

# RACOTUMOMAB – A NOVEL ANTI-IDIOTYPE MONOCLONAL ANTIBODY VACCINE FOR THE TREATMENT OF CANCER

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## SUMMARY

*Racotumomab is a murine gamma-type anti-idiotype monoclonal antibody that specifically induces an antibody response against Neu-glycolyl GM3 ganglioside (NeuGcGM3), which is overexpressed in several solid tumors. It is adjuvanted with aluminum hydroxide for intradermal administration as a cancer vaccine (racotumomab-Alum, known commercially as Vaxira®). Racotumomab is currently being evaluated for a number of cancer indications, including melanoma, breast and lung cancer. In early clinical trials, racotumomab demon-*

*strated high immunogenicity and low toxicity and it advanced to further clinical testing as a treatment for patients with non-small cell lung cancer (NSCLC). On the basis of promising results in a phase II/III study, racotumomab was launched in 2013 in Cuba and Argentina as an intradermal injection for the treatment of patients with advanced stage NSCLC.*

**Key words:** Racotumomab – NeuGcGM3 – Cancer vaccine – Non-small cell lung cancer

## BACKGROUND

The development of immune-based therapies for the treatment of cancer has become an attractive option as the specificity of these therapies has the advantage of

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inducing fewer side effects than the conventional non-specific chemotherapy and radiotherapy treatments. Thus far, the development of passive immunotherapy, such as monoclonal antibodies (MAbs) or cytokines, has proven effective and efforts are now being made to develop vaccines that would induce an active immune protection by boosting the host's immune defense against tumor-associated antigens (TAAs). Cancer vaccines have been designed to stimulate antitumor responses targeting tumor-specific TAAs while preserving surrounding tissue from nonspecific toxicity. Since most TAAs are self-antigens and the body eventually builds up immune tolerance against them, the development of vaccines against these oncoproteins has been challenging. One of the strategies to overcome this immune tolerance barrier consists of the use of anti-idiotypic MAbs, also referred to as Ab2, to function as antigen surrogates and as such modulate the immune response. Immunization with a given antigen leads to the generation of antibodies (Ab1) directed against this specific antigen, and Ab1 antibodies can then be used to generate a series of anti-idiotypic antibodies (Ab2) directed against these Ab1 antibodies. The resulting Ab2 antibodies are often able to mimic the three-dimensional structure of the native antigen and can therefore be used as immunogens to induce a specific immune response similar to the one that would be induced by the initial antigen (1, 2).

An additional advantage of the anti-idiotypic vaccines is that these vaccines are also able to target antigens of a non-protein origin. Tumor-associated carbohydrate antigens (TACA) have been identified as a subset of TAAs of carbohydrate nature that are specifically expressed on tumor tissue as compared to normal tissue due to an aberrant glycosylation in tumor cells. Additionally, it has been demonstrated that TACAs play an essential role in metastasis induction and tumor invasiveness.

Gangliosides are a group of TACAs that have gained special attention as novel targets for cancer immunotherapy, based on the qualitative and quantitative changes they suffer during malignant transformation and due to their importance for tumor biology (3, 4). Gangliosides, especially Neu-glycolyl GM3 ganglioside (NeuGcGM3), are not expressed in normal human cells but are overexpressed in several solid tumors. In metastatic lesions, the presence of NeuGcGM3 reaches 73.4% of total lipid bound sialic acid (5). Racotumomab (formerly known as 1E10) is a murine gamma-type anti-idiotypic MAb (Ab2 MAb) specific to the Ab1 MAb P3 able to react specifically

against the tumor antigen NeuGcGM3. The antibody triggers a strong anti-idiotypic antibody (Ab3) response, which has the same antigenic specificity as Ab1 (P3), mimicking the three-dimensional structure of the N-glycolyl, giving rise to a specific immune response against the tumor antigen NeuGcGM3 and reducing the potential risk of immune crossreactivity. This review describes some of the preclinical and clinical data for this novel oncolytic vaccine candidate.

