LBA2000 **Oral Abstract Session**

Efficacy and safety of STUPP regimen with or without anlotinib for newly diagnosed glioblastoma: Results of a multicenter, double-blind, randomized phase II trial.

Yuanyuan Chen, Guihong Liu, Meihua Li, Liang Wang, Pengfei Sun, Shiyu Feng, Xin Xu, Xuejun Yang, Yanhui Liu, Yonghong Hua, Wen Ma, Hao Jiang, Xianming Li, Juntao Ran, Song Lin, Wei Zheng, Siyang Wang, Xueguan Lu, Zhongping Chen; State Key Laboratory of Oncology in South China, Sun Yat-Sen Univercity Cancer Center, United Laboratory of Frontier Radiotherapy Technology of Sun Yat-sen University and Chinese Academy of Sciences Ion Medical Technology Co., Ltd., Guangzhou, China; Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; Department of Neurosurgery, The First Affiliated Hospital of Nanchang University, Nanchang, China; Tangdu Hospital- Air Force Military Medical University/Department of Neurosurgery, Xian, China; The Second Hospital of Lanzhou University, Lanzhou, China; Chinese People's Liberation Army General Hospital, Beijing, China; HeNan Cancer Hospital Department Neurosurgery, Zhengzhou, China; Tianjin Medical University General Hospital/Neurosurgery, Tianjin, China; West China Hospital of Sichuan University/Neurosurgery, Chengdu, China; Zhejiang Cancer Hospital/Department of Head and Neck Radiation Oncology, Hangzhou, China; Department of Radiotherapy, Gansu Provincial Hospital, Lanzhou, China; The First Affiliated Hospital of Bengbu Medical College, Bengbu, China; Department of Oncology and Radiology, Shenzhen People's Hospital, Shenzhen, China; The First Hospital of Lanzhou University, Lanzhou, China; Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; Sixth Medical Center of PLA General Hospital, Beijing, China; Cancer Center, The Fifth Affiliated Hospital, Sun Yat-Sen University, Zhuhai, China; Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; Department of Neurosurgery/Neuro-Oncology, Cancer Center, Sun Yat-Sen University, Guangzhou, China

2001 Oral Abstract Session

A prognostic classification system for extent of resection in IDH-mutant grade 2 glioma: A report by the RANO resect group.

Philipp Karschnia, Jacob S. Young, Maarten Wijnenga, Arthur Wagner, Oliver Schnell, Levin Häni, Yoshua Esquenazi, Einar Vik-Mo, Roberta Rudà, Michael A. Vogelbaum, Shawn L. Hervey-Jumper, Juergen Beck, Jorg Dietrich, Stefan J. Grau, Yae Won Park, Gilbert Youssef, Asgeir S. Jakola, Lorenzo Bello, Mitchel S. Berger, Joerg Tonn, RANO Resect Investigators; Department of Neurosurgery, Uniklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany; Department of Neurosurgery & Division of Neuro-Oncology, University of San Francisco, San Francisco, CA; Department of Neurology, Erasmus MC Cancer Institute, Rotterdam, Netherlands; Department of Neurosurgery, Technical University Munich, Munich, Germany; Department of Neurosurgery, Inselspital Bern, Bern University Hospital, University of Bern, Bern, Switzerland; Department of Neurosurgery, McGovern Medical School at UT Health Houston, Houston, TX; Department of Neurosurgery, Oslo University Hospital & Institute for Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway; Division of Neuro-Oncology, Department of Neuroscience, City of Health and Science Hospital and University of Turin, Turin, Italy; Department of Neurosurgery, Moffitt Cancer Center, Tampa, FL; Department of Neurosurgery, University of Freiburg, Freiburg, Germany; Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Department of Neurosurgery, University of Cologne, Cologne, Germany; Department of Radiology and Center for Clinical Imaging Data Science, Yonsei University College of Medicine, Seoul, South Korea; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Department of Clinical Neuroscience, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Division for Neuro-Oncology, Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; Department of Neurosurgery, Ludwig-Maximilians-University, Munich, Germany

Background: The effects of resection in IDH-mutant grade 2 gliomas remain controversial since terminology for extent of resection was inconsistently applied across trials. We aimed to (I) establish a standardized classification system for extent of resection and (II) assess the impact of supramaximal resection on survival in IDH-mutant astrocytomas and 1p19q-codeleted oligodendrogliomas. **Methods:** Patients with newly diagnosed grade 2 IDH-mutant glioma meeting the WHO 2021 criteria were identified across sixteen centers in the USA, Europe, and Asia as part of the RANO *resect* effort. Additional patients from UCSF served for validation. Kaplan-Meier analyses and log-rank tests were applied to calculate survival, and Cox's proportional hazard regression model to adjust for multiple variables (significance level: $p \leq 0.05$). **Results:** We identified 1391 newly diagnosed IDH-mutant gliomas grade 2 between 1993-2024, of which 728 patients (379 astrocytoma, 349 oligodendroglioma) received no adjuvant treatment and allowed to study the effects of resection. Smaller post-operative T2/FLAIR tumor remnants were favorably associated with outcome. We classified those patients according to residual T2/FLAIR tumor volumes: patients with 'maximal T2/FLAIR resection' (class 2; 0-5 cm^3 remnant) had superior progression-free and overall survival compared to 'submaximal T2/FLAIR resection' (class 3; 5-25 cm^3 remnant) or 'minimal T2/FLAIR resection' (class 4; >25 cm^3 remnant), with 10-year survival rates of 82.2% *vs.* 75.0% *vs.* 45.6% (respectively; $p = 0.001$). Resection of non-infiltrated structures beyond T2/FLAIR borders provided an additional survival benefit as characterized by a 10-year survival rate of 97.5%; thus defining class 1 'supramaximal T2/FLAIR resection' (HR for OS *vs.* class 2: 0.24, CI 0.1-0.5 / in astrocytoma: 0.26, CI 0.1-0.7 / in oligodendroglioma: 0.21, CI 0.1-0.9). Effects of extensive resection on survival unfolded after 3 years in astrocytomas, whereas survival curves separated after 6-8 years in oligodendrogliomas. The prognostic relevance of the four-tier classification was conserved in a multivariate analysis controlling for clinical markers including pre-operative tumor and 1p19q-codeletion, in subgroups of either astrocytomas or oligodendrogliomas, and in a separate cohort of 586 patients who received adjuvant chemo-/radiotherapy. The prognostic value of the classification was further validated in the external UCSF cohort of 381 grade 2 IDH-mutant gliomas ($p = 0.001$). **Conclusions:** The proposed 'RANO classification for extent of resection' serves as prognostic tool for patient stratification in grade 2 IDH-mutant gliomas. While effects of extensive surgery are evident earlier in astrocytomas, 'supramaximal' resection translates into a survival benefit for both astrocytomas and oligodendrogliomas and should be characterized in clinical trials. Research Sponsor: None.

2002 Oral Abstract Session

Final clinical and molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion: NCT00626990.

Martin J. Van Den Bent, Sara C. Erridge, Michael A. Vogelbaum, Anna K. Nowak, Marc Sanson, Alba Ariela Brandes, Wolfgang Wick, Paul M. Clement, Jean-Francois Baurain, Warren P. Mason, Helen Wheeler, Michael Weller, Kenneth D. Aldape, Pieter Wesseling, Johan M. Kros, Mircea Tesileanu, Golfinopoulos Vassilis, Thierry Gorlia, Pim French, Brigitta Gertrud Baumert, EORTC Brain Tumor Group; Erasmus MC Cancer Institute, Rotterdam, Netherlands; Edinburgh Cancer Centre, Edinburgh, United Kingdom; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; University of Western Australia, Nedlands, Australia; Hôpital La Pitié Salpêtrière, Paris, France; Bellaria Maggiore Hospital, Bologna, BO, Italy; University of Heidelberg, Heidelberg, Germany; UZ Leuven - Leuven Cancer Institute - KU Leuven, Leuven, Belgium; St. LUC University Hospital Medical School, Woluwe-Saint-Lambert, Belgium; Princess Margaret Cancer Centre, Toronto, ON, Canada; Royal North Shore Hospital, Sydney, NSW, Australia; Department of Neurology, University Hospital Zurich, and Brain Tumor Centre, University Hospital and University of Zurich, University Hospital Zurich, Zurich, Switzerland; NCI CCR, Bethesda, MD; Amsterdam UMC, Amsterdam, Netherlands; Erasmus MC, Rotterdam, Netherlands; Yale University, New Haven, CT; EORTC - European Organisation for Research and Treatment of Cancer, Woluwe-Saint-Lambert, Belgium; EORTC Headquarters, Brussels, Belgium; Cantonal Hospital Graubunden, Chur, Switzerland

Background: The 1st and 2nd interim analyses of the CATNON trial on anaplastic glioma (NCT00626990) showed benefit from adjuvant (adj) temozolomide (TMZ) on overall survival (OS) in patients with IDH mutant (mt) tumors, but no benefit of concurrent (conc) TMZ regardless of Isocitrate dehydrogenase 1 and 2 (IDH) mutation (mt) status. We now present the final analysis and the exploratory molecular marker analysis of the study. **Methods:** The 2x2 factorial design phase III CATNON trial randomized 751 adult patients with newly diagnosed non-codeleted anaplastic glioma to either 59.4 Gy radiotherapy (RT) alone; the same RT with concTMZ; the same RT and 12 cycles of adjTMZ or the same RT with both concTMZ and adjTMZ. Methylation status including *MGMT* promoter methylation status were assessed with the Infinium MethylationEPIC Beadchip. IDH mutation (mt) status and glioma specific alterations were assessed with a glioma targeted panel using Agilent SureSelect baits. **Results:** After a median follow-up of 10.9 years and with 499 events observed, in the intent-to-treat population the hazard ratio (HR) for OS adjusted for stratification factors after concTMZ was 0.906 (95%CI 0.760, 1.082; p=0.28) and after adjTMZ 0.647 (95%CI 0.541, 0.773; p <0.0001). In 660 patients IDH status could be determined: IDH was mt in 444 tumors and wild type (wt) in 216 tumors. Median OS was 1.7 yrs in patients with IDHwt tumors and 8.5 years in patients with IDHmt tumors. Benefit to TMZ was limited to patients with anaplastic glioma IDHmt of which 199 were still alive (45%). For patients with IDHmt tumors the HR for concTMZ was 0.81 (95% CI 0.63-1.04; p=0.09) and for adjTMZ 0.54 (95% CI 0.42-0.69,p < 0.0001). No benefit was observed of concTMZ in IDHmt glioma patients that also received adjTMZ (HR 0.92 95% CI 0.63-1.36; p=0.69). In patients with IDHmt tumors that had received any TMZ median OS was 10.3 years, the median OS in patients treated with adjTMZ was 12.5 years (95% CI 9.4-15.0; p<0.0001). In exploratory analysis, high-copy number Amplification of *PDGFR* and *CDK4*; Homozygous deletion of the *CDKN2A/B* locus, total copy number alterations, methylation subtype (A_IDH vs A_IDH_HG, G-CIMP high versus low, *MGMT*-promoter methylation as determined by methylation arrays) were all associated with outcome but none was predictive for benefit to TMZ. **Conclusions:** Despite more follow-up, concTMZ did not improve OS regardless of IDH status. AdjTMZ increased OS in patients with IDHmt tumors but not in patients with IDHwt tumors. Molecular factors of known prognostic significance for IDHmt 1p/19q intact anaplastic glioma did not predict benefit to TMZ. Median OS in patients with IDHmt glioma having received adjTMZ after RT was 12.5 years. Standard of post-operative care in patients with high grade IDHmt astrocytoma should be RT followed by 12 cycles adjTMZ. Funding Source: MSD. Clinical trial information: NCT00626990. Research Sponsor: MSD; Dutch Cancer Socierty; 10685; Brain Tumor Charity; GN-000577; Stijd van Salland.

2003 Oral Abstract Session

A phase 2 study of pemigatinib for pre-treated glioblastoma or other gliomas with activating FGFR1-3 alterations: Results from FIGHT-209.

Enrico Franceschi, Martin J. Van Den Bent, Marc Sanson, Andrew B. Lassman, Giuseppe Lombardi, Maria Vieito Villar, Roy E. Strowd, Juan Manuel Sepulveda Sanchez, Catherine McBain, Rikke Hedegaard Dahlrot, Estela Pineda, Delphine Larrieu, Alessia Pellerino, Yoshitaka Narita, Stephen Joseph Bagley, Lalanthica Yogendran, Natalia Oliveira, Yufei Guo, Louis Viviers, Manmeet Singh Ahluwalia; IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Erasmus MC Cancer Institute, Rotterdam, Netherlands; Hôpital Universitaire Pitie-Salpetriere, Paris, France; Division of Neuro-Oncology, Department of Neurology, and the Herbert Irving Comprehensive Cancer Center, Columbia University Vagelos College of Physicians & Surgeons and New York-Presbyterian, New York, NY; Department of Oncology IOV – Istituto Oncologico Veneto, Padua, Italy; Hospital General Universitario Vall d'Hebron, Barcelona, Spain; Department of Neurology, Wake Forest University School of Medicine, Winston-Salem, NC; Hospital Universitario 12 Octubre, Madrid, Spain; The Christie NHS Foundation Trust, Manchester, United Kingdom; Department of Oncology, Odense University Hospital, Denmark & Department of Clinical Research, University of Southern Denmark, Odense, Denmark; Hospital Clínic de Barcelona, Barcelona, Spain; Oncopole Claudius Regaud, Institut Universitaire du Cancer de Toulouse Oncopole, Toulouse, France; Division of Neuro-oncology, Department of Neuroscience "Rita Levi Montalcini", University and City of Health and Science Hospital, Torino, Italy; National Cancer Center Hospital, Tokyo, Japan; University of Pennsylvania Hospital, Philadelphia, PA; UC Health at Cincinnati, Cincinnatti, OH; Incyte Biosciences International, Morges, Switzerland; Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: FGFR genomic alterations occur in approximately 8% of gliomas. Inhibition of FGFR1-3 with pemigatinib showed antitumor activity in a multihistology basket trial (FIGHT-207) in which approximately 10% of participants (pts) had recurrent/progressive FGFR-altered glioblastoma (GBM). We further investigated pemigatinib activity in primary brain tumors by conducting an international, multicenter, single-arm, 2-cohort, phase 2 study specifically in adults with FGFR-altered pretreated gliomas (FIGHT-209; NCT05267106). **Methods:** Pts were enrolled in 2 cohorts: A, histologically or molecularly defined GBM; or B, other gliomas, glioneuronal tumors, and neuronal tumors. Eligible pts had tumors harboring a FGFR1-3 fusion/rearrangement or mutation detected by an accredited laboratory that had recurred/progressed after ≥1 prior therapy. Pemigatinib (oral, 13.5 mg on days 1-14/21) was intended to continue until progression by Response Assessment in Neuro-Oncology (RANO) criteria determined by an independent review committee (IRC) or unacceptable toxicity. Efficacy of each cohort was evaluated independently. The primary endpoint was objective response rate (ORR; partial plus complete) per RANO (cohort A), with a goal of > 28%. Key secondary and exploratory endpoints were ORR in cohort B, ORR by investigator assessment, progression-free survival (PFS) by IRC, overall survival (OS), safety, neurologic function by Neurologic Assessment in Neuro-Oncology (NANO), and efficacy correlations with diagnosis and specific FGFR-alterations. **Results:** Between May 2022 and December 2023, 74 pts were enrolled in cohort A and 9 in cohort B. FGFR1-3 fusions/rearrangements were the most common genomic alterations in cohort A (n = 65 [88%]) and in cohort B, FGFR1 mutations (n = 8 [89%]). Pts had a median (range) age of 56 (20-79) years; 60% were male. On September 27, 2024 (data cutoff), 16 pts remained on treatment (cohort A, n = 11 [15%]; cohort B, n = 5 [56%]); 67 discontinued, primarily due to progressive disease (n = 59 [71%]). In cohort A, ORR was 8% (6 partial responses [PR], 0 complete responses [CR]); 21 pts (28%) had stable disease (SD); estimated 6-month PFS rate was 17% (95% CI, 8.7-27.8) and 12-month OS rate 48% (95% CI, 35.6-60.2). In cohort B, the ORR was 22% (1 CR, 1 PR); 3 (33%) SD. Most treatment-emergent adverse events (AEs) were low grade in severity (grade ≥3, 36.1%). Hyperphosphatemia, a class effect of FGFR inhibitors, was the most common AE (75%); 6 pts (7%) required dose reduction and 4 pts (5%) discontinued due to AEs. **Conclusions:** ORR did not meet the pre-specified goal of > 28% among pts with GBM harboring pemigatinib-sensitizing FGFR alterations. However, durable disease stabilization was observed, notably in pts with CNS tumors other than GBM, and toxicities were manageable. More mature PFS and OS data will be presented with exploratory molecular correlations. Clinical trial information: NCT05267106. Research Sponsor: Incyte Corporation.

A phase II study of asandeutertinib (TY-9591) in advanced NSCLC patients with EGFR-positive mutations and brain metastases.

Pu-Yuan Xing, Ligang Xing, Ying Cheng, Yongzhong Luo, Zhengguo Li, Qin Xin, Chengqin Li, Xiu Gui Chen, Yusheng Wu, Yuankai Shi; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China; Shandong Cancer Hospital and Institute, The Affiliated Cancer Hospital of Shandong First Medical University, Jinan, China; Department of Medical Oncology, Jilin Cancer Hospital, Changchun, China; Hunan Cancer Hospital & The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China; Department of Respiratory and Critical Care Medicine, Wuwei Cancer Hospital, Wuwei, China; TYK Medicines Inc, Shanghai, China

Background: Asandeutertinib (TY-9591), a deuterated osimertinib derivative, is a new central nervous system-active 3rd generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), that can potently and selectively inhibit *EGFR*- sensitizing mutations (EGFRm+) and T790M resistance mutation. The phase I study for asandeutertinib (NCT04204473) showed had a very superior clinical efficacy on the NSCLC with *EGFR* mutations. This phase II study (NCT05146219) aimed to further evaluate the efficacy and safety of asandeutertinib in patients with locally advanced or metastatic EGFRm+ NSCLC with brain metastases (BM). **Methods:** 29 patients were enrolled and received asandeutertinib treatment at a dose of 160 mg once daily. The 27 patients with *EGFR*-sensitizing mutations (19 Del or L858R) did not take any EGFR-TKI previously, while the 2 patients with *EGFR* T790M resistance mutation previously received 1st or 2nd-generation EGFR-TKIs therapy. The primary endpoints were the intracranial objective response rate (iORR) assessed by investigator (INV) per RANO-BM and the extracranial objective response rate (eORR) assessed by INV per the RECIST v1.1. **Results:** At the time of data cutoff at March 21,2024, the median follow-up time was 16.4 months. The confirmed INV-iORR was 93.1% (95% CI: 77.2%-99.2%) (n = 29). The confirmed INV-iORR for those who were treated with asandeutertinib as first line was 92.6% (95% CI：75.7%-99.1%) (n = 27). The 2 patients with previous EGFR-TKI therapy were intracranial partial response (iPR). The median intracranial duration of response (iDoR) and intracranial progression-free survival (iPFS) were not reached. The 12-month iDoR was 82.8%, and the 12-month iPFS was 96.6%. The median PFS was 13.5 months (95% CI: 12.5-NA) (n = 29) and 15.1 months (95%CI：12.5 - NA) (n = 27) for those without previous EGFR-TKI therapy. Any intracranial or extracranial progression was evaluated as systemic progression, which may lead to underestimation of the systemic PFS. The mean treatment was 402.9 days (n = 29). 27 (93.1%) patients experienced treatment-related adverse events (TRAEs). The most common TRAEs (≥10%) included decreased white blood cell count, decreased absolute neutrophil count, decreased platelet count, elevated serum creatine phosphokinase, diarrhea, etc (majority grade 1/2). Grade 3 TRAEs occurred in 27.6% patients while no grade 4/5 adverse event. Six serious adverse events were reported by five patients (17.2%), of which two patients (6.9%) were study drug-related. The interstitial lung disease, cardiomyopathy and keratitis were not reported. **Conclusions:** Asandeutertinib is highly effective and well-tolerated in locally advanced or metastatic EGFRm+ NSCLC patients with BM. Pivotal phase II study (NCT05948813) and phase II trials (NCT05382728) are onging. Keywords: TY-9591; Deuterated osimertinib derivative; Brain metastases. Clinical trial information: NCT05146219. Research Sponsor: None.

