OS07.3.A Phase 1/2 clinical trial of blood-brain barrier opening with the SonoCloud-9 implantable ultrasound device in recurrent glioblastoma patients receiving IV carboplatin

A Idbaih, A Sonabend, R Stupp, O Chinot, H Dufour, F Ducray, P Menei, J de Groot, C Desseaux, A Carpentier

centage of CRET regardless of other adjuncts used, tumour location and molecular characterisation.

OS07.3.A. PHASE 1/2 CLINICAL TRIAL OF BLOOD-BRAIN BARRIER OPENING WITH THE SONOCLOUD-9 IMPLANTABLE ULTRASOUND DEVICE IN RECURRENT GLIOBLASTOMA PATIENTS RECEIVING IV CARBOPLATIN

A. Idbaih[1], A. Sonabend[2], R. Stupp[3], O. Chinot[4], H. Dufour[4], F. Ducray[5], P. Menei[6], J. de Groot[7], C. Desseaux[8], A. Carpentier[9]; [1]Sorbonne Université, Inserm, CNRS, UMR S 1127, Institut du Cerveau, ICM, AP-HP, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurologie 2-Mazarin, Paris, France, [2]Malnati Brain Tumor Institute, Lurie Comprehensive Cancer Center, Departments of Neurological Surgery and Neurology, Northwestern Memorial Hospital, Northwestern University, Chicago, IL, United States, [3]Malnati Brain Tumor Institute, Lurie Comprehensive Cancer Center, Departments of Neurological Surgery and Neurology, Northwestern Memorial Hospital, Northwestern University, Paris, France, [4]Hôpital de la Timone, Marseille, France, [5]Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France, [6]CHU Angers, Angers, France, [7]MD Anderson Cancer Center, Houston, TX, United States, [8]Carthera, Lyon, France, [9]Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, Service de Neurochirurgie, Paris, France.

BACKGROUND: Low intensity pulsed ultrasound (LIPU) in combination with microbubbles is a promising approach for brain drug delivery. A phase 1/2 clinical study (NCT03744026) was initiated to demonstrate the safety and efficacy of blood-brain barrier (BBB) disruption over a large volume using an implantable ultrasound system (SonoCloud-9) in patients with recurrent glioblastoma receiving carboplatin chemotherapy. MATERIAL AND METHODS: The SonoCloud-9 device (Carthera, Paris, France) was placed at the end of tumor resection and replaced the bone flap. The device was activated 9-14 days after surgery for a duration of 270 seconds every 4 weeks until progression or treatment completion, concomitantly with IV DEFINITY microbubbles (10 µl/kg, Lantheus, Billerica, US). The Phase 1 cohort consisted of an escalation of BBB disruption volume by activation of 3 (n=3), 6 (n=3), then 9 (n=3) emitters of the device. Dose limiting toxicity (DLT) was assessed during the first 2 weeks after the 1st sonication. A subsequent expansion cohort consisted of patients treated with 9 emitters in which the primary endpoint was assessment of BBB opening on MRI using gadolinium (<1 hr after sonication). All patients received carboplatin either after (n=21) or before (n=12) device activation to disrupt the BBB. In addition, a sub-study was performed to investigate carboplatin concentration enhancement in the peritumoral region with sonication at time of device implantation. RESULTS: Study accrual is complete with 38 patients enrolled and 33 patients having been implanted and received at least one sonication+carboplatin. A total of 101 sonications were performed (range=1-10 sonication sessions/patient). No DLTs were observed. A total of 14 SAEs were observed including five events considered as possibly treatment related. BBB disruption was confirmed by gadolinium enhancement after sonication. In an analysis of 60 treatments in 27 patients that had all nine emitters active, 90% of activated emitters led to BBB opening in gray and/or white matter with good repeatability of BBB opening. In 3 patients who underwent intraoperative sonication and carboplatin administration, a 7.58-fold increase in brain/plasma drug levels was demonstrated. Updated and mature outcome results will be presented. CONCLUSION: These results confirm the safety and feasibility of repeated BBB disruption using an implantable ultrasound system. LIPU substantially increases drug levels in the peritumoral brain.

OS07.4.A. REGORAFENIB IN RECURRENT GLIOBLASTOMA PATIENTS: A MULTICENTRIC REAL-LIFE STUDY

F. Bruno[1], A. Pellerino[1], E. Pronello[2], R. Palmiero[1], V. Polo[3], R. Vitaliani[3], E. Trincia[3], V. Internò[4], C. Porta[4], R. Soffietti[1], R. Rudà[1,3]; [1]University and City of Health and Science, Turin, Italy, Turin, Italy, [2]Neurology Unit, Dept. of Translational Medicine, University of Eastern Piedmont, Novara, Italy, Novara, Italy, [3]Multidisciplinary Brain Tumor Board, Ca' Foncello Hospital, Treviso, Italy, Treviso, Italy, [4]Department of Interdisciplinary Medicine, University of Bari Aldo Moro. Division of Medical Oncology, Bari, Italy, Bari, Italy.