## PRECLINICAL DATA

BALB/c mice were immunized seven times at 14-day intervals with intraperitoneal injections of 50 µg racotumomab coupled to keyhole limpet hemocyanin (KLH), racotumomab alone, the carrier KLH alone or the immunological adjuvant alone (PBS control). Three of the doses were administered before and four doses after subcutaneous inoculation with F3II mammary tumor cells. In the control animals, the tumors grew by invading the muscular and adipose layers of the subcutis, and at day 30, the tumor cells invaded the dermis and the dermal papillae causing necrosis in the epidermal layer and visible ulceration on the surface of the tumors. Tumor incidence was 100% and the latency was similar in all groups. A significant decrease in subcutaneous tumor growth was seen in the racotumomab/KLH-immunized animals, while no differences were seen in tumor growth between the control mice and the mice treated with racotumomab or KLH alone. Immunization with racotumomab/KLH also significantly reduced the spontaneous dissemination to lungs of the F3II mammary tumor cells. In the second portion of the experiment, C57BL/6 mice were inoculated with B16 murine melanoma cells, and 10 or 14 days post-inoculation the animals were injected with 10 µg intravenous racotumomab, an irrelevant MAb or PBS alone. The animals given racotumomab had a significantly reduced number of lung metastases compared with the mice that received PBS. Lymph node cells from naive mice and from animals immunized with racotumomab were challenged *in vitro* with the anti-idiotypic MAb or the irrelevant antibody in order to evaluate the ability of racotumomab to induce proliferation of lymphocytes to its idio type. No proliferative response was seen in either of the two groups of cells after challenge with different concentrations of the anti-idiotypic MAb (6).

The nature of the idio type defined by racotumomab was evaluated using a phage-displayed random peptide library. Seven different phagotopes were isolated and all

the sequences were found to bear the basic amino acid-rich motifs KPPR or RRRR/K. It was observed that the P3 MAb completely inhibited the binding of racotumomab to phage peptides, suggesting that the peptides are possible mimotopes of the idiotope recognized by anti-idiotypic antibodies in P3. Previous studies had shown that P3's idiotype is autoimmunogenic and shared by antibodies with different specificities, and now it has been demonstrated that the P3 MAb is able to activate a network cascade involving autologous anti-idiotypic and anti-anti-idiotypic T cells. The results also revealed the immunodominance of P3's heavy chain CDR3 (H-CDR3), showing that it behaves as a potential regulatory idiotope, simultaneously involved in the interaction of P3 MAb with anti-idiotypic B and T cells (7).

In F3II tumor-bearing mice, the administration of racotumomab (100 µg) in combination with low-dose cyclophosphamide (150 mg/m<sup>2</sup>) led to a significant reduction in the F3II mammary carcinoma growth. It was observed that immunization with racotumomab potentiated the antiangiogenic effect of low-dose cyclophosphamide and it also led to a significant reduction in splenic myeloid cells Gr1<sup>+</sup>/CD11b<sup>+</sup> which are associated with a suppressor phenotype. These data demonstrated a combinatorial therapeutic effect based on the complementary antiangiogenic effect of low-dose cyclophosphamide with the tumor apoptosis induced by racotumomab immunization, suggesting that enhanced apoptosis can contribute to tumor control (8).

The therapeutic effect of racotumomab was also evaluated in the poorly immunogenic and highly metastatic 3LL-D122 Lewis lung carcinoma C57BL/6 mouse model. Immunization of the animals with racotumomab in Alum adjuvant induced an antimetastatic effect, which was associated with the increment of T cells infiltrating metastases, the reduction of new blood vessel formation and the increase of apoptotic tumor cells in lung nodules. The results of this study showed that active immunization did not induce measurable antibodies to racotumomab, NeuGcGM3 or tumor cells, suggesting a distinct mechanism of action that needs to be elucidated (9).