2005 Oral Abstract Session

Patritumab deruxtecan (HER3-DXd) in active brain metastases (BM) from metastatic breast (mBC) and non–small cell lung cancers (aNSCLC), and leptomeningeal disease (LMD) from advanced solid tumors: Results from the TUXEDO-3 phase II trial.

Matthias Preusser, Javier Garde, Maria Gion, Manuel Ruiz, Juan José García-Mosquera, Richard Greil, Maria Valero, Miriam Arumí, Giulia Raimondi, Marta Campolier, Paula Gonzalez-Alonso, Jose Antonio Guerrero-Martinez, Antonio Llombart-Cussac, Felicitas Oberndorfer, Maximilian Marhold, Marta Vaz Batista, Anna Sophie Berghoff, Julia Furtner, Thorsten Fuereder, Rupert Bartsch; Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; Arnau de Vilanova University Hospital, Valencia, Spain; IOB Madrid, Institute of Oncology, Hospital Beata Maria Ana, Madrid, Spain; Virgen del Rocío University Hospital, Seville, Spain; Dr. Rosell Oncology Institute (IOR), Dexeus University Hospital, Quironsalud Group, Barcelona, Spain; IIIrd Medical Department, Paracelsus Medical University Salzburg; Salzburg Cancer Research Institute-CCCIT and Cancer Cluster, Salzburg, Austria; Hospital Quirón Sagrado Corazón, Sevilla, Spain; Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain; Medica Scientia Innovation Research (MEDSIR), Hospital Arnau de Vilanova, FISABIO, Translational Oncology Group, Universidad Cardenal Herrera-CEU, Alfara Del Patriarca, Spain; Medical University of Vienna, Department of Pathology, Vienna, Austria; Department of Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria; Hospital Professor Doutor Fernando Fonseca EPE, Medica Scientia Innovation Research (MEDSIR), Barcelona, Lisbon, Portugal; Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria; Research Center for Medical Image Analysis and Artificial Intelligence, Faculty of Medicine and Dentistry, Danube Private University, Krems an Der Donau, Austria; Medical University of Vienna, Department of Medicine 1, Division of Oncology, Vienna, Austria

Background: BM and LMD are common and severe complications of solid cancers with high morbidity, poor prognosis, and limited treatment options. Antibody drug conjugates (ADCs) have shown high intracranial overall response rates (IC-ORR) in HER2-positive mBC and *EGFR*-mutated NSCLC patients (pts). HER3-DXd, an ADC combining an anti-HER3 antibody with a topoisomerase (topo) I inhibitor, has shown promising results in mBC and aNSCLC pts. Since HER3 is highly expressed in aNSCLC and mBC CNS metastases, we hypothesized HER3-DXd may have clinical activity in BM from mBC and aNSCLC pts, and LMD from any solid tumor. **Methods:** TUXEDO-3 (NCT05865990) is an international, multicenter, multicohort, single-arm, phase II trial enrolling pts with BM from mBC (cohort 1), aNSCLC (cohort 2), and LMD from any solid tumor (cohort 3). Key inclusion criteria were: Pts ≥18 years old, histologically documented disease, ECOG PS 0-2, and left ventricular ejection fraction ≥50% in all cohorts; newly diagnosed/progressing BM with ≥1 brain lesions ≥10mm by MRI, and ≥1 line of prior systemic treatment, in cohorts 1 and 2; LMD per EANO-ESMO in cohort 3. Pts received HER3-DXd 5.6 mg/kg IV Q3W until disease progression, unacceptable toxicity or withdrawal for any reason. Primary endpoint was IC-ORR per local investigator according to RANO-BM in cohorts 1 and 2, and 3-month OS in cohort 3. Sample size was based on Simon's two-stage design. Primary endpoint was met if ≥3 IC responses (H0: ≤5%; H1: ≥25%) in cohort 1 and 2; and if ≥3 pts with 3-month OS (H0: ≤5%; H1: ≥25%) in cohort 3. Overall sample size was 60 pts with a target population of 20 pts per cohort. **Results:** Between December 2023 and July 2024, 61 evaluable pts were enrolled from 8 Austrian and Spanish sites. Median age (min; max) was 57.0 (35.0; 75.0), 59.5 (37.0; 72.0) and 51.5 (40.0; 66.0) years in cohorts 1, 2 and 3, respectively. At data cut-off, median follow-up (min; max) was 4.4 (1.4; 10.1), 4.3 (0.2; 11.0) and 3.5 (0.8; 8.6) months in cohorts 1, 2 and 3, respectively. Primary endpoints were met in all three cohorts. In cohort 1, 5/21 (23.8%) pts had IC response irrespective of BC subtype; 2 (40.0%) responders had received previous topo I based ADCs. In cohort 2, 5/20 (25.0%) pts had IC response. In cohort 3, 11/20 (55.0%) pts achieved 3-month OS irrespective of the LMD type. No new signals of toxicity were observed and neurological symptoms, QoL and neurocognitive function remained stable or improved over the treatment period. Tumoral HER3 expression did not correlate with treatment response. **Conclusions:** TUXEDO-3 is the first trial evaluating efficacy and safety of HER3-DXd in pts with BM or LMD. HER3-DXd showed substantial CNS activity in parenchymal metastases and LMD, and may be a potential novel treatment for CNS disease in cancer pts. Clinical trial information: NCT05865990. Research Sponsor: Daiichi Sankyo Company, Limited; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co.

A phase II study of an anti-telomerase CD4+ T-helper vaccine (UCPVax) with or without temozolomide in newly diagnosed glioblastoma.

Antoine Carpentier, Stefania Cuzzubbo, Aurelia Meurisse, Clotilde Verlut, Jean David Fumet, Laura Boullerot, Charlotte Bronnimann, Emmeline Tabouret, Renata Ursu, Claudia Barsan, Catherine Belin, Alice Hervieu, Marion Jacquin, Melanie Moltenis, Anne-Laure Clairet, Christine Fagnoni-Legat, François Ghiringhelli, Dewi Vernerey, Caroline Laheurte, Olivier Adotevi; Hôpital Saint-Louis, Paris, France; Neurology Department, APHP, University Hospital Saint Louis, Paris, France; UMQVC; CHU Jean Minjoz Besançon, Besançon, France; Department of Neurology University Hospital of Besançon, Besançon, France; Centre Georges François Leclerc, Early phase unit, Dijon, France; INSERM, EFS BFC, UMR1098, RIGHT, University of Bourgogne Franche-Comté, Besancon, France; University Hospital of Bordeaux, Department of Medical Oncology, Bordeaux, France; Neuroncology Department, CHU Timone, Marseille, France; Department of Neurology, AP-HP, Saint Louis Hospital, Paris, France; Department of Neurology, AP-HP, Saint Louis Hospital, Paris Cité University, Paris, France; Centre Georges François Leclerc, Medical Oncology Department, Dijon, France; INSERM CIC-1431, Clinical Investigation Center, University Hospital of Besançon, Besançon, France; University Hospital of Besançon, Besançon, France; CHU Besançon, Besançon, France; Department of Pharmacy, University Hospital of Besançon, Besancon, France; Centre Georges François Leclerc, Dijon, France; UMQVC; University Hospital of Besançon, Besançon, France; INSERM, EFS UFC, UMR1098, RIGHT, University of Franche-Comté, Besançon, France; Department of Medical Oncology, University Hospital of Besançon, Besancon, France

Background: UCPVax is a therapeutic vaccine designed to stimulate CD4+ helper T cell responses against telomerase (TERT), a protein highly expressed in glioblastoma (GBM). Temozolomide (TMZ), a standard chemotherapeutic agent in the treatment of GBM, has been shown to induce CD4+ T-cell lymphopenia, which could potentially impair the immune response to the vaccine. We conducted a multicenter, 2-cohort, phase IIa study to evaluate the immunogenicity and efficacy of UCPVax, with or without TMZ, as adjuvant therapy in patients with newly diagnosed GBM following chemoradiation. **Methods:** Patients with non-mutated IDH1 glioblastoma (GBM) were enrolled one month after completing concurrent radiotherapy and temozolomide (TMZ). Cohort A received the vaccine alone, without additional TMZ, while Cohort B was treated with both the vaccine and six monthly cycles of TMZ. The primary endpoint was the induction of TERT-specific CD4+ T cell responses, assessed ex vivo using the INF-γ ELISpot assay. Secondary endpoints included epitope spreading, clinical outcomes, and safety. **Results:** Thirty-one GBM patients with unmethylated MGMT status were included in cohort A, and 30 patients (50% with unmethylated MGMT status) were included in cohort B. The vaccine was well tolerated, with no vaccine-related serious adverse events. Vaccine-expanded TERT-specific CD4+ T cells were detectable *ex vivo* in 25/30 (83%) of patients in cohort A (no additional TMZ) and in 18/26 69% of patients in cohort B (treated with additional TMZ). Epitope spreading was induced in 29 out of 55 evaluable patients (52.7%), corresponding to 15/26 (57.7%) in cohort A and 14/29 (48%) in cohort B. Median overall survival (OS) was significantly improved in patients who developed an epitope spread response compared to those who did not (19.3 vs. 12.8 months, P = 0.03). In the 44 patients with measurable disease at the time of inclusion, the radiological response rate (RR) was 34%, including minor responses. In patients who developed epitope spreading after vaccination (n = 22), the RR was 50%, compared to 18.7% in patients without epitope spreading (P = 0.05). Furthermore, tumor-infiltrating lymphocytes against TERT were detected in 3 vaccinated patients who underwent surgery at recurrence. **Conclusions:** UCPVax demonstrated robust immunogenicity, even when co-administered with TMZ, and was associated with improved overall survival (OS) in GBM patients who developed an epitope spreading response. These findings support further clinical investigation of TERT-derived CD4+ helper vaccine in GBM patients. Clinical trial information: NCT04280848. Research Sponsor: French Eastern Interregional Group of Clinical Research and Innovation (GIRCI-Est - APJ2017); Oligocyte.

2007 Oral Abstract Session

INB-200: Phase 1 study of gene-modified autologous gamma-delta (γδ) t cells in newly diagnosed glioblastoma multiforme (GBM) patients receiving maintenance temozolomide (TMZ).

Mina Lobbous, Lawrence S. Lamb Jr., Kate Rochlin, Thriumaine Pillay, Mariska Anouska ter Haak, Louis B. Nabors; Cleveland Clinic, Cleveland, OH; IN8bio, Inc., New York, NY; IN8bio, New York, NY; University of Alabama at Birmingham, Birmingham, AL; Division of Neuro-oncology, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL

Background: Recent cell therapy and CAR-T initiatives for GBM have shown initial responses but durability has been disappointing. We developed a novel approach to treat newly diagnosed GBM using innate γδ T cells following forced upregulation of tumor stress-associated targets. **Methods:** We leveraged the TMZ-induced activation of the DNA damage response (DDR) pathway to transiently upregulate NKG2D-L targets on GBM. Co-administration of TMZ chemotherapy with γδ T cells engineered for TMZ resistance by insertion of a methylguanine-DNA methyltransferase (MGMT)-expressing lentivector (DeltEx Drug Resistant Immunotherapy – DRI) enables the targeting of residual GBM cells during the standard-of-care Stupp regimen. A total of 23 patients were enrolled, with 13 treated and (62% male; median age 66 (range: 21-74); 92% IDH-WT, 54% MGMT-unmethylated). Cohorts (C) 1, 2 and 3 received 1, 3 or 6 doses (1 x 10^7 DRI cells/dose) into the resection cavity with 150 mg/m^2 of IV TMZ on Day (D) 1 of each Stupp regimen maintenance cycle. **Results:** No Dose limiting toxicities (DLTs) were seen nor were occurrences of cytokine release syndrome (CRS) or neurotoxicity (ICANS). Most common adverse events were related to underlying TMZ and Stupp regimen. As of January 24, 2025, median follow-up is 16.9 months (m). The median PFS for patients is 8.3m for those who received a single dose of INB-200, 9.9m for all patients (a 44% increase over the 6.9m mPFS of the Stupp) and 14.0m for patients who received repeated doses, an 102.4% improvement over Stupp and 69% over single dose patients. A patient with IDH mutant tumor remains progression free for almost 44 months and one with MGMT-unmethylated tumor for 18 months. Biopsy specimens from three patients are available with general immune activation having been demonstrated. **Conclusions:** To date all patients had manageable toxicity with outpatient treatment and a continued encouraging trend in longer PFS from treatment with DRI γδ T cells. Clinical trial information: NCT04165941. Research Sponsor: IN8Bio, Inc.

Subject	Age/ Sex	IDH/ Methylation	Resection	Dose level	TMZ Maint. Cycles Received	Response	PFS (mos)	OS (mos)
001	69/M	IDH-WT, MGMT-unmethylated	Total	1	5	SD	8.3	15.6
003	75/F	IDH-WT, MGMT-methylated	Total	1	6	SD	11.9	17.7
004	21/F	IDH-WT, MGMT-unmethylated	Total	1	3	SD	7.4	9.6
007	75/M	IDH-WT, MGMT-unmethylated	Total	2	2	Un-evaluable	-	5.1
009	32/M	IDH-mutant, MGMT-methylated	Total	2	12	SD		43.7+
011	56/F	IDH-WT, MGMT-methylated	Total	2	6	SD	22.2	28.6
014	73/F	IDH-WT, MGMT-unmethylated	Subtotal	2	6	SD	8.7+	8.7 without progression
015	73/M	IDH-WT, MGMT-methylated	Subtotal	3	5	SD	7.1	11.8
017	74/F	IDH-WT, MGMT-methylated	Subtotal	3	3	SD		21.5+
020	66/M	IDH-WT, MGMT-methylated	Subtotal	3	3	SD		19.6+
021	57/M	IDH-WT, MGMT-unmethylated	Total	3	6	SD		18.1+
022	53/M	IDH-WT, MGMT-unmethylated	Subtotal	3	6	SD	10.0	13.6
023	52/M	IDH-WT, MGMT-unmethylated	Subtotal	3	1		4.2	5.4

Immunological correlates from phase I study of CARv3-TEAM-E in patients with recurrent glioblastoma (GBM): INCIPIENT trial.

Bryan D. Choi, Elizabeth R. Gerstner, William T. Curry, Deshea L. Harris, Maxx King, Md Raihan Chowdhury, Matthew J. Frigault, Marcela Valderrama Maus, Kathleen Gallagher; Massachusetts General Hospital, Boston, MA; Massachusessets General Hospital, Boston, MA; Massachusetts General Hospital, Charlestown, MA

Background: Chimeric Antigen Receptor (CAR) T cells for glioblastoma (GBM) have been limited by the challenge of targeting a single tumor antigen in a heterogeneous disease. To address this barrier, we generated a novel engineered T-cell product (CARv3-TEAM-E) that targets the EGFRvIII antigen while also secreting T-cell-Engaging Antibody Molecules (TEAMs) against wild-type EGFR. **Methods:** The INCIPIENT clinical trial is a first-in-human study of CARv3-TEAM-E in patients with recurrent GBM (NCT05660369). Patients were treated with intraventricular CARv3-TEAM-E T cells (10E6 cells per infusion). A subset of patients were conditioned with lymphodepleting chemotherapy (LDC) consisting of cyclophosphamide and fludarabine. Immune cells were profiled in the cerebrospinal fluid (CSF) and peripheral blood of patients by flow cytometry. **Results:** CAR T cells were detected in the CSF of all patients for an average of 33.6 days (*SD* = 10.33). Granulocytes, NK cells, B cells, and monocytes appeared in the CSF immediately after infusion, decreasing to low levels over the course of several weeks. TEAM-positive T cells persisted in CSF until (median) day 33.6 (*SD* = 10.8) with a range of 21-56 days. CAR T cells were transiently detected in the peripheral blood of 9/10 patients at an average of 14 days (*SD* = 3.5) after infusion. Prior to infusion, CAR T cells were predominantly CD4-positive and remained as such in the CSF over time. Those in the periphery exhibited CD4-to-CD8 polarization. Of patients who received multiple infusions, 3 out of 6 had CAR-positive T cells in the CSF after a second infusion, although their persistence was short-lived and was not detected in the periphery following repeat infusions. LDC increased engraftment of CAR T cells in CSF but not in peripheral blood. Patients with poor CAR persistence demonstrated the development of anti-CARv3-TEAM-E antibodies in the CSF and serum, which increased with reinfusion. **Conclusions:** Following initial infusion, intraventricularly delivered CARv3-TEAM-E T cells were detected in the CSF and peripheral blood in patients with recurrent GBM. Reduced persistence was observed with subsequent infusions. This corresponded with the emergence of anti-CARv3-TEAM-E antibodies in treated patients. Clinical trial information: NCT05660369. Research Sponsor: Gateway for Cancer Research; National Cancer Institute/U.S. National Institutes of Health; 1R01CA294071-01A1.

2009 Clinical Science Symposium

Multicenter trial of microbubble-enhanced transcranial focused ultrasound (MB-FUS) with monthly adjuvant temozolomide for patients with high-grade gliomas.

