

Report of the Fifth Nimotuzumab Global Meeting

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The Center for Molecular Immunology (CIM) celebrated its 15th anniversary with a highly attended international workshop: “Fifth Nimotuzumab Global Meeting” held in November 23rd-25th, 2009 in Havana, Cuba. The meeting was chaired by Dr. Agustín Lage Dávila, General Director of the CIM. This international meeting, with 250 participants, brought together scientists from more than 20 countries who are involved in many aspects of nimotuzumab development, including its mechanism of action, indication targets, different therapeutic interventions, effectiveness and safety profile assessment. The presentations at the 2009 meeting evidenced not only the recent advances made in several clinical areas but also the challenges that lie ahead. To date, nimotuzumab has been administered to over 5000 patients in clinical trials that have concluded and others in progress.

The meeting was opened with a keynote address by Dr. Agustín Lage Dávila. Dr. Lage reinforced the concept that nimotuzumab is not a me-too drug but an innovative drug with a potential differentiation pattern due to its low toxicity and its ability to mobilize cellular immunity. Dr. Lage highlighted the current challenge of the transit from product-oriented to disease-oriented research, targeting special patient niches, evaluating chronic drug use and drug combinations and finally the motivation to learn from expanded-use programs in “real oncology”.

The first session entitled “Nimotuzumab’s Mechanism of Action” was chaired by Dr. Rolando Pérez, Director of Research and Development of CIM. The classical paradigm for EGFR-targeted therapies is based on the association between therapeutic efficacy and cytotoxicity in the presence of significant dermatologic toxicity which is used as a surrogate marker of therapeutic efficacy. It is also stated that the objective clinical response achieved with these therapies correlates with median overall survival and that EGFR gene mutations and K-Ras mutations are response predictor biomarkers. Dr. Pérez presented a new EGFR-targeting paradigm using Nimotuzumab as a case study, based on the unexpected clinical findings according to the current paradigm which are supported by the degree of inhibition of EGF-dependent receptor activation, permitting a basal level of receptor signaling; bivalent binding to cells with high expression of EGFR as a consequence of intermediate affinity and a minimum threshold in receptor number; reduction of CD133⁺ cancer stem cells and neo-angiogenesis and finally the “Vaccinal effect” as an induction of an anti-tumor cellular immune response. This approach has been focused on tumor localizations with EGFR-overexpression, documentation of the evidence of potentiation with radiotherapy (RT), evaluation of chronic treatment to exploit its low toxicity profile and combinations with immuno-modulators.

Throughout this session, there were examples of

how the common understanding on the mechanism of action of Nimo can provide the framework for an optimization strategy to improve the clinical benefit of the patient. One example of this was presented by Arlhee Díaz, from the System Biology Lab of CIM, who described the *in vivo* and *in vitro* testing of nimotuzumab on human glioblastoma cell line U87MG with the aim of confirming that nimotuzumab reduces: tumor volume, angiogenesis, microsatellite formation, CD133 cell number, proliferation, EGFR signaling and increases apoptosis. Dr. Luis E. Fernández, Head of the Vaccine Department at CIM, during his lecture “EGFR Targeting with Antibodies: A Connection between Humoral and Cellular Immune Responses?” illustrated the significant anti-metastatic effect associated to 7A7 MAbs. This is a murine anti EGF-R antibody, with an action that mainly depends on the mobilization of specific anti-tumour effector CD8⁺T cells, evidencing the existence of a pathway connecting the humoral and cellular immune responses.

Another example on the understanding of the molecular basis of the mechanism of action was provided by Dr. Ariel Talavera from the System Biology Lab at CIM, presenting nimotuzumab as an antitumor antibody that targets the EGFR and blocks the binding of the ligand while permitting the conformation of the active receptor.