The antitumor activity of racotumomab was further examined in the 3LL Lewis lung carcinoma model in C57BL/6 mice. This preclinical model of non-small cell lung cancer (NSCLC) is a validated model for the NeuGcGM3 ganglioside, as it shows increased expression of this specific antigen in disseminated nodules with respect to the primary tumor or in vitro cultured cells.

The results of this study demonstrated that biweekly treatment with racotumomab (50-200 µg) was highly effective against the 3LL lung tumor nodules. Additionally, the combination of pemetrexed-based chemotherapy (100 mg/kg weekly) with the biweekly doses of racotumomab showed a significant synergistic effect as compared to each treatment alone, when evaluated in this mouse model of NSCLC. The therapeutic effect of racotumomab was associated with an increase of CD4<sup>+</sup> and CD8<sup>+</sup> cell infiltration, reduced angiogenesis and tumor cell apoptosis in lung nodules. The results of this study support the use of chemo-immunotherapy combinations for the treatment of NSCLC (5, 10).

### CLINICAL STUDIES

The clinical efficacy of racotumomab was evaluated in a number of early clinical trials. The first phase I study was designed to investigate the safety of aluminium hydroxide-precipitated racotumomab in patients with advanced malignant melanoma. The study enrolled a total of 20 subjects, who were treated with 6 intradermal injections of racotumomab, given at 2-week intervals. Seventeen of the patients received at least 4 doses of the vaccine and 16 of the immunologically evaluable subjects developed Ab3 antibodies expressing P3 epitopes, determined by the ability of the patients' immune sera to inhibit racotumomab (Ab2) binding to P3 MAb (Ab1). This was representative of a very strong Ab3 response against N-glycolyl-containing gangliosides in these 16 patients (11).

Toxicity and humoral immune response elicited by racotumomab were also evaluated in a phase I study enrolling 9 patients with histologically confirmed small cell lung cancer who received previous chemotherapy and/or radiotherapy resulting in partial or complete response. The subjects received four biweekly injections of 2 mg of aluminium hydroxide-precipitated racotumomab, followed by additional six doses at 28-day intervals. The patients who maintained a good performance status were then re-immunized. Patients who received at least four doses of racotumomab developed strong specific antibody responses against racotumomab (89% of the patients) and NeuGcGM3 ganglioside (78% of the patients). Additionally, intense staining of small cell lung cancer tumor tissue was evident for patients with the highest anti-NeuGcGM3 post-vaccination titer, showing a clear increase in the reactivity against cancer cells after immunization. Prolonged survival was seen in several patients treated with racotumomab (12).

A total of 10 patients with stage III/IV breast cancer were enrolled in a phase I trial designed to evaluate the immune response of the subjects treated with racotumomab. The women were immunized with 1 or 2 mg of aluminum hydroxide-precipitated racotumomab every other week for a total of six injections, and two patients at each dose were re-immunized 7 to 9 months after completing the induction phase. Eight of the nine patients who received at least four doses of racotumomab and were therefore considered immunologically evaluable, demonstrated strong specific responses both against racotumomab and NeuGcGM3 ganglioside. The Ab3 response in the induction phase was mostly of IgG isotype against racotumomab, with no IgM antibodies detected at the lowest serum dilution tested (13). In contrast, IgG and IgM Ab3 antibodies were detected against NeuGcGM3 ganglioside. Another phase I study in patients with high-risk and/or metastatic breast cancer (N = 20) evaluated three different dose levels of the racotumomab vaccine (0.5, 1 and 2 mg). The study consisted of an induction phase during which the patients received six intradermal injections given in 2-week intervals, followed by a maintenance phase consisting of 10 monthly doses until completing 1 year of treatment. Severe hypersensitivity skin reactions were observed in two patients and one patient experienced a transient loss of consciousness with uncertain relation to the vaccine. Overall, the vaccine was well tolerated and was able to induce a very specific and strong immune response to NeuGcGM3, independent of dose escalation. A specific cellular Th1 response was seen in 40% of the evaluable patients (14). Patients with metastatic breast cancer (n = 34) who were pretreated with at least one line of chemotherapy, were enrolled in another phase I trial and treated with metronomic chemotherapy consisting of daily oral cyclophosphamide (50 mg), bi-daily oral methotrexate (2.5 mg on days 2 and 4 of every week), in combination with intradermal aluminum hydroxide-precipitated racotumomab (1 mg/dose). The first five doses of racotumomab were administered every 14 days and re-immunizations were given every 28 days. Five of the patients achieved objective response, 12 had stable disease and 17 had disease progression. Median time to progression was 6.8 months and the median survival time was 10.07 months (15).