Graeme Woodworth, Pavlos Anastasiadis, Chetan Bettegowda, Jeremi Chabros, Chixiang Chen, Ahmad Ozair, Jakob Gerstl, Chris Douville, Rania Mekary, Timothy Richard Smith, Ying Meng, Ali Rezai, Arjun Sahgal, James R. Perry, Jason Sheehan, Dheeraj Gandhi, Nathan J. McDannold, Alexandra J. Golby, Nir Lipsman, BT008 Trial Investigators; University of Maryland School of Medicine, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Harvard T. H. Chan School of Public Health, Boston, MA; Brigham and Women's Hospital, Boston, MA; Johns Hopkins University, Baltimore, MD; Massachusetts College of Pharmacy and Health Sciences, Boston, MA; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; West Virginia University, Morgantown, WV; Sunnybrook Health Sciences Center, Toronto, ON, Canada; University of Virginia, Charlottesville, VA

Background: High-grade gliomas (HGGs) have few effective therapies targeting tumor cell recurrence, which remain shielded by blood-brain barrier (BBB). MB-FUS allows for controlled BBB opening (BBBO) enabling localized drug delivery and increased tumor biomarker release into systemic circulation. **Methods:** MR-guided MB-FUS with real-time feedback was evaluated for HGG patients in multicenter phase 1/2 trial (BT008: NCT03551249, NCT03616860) for adverse events (AEs) and feasibility [primary endpoints], efficacy [secondary endpoint], and plasma cell-free DNA (cfDNA) post-procedure [exploratory]. After resection and 6 weeks of chemoradiation, peri-resectional infiltrative regions were targeted with MB-FUS during monthly adjuvant temozolomide cycles (MB-FUS+TMZ). For efficacy, overall survival (OS) and progression-free survival (PFS) were compared with an external cohort, created using restriction and coarsened exact matching (CEM). **Results:** Trial cohort had 34 patients enrolled and evaluated from 5 sites in North America. No serious procedure-related AEs were seen, with the most common AEs being mild, self-resolving. BBBO was seen in 100% of treatments, covering 82% targeted volumes with ≤3mm accuracy. Trial cohort had longer mPFS (univariate 13.5 vs. 9.6 months, multivariate HR 0.62, 95%CI: 0.39-0.99, p=0.048) and mOS (36.4 vs. 19.1 months, multivariate HR 0.50, 95%CI: 0.26-0.95, p=0.036), with treatment effect robust in sensitivity analyses. Disease state correlated closely with longitudinal plasma cfDNA changes. **Conclusions:** MB-FUS+TMZ is a safe and feasible therapeutic approach for HGG, potentially improving survival and enabling longitudinal non-invasive monitoring. Clinical trial information: NCT03551249, NCT03616860. Research Sponsor: Insightec Inc; U.S. National Institutes of Health; R21NS113016.

Variables	Trial cohort	Matched Cohort †	
Patients (N)	34	158	
Baseline characteristics used in CEM			SMD†
Age, years, mean±SD	51.5 ±13.0	51.6 ±13.0	0.0
MGMT, Unmethylated, N (%)	16 (47.1%)	74 (47.1%)	0.0
IDH, Wild type, N (%)	29 (85.3%)	135 (85.3%)	0.0
Characteristics tackled through restriction			SMD†
Received resection & 6 weeks of chemoradiotherapy	34 (100%)	158 (100%)	0.0
Non-Hispanic, N (%)	34 (100%)	158 (100%)	0.0
Complete resection, N (%)	34 (100%)	158 (100%)	0.0
KPS ≥70 – N (%)	34 (100%)	158 (100%)	0.0
Other characteristics not used in CEM			wSMD†
Sex, male – N (%)	16 (47.1%)	101 (63.9%)	0.34
Race, White – N (%)	28 (82.4%)	137 (86.7%)	0.13
Preoperative tumor size, median cm^3 (IQR)	19.8 (6.9, 42.9)	47.0 [30.0, 53.0)	0.61
Clinical Outcomes			P
Unadjusted mOS, months (95%CI)	36.4 (21.1, NR)	19.1 (16.2, 22.8)	<0.001
OS HR for treatment adjusted for tumor size, IDH, & MGMT (95%CI)	0.50 (0.26, 0.95)		0.036
Unadjusted mPFS, months (95% CI)	13.5 (9.9, 25.4)	9.6 (7.8, 11.9)	0.032
PFS HR for treatment adjusted for tumor size, IDH, & MGMT (95%CI)	0.62 (0.39, 0.99)		0.048

SMD, weighted standardized mean difference.
†Estimated using CEM weights.

2010 Clinical Science Symposium

Leveraging stimulated Raman histology-based cellularity for random forest prediction of glioblastoma recurrence.

Sanjeev Herr, Niels Olshausen, Jasleen Kaur, Youssef Sibih, Vardhaan Ambati, Katie Scotford, Thiebaud Picart, Akhil Kondepudi, Anna-Katharina Meißner, Melike Pekmezci, Todd Hollon, Albert H. Kim, Shawn L. Hervey-Jumper; Drexel University College of Medicine, Philadelphia, PA; University of California, San Francisco, San Francisco, CA; University of Michigan, Ann Arbor, MI; Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany; Washington University School of Medicine in St. Louis, St. Louis, MO

Background: Glioblastoma is a universally fatal diagnosis with extent of resection being one of the most significant predictors of overall and progression-free survival. Most patients eventually experience recurrence, with sixty percent recurring along the resection cavity. Recent work leveraging Stimulated Raman histology (SRH) and artificial intelligence (AI) has approximated glioma cellularity within the infiltrative margins. It remains unknown if these estimates of glioma burden at the infiltrative margins influence glioblastoma recurrence. This study aims to evaluate a predictive model of focal recurrence in patients with glioblastoma using SRH and AI-generated cellularity scores from tissue samples taken at the resection cavity margins. **Methods:** A multi-center, retrospective cohort study was conducted on patients diagnosed with glioblastoma who underwent resection followed by spatial annotated tissues acquired from the resection cavity margins. Tissues were analyzed using SRH optical imaging, and histopathology analysis was performed using confocal microscopy. Tissue cellularity was measured histologically and by optical imaging. **Results:** Over 400 patients and 2,200 specimens were analyzed, of which a nested subset of 60 patients were selected based on selection criteria. Using preoperative and postoperative imaging, margin samples were determined to be in an area of recurrence (n=58) or nonrecurrence (n=220). Cellularity was significantly higher in the recurrent margin sample group when compared to the nonrecurrent group ($p = 0.026$), which was further confirmed by a pathologist-determined cellularity score (0-3) that demonstrated similar findings ($p = 0.026$). Results were validated across three medical centers. Six classifiers were then trained for recurrence prediction. Using nineteen of the most predictive variables, random forests (RF) performed best with an AUC of 0.848. RF screening for the minimum practical number of variables demonstrated an AUC of 0.805 using only FastGlioma, age and extent of resection as variables. **Conclusions:** AI-generated cellularity scores have the potential to predict focal recurrence of glioblastoma, allowing for more tailored approaches to surgical resection and radiotherapy to increase progression-free survival. Research Sponsor: None.

2011 Clinical Science Symposium

Stereotactic radiation versus hippocampal avoidance whole brain radiation in patients with 5-20 brain metastases: A multicenter, phase 3 randomized trial.

Ayal Aizer, Shyam Kumar Tanguturi, Grant Benham, Paul D. Brown, Daniel Cagney, Paul J. Catalano, Fallon Chipidza, Daphne A. Haas-Kogan, Jaroslaw T. Hepel, Monica Krishnan, Marciana Johnson, Nayan Lamba, Jennifer Nosker, Michael Parsons, Luke Peng, Ivy Ricca, Diana D. Shi, Kee-Young Shin, Patrick Y. Wen, Rifaquat Rahman; Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA; Department of Radiation Oncology, Mayo Clinic, Rochester, MN; Mater Private Hospital, Dublin, Ireland; Dana-Farber Cancer Institute, Boston, MA; DFCI/BWH Cancer Center/Milford Regional Medical Center/South Shore Health, Boston, MA; Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA; Rhode Island Hospital/Brown University , Boston, MA; Brigham and Women's Hospital/Dana-Farber Cancer Institute/Milford Regional Medical Center/South Shore Health, Boston, MA; Brigham and Women's Hospital, Boston, MA; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA; Department of Radiation Oncology, Brigham and Women's Hospital/ Dana-Farber Cancer Institute, Boston, MA; Division of Neuro-Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: Radiation therapy forms the mainstay of management for patients with brain metastases. Published randomized trials have found improved quality of life with stereotactic radiation (SRS/SRT) over whole brain radiation (WBRT) in patients with ≤ 4 brain metastases; comparative trials in patients with >4 brain metastases are lacking. In addition, prior randomized trials have demonstrated the superiority of hippocampal avoidance WBRT (HA-WBRT) over traditional WBRT, but no study has compared SRS/SRT to HA-WBRT. Accordingly, we conducted a multicenter, phase 3 randomized trial comparing SRS/SRT to HA-WBRT in patients with 5-20 brain metastases. **Methods:** Eligible patients were age 18-80 with 5-20 brain metastases secondary to a solid primary other than small cell lung cancer, were naïve to prior brain-directed radiation, and lacked leptomeningeal disease. The primary endpoint was the average of patient-reported symptom severity and interference over the first six months post-baseline relative to baseline, using the MD Anderson Symptom Inventory–Brain Tumor (MDASI-BT) module, a validated instrument assessing 22 symptoms and 6 interference measures integral to quality of life, each scored 0-10 with higher scores indicating greater symptomatology/interference in function. The target effect size was a symptom severity of 0.70, corresponding to 50% of the observed difference between patients with a good (90-100) versus poor (≤80) Karnofsky performance status; with 80% power and a two-sided alpha of 0.05, 196 patients were required. **Results:** Between 4/2017-5/2024, 196 patients enrolled, 98 in each arm. The median number of brain metastases was 14 (IQR 11-18); 25% of patients underwent prior neurosurgical resection. Baseline mean MDASI-BT symptom severity scores were 2.2 (SRS/SRT arm) and 1.9 (HA-WBRT arm), p=0.20; respective interference scores were 3.5 and 3.2 (p=0.40). The average of weighted post-baseline severity and interference scores relative to baseline indicated lower symptomatology/inference in the SRS/SRT arm, meeting the primary endpoint of the study (difference between SRS/SRT and HA-WBRT: -1.06, $p<0.001$). Averaged post-baseline symptom severity scores minus baseline were -0.03 and 0.59 in the SRS/SRT and HA-WBRT arms, respectively (difference -0.62, with lower symptom severity in the SRS/SRT arm, $p<0.001$); respective interference estimates were -0.62 and 0.89 (difference -1.50, with lower interference in the SRS/SRT arm, $p<0.001$). Median survival was 8.3 and 8.5 months in the SRS/SRT and HA-WBRT arms, respectively (p=0.30). **Conclusions:** This phase 3 randomized trial indicates that patients with 5-20 brain metastases experience fewer symptoms and less interference in function after SRS/SRT as opposed to HA-WBRT, without compromise of survival, supporting SRS/SRT as the standard of care in this population. Clinical trial information: NCT03075072. Research Sponsor: Varian.

2012 Rapid Oral Abstract Session

Utidelone in combination with etoposide and bevacizumab in HER2-negative breast cancer patients with brain metastasis: A prospective, single-arm, phase II trial.

Yehui Shi, Peng Wang, Yuehong Zhu, Yu Zheng, Chunfang Hao, Yongsheng Jia, Xu Wang, Shufen Li, Zhengjun Yang, Bin Zhang, Weipeng Zhao, Ning Lu; Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; Tianjin Medical University Cancer Institute & Hospital / Tianjin Cancer Hospital Airport Hospital, Tianjin, China; Tianjin Medical University Cancer Institute & Hospital, Tianjin, Tianjin, China

Background: For advanced HER2 negative breast cancer patients with brain metastasis, systematic therapy has failed to yield satisfied efficacy, although bevacizumab and etoposide have shown some effectiveness as mono- or combination therapy. Novel microtubule inhibitor utidelone demonstrated good efficacy in advanced breast cancer patients in several clinical trials, and was also suggested a capability of blood-brain barrier penetration. Therefore, utidelone in combination with bevacizumab and etoposide would be a promising regimen for HER2 negative breast cancer patients with brain metastasis. **Methods:** Breast cancer patients with brain metastasis were enrolled and Simon's two-stage optimal trial design was used for this trial. If more than 3 out of 13 patients showed central nervous system (CNS) response, 30 more patients would be further enrolled. The acceptable ORR was set to be 40% for the trial. Utidelone (30mg/m^2/day, iv, d1-5), and etoposide (100mg/m^2, iv, d1-3) were concurrently administered with bevacizumab (10mg/kg iv, d1) every 21 days for 6 cycles, followed by maintenance treatment with utidelone and bevacizumab until disease progression or unacceptable toxicity. The primary endpoint is CNS-ORR. Secondary endpoints include CNS-clinical benefit rate (CNS-CBR), CNS-PFS, PFS, and safety. **Results:** 34 female HER2 negative patients were enrolled, including 11 triple negative breast cancer patients and 23 patients of luminal subtype, with a median age of 52 years (range 34-74) and a median treatment lines of three. Five patients had prior brain radiotherapy and 2 patients were previously treated with brain surgery. As of December 2, 2024, the median follow up duration was 11.5 months. The CNS-ORR was 67.6% (23/34), and the CNS-CBR was 88.2% (30/34). The median PFS was 6 months (95% confidence interval [CI], 4.265-7.735). The median CNS-PFS was 15 months (95% CI, 6.760-23.240), with supportive treatment for some of the patients after extracranial progression which included etoposide re-administration, or abraxane, endocrine therapy, radiotherapy and immunotherapy. The major AE was peripheral neuropathy with 8.8% (3/34) of Grade 3, primarily classified as sensory. Most of the treatment-related AEs were grade 1 or 2 and were considered manageable and reversible. **Conclusions:** Utidelone in combination with etoposide and bevacizumab has shown promising anti-tumor activity and manageable toxicity in HER2 negative breast cancer patients with brain metastasis, and a randomized control trial is warrantied. Clinical trial information: NCT05781633. Research Sponsor: Tianjin Science and Technology Funding; 18ZXXYSY00070; Tianjin Municipal Education Commission Funding; 2016YD03; Beijing Biostar Pharmaceuticals; "358"Project, TJMUCH; 358-2023-06.

2013 Rapid Oral Abstract Session

Phase 1 study of HMPL-306, an inhibitor of mutant IDH1/IDH2 (mIDH1/2), in western patients (pts) with advanced mIDH solid tumor, including glioma.

Jordi Rodon Ahnert, Juan Manuel Sepulveda Sanchez, Olatunji B. Alese, Georgia Anguera, Chandrikha Chandrasekharan, Sant P. Chawla, Melissa Amber Burgess, Maen Abdelrahim, John L. Villano, Bo Zhang, Yukang Wang, Xiuya Yu, Zeyu Zhong, Xian Luo, Songhua Fan, Michael Shi, Weiguo Su, Maria Vieito Villar; The University of Texas MD Anderson Cancer Center, Houston, TX; Hospital Universitario 12 Octubre, Madrid, Spain; Winship Cancer Institute of Emory University, Atlanta, GA; Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Uiversity of Iowa Heatlh Care Medical Cancer, Iowa City, IA; Sarcoma Oncology Research Center, Santa Monica, CA; University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; Houston Methodist Cancer Center, Houston, TX; University of Kentucky Markey Cancer Center, Lexington, KY; HUTCHMED Limited, Shanghai, China; Vall d'Hebron Unversity Hospital, Barcelona, Spain

Background: Isocitrate dehydrogenase (IDH) 1 or IDH2 mutations or co-mutations have been associated with various tumors, including glioma. HMPL-306 ('306) is a novel, small-molecule, orally available, highly selective, and potent dual inhibitor of both mIDH1 and mIDH2. This is a phase 1 study of '306 in pts with locally advanced or metastatic solid tumors with mIDH. Here, we report the results of the dose escalation stage. **Methods:** Pts with locally advanced or metastatic solid tumors with any mIDH were enrolled to receive '306 once daily (QD) for 28-day cycles. The mTPI-2 design was used for dose escalation, having explored in 8 successive cohorts (50-400 mg). The study aims to determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), evaluate safety, tolerability, preliminary efficacy and pharmacokinetics/ pharmacodynamics (PK/PD). **Results:** As of Aug 9, 2024, 42 pts were administered '306 across 8 doses (n = 3, 3, 5, 12, 6, 4, 4, 5 in 50, 100, 150, 200, 250, 300, 350, 400 mg QD cohorts, respectively), with 17 (40.5%) lower-grade glioma (LGG, grade 2 and grade 3 glioma) pts, 3 (7.1%) grade 4 glioma pts and 22 (52.4%) non glioma pts. The median age was 55 years, and 25 (59.5%) pts were male. During the dose escalation from 50 mg to 400 mg QD cohort, 1 pt given 250 mg QD experienced a dose-limiting toxicity (DLT) of grade 3 lipase increased. MTD was not reached. 12 (28.6%) pts reported grade ≥3 adverse events (AEs), which reported in ≥ 2 pts was abdominal pain. Efficacy signals were observed especially in LGG pts, in the efficacy evaluated set (N = 14), objective response rate (ORR) was 7.1%, disease control rate was 100%; in the safety analysis set (N = 17), median progression-free survival (PFS) was 20.5 months (95% confidence interval [CI]; 5.5-not estimable). One grade 2 glioma pt with multiple previous treatment on the 200 mg QD achieved minor response lasting 16.8 months. The ORR of grade 4 glioma pts and non glioma pts were not reached, the disease control rate were 33.3% and 25%, respectively. Drug exposures were dose-proportional from 50 mg to 400 mg. Steady-state with ~5-fold accumulation was reached after ~28 days of repeated daily dosing. In non-glioma pts, 2-HG inhibition plateaued after ~28 days, increasing with dose, reaching ~90% at ≥150 mg at C2D1. **Conclusions:** '306 was well-tolerated in pts with mIDH1/2 solid tumors, showing target inhibition and durable responses in LGG. Clinical trial information: NCT04762602. Research Sponsor: HUTCHMED Limited.

2014 Rapid Oral Abstract Session

Vaccination by homologous antigenic loading with DOC1021 as adjuvant therapy for glioblastoma: Phase I clinical trial results.