There has been considerable progress in demonstrating the clinical benefits of the treatment with nimotuzumab in pediatric and adult patients with glial tumors, as illustrated in several presentations during the second session of the meeting. Dr. Javier Figueredo, Head of the Neurosurgery Service of the Center of Medical and Surgical Research of Cuba, updated the results of a randomized, placebo-controlled, double-blind study using the nimotuzumab antibody combined with radiotherapy (RT) on newly-diagnosed patients with high grade malignancy astrocytic tumors, anaplastic astrocytoma (AA, grade III) and multiform glioblastoma (GBM, grade IV). Overall survival, response rate and safety are the endpoints of the trial, where 74 patients out of 80 have been recruited to receive nimotuzumab combined with radiotherapy vs. a group of patients treated with placebo plus radiotherapy. Preliminary results show that the median survival of GBM patients was 16.43 months after their enrollment in the trial and after receiving at least 6 or more doses of nimotuzumab, vs 8.67 months in the placebo group; while in anaplastic astrocytoma patients the median survival has not yet been reached in the nimotuzumab group vs 17.57 in the placebo group.

On the other hand, intrinsic pontine gliomas (IPG) account for approximately 8% of pediatric brain tumors and appear almost exclusively during childhood and adolescence. The peak age of onset is 5-10 years with an extremely poor prognosis: median overall survival (OS) ranges from 3 to 8.5 months and 1-year-OS

is 25%, with no standard chemotherapy (CT) available. Results of a phase III study using nimotuzumab together with concomitant standard radiotherapy for the treatment of newly diagnosed diffuse IPG in children was presented by Dr. Ferdinand Bach from Oncoscience, Germany. This clinical study was led in Europe by Dr. Gudrun Fleischhack and his colleagues from the University of Bonn, Children's Hospital, Pediatric Hematology and Oncology, Bonn, Germany. The results proved that repeated and simultaneous applications of nimotuzumab and radiotherapy were well tolerated and safe. No patient abandoned the treatment due to adverse events that would possibly be related to the drug under study. This combination therapy had transient cytotoxic efficacy in most of the patients with a median progression-free survival (PFS) of 5.5 months, median OS of 9.6 months, 1-year-PFS of 7.3% and 1-year-OS of 34.1%. Patients classified as responders had an OS of 11.4 months. The speaker concluded that results are comparable to other combination therapies including intensive chemotherapy and that data suggest that nimotuzumab has a role devoid of toxicity in children with DIPG. A similar phase II study in newly-diagnosed children with brain stem glioma is being conducted in Cuba. The results of this trial were presented by Dr. Ricardo Cabanas, Head of the Oncology Service of the Pediatric Hospital "Juan Manuel Márquez" in Havana, Cuba. From December 2007 to December 2009, 12 patients had been enrolled in this trial. The mean survival time was 14.54 months and the median was 15.13 months; only adverse events that were mild or moderate in intensity (grade I/II according CTCAE Version 3 NCI) were reported as well as non-severe adverse events related to Nimotuzumab.

The combination of nimotuzumab with Interferon (IFN) may achieve an enhanced antiproliferative activity in neuroepithelial tumors and this was explored by Dr. Silvia Salva from the Neurosurgery Service of the "Hermanos Ameijeiras" Hospital of Cuba, in a presentation on the clinical benefit and safety profile of nimotuzumab in patients with low grade glioma. Dr. Salva demonstrated that nimotuzumab had a broad safety profile after being administered during a long treatment period and combined with RT and IFN, improving the functional condition of those patients. In the group of newly-diagnosed patients ($n = 17$), the PFS rate after 6 and 12 months were 94.12% and 88.24%, respectively. This was considered as being very favorable compared to reports from the literature of 76% and 39% for similar groups of patients.

The current status of ongoing trials of highly malignant gliomas in adult and pediatric patients was presented. Dr. Neera Gupta from Biocon, India showed results from an open label, prospective, multicentric study, evaluating the safety and efficacy of nimotuzumab as an induction and maintenance therapy, in combination with RT plus temozolomide during the concomitant and adjuvant treatment in Indian patients with multiform glioblastoma. Preliminary data of the ongoing adult trial conducted in India indicated that the median PFS and OS were 11.34 and 14.53 months, respectively. Another trial was presented by Dr. Leonardo Viana from York Medical Bioscience, Canada. It was a phase II study of the safety and efficacy

of Nimotuzumab in pediatric patients with recurrent diffuse Intrinsic pontine glioma. The overall survival and the objective response rate (PR + CR) are the primary objectives of these trials and no safety concerns related to nimotuzumab have been observed.