Racotumomab vaccination was also applied in a case of pediatric relapsed neuroblastoma in which it demonstrated the ability to elicit an immune response with a favorable toxicity profile. The results of this case study suggest that the novel vaccine could become an innova-

tive alternative for the treatment of neuroblastoma and other embryonal pediatric malignancies (16).

In more advanced lung cancer trials, patients with stage IIIb (n = 34) or stage IV (n = 37) NSCLC were treated with intradermal injections of 1 mg of aluminum hydroxide-precipitated racotumomab. The first 5 injections were administered biweekly and the remaining 10 doses were administered every 28 days. If the patients maintained a favorable clinical status, additional re-immunizations were administered at 28-day intervals. The overall survival (OS) time of the patients from the start of vaccination was 9.93 months and the 1-year survival rate was 34%. When the survival time of the vaccinated patients was compared with that of a nonrandomized control group, the median survival time of these controls was significantly lower (4.53 months). There were no significant differences in survival between vaccinated patients according to disease stage, sex, age or tumor histology (17, 18). A strong specific antibody response of both IgM and IgG isotypes against NeuGcGM3 ganglioside was observed in the hyperimmune sera from 16 of the 20 racotumomab-treated patients evaluated for the immune response elicited by the racotumomab immunotherapy. The antibody response against NeuGcGM3 ganglioside was increased with the course of vaccination, and it reached a peak after patients received the fourth or fifth doses of the anti-idiotypic MAb. There was a statistically significant difference between the median survival time of the patients that developed IgG and/or IgM antibodies against NeuGcGM3 (14.26 months) and the median survival time of the patients that did not develop antibodies against the ganglioside (6.35 months) (19).

A multicenter, controlled, randomized, double-blind, phase II trial evaluated the effects racotumomab treatment in patients with advanced NSCLC (N = 176) who had achieved partial or complete response or disease stabilization after completion of onco-specific treatment. The induction phase of the study consisted of a total of five doses of racotumomab, each administered every 14 days, followed by a maintenance period of one racotumomab dose given every 28 days until patient refusal or worsening of ECOG status. The results of this study demonstrated an OS benefit in the racotumomab-treated group as determined both by the intent-to-treat (ITT) and per-protocol-population (PPP) survival analysis. The final results revealed a median OS of 8.3 and 6.3 months for the racotumomab- and placebo-treated groups, respectively, as determined by ITT analysis. The

respective OS values achieved through PPP analysis were of 10.9 and 6.9 months. The survival benefit appeared to increase when the patient's condition allowed for completion of the induction period of vaccination, consisting of the first five biweekly injections (20-22).