Joseph Georges, Christina Marie Clay, Sabina Amin, Joseph Ifrach, Briana A. Burns, Akshar Trivedi, Wei Liu, Madhuri Namekar, Keenan Ernste, Vinod Ravi, Sigmund H. Hsu, Jay-Jiguang Zhu, Rodrick C. Zvavanjanja, Yoshua Esquenazi, Nitin Tandon, Alan Turtz, Laura K. Aguilar, Vanaja Konduri, William Karl Decker; Banner University Medical Center, Phoenix, AZ; The University of Texas MD Anderson Cancer Center at Cooper University, Camden, NJ; Cooper University Health, Camden, NJ; Cooper Neurological Institute, Camden, NJ; Baylor College of Medicine, Houston, TX; Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; UTHealth Neurosciences, Houston, TX; The University of Texas Health Science Center at Houston, McGovern Medical School, Houston, TX; The University of Texas Health Science Center at Houston, Houston, TX; Department of Neurosurgery, McGovern Medical School at UT Health Houston, Houston, TX; Diakonos Oncology Corporation, Houston, TX

Background: Glioblastoma is a devastating tumor for which median overall survival (mOS) remains 14-18 months despite aggressive standard of care (SOC) treatment. Clinical studies of dendritic cell (DC) vaccination for GBM have shown promise but have been largely inconclusive. DC homologous antigenic loading leverages p38MAPK and mTORC1 signaling cascades to initiate cDC1-like skewing of monocyte-derived DC, leading to potent downstream induction of tissue-homing cytolytic memory effector T cells. Here we report results of a completed phase I study for glioblastoma (IDH-wt). **Methods:** This clinical trial evaluated autologous DC vaccine DOC1021 prepared from mobilized peripheral blood mononuclear cells (PBMC), loaded with autologous tumor lysate and amplified tumor mRNA, and administered bilaterally near deep cervical lymph nodes. Three courses of vaccine every 2 weeks plus weekly peg-IFN were administered after completion of chemoradiation. Four dose levels from 3.5 x 10^6 to 3.6 x 10^7 total vaccine cells were tested. Patients with subtotal resection or tumor progression prior to vaccination were not excluded. **Results:** Sixteen newly diagnosed patients completed treatment, median age 61 years (range 47-73), 94% MGMT unmethylated, 25% subtotal resected. OS at 12-months was 88% compared to expected ~60% for SOC and 5 patients are still alive at 19-30 months of follow-up. Two recurrent glioblastoma patients were also treated and survived for 10-12 months. Most common AEs were mild flu-like symptoms and injection-site reactions, and there were no dose limiting toxicities. Analysis of post-vaccination PBMC indicated expansion of $CD4^+$ (13/13 patients) and $CD8^+$ (11/13) central memory T-cell compartments ($p < 0.00006$ and $p < 0.003$, respectively) as well as expansion of $CD8^+CD127^+$ MPECs (12/13; $p < 0.002$). Among 3/3 patients analyzed by spatial transcriptomics, intense $CD25^+$ foci correlating with co-expression of effector memory T-cell and migratory microglial markers were observed in post-vaccination but not pre-vaccination samples. For 8 patients who were observed rather than re-operated for worsening T1-weighted signal on MRI in the 23 weeks after vaccination, signal gradually resolved and GBM-specific mOS is not yet reached compared to 15.1 months for 8 patients who received reoperation despite comparable clinical characteristics, suggesting an immune-reactive microenvironment manifesting as pseudo-progression. **Conclusions:** DOC1021 combined with SOC is safe and potentially efficacious in this challenging population that included subtotal resections, pre-treatment progression and 15/16 MGMT unmethylated. A randomized phase II trial is being launched including criteria to avoid early re-operation for enhancing T1-weighted signal that may be pseudo-progression. Clinical trial information: NCT04552886. Research Sponsor: Cancer Cures 4 Kids; N/A; Diakonos Oncology; N/A.

2015 Rapid Oral Abstract Session

Results from phase 1 study of mycophenolate mofetil with chemoradiation in newly diagnosed glioblastoma to target de-novo purine metabolism to overcome treatment resistance.

Yoshie Umemura, Nathan Clarke, Wajd Al-Holou, Ameer L. Elaimy, Andrew Scott, Denise Leung, Michelle Miran Kim, Sean Ferris, Jennifer Thomas, Jason Heth, Matthew J. Schipper, Krithika Suresh, Theodore Lawrence, Daniel Richard Wahl; Ivy Brain Tumor Center at Barrow Neurological Institute, Phoenix, AZ; University of Michigan, Ann Arbor, MI

Background: Mycophenolate mofetil (MMF) inhibits IMPDH and disrupts *de novo* purine synthesis which is preferred by glioblastoma (GBM) whilst normal brain prefers resource efficient salvage pathway. A phase 0 study demonstrated the active drug metabolite reaching both enhancing and non-enhancing GBM tissues in humans, and effective target engagement, noted by reduced GTP/IMP ratio. This phase 1 trial assessed the tolerability of MMF with chemoradiation in newly diagnosed GBM patients (NCT04477200). **Methods:** Thirty adult patients with newly diagnosed GBM were given MMF, dosed BID, 1 week prior to and concurrently with standard of care (SOC) radiotherapy (RT) of 60 Gy in 30 fractions with concomitant temozolomide (TMZ) 75mg/m2, followed by MMF 1 day before + 5 days of each SOC TMZ 150-200mg/m2 x 5/28-day cycle up 12 cycles. Optune was optional. Primary endpoint was dose limiting toxicity (DLT) and maximally tolerated dose (MTD) of MMF combined with SOC GBM chemoradiation. Time-to-event continual reassessment method was used to determine MMF dosing, with MTD defined as estimated rate of dose-limiting toxicity (DLT) closest to but not exceeding 30%. DLT periods were during and up to 4 weeks after concurrent chemoradiation (DLT1), and first two 28-day cycles of MMF with temozolomide (DLT2). Transient grade 4 neutropenia x $<$ 7 days and asymptomatic grade 4 lymphopenia were excluded from DLT. Kaplan Meier method was used to estimate overall survival (OS). **Results:** The median age was 57 (range 20-75). The majority had KPS $>$ 80 (67%) at baseline, and unmethylated MGMT (70%). During DLT1 period, 5 DLT1 was noted out of 16 subjects on 2000mg BID (grade 3 hemiparesis, cognitive disturbance, fatigue, and grade 4 thrombocytopenia x2), and none at 1500mg (N = 10) and 1000mg (N = 4). During DLT2 period, 1/6 subjects at 1500mg BID experienced DLT of grade 3 fatigue, and none at 1000mg (N = 4) and 2000mg (N = 16). All DLTs were reversible. Four patients did not receive MMF during DLT2 period due to withdrawal from the study (N = 2) and progression of disease (N = 2). The most common treatment related adverse events were fatigue (77%), leukopenia (67%), and nausea (53%). Of the dose levels studied, the MTD for DLT1 and DLT2 were both 2000mg BID (posterior probability of DLT1: 18.5%, posterior probability of DLT2: 7.5%), however, due to frequent fatigue and nausea, DLT1 period starting dose was lowered to 1500mg BID for the last 7 subjects. The recommended phase 2 dose is 1500mg BID combined with concurrent RT+TMZ followed by TMZ. Median OS was 16.8 months with 25.5 months median follow up duration (NR & 25.5 months in MGMT methylated, 14.2 & 24.9 months in MGMT unmethylated respectively). **Conclusions:** MMF can penetrate enhancing and non-enhancing GBM with evidence of successful inhibition of *de-novo* purine synthesis in humans, and is reasonably well tolerated when combined with chemoradiation newly diagnosed GBM patients. These promising results have led to a planned phase 2/3 randomized controlled trial through Alliance for Clinical Trials in Oncology. Clinical trial information: NCT04477200. Research Sponsor: Gateway for Cancer Research.

2016 Rapid Oral Abstract Session

Use of lucicebtide (ST101) in glioblastoma patients by antagonism of C/EBPβ-dependent mesenchymal cell transition and immunosuppressive M2 macrophage polarization.

Fabio Massaiti Iwamoto, Osama Al Dalahmah, Jim Rotolo, Franco Abbate, Clara Levrero, Joyce Gakuria, Robin Arthur Buerki, Abi Vainstein Haras; Columbia University Irving Medical Center, New York, NY; Sapience Therapeutics, Inc., Tarrytown, NY; Columbia University Medical Center, New York, NY; Northwestern Medicine Cancer Center, Warrenville, IL

Background: C/EBPβ is a master regulator of the mesenchymal phenotype in GBM and has an essential role in the maintenance of immunosuppressive M2 tumor-associated macrophages (TAMs). Lucicebtide is a first-in-class antagonist of C/EBPβ that has shown direct anti-tumor activity in GBM as well as the ability to reprogram TAMs in the TME toward immunostimulatory M1 macrophages. In a recent recurrent GBM (rGBM) P2 study, lucicebtide was well-tolerated and resulted in disease control in 9/30 patients, including two PRs lasting > 1 year. With strong rationale for targeting C/EBPβ in GBM, additional cohorts we explored in a window-of-opportunity (WoO) study (NCT04478279). **Methods:** The WoO study enrolled 2 cohorts; 9 pts with rGBM that received 2-4 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide after surgery to progression and 9 ndGBM pts that received 2-3 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide + chemoradiation after surgery until progression. Endpoints include efficacy parameters of PFS and OS, safety as a single agent and in combination with chemoradiation, and pharmacodynamic analyses including spatial transcriptomics and TME characterization. **Results:** Lucicebtide was well-tolerated as a single agent and in combination with chemoradiation. Tissue analysis indicates penetration past the BBB and tumor uptake, as well as C/EBPβ target engagement. Lucicebtide + chemoradiation in ndGBM extended PFS beyond historic benchmarks, with the majority of patients remaining on study without progression (7-22+ months). As of January 25, 2025, mOS could not be evaluated, with 8/9 patients alive. In rGBM, lucicebtide improved mPFS to 3.4 months and mOS to at least 11.8 months, exceeding historical data with chemotherapy (historic mPFS ~ 2 months and mOS 5.6-9.8 months). Pathologic evidence of treatment effect, i.e. geographic necrosis, was observed in 5/6 pts including otherwise treatment naïve ndGBM patients. Spatial transcriptomics analysis revealed a significant reduction in the mesenchymal gene signature following lucicebtide, consistent with on-target antagonism of C/EBPβ. Further, immune activation in the TME, as indicated by increased M1/M2 ratio and CD8+ T cell infiltration, was associated with disease control. **Conclusions:** Lucicebtide is well-tolerated as monotherapy and in combination with SoC. Improvements in PFS and OS in GBM patients following lucicebtide exposure demonstrated penetration across the BBB and target engagement, resulting in on-target pharmacodynamic activity including a dramatic reduction in mesenchymal gene signature in tumor cells and a remodeling towards a more permissive immune TME. These data provide the mechanistic rationale for continued clinical evaluation of lucicebtide as a novel approach for patients with GBM. Clinical trial information: NCT04478279. Research Sponsor: None.

2017 Rapid Oral Abstract Session

Safety and tolerability of intraventricular CARv3-TEAM-E T cells following lymphodepleting chemotherapy in recurrent glioblastoma: INCIPIENT trial.

Elizabeth R. Gerstner, William T. Curry, Deborah Anne Forst, Alona Muzikansky, Estelle Emmanuel-Alejandro, Gabrielle Furman, Daniella Cook, Danielle Bernier, Lu Huang, Jeremy Ford, Karen Buch, Sarah Nikiforow, Kathleen Gallagher, Matthew J. Frigault, Marcela Valderrama Maus, Bryan D. Choi; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital, Charlestown, MA; Dana-Farber Cancer Institute, Boston, MA

Background: CAR T therapy is a novel, promising approach in glioblastoma (GBM) but tumor heterogeneity can limit efficacy when a single antigen is targeted. We designed a second-generation CAR T molecule that targets epidermal growth factor receptor vIII (EGFRvIII) and also secretes a T-cell–engaging antibody molecule (TEAM) against wild-type EGFR. **Methods:** In a phase 1, first-in-human study (INCIPIENT, NCT05660369), patients with recurrent GBM with EGFRvIII mutation and/or EGFR amplification were eligible to receive up to 6 intraventricular doses of 10x106 CAR T cells via Ommaya catheter after lymphodepleting chemotherapy (LDC) with fludarabine and cyclophosphamide. Primary objective was safety and tolerability and secondary objective was preliminary tumor response determined by iRANO criteria. **Results:** CAR T manufacturing was successful for all patients. Seven patients (5 male) received at least 1 intraventricular infusion. Two patients received 2 infusions (1 for progressive disease (PD) and 1 without PD). One patient received 3 infusions after experiencing initial PD. No DLTs occurred. All patients experienced cytokine release syndrome (CRS) grade 1 lasting 0-9 days with only 1 patient experiencing CRS grade 2 for 1 day. One patient experienced ICANS grade 1 that lasted 2 days. All patients experienced tumor inflammation-associated neurotoxicity grade 1 with a duration of 2-9 days. Adverse events (grade 3-4) at least possibly related to CAR T were febrile neutropenia (N = 1) and neutrophil count decrease (N = 1). Toxicity was managed with supportive care without need for ICU monitoring and 3 patients received at least 1 dose of anakinra (max duration = 4 days, median = 1 day). Best response was stable disease (SD) in 5 patients with 1 patient achieving SD for 6 months after a single infusion and another experiencing a 33% decrease in tumor diameter after 2 infusions. All patients are alive 3-8 months after first infusion. From the preceding safety run-in arm of the study (without LDC), one patient survived 12 months and another is still alive $>$ 20 months after infusion. **Conclusions:** Intraventricular CARv3-TEAM-E infusions were well tolerated, even with multiple doses, and no DLTs were noted. Toxicity was manageable in all patients with supportive care and anakinra was administered to 3 patients. Steroids were not required to manage toxicity. A subset of patients experienced SD for several months. Clinical trial information: NCT05660369. Research Sponsor: Gateway for Cancer Research; National Gene Vector Biorepository at Indiana University, which is funded under National Cancer Institute contract HSN261201500003I Task Order No. HHSN26100077; Philanthropic support to the Cellular Therapy Program at MGH.

2018 Rapid Oral Abstract Session

A phase 1 study of B7H3 CAR-T cells administered intracranially in recurrent glioblastoma.

Gordon Li, Brian R. Stocksdale, Kun-Wei Song, Jasia Mahdi, Kelly Tanner, Sophie Bertrand, Michael Iv, Zachary Threlkeld, Sneha Ramakrishna, Bita Sahaf, Emily Egeler, Vivek Charu, Ramya Tunuguntla, Kate Therkelsen, Seema Nagpal, Michael Lim, Michelle Monje, Brian Scott, Crystal Mackall, Reena Parada Thomas; Stanford University, Stanford, CA; Department of Radiology, Stanford University School of Medicine, Stanford, CA; Quantitative Science Unit, Department of Medicine, Stanford University School of Medicine, Stanford, CA

Background: Glioblastoma (GBM) is an aggressive malignancy with median survival of approximately 2 years from initial diagnosis and 9 months after first progression. Effective treatments in the recurrent setting following upfront chemoradiation and adjuvant temozolomide are limited. The transmembrane glycoprotein B7H3 is over-expressed in GBM and chimeric antigen receptor T cells targeting B7H3 (B7H3-CART) have shown activity in several preclinical cancer models. Intracranial delivery of B7H3-CART may optimize targeting the immune response to the tumor microenvironment while limiting systemic toxicity. **Methods:** We conducted a single-arm phase 1 study in patients with recurrent GBM undergoing repeat resection. B7H3-CART was administered via intratumoral and intraventricular Ommaya reservoirs monthly for a planned 6 months or until confirmed disease progression. When possible per investigator discretion, the dose was divided evenly between the two reservoirs. The primary endpoints were safety and manufacturing feasibility, with secondary endpoints focused on preliminary efficacy. Dose escalation was planned according to a standard 3+3 design (dose level 1: $10x10^6$ cells; level 4 (max): $100x10^6$). Adverse events within 28 days of first dose and at least possibly related to B7H3-CART were considered dose-limiting toxicities (DLTs) if meeting additional criteria: any grade 5 toxicity, grade 4 cytokine release syndrome, neutropenia, or thrombocytopenia lasting $>$ 14 days, or any non-hematologic grade 3 toxicity lasting $>$ 72 hours. Neurotoxicity was considered a DLT if grade 4 for $>$ 96 hours or new-onset grade 3 for $>$ 28 days. Serial CSF and serum samples were collected for translational studies to determine immune cell kinetics and the mechanisms of activity and resistance. **Results:** Eleven patients were enrolled, underwent apheresis, and had B7H3-CART successfully manufactured. Nine received at least one dose of B7H3-CART and were evaluable in the dose escalation cohort. One patient in dose level 2 ($25x10^6$ cells) experienced a DLT (grade 3 hypertension). No additional DLTs were observed in this dose level after expansion to 6 patients, and the recommended phase 2 dose was established at $25x10^6$ cells. Toxicity otherwise has been primarily related to tumor inflammation-associated neurotoxicity (TIAN), observed after 29 of 36 infusions (81%), and managed acutely with anakinra and dexamethasone. The median overall survival (mOS) from date of enrollment for patients receiving at least one dose of B7H3-CART is 14.6 months (95% CI: 2.3 - 26.8 months). One patient is currently receiving B7H3-CART and 4 others are being clinically followed up to 22 months from enrollment. **Conclusions:** Intracranial administration of B7H3-CART in recurrent GBM is technically feasible and safe. TIAN was common but manageable and reversible with immunomodulators. Correlative analyses on surgical tissue, CSF, and serum are ongoing. Clinical trial information: NCT05474378. Research Sponsor: California Institute for Regenerative Medicine; CLIN2-15094.

2019 Rapid Oral Abstract Session

Tirabrutinib for the treatment of relapsed or refractory primary central nervous system lymphoma: Efficacy and safety from the phase II PROSPECT study.

Lakshmi Nayak, Christian Grommes, Avyakta Kallam, David M. Peereboom, Prakash Ambady, Joe S. Mendez, Dawit Gebremichael Aregawi, Ashley Love Sumrall, Antonio Marcilio Padula Omuro, Fabio Iwamoto, Jorg Dietrich, Yoshie Umemura, Reinhold Munker, Ugonma Nnenna Chukwueke, Lauren Schaff, Sergio Prados, Akira Takazawa, Arata Aoi, Tracy Batchelor; Dana-Farber Cancer Institute, Boston, MA; Department of Neuro-oncology, Memorial Sloan Kettering Cancer Center, New York, NY; City of Hope Cancer Center, Duarte, CA; Cleveland Clinic Brain Tumor and Neuro-Oncology Center, Cleveland, OH; Providence Brain and Spine Institute, Portland, OR; University of Utah and Huntsman Cancer Institute, Salt Lake City, UT; Penn State Cancer Institute, Hershey, PA; Atrium Health Levine Cancer Institute, Charlotte, NC; Stanford Cancer Institute, Stanford, CA; Columbia University Irving Medical Center, New York, NY; Massachusetts General Hospital, Boston, MA; Ivy Brain Tumor Center at Barrow Neurological Institute, Phoenix, AZ; Markey Cancer Center, Lexington, KY; Memorial Sloan Kettering Cancer Center, New York, NY; ONO Pharma USA, Inc., Cambridge, MA; Brigham and Women's Hospital, Boston, MA

Background: Primary central nervous system lymphoma (PCNSL) is a rare, aggressive form of non-Hodgkin lymphoma localized to the brain, cerebrospinal fluid, or eyes. For patients with PCNSL, treatment options are limited, standard of care is not well established, and prognosis is poor, particularly in the relapsed or refractory (r/r) setting. Tirabrutinib, a highly potent selective second-generation Bruton's tyrosine kinase inhibitor, is approved in Japan, Taiwan, and South Korea based on a phase I/II study that demonstrated clinical activity in Japanese patients with r/r PCNSL. There are no currently approved drug therapies for PCNSL in the US or Europe. Here we report results from the PROSPECT study (NCT04947319) conducted in the US. **Methods:** In this open-label phase II study, patients with r/r PCNSL received oral tirabrutinib 480 mg as monotherapy once daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by Independent Review Committee. Secondary endpoints included duration of response (DOR), time to response (TTR), best overall response (BOR), and safety. Overall survival (OS) and progression-free survival (PFS) were exploratory endpoints. **Results:** Forty-eight patients were enrolled. Median age was 65.5 y (range, 34-87). With a median follow-up of 11.2 mo as of November 1, 2024 (data cut-off), ORR was 66.7% (n = 32), with a complete response rate (CRR), confirmed (CR) + unconfirmed (CRu), of 43.8% (n = 21) and a partial response rate of 22.9% (n = 11). Median DOR was 9.3 mo (range, 0.0-23.5), and median TTR was 0.95 mo (range, 0.9-3.7). Median OS was not reached (range, 1.0-33.0); median PFS was 6.0 mo (range, 0.0-26.0). Overall incidence of any-grade treatment-emergent adverse events (TEAEs) was 97.9% (n = 47) and grade ≥3 was 56.3% (n = 27). Any-grade treatment-related adverse events (TRAEs) were experienced by 75.0% (n = 36), most frequently anemia (18.8%), fatigue (14.6%), neutrophil count decreased (14.6%), pruritus (14.6%), rash (14.6%), and maculo-papular rash (14.6%). Grade ≥3 TRAEs were experienced by 27.1% (n = 13), most frequently neutrophil count decreased (8.3%) and rash maculo-papular (4.2%). Deaths related to TEAEs occurred in 2 (4.2%) patients: 1 patient died from seizure and pneumonia, and the other from a fall; these grade 5 TEAEs were considered unrelated to study treatment. At data cutoff, 27.1% (n = 13) of patients remain on tirabrutinib treatment. Main reasons for discontinuation were disease progression (54.2%, n = 26) and death (8.3%, n = 4), and 1 (2.1%) patient discontinued due to an AE; deaths included the 2 patients with grade 5 TEAEs. **Conclusions:** With an ORR of 66.7%, CR/CRu rate of 43.8%, median DOR of 9.3 mo, and a manageable safety profile, the PROSPECT trial supports tirabrutinib monotherapy as a potentially effective treatment option for patients with r/r PCNSL. Clinical trial information: NCT04947319. Research Sponsor: ONO Pharmaceutical Co., Ltd.