Additionally, new approaches using the intracavitary administration of nimotuzumab are under development. Dr. Iosmill Morales, from the Neurosurgery Services of the "Luis Díaz Soto" Hospital discussed the results of the direct infusion of nimotuzumab into the postsurgical resection cavity. It was a safe procedure, being used to treat patients suffering from high-grade gliomas. The clinical efficacy of this therapy must still be evaluated in a clinical trial.

Squamous cell cancer of the head and neck (SCCHN) would be considered as the ideal malignancy for the treatment with EGFR inhibitors. Nimotuzumab has the advantages of tumoral tissue specificity and is also devoid of toxicity. The impact of Nimotuzumab as the most recent treatment available to improve clinical outcomes in SCCHN was discussed through several presentations in the last session on the first day of this Fifth Nimotuzumab Global Meeting.

Dr. N. Gupta, on behalf of the Indian clinical investigators (Dr. Lokesh Viswanth and his colleagues from the Kidwai Memorial Institute of Oncology in Bangalore, the Shirdi Sai Baba Cancer Hospital in Manipal and the KMC Hospital in Mangalore), presented the updated data of the proof-of-concept phase IIb, 4-arm, open label and randomized trial of nimotuzumab in combination with chemoradiotherapy or RT alone. It was carried out in patients with locally advanced and inoperable head and neck cancers. The median OS for the RT alone arm was 12.8 months vs. 14.4 months for the RT plus nimotuzumab group but the difference did not reach statistical significance in this small sample size. The hazard ratio was 0.74 which is well in line with the expected differences between RT alone and RT in association with an anti-EGFR monoclonal antibody. The median overall survival for the chemoradiotherapy group was 25.1 months, and it has not yet been reached for the chemoradiotherapy plus nimotuzumab group which surprisingly showed statistical significance for this small population. Dr. N. Gupta expressed that the concurrent use of nimotuzumab with chemoradiation has enhanced long term local regional control and survival in long term follow-up, with a surprisingly benign toxicity profile, preferentially targeting the tumor.

Dr. YI Jun Lin from the Cancer Institute & Hospital of the Chinese Academy of Medical Sciences presented the evolution of clinical trials of nimotuzumab in nasopharyngeal carcinoma (NPC) in China. The updated data of a phase Ib/II trial of nimotuzumab combined with RT for local advanced NPC showed a 3-year survival rate for nimotuzumab + RT treated patients of 84.29% vs 77.61% for the patients that received only RT. Dr. YI Jun Lin also presented the design of a new phase III trial combining nimotuzumab with RT for local advanced NPC in China.

The clinical strategy of nimotuzumab development for Head and Neck cancer in Singapur was discussed by Christie Yang, a representative of Innogene Kalbiotech. Two ongoing trials, phase II and III respectively, are evaluating the use of nimotuzumab concurrently

with Cisplatin (CDDP)/RT in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) and the concurrent use of post-operative adjuvant chemoradiotherapy with or without nimotuzumab for stage III/IV SCCN.

The second day of the meeting was devoted to presentations and discussions of breakthrough results in esophageal cancer and non-small cell lung cancer (NSCLC) among other results from different tumor localizations.

Lung cancer is the leading cause of cancer-related death for both men and women worldwide, and its global incidence has been steadily increasing for decades. NSCLC accounts for approximately 85% of all the cases and in 40% of these it coincides with the locally advanced disease (stage III) and in 45% with the metastatic stage (stage IV). Despite the modest benefits from CT and chemoradiation in the locally-advanced and metastatic disease, more effective treatments are needed because of the large percentage of patients dying from systemic or local progression and the short survival period after conventional therapy (4-6 months). Dr. Elia Neninger, leader clinical researcher of the "Hermanos Ameijeiras" Hospital, described the results of an exploratory study in 9 Cuban hospitals. The study included 164 patients with histologically or cytologically confirmed NSCLC in advanced cancer, with no possible curative therapy, who showed the recurrent or progressive disease after the conventional treatment. The patients received nimotuzumab (200 mg/dose) as a weekly induction for 6 weeks, followed by maintenance treatment at the same dose every two weeks. The median survival in patients treated with nimotuzumab was 8.11 months, which according to Dr. Neninger's opinion is very favorable compared to the institutional control of 5.33 months, and with the second line treatment options: 7.5 months (Docetaxel); 8.3 months (Pemetrexed); 6.7 months (Erlotinib) and 5.6 months (Gefitinib). The study demonstrated that nimotuzumab was very well tolerated and safe, there were no treatment interruptions due to adverse events and there were survival advantages in all treated patients.