An open, nonrandomized study evaluated racotumomab as second-line therapy in patients with recurrent and advanced stages (IIIB/IV) of NSCLC that was in progression after the completion of first-line onco-specific treatment. Most of the patients received four to six cycles of cisplatin/vinblastine therapy. Racotumomab was administered in five intradermic doses given once every 14 days, followed by one dose every 28 days until patient refusal or worsening of ECOG status. After 10 months of follow-up, results from 180 patients that received racotumomab were analyzed using the ITT survival analysis, revealing a median survival of 8.06 months and an OS rate of 21% at 24 months in this patient group. The median survival and OS at 24 months for a control group of 85 patients who did not receive second-line therapy or racotumomab was 6.26 months and 7%, respectively. Finally, per-protocol survival analysis of 124 patients who received  $\geq 5$  doses of racotumomab showed a median survival of 12.1 months and an OS at 24 months of 30%. Overall, these results showed that treatment with racotumomab leads to promising survival improvement in patients with advanced NSCLC in progression after first-line onco-specific treatment (23). A separate phase III, multinational, randomized, open-label trial was designed to evaluate the efficacy and safety of racotumomab plus best supportive care in 1,082 patients with stage III or IV NSCLC who showed response or stable disease after standard first-line platinum-based chemotherapy and radiotherapy. The vaccination consisted of five intradermic doses given once every 14 days, followed by one dose every 28 days until worsening or unacceptable toxicity (24).

## SAFETY

The safety of racotumomab-Alum was also evaluated in the clinical studies described above. Overall, the vaccine candidate was found to be safe and well tolerated, with minimal toxicity reported. In the phase I trials in melanoma patients, no unexpected or serious adverse effects were seen as a result of the racotumomab injection, with some of the main toxicity reported being a local reaction at the site of the injection with induration and local erythema, and sometimes associated with

mild pain. This local reaction was usually resolved within 1 to 3 days. Other adverse events reported were grade 1-2 fever as well as chills and mild cephalgia. Routine hematology and hemochemistry tests revealed grade 1-2 anemia, grade I-II increase of alkaline phosphatase and grade 1 leukopenia. These adverse events were interpreted as nonrelated to the treatment and the symptoms occurred independently of the number of doses administered to the patients (11). The same mild toxicity of local reaction at injection site was also reported in patients with lung and breast cancer (12, 13, 15). Some other grade 1-2 adverse events reported in the phase I trials in lung cancer patients were fever, arthralgias, cephalgia, and paresthetic alterations of inferior and superior limbs, which were related to the platinum-based therapy regimen that patients received as part of the standard treatment. Similar to the melanoma study, adverse events did not exacerbate with increasing number of vaccine doses and no biochemical or hematological abnormalities were reported (12). In the phase I trial evaluating 1 or 2 mg doses of aluminum hydroxide-precipitated racotumomab in breast cancer patients no differences in immunogenicity and toxicity were seen between the two dose levels tested and there were no serious or unexpected adverse events reported during the treatment or the follow-up period. Some other adverse reactions that were reported were chills, cephalgia and grade 1-2 fever. Increased blood pressure was observed in three patients; however it was not considered treatment-related (13). Once again, the overall toxicity of the treatment was generally mild, with the most common side effect being pain at the injection site. Only three of the patients reported grade 3 adverse events, such as vomiting and nausea (15).

Just like in the previous trials, the toxicity data from the more advanced clinical studies in patients with NSCLC did not reveal any biochemical or hematological abnormalities. The most common side effects reported were the same as in the phase I trials, consisting of local injection site reactions with erythema and induration occasionally associated with mild pain. Some cases of fever, pruritus, arthralgias and headache were also reported. The overall toxicity of the racotumomab anti-idiotype vaccine was classified as grade 1 and 2 (20-22).

## INDICATIONS AND CURRENT DEVELOPMENT

Racotumomab was originally developed by researchers at Centro de Inmunología Molecular (CIM) in Cuba and is currently being developed as a vaccine for various cancer

indications including melanoma, breast and lung cancer at RECOMBIO (Spain), Eurofarma Laboratórios (Brasil), Laboratorio ELEA (Argentina) and Innogene Kalbiotech (Singapore). In 2013, racotumomab-Alum (Vaxira®) was launched by CIMAB in Cuba and Laboratorio ELEA in Argentina as an intradermal injection for the treatment of advanced stage NSCLC in patients undergoing chemotherapy and radiotherapy treatment or in patients who have not responded to first-line therapy.

## DISCLOSURES

The author states no conflicts of interest.

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