2020 Rapid Oral Abstract Session

Using single-cell transcriptomics to reveal CD226 upregulation and enhancement of CD19-CAR-T function in the inhibitory CNS microenvironment of refractory CNS lymphoma.

Ulrike Gerdemann, James Kaminski, Alexandre Albanese, Isabella Schichter, Paula Keskula, Ryan A. Fleming, Fran Alvarez-Calderon, Lorenzo Cagnin, Jillian Zavistaski, Austin Moore, Soumya Poddar, Ugonma Nnenna Chukwueke, Lea Steinberg, Michael Mattie, Caroline Falvey, Riemke Bouvier, Alexandra Torres, Caron Jacobson, Lakshmi Nayak, Leslie Kean; Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA; Boston Children's Hospital, Boston, MA; Kite Pharma, Santa Monica, CA; Dana-Farber Cancer Institute, Boston, MA; Kite Pharma, Sana Monica, CA

Background: Refractory CNS lymphoma (CNSL) has a poor prognosis, with 5-year survival of ~30%. We conducted a trial of axi-cel for CNSL, where we achieved a CR of 67%. To deeply interrogate the immune mediators of response, we collected daily paired CSF and peripheral blood (PB) samples post-CAR T infusion. This enabled single-cell transcriptional profiling at an unprecedented depth, identifying key drivers of CD19 CAR T responses and compartment-specific mechanisms of CAR T function. **Methods:** CNSL patients were enrolled in the 'Axi-cel in CNS Lymphoma' Trial, NCT04608487. PB and CSF samples were collected daily from Day 0–14 post-infusion, and 5'10x scRNA /TCR-Seq was performed. This analysis focused on peak CAR T expansion (Day 5-10) and included 1,224,178 T cells from 17 patients. Samples were tested for compartment (CSF vs PB) and response-specific (CR vs PD) transcriptomic differences using a mixed-effects model and GSEA. Functional assays were conducted with CD19 CAR Ts and CD19 CAR+ Jurkat-NFAT reporter cells. **Results:** Transcriptomic analysis identified distinct compartmental differences in CAR Ts, with PB CAR Ts displaying a robust proliferation signature, while CSF CAR Ts were enriched for type I interferon and T-cell dysfunction signatures, including upregulation of inhibitory genes PD-1, TIGIT, TIM3, LAG3. *In vitro*, CSF-exposed CD19-CAR Ts showed increased expression vs culture-media controls for TIGIT (up 40.1%, SEM 7.4), PD-1 (18.9%, SEM 3.8), and Tim3 (60.6%, SEM 7.5). CAR T NFAT expression was reduced from 18.4, 0.1 SEM (media) to 7.2, 0.2 SEM (CSF) relative to unstimulated controls. Differential expression analysis comparing CSF CD8+ CAR Ts from patients achieving CR (n = 11) or PD (n = 4) showed upregulation of Type I interferon signaling (IFIT1, IFIT3) in PD patients. In contrast, CR patients exhibited increased expression of counter-inhibitory genes (TCF7, CD226) in CSF CAR Ts, suggesting a functional advantage of these CAR Ts in the inhibitory CNS environment. Functional assays of CD19-CAR Ts overexpressing the costimulatory molecule CD226, demonstrated higher lymphoma-cell killing vs WT-CAR Ts (48.6%, SEM 4.1 vs 24%, SEM 2.2, p = 0.01) and greater IFNγ production (63.2%, SEM 1.6 vs 49.4%, SEM 1.7, P = 0.006). CD226 acts as a costimulatory receptor and counteracts TIGIT signaling by competing for its shared ligands, CD112 and CD155. Notably, scRNA-Seq receptor-ligand analysis identified CD112 exclusively expressed in myeloid cells, highlighting a critical myeloid-CAR T interaction that enhances CD226^{high} CAR T efficacy. **Conclusions:** ScRNA-Seq suggests tissue-specific CAR T dysfunction in the CNS microenvironment, with CR patients demonstrating upregulation of counter-inhibitory genes, including CD226. This study offers novel insights into axi-cel's mechanism of efficacy and identifies targets to improve CNSL CAR T therapy. Research Sponsor: Kite/Gilead.

2021 Poster Session

Brain metastasis: Incidence, trend analysis, and impact on survival using SEER database (2010-2020).

Shaimaa Fadel, Asmaa Ellaithy; Faculty of Medicine, Suez Canal University, Ismailia, Egypt; Faculty of Medicine, Suez Canal University Hospital, Ismailia, Egypt

Background: Brain metastasis has a poor prognosis in cancer patients with high morbidity and mortality rates. An updated comprehensive analysis of patients with brain metastasis across all primary cancer sites is lacking. So, the study aims to provide the literature with updated evidence about recent trends and survival analysis of brain metastasis. **Methods:** Data of 75,797 patients with brain metastasis, diagnosed in 2010-2020, were extracted using the Surveillance, Epidemiology, and End Results (SEER) software. We used a rate session to calculate the incidence, percent change (PC), and annual percentage change (APC). Rates are per 100,000 and age-adjusted to the 2000 US Std population. Confidence intervals (CI) are 95% per rate with statistical significance at $P > 0.05$. We used SPSS version 23 for data analysis and Kaplan Meier Curve and log-rank test for survival analysis. **Results:** Brain metastasis represented 1.9% of all cancer cases with a mean age of 64.4 (Sd = 11.2). The age-adjusted incidence rate of brain metastasis was 7.1 with a PC of -9.6 from 2010 to 2020 (APC = -0.60; 95% CI: -1.2-0.001, $P < 0.05$). The APC was significantly declining in Caucasians (-0.70; $P > 0.05$) and African Americans (-1.2; $P < 0.05$) with a significant decrease in males (-1, $P < 0.05$) while the Asian or Pacific islanders (API) race had PC of 11.7 and APC of 1.30 ($P < 0.05$). Lung, breast, skin melanoma, and kidneys were the most common primary sites for brain metastasis (78.5%, 3.8%, 3.7%, and 3.2%). The 5-year relative survival of patients with brain metastasis was 6.1% compared to the non-metastatic group 71.5%. The 5-year age standardized relative survival was 5.7% for the metastatic group. The 5-year relative survival of brain metastasis was higher in the API race compared to Caucasians and African Americans (10.1%, 5.9%, and 5.3%). **Conclusions:** The results of this study show a very poor survival outcome for brain metastasis. However, there was a significant decline in brain metastasis trends over the years, which highlights promising improvements in the early detection of primary cancers. Further stratifications showed disparities according to race and primary cancer site. These data may have clinical-directed variations in screening and counseling for subpopulations with cancer. Research Sponsor: None.

2022 Poster Session

A phase I/II study to assess safety and preliminary evidence of a therapeutic effect of azeliragon combined with stereotactic radiation therapy in patients with brain metastases (ADORATION).

Rupesh Kotecha, Yazmin Odia, Zhijian Chen, Amy K. Starosciak, Lydia Hodgson, Alonso La Rosa, Antoinette M. Pimentel, Dilanis Perche, Matthew D. Hall, Robert H. Press, Manmeet Singh Ahluwalia, Minesh P. Mehta; Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Azeliragon is an oral, brain penetrating small molecule inhibitor of the receptor for advanced glycation end-products (RAGE), reducing neuroinflammation by inhibiting peritumoral edema/vascular leakage and overcoming radiation resistance. The primary objective of this study is to evaluate the safety and tolerability of azeliragon plus stereotactic radiosurgery (SRS) for patients with brain metastasis substituting for peri-procedural corticosteroids (loading dose [LD] and corticosteroid taper [CT]) and secondarily to assess the potential efficacy of this novel therapeutic combination. **Methods:** ADORATION (NCT05789589) is a single center, open-label, phase I/II trial. Eligible adults have a confirmed cancer diagnosis within 5 years, maximum brain metastasis diameter of $\leq$2 cm, and have discontinued corticosteroids at least 5 days prior to SRS. In phase I, participants were enrolled into sequential cohorts, starting with azeliragon + SRS + LD; depending on dose-limiting toxicities (DLTs), the next cohorts could be either azeliragon + SRS or azeliragon + SRS + LD + CT. A DLT was defined as any CNS-specific Grade $\geq$ 2 toxicity requiring corticosteroid treatment or any Grade $\geq$ 3 events not clearly due to the underlying disease or extraneous causes. **Results:** In the completed phase 1 portion, 3 patients were initially treated with azeliragon at 30 mg twice daily for 6 days followed by SRS+LD within 7 days of starting drug then a continuous dose of 20 mg daily for at least 8 weeks. As no DLTs were observed, the second cohort of 3 patients was treated with azeliragon and SRS without any corticosteroids (LD or CT). Of the 6 evaluable patients treated to 46 brain metastases, the most common primary histology was lung adenocarcinoma (n = 4). At data cutoff (1/8/2025), the median follow-up was 4.9 months (3.8-9.4 months) and no DLTs were observed. Early response rate (RR) to the combination therapy was assessed at week 8, with a per-patient RANO RR of 100% (partial response [PR] for all 100%), and a per-lesion RANO RR for all RANO-defined target lesions (n = 18) of 100% (PR 95.5%, complete response [CR] 4.5%). For all brain metastases treated (n = 46) the RR was 93.5% (PR for 69.6% and CR for 23.9%). Neurocognitive function batteries, symptom inventories, and quality of life evaluations remained stable during the 8-week early assessment period. **Conclusions:** Azeliragon was safely substituted for corticosteroids in this phase 1 study with no DLTs observed. The early response rate appears encouraging and accrual to the phase II expansion cohort (n = 40) with a primary endpoint of objective response rate is ongoing. Clinical trial information: NCT05789589. Research Sponsor: Cantex Pharmaceuticals.

2023 Poster Session

Efficacy of immune checkpoint inhibitors (ICI) in patients (pts) with central nervous system (CNS) metastases (mets) from solid tumors: A systematic review and meta-analysis.

Soraia Martins, Diogo Martins-Branco, Camila Bobato Lara Gismondi, Marco Bruzzone, Guilherme Nader Marta, Tiago Pina Cabral, Joana Gonçalves, Elisa Agostinetto, Marco Tagliamento, Nuria Kotecki, Matteo Lambertini, Eva Blondeaux, Matthias Preusser, Priscilla Kaliopi Brastianos, Evandro de Azambuja; Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Brussels, Belgium; Hospital Israelita Albert Einstein, São Paulo, Brazil; U.O. Epidemiology Unit, IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy; Unidade Local de Saúde Lisboa Ocidental, Hospital São Francisco Xavier, Lisbon, Portugal; Unidade Local de Saúde Arco Ribeirinho - Hospital Nossa Senhora do Rosário, Montijo, Portugal; U.O. Clinical Oncology, IRCCS Ospedale Policlinico San Martino, University of Genova, Villejuif, France; U.O. Clinical Oncology, IRCCS Ospedale Policlinico San Martino, University of Genova, Genova, Italy; Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; Division of Neuro-Oncology, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; Department of Medical Oncology, Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), Université Libre de Bruxelles (ULB), Brussels, Belgium

Background: Brain metastases, a common complication of solid tumors, are associated with poor outcomes. The role of ICIs in this setting remains unclear. This meta-analysis aims to assess intracranial efficacy of ICI-based systemic treatment in pts with CNS mets from solid tumors. **Methods:** A systematic literature search of PubMed, Embase, CENTRAL, and conference proceedings (ESMO and ASCO) up to 15-Mar-24 (PROSPERO: CRD42021242755), was conducted to identify single-arm phase II or III, or randomized controlled trials of pts with CNS mets from solid tumors at baseline treated with ICI-based systemic treatment. The primary objective, CNS efficacy, was measured by pooled CNS objective response rate (CNS-ORR) and weighted median CNS progression-free survival (mCNS-PFS). Subgroup analyses evaluated the impact of disease and treatment characteristics. Overall effects were pooled using random-effects models. **Results:** Out of 1 690 records screened, a total of 1 224 pts enrolled in 32 clinical trials were included. Overall, ICI-based systemic therapy led to a CNS-ORR of 38.0% (95% confidence interval [CI] 31.8-45.5) and a mCNS-PFS of 9.1 months (mos). CNS efficacy was numerically higher in pts with non-small cell lung cancer (NSCLC, n=383, CNS-ORR 45.8% [34.4-60.9]; mCNS-PFS 9.6 mos) and melanoma (n=554, CNS-ORR 37.7% [30.6-46.5]; mCNS-PFS 11.4 mos) vs multi tumors (n=128, CNS-ORR 24.8% [7.7-80.1] and mCNS-PFS 2.8 mos). Efficacy was also greater in first-line therapy (n=553, CNS-ORR 45.2% [36.7-55.7]; mCNS-PFS 8.6 mos) vs second or later lines (n=190, CNS-ORR 14.9% [7.6-29.2]; and mCNS-PFS 2.6 mos). Dual ICI (n=279, CNS-ORR 43.9% [35.5-54.2]; mCNS-PFS 17.8 mos) and ICI plus non-ICI agents (n=432, CNS-ORR 48.7% [39.6-59.9]; mCNS-PFS 7.1 mos) were more effective than single ICI (n=419, CNS-ORR, 20.4% [11.9-34.9]; mCNS-PFS 4.8 mos). Subgroup analyses showed superior CNS outcomes in cerebral mets, treated lesions, asymptomatic pts, and low/no steroid use (table). **Conclusions:** ICI-based regimens demonstrate CNS efficacy in pts with solid tumors, particularly in pts with NSCLC and melanoma treated with first-line combination therapies. Research Sponsor: None.

Subgroup analyses by CNS characteristics	Category (*n* of pts for CNS-ORR)	CNS-ORR, % (95% CI)	mCNS-PFS, mos
Type of CNS mets	Cerebral (1063)	38.3 (31.9-45.9)	9.6
	Leptomeningeal (51)	34.6 (15.9-75.2)	2.4
CNS local therapy	Treated (197)	37.6 (26.8-52.8)	8.9
	Untreated (307)	43.1 (35.0-53.0)	5.2
Symptoms	Asymptomatic/mild (832)	40.4 (34.5-47.3)	10.3
	Symptomatic (80)	31.3 (18.3-53.4)	2.5
Concomitant steroids	No (391)	30.6 (21.6-43.4)	15.1
	Low dose (434)	40.7 (31.5-52.6)	7.6
	Any dose steroids (144)	41.6 (31.7-54.7)	3.3

2024 Poster Session

Irradiated tumor volume as a predictor of local recurrence and radionecrosis in lung cancer with brain metastases treated with stereotactic radiosurgery.

Andreas Koulouris, Oscar Grundberg, Marcus Skribek, Caroline Kamali, Michael Gubanski, Simon Ekman, Georgios Tsakonas; Karolinska University Hospital, Solna, Sweden; Karolinska Institutet, Solna, Sweden; Department of Oncology, Karolinska University Hospital, Stockholm, Sweden

Background: Stereotactic radiosurgery (SRS) is a standard local treatment for brain metastases (BM), but it may result in local recurrence (LR) or radionecrosis (RN). This study evaluates irradiated tumor volume as a predictor of LR and RN in SRS-treated lung cancer patients with BM. **Methods:** We retrospectively analyzed 431 lung cancer patients with BM who underwent SRS at Karolinska University Hospital, Sweden, (2009-2020), encompassing all-comers from the Stockholm region. Associations among irradiated tumor volume and risks of RN, symptomatic RN, as well as LR at 6 and 12 months, were assessed using Cox regression models. Furthermore, we evaluated the diagnostic performance of Methionine PET-CT in differentiating RN from LR. **Results:** 40 patients (9.2%) developed asymptomatic RN, 37 (8.3%) symptomatic RN, and 67 (15.5%) LR. Larger tumor volumes significantly increased the risks of RN and LR. At 6 months, a tumor volume of 4.75 cm^3 was associated with an RN risk reaching the upper limit of 20%. By 12 months, substantially smaller volumes, such as 1.13 cm^3, were related to same risk levels. Symptomatic RN followed a similar trend, with a volume of 13.58 cm^3 presenting a risk of up to 20% at 6 months, while at 12 months, considerably smaller volumes, such as 3.8 cm^3, corresponded to a symptomatic RN risk as high as 40%. 20% risk of LR was observed with volumes of 5.66 cm^3 and 3.28 cm^3 at 6 and 12 months, respectively. The sensitivity and specificity of Methionine PET-CT are 0.909 and 0.600 when MRI was considered the gold standard. **Conclusions:** Larger irradiated tumor volumes were positively correlated with an increased risk of both RN and LR. At 12 months post-SRS, smaller tumor volumes were associated with higher RN and LR risks in comparison with 6 months. Methionine PET-CT, when used alongside MRI, did not demonstrate a clear advantage in differentiating LR from RN. Research Sponsor: European Society for Medical Oncology (ESMO); Hellenic Society of Medical Oncology (HeSMO); Elena Iliopoulou Giama (EIG) Cancer Research & Scholarship Foundation; Scholarship - Legacy “M. M. Manassaki” by the University of Crete; Region Stockholm (clinical postdoctoral appointment); Stockholm Cancer Society; 204053.

2025 Poster Session

Efficacy of systemic therapy in breast cancer with CNS metastases: “Real-world” experience.