Several presentations showed the current status of a number of trials assessing the efficacy and safety of nimotuzumab in advanced NSCLC. The phase II study of nimotuzumab for stage III NSCLC in combination with CDDP + Vinorelbine (VNR) + Thoracic RT was sponsored by Daiichi-Sankyo Co., Ltd, and presented by Hiroshi Tsubouchi, Japan. The phase II trial has already started the recruitment of patients according the representative of Daiichi-Sankyo; in 2010 a pivotal phase III study will corroborate the benefits of nimotuzumab in NSCLC patients. Dr. Leonardo Viana from York Medical Bioscience, Canada, discussed the design of a randomized, phase II, double-blind study of nimotuzumab plus whole-brain RT (WBRT) compared with WBRT alone, which is ongoing in Canada, USA, Singapore, India, Europe, Pakistan, South Korea and Cuba in patients with NSCLC brain metastases. According to Dr. Viana, the previous phase II data of Dr. Amparo Macías suggested that the effect of adding nimotuzumab produces an increase in local control rate that changes from 50% to 83%. The main reason for the internationalization of the current

protocol is to prepare the scenario for the phase III trial. Dr. Viana also presented the design of a Phase I/II Clinical Study of Nimotuzumab combined with external RT in stages IIB, III and IV NSCLC, and Dr. Neera (Biocon, India) presented the current state of an ongoing open label, randomized, comparative, multicentric study assessing the safety and efficacy of nimotuzumab combined with CT vs. CT alone to treat patients with stage IIIB/IV NSCLC.

The main breakthrough in the Gastrointestinal Cancer Session was the presentation by Dr. Mayté Lima, Clinical Researcher of the "Hermanos Ameijeiras" Hospital, Cuba, on the outcome of the phase II randomized study using nimotuzumab plus radiochemotherapy vs. radiochemotherapy alone in unresectable esophageal tumors, which was sponsored by CIM. Dr. Lima showed the data of the 68 patients included and receiving nimotuzumab plus radiochemotherapy (CDDP 75 mg/m² for 4 cycles, 5-Fluorouracil (5-FU) 750 mg/m², for 4 cycles + RT: 50.4 Gy), vs. radiochemotherapy alone. The primary endpoint of the trial was the overall response rate (ORR) and the hypothesis was the improvement of the ORR in 30% with immune-chemo-RT. The positive conclusion of the trial demonstrated the superiority of the addition of nimotuzumab to the standard therapy, with an ORR of 52.6% vs. 12.5% ($p = 0.004$). On the other hand, the combination studied confirmed its advantage on the OS (7.03 months in the group treated with nimotuzumab vs. 2.97 months in the control group). During the trial, nimotuzumab was safely administered with the CT-RT combination in advanced esophageal cancer patients without showing skin rash or any other dermatologic disorders.

The Gastrointestinal session continued with the updating information on the current state of a phase II study of nimotuzumab combined with Irinotecan. Masanori Suzuki, from Daiichi Sankyo Co., Ltd., Japan, informed that the study is being conducted in Japan and Korea. At present, 89 patients (Japan 39, Korea 40) have been enrolled in the trial without any important findings of AEs associated to CPT-11. Masanori Suzuki explained that nimotuzumab did not affect the pharmacokinetics of CPT-11 and that tumor and serum samples were provided in 70% and 90% of the patients respectively, from which essential biomarkers will be measured in 2010. A pivotal study with nimotuzumab in second line gastric cancer patients who had previously been treated with a 5-FU regime will be conducted in Japan.

During the Genitourinary Cancer Session, the most recent results in cervical cancer, prostate cancer and in the polycystic disease using nimotuzumab were discussed.