BACKGROUND: Few options are still available for recurrent glioblastoma (GBM). In the Italian phase 2 REGOMA trial, regorafenib improved overall survival, as compared to lomustine, for GBM patients at first progression after chemoradiation. Here, we present the results of a real-life multicentre study that analysed clinical and radiological features, response to treatments, tolerability, and outcome of a cohort of GBM patients treated with regorafenib at first tumour progression. PATIENTS AND METHODS: We enrolled GBM patients at first tumour progression in three Italian Institutions (Turin, Treviso, Bari). Regorafenib was administered following an escalation dose protocol (1st cycle: 80 mg/day for 2 weeks, then 120 mg/day for one week; 2nd cycle: 120 mg/day for 2 weeks, then 160 mg/day for one week; 160 mg/day from the 3rd cycle). MRI scans were obtained at baseline and every 3 months. Progression-free survival (PFS) and overall survival (OS) were defined as time from regorafenib initiation and disease progression or death. RESULTS: From January 2020 to January 2022, 66 GBM patients were included. Median age was 60.0 years. MGMTp methylation was found in 30 patients (45.5%). First-line treatment consisted in chemoradiation in 61 (92.4%), in upfront TMZ (3, 4.5%) or RT alone followed by TMZ (2, 3.0%). Median dose was 120 mg/day 21q28 day, which was lower than that used in REGOMA trial (149 mg). Median PFS (mPFS) was 2.7 months (2.4 - 3.0 95% CI) and median OS (mOS) 7.1 months (5.4 - 8.9 95% CI). Best RANO response to regorafenib was partial response (PR) in 10 (15.1%), stable disease in 14 (21.2%), and progressive disease in 42 (63.7%) patients. All PRs were observed within the first three months of treatment. Patients who completed treatment up the 6th, 9th, and 12th cycles were 20, 3 and 2, respectively. Forty-six (69.7%) patients presented adverse events of any grade, and 21 (31.8%) grade III-IV toxicity. The most frequent adverse events were fatigue (33.3%), hand-foot syndrome (27.3%), and liver enzymes increase (15.2%). Two patients only (3.0%) interrupted regorafenib due to toxicity.In a multivariable analysis, factors significantly associated with disease progression were higher age ($p = 0.035$) and absence of *MGMT*p methylation ($p = 0.024$). CONCLUSION: In this real-life study on 66 patients, mPFS and mOS were similar to those of the 59 patients enrolled in the regorafenib arm of REGOMA trial (2.7 vs 2.0 months; 7.1 vs 7.4 months, respectively). However, we observed a higher rate of PRs as compared to REGOMA (15% versus 3.0%). Type and severity of adverse events were similar between the two studies. Moreover, we had a lower incidence of discontinuations of regorafenib due to toxicity, maybe attributable to the lower dose intensity.We are further analysing the data of MRI-perfusion, with the aim to explore whether it can predict an early response or progression in comparison to standard MRI.

OS07.5.A. REPORT FROM THE POOLED ANALYSIS OF THE RANDOMIZED TRIALS NORDIC, NOA-8 AND CE.6 ON ELDERLY PATIENTS WITH GLIOBLASTOMA

T. Gorlia[1], F. Oppong[1], C. O´Callaghan[2], W. Wick[3,4], N. Laperriere[5], M. Weller[6], J. Perry[7], G. Reifenberger[8], B. Tavelin[9], A. E. Malmström[10,11]; [1]EORTC Headquarters, 1200 Brussels, Belgium, [2]Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada, 31 Neurology Clinic and National Centre for Tumour Diseases, University Hospital Heidelberg,, Heidelberg, Germany, [4]DKTK and Clinical Cooperation Unit Neurooncology, DKFZ, Heidelberg, Germany, [5]Department of Radiation Oncology PrincessMargaret Cancer Centre University of Toronto, Canada, Toronto, ON, Canada, [6]University Hospital Zurich, Department of Neurology, Frauenklinikstrasse 26, 8091 Zürich, Switzerland, [7]Dept of Medicine, Sunnybrook Hospital, University of Toronto, Toronto, ON, Canada, [8]Institute of Neuropathology, Heinrich Heine University, Duesseldorf, Germany, 9, Department of Radiation Sciences, Oncology, Umeå University, 90187 Umeå, Sweden, [10]Dept of Advanced Home Care, Linköping University, Linköping, Sweden, [11]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden.

BACKGROUND: The majority of patients diagnosed with glioblastoma are over 60 years old. Three randomized trials addressed the roles of radiotherapy (RT) and temozolomide (TMZ) for these patients. Two, the NORDIC and NOA-08 (N&N) compared RT versus TMZ head-to-head, the third, CE.6, randomized between hypofractionated RT and the combination of RT+TMZ. All showed significant benefit for the TMZ arms, especially for patients with *MGMT* promoter methylated tumors. An ongoing pooled analysis of these three trials focuses on identifying significant baseline prognostic factors and assess their value for predicting outcome in relation to treatment. The aim is improved selection of elderly patients with glioblastoma for their optimal treament; RT alone, TMZ with or without concomitant RT or palliative care. METHODS: The data of two phase 3 studies (N&N) were pooled to build a large dataset and findings are compared to CE.6 trial data. A re-assessment of the clinically most relevant *MGMT* cut-off is performed. The prognostic value of baseline clinical factors and quality of life scores, determined by the EORTC QLQ-30 and BN-20 questionnaires, are investigated. Data is also analysed to account for a possible impact of sex. RESULTS: The N&N dataset includes 715 and the comparative dataset (CE.6) 562 patients. Median age for N&N is 71 years and 73 for CE.6. In N&N and CE.6 respectively, 66.2% versus 70.5% underwent resection and 50.9% and 75.3% were on steroids at the time of study inclusion. In N&N, 401 patients received RT alone and 281 in CE.6, while 314 were randomized to TMZ alone in N&N and 281 to concomitant RT and TMZ in CE.6. For N&N *MGMT* promoter methylation status was successfully determined for 412 (57.6%) and 354 (63.0%) for CE.6. In a first report, patients with the combination of the comorbidities hypertension, diabetes and/or cerebrovascular insult had poorer prognosis when treated with TMZ. CONCLUSION: An ongoing pooled analysis of the trials NORDIC, NOA-08 and CE.6 is expected to identify factors that will improve personalized medicine for elderly patients with glioblastoma. Reanalyzed *MGMT* promoter methylation data and the role of baseline quality of life for outcome will be reported.