Bipin Ghimire, Maria Jamil, Lisa R. Rogers, Marian Girgis; Henry Ford Health System, Detroit, MI

Background: The incidence of CNS metastases in breast cancer is rising. While local therapies such as surgery and radiation remain standard, data on upfront systemic therapies for active brain metastases, especially HER2-negative patients, is limited. This study examines upfront systemic therapy efficacy for CNS metastases in breast cancer patients at a single institution, including a majority African American (AA) population. **Methods:** A retrospective chart review included breast cancer patients with CNS metastases treated at Henry Ford Health (January 2014–July 2024). Eligible patients had not received concurrent local therapy; prior local therapy was permitted if unrelated to the studied lesions. CNS response was to be assessed using RANO-BM (defines measurable disease as lesions $>$ 10 mm) for parenchymal and modified RANO-LM criteria for leptomeningeal disease (LMD). **Results:** Among 35 patients (20 AA, 13 Caucasian), with a median age of 54 years, HER2-positive was the most common receptor type (49%), followed by HR-positive (37%) and triple-negative (14%); nearly half (46%) had HER2-low disease. Parenchymal metastases were predominant (86%); three had co-existing LMD, and two others had only LMD. Most metastases were multiple; 91% had lesions $<$ 10 mm. 43% had prior WBRT or SRS to unrelated lesions. HER2-positive patients had the highest CNS overall response rate (ORR, 53%) and disease control rate (DCR, 94%), followed by HR-positive (ORR 31%, DCR 69%) and triple-negative (ORR and DCR 20%). Median PFS did not significantly differ between receptor groups (p = 0.130). Trastuzumab-deruxtecan (T-Dxd) was the most common regimen (10/35) and within HER2-positive and HR-positive groups. T-Dxd achieved CNS ORR of 60%, DCR of 90%, and median PFS of 16 months. Tucatinib-based regimens showed a 100% DCR with median PFS of six months. Other therapies, including sacituzumab, abemaciclib, and trastuzumab-emtansine, showed stable disease as the best response. Among AAs, HR-positive was the most common receptor type (50%). These patients had ORR of 35% and DCR of 65%. T-Dxd maintained ORR of 60% and DCR of 80%. Of five patients with LMD, three were HER2-positive, and two were HR-positive, with an ORR of 60%, and DCR of 80%. **Conclusions:** This “real-world” experience highlights that, at our institution, most patients with breast cancer and CNS metastases considered for upfront systemic therapy lack measurable disease (91% having lesions $<$ 10 mm) typically required for clinical trials. Nonetheless, the response rate aligns with published experiences. In addition, we included patients with LMD, who are often excluded in trials. Our data also suggests impressive CNS responses with T-Dxd, both overall and in AA patients. The management of brain metastases and LMD in these patients is best approached in a multidisciplinary format. Research Sponsor: None.

Whole brain radiotherapy and intrathecal injection of thiotepa, combined with systemic treatment for the primary tumor, to treat solid tumor leptomeningeal metastasis: A prospective, single center, single arm, phase II clinical study.

Siyu Guo, Bicheng Zhang, Dang Wu, Jing Zhao, Ting Zhang; Zhejiang University, Hangzhou, China; The Second Affiliated Hospital of Zhejiang University, Hangzhou, China; Department of Radiation Oncology,The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Medical Oncology, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: To evaluate the efficacy and toxicity of a triple therapy regimen consisting of Hippocampal-sparing whole-brain radiotherapy (HS-WBRT), intrathecal Thiotepa (ITT), and primary lesion treatment for solid tumor leptomeningeal metastasis (LM). (NCT06376292). **Methods:** Based on the comprehensive results of MRI and cytology evidence, patients diagnosed with LM according to the diagnostic criteria in the EANO-ESMO guidelines meet the criteria. Patient began ITT twice a week, and underwent HS-WBRT as soon as possible. Before each ITT, cerebrospinal fluid (CSF) pressure is measured and CSF is collected for testing, including protein, tumor markers, IgG, albumin levels of CSF, and albumin ratio. MRI reexamination is conducted every three months, and the RANO-LM criteria is used to evaluate the response of patients after treatment. Besides,the LM-PROG SCORE we designed can be used as an indicator to evaluate the treatment effect and adjust the medication frequency or switch the treatment line of intrathecal Pemetrexed (IP). The primary endpoint is overall survival. **Results:** As of December 1, 2024, a total of 57 patients have been enrolled. 40 patients were included in the statistics. Most cases are lung cancer (27, 67.5%), in addition to breast cancer(8, 20%), gastric cancer (3, 7.5%), rectal cancer (1, 2.5%) and cervical cancer (1, 2.5%). The mOS was 7.8 months (95% CI 2.06-13.54 months). The mPFS was 5.63 months (95% CI 0.76-10.51 months). The RANO-assessed ORR to treatment was 62.5% (10/16), DCR was 87.5% (14/16), with 24 patients (60%) not reaching the follow-up time. The three longest survival among alive patients are 21.3 months, 14.9 months, and 12.7 months. The most significant effect of combination therapy is the rapid relief of symptoms. 25% of patients (10/40) had already experienced unconsciousness (RASS≠0) at the time of diagnosis. After our treatment, all patients regained consciousness (RASS = 0). The long-term therapeutic effect also significantly reduces tumor markers, protein content, albumin and IgG content, pressure drop, and albumin ratio in CSF, indicating the recovery of the blood-brain barrier. 85% of patients experience varying degrees of bone marrow suppression during treatment, but most are mild and can tolerate subsequent ITT maintenance after treatment. **Conclusions:** Under the efficacy guidance of LM-PROG SCORE we designed, our combination therapy can greatly improve patients' overall survival, progression free survival, and quality of life. And it was found that in addition to imaging, indicators such as protein content, IgG and albumin content, Albumin Ratio and tumor markers in CSF can serve as efficacy evaluation indicators. Clinical trial information: NCT06376292. Research Sponsor: None.

Effect of CD4+PD-1+CXCR6+ T cells on the response of immune checkpoint inhibitor therapy in brain metastases of NSCLC.

Yang-Si Li, Wenpu Lai, Kai Yin, HaiYan Tu, Liang Li, Shou-Heng Lin, Peng Li, Jin-Ji Yang, Qing Zhou, Wen-Zhao Zhong, Xuchao Zhang, Xue-Ning Yang, Lu Zeng, SiYang Maggie Liu, Yangqiu Li, Oscar Junhong Luo, Meimei Zheng, Yi-Long Lung Cancer Wu; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital, Guangzhou, China; Jinan University, Guangzhou, China; Guangdong Provincial People's Hospital, Guangzhou, China; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China; Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, Guangdong, China; Jinan University, Guangdong, China

Background: Brain metastases (BrM) in non-small cell lung cancer (NSCLC) presented a significant challenge due to poor prognosis. While immune checkpoint inhibitors (ICIs) have been standard treatments for NSCLC, their efficacy in BrM is variable, emphasizing the urgent need for predictive biomarkers and fundamental mechanisms. **Methods:** We prospectively collected 20 cerebrospinal fluid (CSF) and 4 BrM tumors from 18 NSCLC patients with BrM undergoing ICI therapy for single-cell RNA sequencing (scRNA-seq), complemented by integrating data from multiple published datasets. Three independent cohorts (8 and 25 CSF, and 31 BrM tumors) underwent flow cytometry, proteomics, and multiplex immunohistochemistry for validation, respectively. **Results:** Our study provided a high-resolution atlas of cellular dynamics in the CSF and BrM during ICI therapy in NSCLC patients with BrM. Notably, we identified a key immune cell subset, $CD4^+PD\text{-}1^+CXCR6^+$ T cells, as a positive predictor of ICI intracranial tumor responses, which presented highly functional and transcriptomic similarities in both CSF and BrM tumor environment. Moreover, CXCR6 could serve as a specific marker for $CD4^+PD\text{-}1^+$ T cells linked to ICI response. Further, we revealed that the novel cluster of $CD4^+PD\text{-}1^+CXCR6^+$ T cells was closely associated with lymphocyte activation and aggregation in CSF and BrM of ICI responders, and cDCs of ICI responders interacted with $CD4^+PD\text{-}1^+CXCR6^+$ T cells for enhanced antigen presentation and inflammatory activation. **Conclusions:** Our findings revealed critical insights into the immune landscape of NSCLC BrM under ICI therapy, highlighting $CD4^+PD\text{-}1^+CXCR6^+$ T cells in CSF as a promising biomarker and illuminating fundamental mechanisms underlying ICI efficacy. Research Sponsor: None.

IT-IO: Intrathecal administration of nivolumab and ipilimumab in combination with systemic combination of nivolumab and ipilimumab in patients with non-small cell lung cancer or melanoma and newly diagnosed leptomeningeal metastasis, a multicentric phase I study.

Emilie Le Rhun, Dorothee Gramatzki, Lukas Kraehenbuehl, Joanna Mangana, Egle Ramelyte, Christian Britschgi, Ulrich Richter, Andreas Wicki, Susanne Weindler, Denis Migliorini, Heinz Philipp Laubli, Urania Dafni, Markus Vaas, Tobias Weiss, Reinhard Dummer, Michael Weller; University Hospital Zurich, Zurich, Switzerland; Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland; Department of Dermatology and Allergology, Cantonal Hospital Aarau, Zurich, Switzerland; Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; University Hospital Zurich- Department of Medical Oncology and Hematology, Comprehensive Cancer Center Zurich, Zurich, Switzerland; University Hospital Zurich, Department of Medical Oncology and Hematology, Zurich, Switzerland; Department of Medical Oncology and Hematology, University Hospital Zurich, Zurich, Switzerland; Department of Medical Oncology, Kantonsspital St. Gallen, St Gallen, Switzerland; Geneva University Hospitals, Geneva, Switzerland; University Hospital Basel, Basel, Switzerland; National and Kapodistrian University of Athens and Frontier Science Foundation Hellas, Athens, Greece; University Hospital Zurich, Clinical Trial Center, Zurich, Switzerland; Department of Neurology, University Hospital Zurich, Zurich, Switzerland; Department of Neurology, University Hospital Zurich, and Brain Tumor Centre, University Hospital and University of Zurich, University Hospital Zurich, Zurich, Switzerland

Background: The optimal management of patients with leptomeningeal metastases (LM) from non-small cell lung cancer (NSCLC) or melanoma remains controversial. IT-IO (NCT05598853) is a prospective phase I, multicenter, open label, interventional clinical study aiming at determining the recommended phase 2 dose (RP2D) of intrathecal nivolumab and ipilimumab in patients with newly diagnosed LM from NSCLC or melanoma. **Methods:** The diagnosis of LM had to be confirmed or probable by EANO ESMO criteria. Planned whole brain radiotherapy (WBRT) was not allowed. Planned or prior craniospinal irradiation were not allowed. The treatment regimen consisted of intrathecal nivolumab (fixed dose 50 mg) / ipilimumab (increasing doses) in combination with systemic combined nivolumab/ipilimumab. Three dose levels of IT ipilimumab were planned: 5 mg (dose level 1), 10 mg (dose level 2), and 20 mg (dose level 3). RP2D, the primary endpoint, was determined in a 3+3 design. Secondary endpoints included compartmental efficacy and survival. **Results:** A total of 19 patients, 6 female and 13 male patients, 12 with melanoma and 7 with NSCLC, were enrolled between February 2022 and August 2024. Median KPS at study entry was 80, 12 patients had a positive CSF. The dose escalation phase (n = 12) was completed without dose-limiting toxicity until dose level 3. The RP2D is nivolumab 50 mg and ipilimumab 20 mg. Sixteen SAE were noted, all unrelated or unlikely related to intrathecal therapy. Three patients are still alive. For the whole cohort, median overall survival was 3 (range 0.6-10.3) months, for patients with a diagnosis of melanoma 2.9 (range 0.6-8.2) and for patients with NSCLC 4.5 (range 0.8-10.3) months. OS at 6 months was 20% (one patient ongoing at 5.1 months). Translational research is ongoing. **Conclusions:** No safety issue was noted. Efficacy data are preliminary and need to be confirmed in larger trials. Clinical trial information: NCT05598853. Research Sponsor: Bristol Myers Squibb.

Evaluating the utility of DNA methylation signatures in tissue and biofluids for lung adenocarcinoma brain metastasis prediction and non-invasive detection.

Jeffrey Zuccato, Yasin Mamatjan, Farshad Nassiri, Andrew Ajisebutu, Jeff Liu, Mathew Voisin, Suganth Suppiah, Olli Saarela, Ming-Sound Tsao, Kenneth D. Aldape, Vikas Patil, Gelareh Zadeh; Oklahoma University Health Sciences Center, Oklahoma City, OK; University Health Network, Toronto, ON, Canada; Princess Margaret Cancer Center, Toronto, ON, Canada; University of Toronto, Toronto, ON, Canada; Department of Medical Oncology and Hematology, University Health Network, Princess Margaret Cancer Centre, Toronto, ON, Canada; NCI CCR, Bethesda, MD; Mayo Clinic, Rochester, MN

Background: Brain metastases (BM) are common and arise in 30% of lung adenocarcinoma (LUAD) patients. Patients with LUAD that develop BM have significantly poorer outcomes, with a 10-16 month median overall survival. Unfortunately, current clinical practice for BM prediction is limited and so BM are typically detected after they develop and grow to cause neurological symptoms. Once BM are detected, currently neurosurgical tumor biopsies are performed to enable BM diagnosis via neuropathological evaluation. The aims of this study were to develop DNA methylation-based models that predict LUAD BM and non-invasively detect BM in blood to enable early diagnosis and treatment. **Methods:** DNA methylomes were acquired from 402 tumor tissue and plasma samples in a cohort of 346 LUAD and BM patients. Machine learning models were built using DNA methylation signatures that stratify BM risk in tissue and detect BM in plasma. Models were evaluated in independent validation datasets. A predictive nomogram was developed using the BM prediction model together with clinical factors to provide composite patient-specific scores reflecting BM risk. **Results:** The methylation-based BM predictor accurately stratified BM risk in a univariable Cox model using validation set data (HR = 5.65, 95%CI 1.85–17.2, p = 0.0023). Model utility was independent of the predictive value of clinical factors in a multivariable Cox model using validation set data (Table 1: HR = 8.92, 95%CI 1.97–40.5, p = 0.0046). The 5-year model accuracy was 0.81 and significantly higher than a similarly built cancer stage-based model (0.65), demonstrating utility over current practice. The combinatorial clinical-methylomic predictive nomogram had enhanced utility with an accuracy of 0.82 univariable Cox HR of 17.2 (95%CI 4.13–71.3, $p < 0.0001$), demonstrating comprehensive patient-specificity. The plasma-based model accurately classified BM from gliomas and lymphomas (AUROC=0.80), as typical clinical differential diagnoses, in validation set data. The models were validated further in additional external data. **Conclusions:** DNA methylation-based modeling of BM can accurately predict LUAD patients at risk for BM development and can non-invasively detect BM that develop. Future treatment approaches may tailor initial LUAD treatment and ongoing cancer surveillance to a patient's BM risk, allowing for the potential to prevent and treat BM early. Research Sponsor: None.

DNA methylation-based BM prediction is independent of clinical factors in a multivariable Cox proportional hazards model.

Variable		HR	95% CI	p
Methylome risk score		8.92	1.97–40.5	0.005
Age	Years	0.96	0.92–1.02	0.177
Smoking	Pack-years	0.99	0.95–1.03	0.496
EGFR	Mutant vs wildtype	0.92	0.25–3.34	0.895
T	T2 vs T1	1.58	0.41–6.04	0.505
	T3–4 vs T1	1.49	0.28–7.98	0.642
N	N1 vs N0	1.05	0.31–3.58	0.943
	N2–3 vs N0	1.00	0.27–3.69	0.995
M	M1 vs M0	145	12.2–1730	<0.001

Effect of early integrated neuropsychological care in patients with brain metastases: A phase 2 randomized controlled trial (ATHENA trial).

Haley Kopp Perlow, Erica L. Dawson, Khaled Dibs, Alex R. Ritter, Yilun Sun, Daniel Boulter, Ansel P. Nalin, Raj Singh, Sasha Beyer, Simeng Zhu, Dukagjin M. Blakaj, John C. Grecula, Raju R. Raval, Shayla Vazquez, Samantha Whitman, Carolyn J. Presley, Clement Pillainayagam, Pierre Giglio, Evan M. Thomas, Joshua David Palmer; Department of Radiation Oncology, Seidman Cancer Center University Hospitals/Case Western Reserve University, Cleveland, OH; Department of Neurology, Ohio State University, Columbus, OH; Department of Radiation Oncology, Ohio State University, Columbus, OH; Department of Radiation Oncology, West Virginia University, Morgantown, WV; Department of Population Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH; Department of Radiology, Ohio State University, Columbus, OH; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The Ohio State University, Columbus, OH; Ohio State University, Columbus, OH; Department of Neuro-Oncology, University Hospitals Seidman Cancer Center/Case Western Reserve University, Cleveland, OH; Department of Neuro-Oncology, Ohio State University, Columbus, OH

Background: Advancements in radiotherapy delivery through both hippocampal sparing whole brain radiotherapy (WBRT) and stereotactic radiosurgery (SRS) can better preserve QOL and reduce cognitive decline. However, even patients treated with advanced brain radiotherapy techniques have a reduction in their QOL and cognitive abilities either due to their radiation treatment, systemic therapy, or progression of disease. This Phase 2 Randomized Controlled Trial (NCT05503251) aims to evaluate the impact of a neuropsychological evaluation and intervention with a certified neuropsychologist on QOL and cognitive function for brain metastases patients treated with radiotherapy. **Methods:** Brain metastases patients were randomized 1:1 to either neuropsychology evaluation and intervention plus brain radiotherapy or brain radiotherapy alone. The intervention arm included five appointments with the neuropsychology team for testing, evaluation, and counseling over a three-month period. Patients with any number of brain metastases and an estimated survival of $\geq$ 6 months were included. Exclusion criteria included prior WBRT and pre-existing mental disability. Stratification factors for randomization were Karnofsky performance status (KPS, $>$ 70 vs. $\leq$ 70) and radiation cohort ($>$ 15 brain metastases received WBRT, $\leq$15 received SRS). All patients receiving WBRT were prescribed memantine. The primary endpoint was deterioration of QOL at 3 months as measured by Fact-Br. Repeated measures analysis of variance was used to measure QOL. Cognition was measured by Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association Test, and Trail Making Test A/B, with cognitive decline defined as decline on at least one assessment using reliable change index. **Results:** Between August 2022 and June 2024, 110 patients were randomized. Baseline characteristics were balanced between arms and included a median KPS of 90 (IQR 80, 90), median age of 62.5 (IQR 54, 70), 53% female patients, 43% of patients with a primary lung cancer, and most patients (74%) with $\leq$15 brain metastases. The median overall survival or time to last follow-up was 8.5 months. The primary endpoint, deterioration of QOL at 3 months, was not different between the control and intervention arms ($p = 0.93$). Cognitive decline differences at 3 months were not significant between the control and intervention arms (24.1% vs. 27.3%, $p = 0.33$). Additionally, there were no differences at 3 months with verbal fluency, executive function, immediate recall, delayed recall, or delayed recognition between arms. **Conclusions:** This study did not meet its primary endpoint, better preserved QOL at 3 months for patients receiving early integrated neuropsychological care. Further evaluation of the delayed impact ($>$ 6 months) of neuropsychology intervention on QOL and cognitive function will be reported when data are available. Clinical trial information: NCT05503251. Research Sponsor: None.