Dr. José Dávalos, from the National Institute of Nephrology, Cuba, presented the background and characterization of the EGF system as the therapeutic target in the autosomic dominant polycystic kidney disease (ADPKD), concluding that the EGF system could be a potential target for the treatment of the ADPKD using MAbs that inhibit the EGF receptor. Dr. Dávalos showed preliminary data of an ongoing phase I/II clinical trial using nimotuzumab in the treatment of the ADPKD, which is aimed to assess safety and the optimal biological dose or the maxi-

mum tolerated dose of nimotuzumab. Currently, 14 patients have been included without any safety concern arising from the trial.

Cervical cancer is a major world health problem; it is the second most common malignancy in women worldwide with approximately 500 000 new cases every year. About 78% of the cases occur in developing countries, where it is considered to be the second cause of death by cancer in women. The current standard of care includes concomitant chemoradiotherapy that provides additional efficacy (40 to 30%) in global survival over the former standard with RT. Despite this advantage, up to 35% of the patients will develop the recurrent/metastatic disease. In this phase of the disease, CDDP is the most active single agent providing overall response rates ranging from 20% to 30%. Several combination therapies, containing CDDP, provide benefits in terms of OS from 7.3 to 12.9 months, while the use of anti-EGFR combined with CT has shown that the OS is of 3.5 and 4.96 months with the small tyrosine kinase inhibitors Gefitinib and Erlotinib, respectively, or even by adding Cetuximab the OS was of 7.3 months.

Defining the role of Nimotuzumab in this subset of patients was the goal of the work presented by Dr. Sailyn Alfonso, of the "Celestino Hernández Robau" Hospital in Villa Clara, Cuba. The Expanded Access Program in advanced cervical cancer (May 2008 - September 2009) included 58 patients with a histological diagnosis of recurrent or metastatic cervix cancer previously treated with chemo-RT and without any therapeutic alternative. Survival and safety after monotherapy with Nimotuzumab was evaluated during the study in patients ≥ 18 years of age who signed the consent form and having a performance status ECOG ≤ 3 . Nimotuzumab was administered during the induction phase in the form of a 200 mg intravenous infusion weekly for 12 weeks and 200 mg intravenously in the maintenance phase every 2 weeks until the deterioration of the performance status. Almost 60% of the patients received a maintenance treatment with nimotuzumab and only 13% of the events reported were related to nimotuzumab, among them the usual mild and moderate constitutional symptoms were predominant. Dr. Sailyn Alfonso confirmed that for this group of patients, the OS mean was 12.11 months and the median has not yet been reached, while OS rate was 66% at 15 months after inclusion. The results provided by Dr. Alfonso emphasized the benign safety profile of nimotuzumab even during prolonged administration and the very promising efficacy results prolonging survival.

The application of nimotuzumab in stage III A/B epithelial origin cervical cancer, without any prior treatment is being evaluated in a phase II, single-arm, open-label study conducted by the Cipto Mangunkusumo General Hospital in Jakarta, Indonesia. The rationale, design characteristics and current status of the study were presented by Francine Tay from Innogene Kalbiotech, Singapur. Ms. Francine Tay expressed that 71 new diagnosed patients will be included in the trial to received nimotuzumab (200 mg weekly for 9 cycles) plus RT (2 Gy for 5 days per week for 5 weeks) and brachytherapy (7 Gy weekly for 3 weeks). Patients with objective response rate will be submit-

ted to a 200 mg nimotuzumab biweekly maintenance treatment, while patients with a stable or progressive disease will be randomized to 1 nimotuzumab beyond the progression until there is a worsening of the performance status or toxicity, or 2 observations. The trial endpoints are ORR, TTP, 2 years of survival and safety. Ms. Francine Tay informed that 25 patients had been currently included and 3 out of the 21 patients that can be evaluated are in progression. No safety concerns have emerged from this application approach.

