in the 20 mg/kg cohort. The 10 mg/kg cohort was expanded up to 12 patients, with a total of 4 DLTs.

The 20 mg/kg cohort was also planned to be expanded as of November 2006. Nine patients achieved a PR (7 patients with confirmed PR), including 3 patients with pancreatic cancer, 2 patients with biliary tract cancer, 1 patient with carcinoma of unknown primary, 1 patient with head and neck cancer and 2 patients with adenocarcinoma of unknown primary. Additionally, 14 patients had stable disease, including 1 patient with pancreatic cancer who completed 54 weeks on study (48).

Evidence from preclinical studies suggested that bortezomib abolishes the resistance to TRAIL (47). These results together with other preclinical data (39, 42) provide a strong argument for clinical studies combining TRAIL-R1 monoclonal antibodies with bortezomib. A randomized phase II study of mapatumumab in combination with bortezomib is ongoing in patients with multiple myeloma, and other studies are planned (49).

The favorable safety profile and preliminary evidence of antitumor activity for mapatumumab in phase I trials led to disease-specific evaluation of the drug. Data from three phase II studies with single-agent mapatumumab in patients with non-Hodgkin's lymphoma (NHL), NSCLC and colorectal cancer have been presented.

Forty patients with NHL were treated with mapatumumab in two treatment groups receiving either 3 mg/kg every 21 days (8 patients) or 10 mg/kg every 21 days (32 patients) (50). The median age of the patients enrolled in the study was 62 years and the majority of patients had received more than 3 prior therapeutic regimens. One complete response (CR) and 2 PRs were obtained in the follicular lymphoma subgroup. Additionally, 12 patients had stable disease. The overall tolerance of the antibody was excellent, with no grade 3 or 4 toxicities reported.

In another phase II study, 32 patients with relapsed or refractory NSCLC were treated with mapatumumab at the dose of 10 mg/kg every 21 days. The majority of patients were heavily pretreated and had received up to 7 previous therapeutic regimens (median of 3). No severe treatment-related adverse events were reported. Nine patients (29%) had stable disease with a median duration of 2.3 months (51).

Thirty-eight patients with relapsed or refractory colorectal cancer received mapatumumab at a dose of 20 mg/kg every 14 days in cycles 1 and 2 and 10 mg/kg every 14 days in cycles 3-6. Adverse events were mild to moderate and included fatigue, diarrhea, nausea and vomiting and dyspnea. Severe adverse events were reported as not treatment-related and included renal failure, hemorrhagic gastritis, ileus, hepatic failure, deep venous thrombosis (DVT) and hematemesis. Twenty-one patients (32%) had stable disease for a median of 2.6 months (52).

Conclusions

Targeting the extrinsic apoptotic pathway through death receptors is a novel and promising area of research. The fully human monoclonal antibody mapatumumab selectively binds TRAIL-R1 and induces the activation of the receptor similar to the natural ligand TRAIL. Data from phase I and II clinical studies with mapatumumab demonstrated a good safety profile, reproducible pharmacokinetic parameters and clinical activity. Moreover, the hepatic toxicity described in preclinical models with TRAIL was not seen in humans with TRAIL-R1 monoclonal antibodies. However, despite impressive antitumor activity in preclinical models, clinical studies to date have not reported the expected efficacy. Additionally, tumors initially responsive to mapatumumab seem to develop secondary resistance after several months of exposure to the drug. Primary or acquired resistance to TRAIL-R1 monoclonal antibodies may be explained by several mechanisms, including the relative balance between functional death and decoy receptors, activation of intracellular signaling downstream of TRAIL ligand binding, such as the phosphatidylinositol 3-kinase (PI3K)/Akt or MAPK pathways, the activation status of several proteins, including caspase-8 and c-FLIP, increased XIAP expression, deletion of the *BAX* gene and others. Several therapeutic approaches have been envisioned to reverse or overcome HGS-ETR1 and HGS-ETR2 resistance. One option is to combine mapatumumab with chemotherapeutic or targeted agents that may synergize with the antibody. Another approach is to better identify tumors that are primarily resistant to TRAIL activation and/or that become resistant. A better understanding of the mechanism behind the resistance to agents targeting death receptors would allow rational combinations and optimization of the use of mapatumumab for the treatment of different malignancies.

In view of preclinical and clinical data available to date, mapatumumab and other monoclonal antibodies targeting death receptors represent an effective, well-tolerated treatment that could become relevant for cancer therapy. Future clinical as well as preclinical studies with mapatumumab should prioritize defining the optimal population of patients that derive benefit from the treatment, defining the optimal dose that would yield a relevant pharmacodynamic effect with few or no side effects, as well as identifying the ideal candidates for combinations with mapatumumab, such as cytotoxics or targeted agents, that will allow to circumvent resistance and derive the maximal clinical benefit.

Mapatumumab administered as a single agent may have a role in treating tumors that are dependent on aberrant apoptosis for growth and signal primarily through TRAIL-R1. In contrast, combination therapies with cytotoxics or targeted agents will probably represent an indication of choice for several solid tumors for which cytotoxics alone allow only limited efficacy.

Sources

Human Genome Sciences, Inc. (US); originally developed in collaboration with Cambridge Antibody Technology (GB, US).

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