Intrathecal deferoxamine in patients with leptomeningeal metastases: Phase 1a analysis.

Jessica Wilcox, Anne S. Reiner, Robert J. Young, Laleh Emadi-Paramkouhi, Benjamin Weill, Lindsey Myers, Yasemin Tulca, Ashley Gonzalez, Rachel Estrera, Isaiah Osei-Gyening, Kiana Chabot, Tiffany Thomas, Vanessa R Thompson, Elisa de Stanchina, Lisa R. Modelevsky, Thomas Joseph Kaley, Katherine Panageas, Ingo K. Mellinghoff, Helena Alexandra Yu, Adrienne Boire; Memorial Sloan Kettering Cancer Center, New York, NY; Columbia University Medical Center, New York, NY; Sloan Kettering Institute, New York, NY

Background: Leptomeningeal metastases (LM), the spread of cancer to the cerebrospinal fluid (CSF), is associated with high morbidity and mortality. LM employ the iron-binding transporter and receptor system, lipocalin-2/SLC22A17, to scavenge iron from the CSF to sustain their metabolic needs. In preclinical models of LM, intrathecal administration of deferoxamine (IT-DFO), an iron chelator, resulted in reduction of LM growth and improvement of survival. We evaluated this novel treatment strategy in this first-in-human clinical trial in patients with solid tumor LM. **Methods:** This is a phase 1a, single-institution, clinical trial to determine safety and maximum tolerated dose (MTD) of IT-DFO in patients with LM. Eligibility criteria included LM from any solid tumor, age $\geq$ 18 years, Karnofsky Performance Status $\geq$ 60, life expectancy $\geq$ 8 weeks, and Ommaya reservoir. Patients were enrolled in an accelerated 3+3 dose escalation design with a primary endpoint of dose-limiting toxicity (DLT), defined as a grade 3 non-hematologic or grade 4 hematologic toxicity in the first cycle of treatment. All patients received IT-DFO twice weekly (cycle 1), once weekly (cycle 2), then once every two weeks (cycle 3+) in 28-day cycles. Patients were monitored for LM progression by neurological examination, neuraxial magnetic resonance imaging, and CSF cytology as per modified Response Assessment in Neuro-Oncology LM criteria. **Results:** A total of 8 patients received treatment with IT-DFO from May 2022 to January 2025 at the time of data cut-off. The median age at enrollment was 50 years (range, 26-69). The primary malignancy included breast (n = 4), lung (n = 2), colon (n = 1), and sarcoma (n = 1). Patients were treated with IT-DFO at doses of 10 mg (level 1, n = 4) and 30 mg (level 2, n = 4). IT-DFO was well tolerated, and the majority of adverse events (AEs) were grade 1-2. The most common any grade AEs were vomiting (50%), nausea (37.5%), chills (25%), myalgias (25%), and tremor (25%). Two patients experienced DLTs at 30 mg (grade 3 vomiting, grade 3 syncope). No grade 4-5 AEs were observed. The MTD was determined to be 10 mg. In this heterogenous heavily pretreated population, median overall survival for the evaluable cohort (n = 7) was 10.0 months (95% CI, 6.5 – NA). **Conclusions:** IT-DFO is a novel, well tolerated investigational treatment for LM. A phase 1b dose expansion study at a dose of 10 mg is currently underway to better define safety and efficacy endpoints. Clinical trial information: NCT05184816. Research Sponsor: MSK Center for Experimental Therapeutics; F. M. Kirby Foundation; ASCO Conquer Cancer Young Investigator Award 2021.

Improving adherence to cancer care for socioeconomically disadvantaged patients with central nervous system tumors.

Joshua Amit Budhu, Cleopatra Elshiekh, Bharat Narang, Ashley Marie Rodriguez, Ashley Phillips, Francesca Gany; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Socially disadvantaged patients often face significant barriers to adhering to and completing cancer treatment. Patients with central nervous system (CNS) tumors experience cognitive, neuropsychiatric, speech, motor, sensory, and gait symptoms that exacerbate socioeconomic barriers to care. The Integrated Cancer Care Access Network (ICCAN) is a multi-institutional program developed by Memorial Sloan Kettering Cancer Center's Immigrant Health and Cancer Disparities Service (IHCD). Through ICCAN, patients are provided with patient navigation and resources to mitigate barriers to treatment adherence and completion. While ICCAN has been shown to increase treatment adherence and completion for patients with other cancers, it has not historically enrolled patients with CNS tumors. **Methods:** Under this pilot ICCAN-CNS program, 58 patients with either primary brain tumors or brain metastases were referred to the program. Of these, 45 patients enrolled, 5 patients died before contact was made, 2 patients declined participation, and 4 patients could not be reached. The patient population was evenly split between primary brain tumors (mainly glioblastomas and low-grade gliomas) and brain metastases. Patients were eligible if they were 18 years or older and receiving active treatment or were under active surveillance. If a patient was eligible, they were administered an extensive needs assessment survey that took 60 minutes to complete. The interviews consisted of basic demographic questions, Alliance Distress Screening Tool, Health Related Social Needs (HRSN) Assessment, Essential Needs Assessment, Patient Satisfaction with Cancer Care questionnaire, and an ICCAN-CNS specific questionnaire for patients with brain tumors. Caregivers were allowed to assist patients with neurocognitive or speech deficits in completing the survey questions. Patients were then provided with both patient navigation and resources depending on their needs. Follow-up assessments were conducted at the 2-, 4-, and 6-month marks. **Results:** Patients with CNS tumors completed the initial needs assessments and additional questionnaires. Trends of delayed responses and the need for questions to be repeated were observed, however, patients were still able to express socioeconomic needs. The main needs expressed among these patients were income, employment issues due to lack of ability to work from their cancer, food access, and transportation to appointments. Overall, the response to the program was positive from patients, with many patients accessing resources with the assistance of the access facilitator. **Conclusions:** This pilot demonstrates the feasibility and value of including CNS tumor patients in patient and resource navigation programs. Future plans include a randomized controlled trial using the ICCAN intervention for patients with glioblastoma. Research Sponsor: None.

Risk of intracranial hemorrhage with DOACs vs LMWH in patients with cancer-associated thrombosis and brain metastases.

Ali Mushtaq, Omer Ashruf, Alok A. Khorana, Ahmad Safdar, Sean Hergenrother, Dana E. Angelini; Cleveland Clinic Foundation, Cleveland, OH; Northeast Ohio Medical University, Rootstown, OH; Taussig Cancer Institute, Cleveland, OH

Background: Intracranial hemorrhage (ICH) is a major and often devastating complication in patients with brain metastases requiring therapeutic anticoagulation for cancer-associated thromboembolism (CAT). While direct oral anticoagulants (DOACs) provide a convenient alternative to low-molecular-weight heparin (LMWH), their safety in this population remains unclear. Comparing ICH risk between DOACs and LMWH is crucial for optimizing anticoagulation in these high-risk patients. **Methods:** This retrospective cohort study utilized TriNetX, a multi-institutional database, to analyze adults with solid tumors who developed CAT within six months of brain metastasis diagnosis. Patients receiving therapeutic-dose DOACs (apixaban, rivaroxaban, edoxaban) or LMWH within ten days of venous thromboembolism diagnosis were compared. 1:1 propensity score matching for over 50 covariates, including age, sex, and cancer type (Table 1). We assessed ICH incidence, bleeding events, ICU admissions, and all-cause mortality using Kaplan-Meier survival analysis and Cox proportional hazards models. Subgroup analyses examined ICH risk by cancer type. **Results:** After matching, 4,275 patients were included in each group. DOACs were associated with a statistically significant lower risk of ICH (HR 0.855, 95% CI 0.731-0.999, p=0.049). Additionally, significantly lower rates of ICU admission (16.7% vs. 20.3%; p<0.001) and all-cause mortality at 12 months (42.4% vs. 48.9%; p<0.001) were observed in the DOAC group. Subgroup analyses showed a trend toward lower ICH with DOACs in lung cancer (5.9% vs. 6.1%, p=0.726), melanoma (13.7% vs. 15.9%, p=0.432), and renal cell carcinoma (5.7% vs. 9.0%, p=0.103), but these differences were not statistically significant. No significant differences were found for breast (3.6% vs. 4.5%, p=0.375) or colorectal cancer (4.0% vs. 5.4%, p=0.331). **Conclusions:** DOACs were associated with significantly lower ICH, ICU admission, and mortality compared to LMWH in patients with brain metastases requiring anticoagulation, supporting their role as a viable and well-tolerated alternative. While subgroup analyses did not show significant differences in ICH risk by cancer type, the overall findings indicate a favorable profile for DOACs. These results highlight the need for individualized anticoagulation strategies and warrant further prospective validation.
Research Sponsor: None.

Baseline characteristics after matching.

Characteristic	DOAC (n=4275)	LMWH (n=4275)
Age (years), mean ± SD	63.4 ± 11.9	63.5 ± 11.9
Female, n (%)	1969 (46.1%)	1958 (45.8%)
Lung Cancer, n (%)	2218 (51.9%)	2229 (52.1%)
Breast Cancer, n (%)	692 (16.2%)	672 (15.7%)
Melanoma, n (%)	280 (6.5%)	279 (6.5%)
Renal Cell, n (%)	241 (5.6%)	244 (5.7%)
Colorectal, n (%)	408 (9.5%)	413 (9.6%)

Risk factors (RF) for brain metastases (BM) in patients (pts) with metastatic breast cancer (MBC): An analysis of US electronic health records (EHRs).

Jose Pablo Leone, Sarah L. Sammons, Peter Lambert, Yunru Huang, Filippo Montemurro, Mahesh Shivhare, Eleonora Restuccia, Adam Knott, Thibaut Sanglier, Sara M. Tolaney, Nancy U. Lin; Dana-Farber Cancer Institute, Boston, MA; Genentech, Inc., South San Francisco, CA; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Roche Products Limited, Welwyn Garden City, United Kingdom

Background: BM are a significant clinical challenge in pts with MBC yet risk stratification for early identification is suboptimal. We leveraged a large, contemporary, real-world database to characterize RF associated with BM to inform strategies for enriched surveillance and early detection. **Methods:** Selected pts from the nationwide Flatiron Health de-identified EHR-derived database had MBC, had initiated first-line treatment (1L tx) before March 2023 (allowing for >1 year [yr] of potential follow-up [FU]), and were free of BM at tx initiation. Clinical characteristics were examined as potential RF for BM incidence at any time during FU, using univariate sub-distribution (sd) and cause-specific (cs) hazard ratios. Additional analyses focused on BM risk at 3 yrs from tx initiation and included longitudinal data sequential Cox models with landmarks at every 6 months of FU, and a nested case-control (NCC) design for concurrent BM detection. Analyses were conducted on complete cases, no imputation method was used for missing data, and regression methods using multivariate analyses were used to mitigate confounding. Predictive, modeling-based machine learning (LASSO Cox regression, random survival forests) was conducted using cs hazard ratios to identify potential predictors amongst 90 candidates (data-driven approach using most of the dataset). Analyses were conducted in the overall cohort and stratified by subtype: HER2-negative/hormone receptor-positive (HER2−/HR+), HER2-positive/HR-negative (HER2+/HR−), HER2+/HR+, and triple-negative breast cancer (TNBC). **Results:** The study included 21,368 female pts initiating 1L tx (n = 14,898 HER2−/HR+, 1006 HER2+/HR−, 3468 HER2+/HR+, 1996 TNBC), with 2,530 BM events. Younger age, HER2+ and TNBC subtypes, and more extensive metastasis ($\geq$2 organ sites, particularly liver, lung, or lymph nodes) were associated with higher BM risk (Table); bone-only metastases conferred a lower risk. sd and cs hazard ratios were largely concordant. NCC analyses identified similar predictors for concurrent BM. LASSO Cox modeling yielded a C-index of 0.74 overall (HER2+ 0.70; HER2−/HR+ 0.73; TNBC 0.62). Similar C-indices were seen with random survival forests. **Conclusions:** Clinical characteristics, including metastatic distribution and tumor subtype, can help identify pts at higher BM risk within 3 yrs of initiating MBC tx. Competing risks (of BM and death) did not appear to substantially affect results, except for recurrence time and ECOG PS. Although these findings are encouraging, further refinement of predictive models is needed to improve discrimination and guide targeted neuroimaging and early intervention strategies. Research Sponsor: F. Hoffmann-La Roche Ltd.

		sd hazard ratio
Age, yrs (reference [ref]: <45)	45–55	0.81
	56–65	0.62
	66+	0.31
Subtype (ref: HER2−/HR+)	HER2+/HR+	2.45
	HER2+/HR−	3.40
	TNBC	2.33
Metastatic sites, n (ref: 1)	2–3	1.55
	4+	2.63

Memantine in radiation-induced cognitive dysfunction in brain metastases: A double-blinded, randomized, placebo-controlled trial (CTRI/2022/01/039599).

Haripriya Parapparambil Surendran, Debnarayan Dutta, Wesley Mannirathil Jose, Sruthi Kalavagunta, Parasuraman Ayiramuthu, Narmadha Mukunthu Poornachary, Dhanya Chandran, Sabitha Mangalath, Unnikrishnan Mazhuvancherry Kesavan; Amrita Institute of Medical Sciences and Research, Kochi, India; Amrita Institute of Medical Science and Research Centre, Amrita Vishwa Vidyapeetham, Kochi, India; Amrita Institute of Medical Sciences and Research Centre, Ernakulam, India; Amrita institute of Medical Sciences, Kochi, India; Amrita Institute of Medical Sciences and Research, Ernakulam, Kerala, India

Background: Prospective double-blinded, placebo-controlled randomized study to evaluate the role of memantine in brain metastasis (BM) in preserving cognitive function. **Methods:** Clinic-radiologically diagnosed of BM patients planned for radiation therapy (RT) (SRS or whole brain RT) were randomized to receive memantine or placebo (20 mg/day) over 24 weeks. Cognitive function assessed by Addenbrooke's Cognitive Examination (ACE). Secondary outcomes included QoL, white matter volume changes (MRI T2 FLAIR), and plasma memantine levels (by LC-MS/MS). Safety was assessed using CTCAE v5.0 criteria. **Results:** 130 BM patients were enrolled after randomization [placebo 64 & memantine (experimental arm n = 66]. In placebo and memantine arm mean age was 56.5 & 56.7; female 39 & 40; high school education status 39 (30%) & 37 (28%); SRS in 40 (30%) & 35 (27%); frontal lobe lesion 43 (33%) & 55 (42%); PS 0-1 55 (42%) & 54 (41%) respectively. In the placebo arm, ACE scores at baseline in placebo and memantine arm 83.0 ± 10.1 and 77.7 ± 12.7 (p = 0.78) respectively. At 4 months, ACE score in placebo and memantine arm 76.2 ± 14.3 and 82.2 ± 12.7 (p = 0.04). At 6 months in placebo and memantine arm were 72.9 ± 20.2 and 83.9 ± 10.8 (p = 0.005). At 24 weeks, ACE scores change was +4.0 in memantine & -9.5 in placebo arm; p = 0.001. Memantine arm had better preservation of memory (-3 vs. -2.5, $p < 0.001$), delayed recall (-1 vs. -1, $p < 0.001$), and verbal fluency (-1 vs. 0, p = 0.007). In the SRS subgroup, ACE scores in placebo and memantine at baseline, 4 and 6 month was 83.5 (± 9.5) & 79.7 (± 12.5); 76.6 (± 14.7) & 85.3 (± 10.6); 72.5 (± 23.1) & 86.4 (± 9.5) respectively. At 24 weeks, memantine arm improved ACE scores by +4 (0 to 12) compared to placebo -8 (-15.5 to -2.5) ($p < 0.001$). At 24 weeks in WBRT, memantine arm sustained cognitive improvement (ACE score +3) compared to further decline in placebo (-9.5, $p < 0.001$). At 24 weeks, percentage change in global health status in placebo & memantine arms were -5.57%. & +63.3% respectively. 21% required dose reductions due to adverse events. Loss of appetite (25.7% vs. 12.5%, p = 0.05); gastric irritation (0 vs 7.5%; p = 0.02) were higher in memantine arm. White matter volume changes in the placebo group correlated negatively with cognitive decline (r = -0.544, p = 0.055), suggesting a potential role of edema in radiation-induced cognitive dysfunction. Memantine at a 5 mg BID dose achieved a median trough concentration of 118.06 ng/mL (IQR: 68–211), within the desirable therapeutic range (70–150 ng/mL). 10 mg BID dose trough was 172 (85-290) and peak concentration 397 (258-499 ng/mL) exceeded alert threshold of 300 ng/mL. **Conclusions:** Memantine preserved cognitive function and QoL in RT for BM. Cognitive benefits were more in SRS than HA/WBRT. White matter volume change was negatively correlated to cognitive outcomes. 5 mg BID dose optimally balances efficacy with tolerability. Clinical trial information: CTRI/2022/01/039599. Research Sponsor: None.

Predictors of overall survival in patients with brain metastases from HER2+ breast cancer.

Qinmei Xu, Banu Yagmurlu, Sandhini Agarwal, Michael Iv, Mark D. Pegram, Haruka Itakura; Stanford University School of Medicine, Stanford, CA; Stanford University, Stanford, CA; Department of Radiology, Stanford University School of Medicine, Stanford, CA

Background: Predictors of overall survival (OS) after brain metastasis (BM) in HER2-positive breast cancer (BC) are not well characterized. This study aimed to identify clinical and imaging-derived (radiomic) features that predict OS and develop a combined model for better prognostic performance. **Methods:** Our retrospective study analyzed 289 patients initially diagnosed with non-metastatic HER2-positive BC who later developed BM. We used 25 clinical characteristics and 12 treatment parameters to develop a Clinical model. We developed an Imaging model using a subset of 120 patients, who possessed evaluable pre-treatment brain MRI for delineating tumor segmentations on all brain metastatic lesions. We extracted 1078 radiomic features from each tumor segmentation using PyRadiomics, generating 8 feature sets based on 2 segmentation strategies (largest tumor per patient versus all tumors combined) and 4 tumor feature types (entire tumor, solid component, necrotic component, combined solid and necrotic features with statistical transformations). Morphological features, including lesion number, total size/volume, and necrotic-to-solid ratios, were also incorporated, along with tumor intracranial location. Cox proportional hazards regression model with Coxnet, integrating LASSO and Elastic Net regularization, was used to predict OS. For fair comparison, we randomly selected 30% (n = 31) of the smallest subset (n = 103, largest brain metastasis with both necrotic and solid components), all of which overlap with other model subsets, as validation cohort. Three model types—Clinical, Imaging and Combined—were compared using the concordance index (C-index) to assess performance based on validation cohort. **Results:** Clinical model, built on the whole cohort (286 women, 3 men; mean age 54.52 ± 12.79 years), identified 3 predictors of OS. Imaging model, built on a subset of 120 patients with brain MRI data, identified a radiomic signature (RS) consisting of 4 radiomic features most predictive of OS. Using the same subset, the Combined model (C-index: 0.728 [95% CI: 0.590–0.855]) outperformed Clinical (C-index: 0.62 [95% CI: 0.44–0.78]) and Imaging (C-index: 0.62 [95% CI: 0.46–0.77]) models in the held-out validation cohort (n = 31). Significant features associated with increased mortality risk in the Combined model included a higher RS, absence of tucatinib treatment for the primary BC prior to BM development, elevated Ki-67 expression, Black race, higher N stage, and brainstem metastases. Among these factors, RS, with the largest absolute coefficient in the Combined model (0.38), emerged as the most important predictor of OS (hazard ratio: 20.03 [95% CI: 4.92–81.48], $p < 0.005$). **Conclusions:** A distinct RS from brain MRI is the strongest predictor of OS in patients with BM from HER2-positive BC, surpassing clinical factors. RS may refine risk stratification and guide treatment or clinical trial prioritization. Research Sponsor: Susan G. Komen.