The application of nimotuzumab in castration-resistant prostate cancer patients was discussed by Dr. Joaquín González, from "Hermanos Ameijeiras" Hospital, Cuba. Dr. González presented the preliminary results of a phase II, multicenter, open-label, controlled-randomized trial that plans to include 70 patients (35 per arm) to demonstrate survival benefits compared to the control group; additional endpoints are time to disease progression (biochemical progression), overall response rate, QoL, pain control and safety. The patients are being randomized to receive nimotuzumab (200 mg every 14 days) plus mitoxantrone vs. a group of patients that receive mitoxantrone. Dr. Joaquín González, the principal investigator, reported that 66 patients had been included in the study up to that time, confirming the survival benefit for the nimotuzumab treated patients who reached a median OS of 21.30 months vs. 14.57 months for the patients receiving only CT. The benefit is significantly higher in the group of patients with at least 8 doses of nimotuzumab plus 6 doses of CT, with a mean OS of 34 months (median not yet reached) vs. patients with 6 doses of CT with mean OS of 22.38 months and median OS of 16.33 months. In this subset of nimotuzumab-treated patients, 70% were alive after 24 months compared to only 39% of non-nimotuzumab-treated patients. Dr. González concluded that nimotuzumab was safe when administered in combination with CT and emphasized the preliminary evidence of OS benefits in this group of patients treated with nimotuzumab.

Several examples of post approval surveillance strategies and other safety issues were presented on the last day, November 25th, of the Nimo-meeting 2009. The Medical Division of CIM presented the results of an Observational study in advanced stage cancer patients treated with Nimotuzumab, covering the period from December 2005 – December 2008. Dr. Patricia Piedra, from CIM, Cuba, described the objectives and design features of the study in cancer patients with advanced stage epithelial tumors treated with nimotuzumab combined with standard therapies or as a monotherapy. A total of 671 patients were included according the following criteria: histological or imaging diagnosis of advanced epithelial tumors; life expectancy of at least 12 weeks; Karnofsky $\geq 40\%$; patients who do not meet the inclusion criteria for any other clinical study. Any evidence of adverse events was recorded during the study to evaluate safety, and the adverse events were classified according to the CTCAE toxicity, NCI version 3 scale. The survival of patients included in the study was evaluated. Nimotuzumab was safe in all the therapeutic modalities used and during prolonged treatment schedules. The percentage of the adult and pediatric populations re-

ceiving nimotuzumab for the maintenance treatment, either the prolonged or chronic treatment, was 88.8% and 66.9%, respectively. Only 19.1% of the adult and 22.5% of the pediatric populations presented at least one adverse event during treatment with nimotuzumab. The superior safety profile was corroborated, with less than 20% of the reported adverse events considered as being related to nimotuzumab regardless the number of doses received; more than 70% of them were mild or moderate, without grade III/IV dermatologic reactions. The dermatologic side effects related to nimotuzumab were mild, and the occurrence was < 5% which is significantly lower than the dermatologic effects reported with other anti EGF-R drugs (> 80%). The treatment with nimotuzumab is associated to clinical benefits related to patient survival and corroborates the results from previous clinical studies; the advantage of the intervention was demonstrated in the "Real Oncology" setting. Newly diagnosed advanced head and neck tumor patients had a mean survival rate of 28.63 months; the median had not yet been reached at the time of the analysis. The patients that had recurrent or metastatic tumors had a mean survival rate of 17.5 months and a median of 9.10 months. Patients with a new diagnosis of multiform glioblastoma had an average survival rate of 15.73 months and the median was 13.97 months. These results are similar to the survival rates resulting from combining RT with temozolomide; nevertheless, the therapy with nimotuzumab is far better in terms of safety profile.

Dr. Giselle Saurez, from CIM, Cuba, presented the steps taken for the regularization of post approval clinical data collection in Cuba. Dr. Saurez said that CIM is conducting formal phase IV clinical trials for the approved indication, advanced head and neck cancer and high grade malignant glioma. These studies are being complemented by a prescription and utilization study conducted in collaboration with the Cuban Center for the Development of Pharmacoepidemiology. The results of the pharmacoepidemiologic research are expected to provide predictions confirming the effectiveness and safety of the nimotuzumab treatment in open populations with the main goal of positively transforming the natural fatal course of cancer, and turning it into a chronic and treatable disease.

Post approval clinical experiences in India were discussed by Dr. Neera Gupta from Biocon India. A phase IV clinical trial started in 2006 after the regulatory authorization, with safety assessment as the primary objective. The main indication explored was head and neck cancer and 150 patients were enrolled. The treatment regime was nimotuzumab, with 6 weekly-administered doses of 200 mg i.v., combined with the standard care according to the condition of the disease and the hospital. The adverse events related to nimotuzumab were mild and moderate, and the most frequent ones were mucositis, hypotension, rash and anemia.

Additional safety information related to the completed Cuban efficacy trial in advanced head and neck cancer patients was presented by Dr. José Alert from the National Institute of Oncology, Cuba, and by Dr. Raymed Bacallao from the National Institute of Nephrology. Dr. Alert's presentation reviewed the literature for details on radiation dermatitis and

mucositis in advanced head and neck cancer treated with antiEGFR therapy. He emphasized stressed the effects of Nimotuzumab plus RT. The reference study included 106 advanced cancer patients, divided into two groups. The study group received RT: 66 Gy in 33 fractions of 2 Gy/day plus nimotuzumab (200 mg every week for 6 weeks), compared to a placebo control group. According Dr. Alert's conference, the incidence of dermatologic adverse events with the nimotuzumab plus RT combination during the study was as follows: acne-like rash was absent; oral toxicity grade 3-4 was of 16.1%; radiation dermatitis grade 3-4 in 12.2% of the patients. Most importantly, Dr. Alert reported that the incidence of complications was similar in both groups.

Supplementary safety information arising from the same clinical trial was presented by Dr. Bacallao, who discussed the results of magnesium levels in patients treated with Nimotuzumab. This presentation gave additional evidence on the fact that Nimotuzumab does not produce hypomagnesaemia or secondary hypocalcemia in patients treated with 200 mg/week for 6 weeks. The absence of hypomagnesaemia seems to be related to the intrinsic characteristics of Nimotuzumab and its interaction with the target. Dr. Bacallao highlighted the idea that hypomagnesaemia does not seem to be part of the anti-tumoral mechanism of action of Nimotuzumab.

On November 25th, the last session opening remarks were given by Dr. Rolando Pérez, from CIM, Cuba. To summarize, Dr. Rolando referred to the main aforementioned results pointing out the novel and differential approaches of nimotuzumab. In the following presentation, Dr. Ilia A. Tikhomirov, from CIMYM Canada, recapitulated the binding properties of nimotuzumab as a monovalent binding interaction in lower EGFR expression tissues (healthy tissues), which support the finding that nimotuzumab interacts less with normal tissues, reducing debilitating toxicity. According Dr. Ilia A. Tikhomirov, nimotuzumab relies on bivalent binding (avidity) for its attachment to the cellular surface. The binding of Nimotuzumab and its activity will be facilitated by the EGFR overexpression and/or therapies increasing EGFR expression as RT.

The final presentation of the session was given by Dr. Tania Crombet Ramos, Head of Clinical Research of CIM, Cuba. Dr. Crombet summarized what we have learned about nimotuzumab and presented the future global development plan. According to the results presented in this edition of the meeting, nimotuzumab does not produce the disruption of the basal level of EGFR signaling, supporting that skin rash will not predict its efficacy. On the other hand, for intermediate affinity monoclonal antibodies as nimotuzumab, receptor density (expression) may predict sensitivity, thereby explaining why nimotuzumab is preferentially effective on tumors with high EGFR expression. Dr. Crombet also discussed how combination trials with irradiation enhance the efficacy of nimotuzumab, supporting her discussion on the above clinical results in advanced head and neck cancer, nasopharyngeal carcinomas, high malignant gliomas, unresectable esophageal cancer and advanced stage cervix carcinoma. Finally, to support the statement that

nimotuzumab is safe and that its chronic use is feasible and associated with an increased efficacy, Dr. Crombet showed a compilation of all the clinical results where chronic therapy with nimotuzumab has been implemented. Finally, Dr. Crombet offered details on the design of new clinical trials to explore the use of nimotuzumab beyond the progressive disease; also, the CT combination in different indications, such as NSCLC, glioma,

esophageal, cervical, gastric, and colorectal cancer. The clinical development program includes 36 clinical trials, some of them are in progress to investigate the safety and efficacy of nimotuzumab for cancer of the esophagus, head and neck, gastric, prostate, and pancreas, NSCLC, uterine cervical cancer, and adult and pediatric glioma.

The next Nimo-meeting is scheduled for November 2010.