Hippocampal-avoidance whole-brain radiotherapy with dose escalation on metastases: A prospective randomized trial (HIPPORAD).

Anca-Ligia Grosu, Claudia Schmoor, Erika Graf, Lars Frings, Thomas Rothe, Sabine Schneider-Fuchs, Oliver Oehlke, Ursula Nestle, Florian Würschmidt, Maximilian Niyazi, Raphael Bodensohn, Frank Paulsen, Victor Lewitzki, Jürgen Dunst, Emmanouil Fokas, Sophie Wetzel, Ilja Ciernik, Christian T. Dietzel, Marcel Ott, Ilinca Popp, on behalf of the HIPPORAD Study Group; Department of Radiation Oncology, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany; Clinical Trials Unit Freiburg, Medical Center, University of Freiburg, Freiburg, Germany; Institute of Medical Biometry and Statistics, Medical Center-University of Freiburg, Faculty of Medicine, Freiburg, Germany; Department of Nuclear Medicine, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany; Clinical Trials Unit, University Medical Center Freiburg, Freiburg, Germany; Department of Radiation Oncology, Kliniken Maria Hilf Gmb, Mönchengladbach, Germany; Department of Radiotherapy and Radiation Oncology, Kliniken Maria Hilf, Moenchengladbach, Germany; Radiologische Allianz, Strahlentherapie, Hamburg, Germany; Department of Radiation Oncology, University Hospital, Ludwig Maximilians University of Munich, Munich, Germany; Department of Radiation Oncology, University Hospital Tübingen, Tübingen, Germany; Department of Radiation Oncology, University Hospital Tübingen, University of Tübingen, Tübingen, Germany; Department of Radiation Oncology, University Hospital Wuerzburg, Würzburg, Germany; Christian-Albrechts-Universitat zu Kiel, Kiel, Germany; Department of Radiotherapy and Oncology, University Hospital, Goethe University Frankfurt, Frankfurt, Germany; Department of Radiation Oncology, Krankenhaus Nordwest, Frankfurt, Germany; Department of Radiation Oncology, City Hospital Dessau, Dessau, Germany; Department of Radiation Oncology, University Hospital Halle (Salle), Halle, Germany; Department of Radiation Oncology, Klinikum Wolfsburg, Wolfsburg, Germany

Background: The HIPPORAD trial aimed to evaluate a new method of whole brain radiation therapy (WBRT) with simultaneous integrated boost (SIB) to the metastases, with versus without hippocampal avoidance in patients with brain metastases. **Methods:** We conducted a prospective, multicentre, randomised, double-blind trial (DRKS00004598). Patients with 4-10 brain metastases > = 5mm were randomised at 13 centres in Germany 1:1 between WBRT+SIB with hippocampus avoidance (HA-WBRT+SIB) (arm A) and WBRT+SIB (arm B). Patients and assessors of outcome were blinded to the randomised arm. All patients received WBRT with 30 Gy and SIB with 51 Gy or 42 Gy in 12 fractions, 5x/week. The primary endpoint was the change in neurocognitive function (assessed by the Verbal Learning and Memory Test [VLMT]) 3 months after treatment. Secondary endpoints included neurocognitive changes at 9 and 18 months, development of anxiety and depression, quality of life and measures of oncological outcome. **Results:** Between August 2nd, 2016 and September 7th, 2021, 170 patients were recruited and 136 were randomised between HA-WBRT+SIB (n = 67) and WBRT+SIB (n = 69). Of these, 38 patients in arm A and 42 in arm B were known to be alive 3 months after treatment and were included in the primary endpoint analysis. The change in overall learning performance at 3 months was not significantly different between arms (p = 0.83). VLMT-scores decreased after 3 months, but improved at 9 and 18 months, with HA-WBRT+SIB showing an overall superior trend over WBRT+SIB. At 18 months, VLMT-scores improved to values above baseline in both arms. Patients treated with HA-WBRT+SIB had significantly less depression compared to patients treated with WBRT+SIB at 3 (p = 0.047) and 18 months (p = 0.048). The 12-month-tumor control for boosted metastases was 96% in Arm A and 88% in Arm B, while for the WBRT area it was 78% in both arms. Time to hippocampal tumour progression was comparable between arms (p = 0.98). After 12 months, 4% of patients in arm A and 12% in arm B had suffered neurological death. **Conclusions:** To our knowledge, this is the first prospective trial to show that hippocampal avoidance during WBRT leads to significantly lower rates of depression. The development of VLMT values after HA-WBRT+SIB and WBRT+SIB with 30 Gy in 2.5 Gy-fractions was comparable and a good recovery was observed at 18 months in both arms. The method showed a considerably higher intracerebral tumour control with lower neurological mortality rates compared to historical cohorts. Clinical trial information: DRKS00004598. Research Sponsor: German Cancer Aid.

Initial report of memory avoidance whole brain radiotherapy to treat brain metastases: A prospective phase 2 trial.

Joshua David Palmer, Erica L. Dawson, Khaled Dibs, Alex R. Ritter, Yilun Sun, Daniel Boulter, Ansel P. Nalin, Raj Singh, Sasha Beyer, Simeng Zhu, Dukagjin M Blakaj, John C. Grecula, Raju R. Raval, Shayla Vazquez, Samantha Whitman, Carolyn J. Presley, Clement Pillainayagam, Pierre Giglio, Evan M. Thomas, Haley Kopp Perlow; Department of Radiation Oncology, Ohio State University, Columbus, OH; Department of Neurology, Ohio State University, Columbus, OH; Department of Radiation Oncology, West Virginia University, Morgantown, WV; Department of Population Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH; Department of Radiology, Ohio State University, Columbus, OH; Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; The Ohio State University, Columbus, OH; Ohio State University, Columbus, OH; Department of Neuro-Oncology, University Hospitals Seidman Cancer Center/ Case Western Reserve University, Cleveland, OH; Department of Neuro-Oncology, Ohio State University, Columbus, OH; Department of Radiation Oncology, Seidman Cancer Center University Hospitals/Case Western Reserve University, Cleveland, OH

Background: A common approach for patients with extensive brain metastases requiring radiation is hippocampal avoidance whole brain radiotherapy (HA-WBRT) prescribed with memantine; this was proven to be efficacious based on NRG CC001. However, a subset of patients who receive HA-WBRT with memantine still experience cognitive decline. Other brain structures with important roles in memory and cognition include the corpus callosum, fornix, amygdala, hypothalamus, and pituitary; these structures all have a low propensity for brain metastases and therefore can be safely spared in a radiotherapy plan without increasing the risk of relapse. A subset of patients enrolled on a Phase 2 Randomized Controlled Trial (NCT05503251) received an advanced "memory-avoidance WBRT (MA-WBRT) approach that spared these substructures in addition to the hippocampus, with a primary endpoint of improved cognition compared to a historical control (NRG CC001). **Methods:** All patients with $>$ 15 brain metastases on a prospective clinical trial, which randomized patients to either neuropsychology evaluation and intervention plus brain radiotherapy or brain radiotherapy alone, received MA-WBRT. Exclusion criteria included prior WBRT, pre-existing mental disability, and metastases within the avoidance neurocognitive substructures. All patients received 30 Gy in 10 fractions of MA-WBRT and were prescribed memantine. Cognition was measured by Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association Test, and Trail Making Test A/B, with cognitive decline defined as decline on at least one assessment using reliable change index (same tests and definition as NRG CC001). **Results:** Between August 2022 and May 2024, 29 patients received MA-WBRT. Baseline characteristics included a median KPS of 80 (IQR 70, 90), median age of 64 (IQR 54, 69), 62% female patients, and a plurality of patients with a primary lung cancer (48%), The median overall survival or time to last follow up was 7.9 months. The three-month decline in neurocognitive function comparing the control and intervention groups for patients receiving MA-WBRT was 15.4% and 18.8%, respectively ($p = 0.39$). There was one failure in the right fornix 10 months after enrollment, but this was associated with concurrent distant intracranial failure outside the memory avoidance zone. **Conclusions:** The cognitive decline rate of approximately 17% at three months for patients receiving MA-WBRT compares favorably to a 3-month cognitive decline rate of 50% seen on NRG CC001. Additionally, MA-WBRT does not appear to significantly increase the risk of intracranial failure. Further evaluation of the delayed impact ($>$ 6 months) of MA-WBRT on cognitive function will be reported when data are available. A direct comparison of MA-WBRT plus memantine vs. HA-WBRT plus memantine is forthcoming with a randomized phase 3 trial. Clinical trial information: NCT05503251. Research Sponsor: None.

Genomic predictors of brain metastases in breast cancer.

Anton Safonov, Deborah Ruth Smith, Subhiksha Nandakumar, Emanuela Ferraro, Junchao Shen, Ishaani S. Khatri, Rahul Kumar, Julia Ah-Reum An, Justin Jee, Mark E. Robson, Adrienne Boire, Nikolaus Schultz, Nelson S. Moss, Walid Khaled Chatila, Luke Roy George Pike, Pedram Razavi; Memorial Sloan Kettering Cancer Center, New York, NY; Weill Cornell Medical Center, New York, NY; Brown University, Providence, RI; University of Miami, Miami, FL

Background: Despite therapeutic advances in metastatic breast cancer (MBC), the rising incidence of brain metastases (BM) remains a major challenge, contributing to poor prognosis and significant morbidity. Due to the absence of consensus screening strategies for BM, they are often detected only after clinical symptoms emerge. There is therefore a pressing need for predictive biomarkers to identify breast cancer patients at risk of BM. **Methods:** This study included 3908 patients who underwent sequencing of primary tumor (n = 1885) or non-brain metastasis (n = 2023) with MSK-IMPACT, a custom tumor-normal next generation sequencing assay. First, we performed penalized logistic regression on a gene level to identify alterations in extracranial metastases or primary tumors associated with development of BM. We adjusted for multiple hypothesis testing using Benjamini-Hochberg. Lastly, we developed a lasso machine-learning (ML) model, incorporating baseline genomic and clinicopathologic features, to predict onset and timing of BM from initial diagnosis (for early stage cases) or metastatic disease (for MBC). Each analysis was stratified by receptor status, and repeated to account for loss of heterozygosity (LOH) of tumor suppressor genes. **Results:** Our cohort included 528 BM events over a median follow-up of 58 mos. Pathogenic variants in several genes were associated with subsequent BM development. In the HR+/HER2- subset (n = 2624), pathogenic variants in the following genes portended the onset of BM: *RB1* (OR 2.59 [1.39 - 4.81], q = 0.011), *NF1* (OR 2.22 [1.21 - 4.06], q = 0.039), *TP53* (OR 1.91 [1.43 - 2.54], q < 0.001), *PIK3CA* (OR 1.47 [1.21-4.06], q = 0.028). Pre-existing LOH of *RB1,* in the absence of an *RB1* functional alteration, was associated with BM development (OR 1.37 [1.03 - 1.83], q = 0.090). *TP53* LoF .OR 5.14 [2.21 - 11.9], q < 0.001) was enriched in the BM group in HER2+ tumors, while amplification of *CDKN2A* (OR 11.6 [2.44 - 55.5], q = 0.01) or *EGFR* (OR 4.60 [1.54 - 13.8], q = 0.03) were enriched in TNBC. *TP53* emerged as an important feature across all receptor subtypes in our machine-learning model; *RB1* LoF was also selected as an important feature in the HR+/HER2- group. Validation of the ML model in an external cohort will be presented at the meeting. **Conclusions:** In a large cohort of genomically profiled breast cancer samples, we found several biologically plausible candidates for molecular harbingers of BM. For instance, the recurrent involvement of genes involved in cell cycle regulation (*RB1, CDKN2A, TP53)* has been implicated as candidates for BM tropism in other cancer types. Our approach also uncovers several alterations for which targeted therapies exist or are actively in development *(NF1, PIK3CA)*. Our clinically actionable multimodal model of BM risk is poised to facilitate the development of early detection strategies and guide-high risk patient selection for novel clinical trials to intercept this devastating complication. Research Sponsor: None.

Characterizing functional connectivity in brain tumor patients.

Alexander B. Remsik, Camille Garcia-Ramos, Jon Wieser, Krithi Gopinath, Michael Veronesi, Mustafa K. Baskaya, Mahua Dey, Pallavi Tiwari, Ankush Bhatia, Veena Nair, Vivek Prabhakaran; University of Wisconsin System, Madison, WI; University of Wisconsin-Madsion, Madison, WI; University of Wisconsin Madison, Madison, WI; UW-Madison, Madison, WI; University of Wisconsin, Madison, WI; University of Wisconsin-Madison, Madison, WI

Background: Brain tumors (affecting 25,500 individuals in the US alone) cause unique changes to neural function and connectivity resulting in impairments in various functional domains, including cognition. **Methods:** Between 2012 and 2018, as part of their preoperative surgical planning, 91 brain tumor patients with tumors in right (R) or left (L) temporal (T), parietal (P) or frontal (F) lobes received resting-state functional magnetic resonance imaging (rs-fMRI) and the COWAT verbal fluency (VF) test. UW Hospital and Clinics uses 1.5 T (112 axial slices, 1.0 $\times$ 1.0 $\times$ 1.5 mm) and 3 T (136 axial slices, 1.0 $\times$ 1.0 $\times$ 1.2 mm) GE MRI scanners and includes high-resolution 3D BRAVO T1-weighted imaging, and rs-fMRI scans (eyes closed, 28 axial slices, 3.75$\times$3.75$\times$5.0mm) were also acquired during this imaging protocol. These individuals were compared to each other and to 40 age-matched non-tumor controls (Cs). **Results:** Groups were similar in age, and sex ($p>0.05$), but different in education ($p=0.028$) and VF scores ($p=0.001$). There were significant differences in post-hoc p-values when comparing VF scores between Cs and RT tumor patients ($p=0.039$). Qualitative observations indicate Cs are more integrated have greater network strength and connectivity higher transitivity, efficiency, and modularity index compared to patients. There were significant differences in VF scores between Cs, LF ($p=0.001$), RF ($p=0.012$), RT ($p=0.021$), RP ($p=0.015$). Patients show hypo-frontality of hubs and a unique cerebellar module. LF patients showed correlation to transitivity at 25% ($R=0.404$, $p=0.041$), and patients with RP tumors had significant correlations to transitivity ($R=0.654$, $p=0.029$) and global efficiency ($R=0.607$, $p=0.048$). Cs and L tumors did not show any significant correlation to VF scores, R tumors showed correlation with global efficiency at 25% sparsity ($R=0.374$, $p=0.025$). All remained significant after FDR correction. **Conclusions:** Tumor location impacts rs-fMRI-derived GT network structure and VF scores, suggesting tumors in left hemisphere and frontal areas caused the greatest impact to cognition. These methods may be used in future research and clinical care to map, track, and predict functional connectivity changes resulting from brain tumor and can help inform clinicians and care trajectories. Research Sponsor: NIH (NINDS); T32CA009206, R01NS117568, R01NS123378, TL1TR002375, R01CA264017, R01CA277728, UL1TR002373, P30CA014520; WI Partnership Program; VA; BX005842-01A2; Wisconsin Alumni Research Foundation; MSN281757.

AI-driven transcriptomic classification of glioblastoma: Associations with survival and tumor microenvironment.

Juan Manuel Fernandez-Muñoz, Román Oberti, David A. Reardon, Francisco Quintana, Guido Nicolas Molina, Martin Eduardo Guerrero-Gimenez; SphereBio, Mendoza, Argentina; Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; SphereBio, Buenos Aires, Argentina

Background: Glioblastoma (GBM) is the most lethal primary brain tumor in adults, with a median survival of ~15 months despite current therapies (surgery, radiation, temozolomide). Advances like immune checkpoint inhibitors, anti-angiogenic agents, and tumor vaccines have shown suboptimal results. The 2021 WHO classification highlights molecular markers (e.g., IDH, MGMT) for better stratification, but these fail to fully capture tumor microenvironmental dynamics. Using an AI-driven transcriptomic approach, we identified novel prognostic subtypes in IDH-wildtype GBM, aiming to refine stratification, enhance understanding of tumor biology, and guide personalized therapeutic strategies. **Methods:** We accessed microarray data from The Cancer Genome Atlas (TCGA) (n=353 newly diagnosed, IDH-WT GBM) for a training set and RNA-seq data from the Chinese Glioma Genome Atlas (CGGA) (n=170 primary and n=106 recurrent tumors) for validation. A proprietary SphereBio machine learning–based algorithm was used to derive transcriptomic signatures with prognostic relevance. Subtypes were assessed via Kaplan–Meier analyses in the training cohort and tested in both primary and recurrent validation cohorts. Immune/stromal infiltration was quantified using a tumor deconvolution tool (DA_505), and pathway enrichment (GAGE) was performed on the validation sets. **Results:** AI-driven clustering revealed three transcriptomic subtypes with significant survival differences in both the training ($p<0.0001$) and primary validation ($p=0.0004$) cohorts. In the recurrent cohort, a similar survival trend by subtype was observed, though significance was diminished ($p=0.12$), likely due to limited sample size and therapy-related changes. Immune/stromal deconvolution showed distinct infiltration patterns: subtypes enriched for CD4+ and CD8+ T cells correlated with prolonged survival. Pathway enrichment analysis in both primary and recurrent tumors highlighted potential targets involving embryogenesis, immune modulation, cell cycle, and stress response. The persistence of a consistent survival trend and comparable microenvironment and pathway patterns suggest that these transcriptomic subtypes remain biologically relevant even after standard treatment. **Conclusions:** Our integrated transcriptomic and microenvironment-focused approach identified three prognostically distinct GBM subtypes, validated across independent cohorts. These findings underscore the utility of AI-driven transcriptomic signatures for personalized stratification, with the potential to guide targeted therapeutic strategies and inform clinical trial design in GBM. Research Sponsor: None.

Impact of neuroradiologists' input on peer review meetings for CNS radiotherapy treatment planning.

Abhishek Mahajan, Chloë May, Shaveta Mehta, Aditya Shenoy, Noon Altijani, Robert Brass; The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, Merseyside, United Kingdom; The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, United Kingdom; The Clatterbridge Cancer Centre, Liverpool, United Kingdom; Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom

Background: Evidence shows radiologists' involvement improves planning accuracy, especially in complex anatomical areas. However, their participation remains limited. This prospective observational study evaluates the impact of neuroradiologists' input on changes to radiotherapy (RT) plans during peer review meetings. **Methods:** Data were collected from 205 patients with CNS tumours planned for radiotherapy between May 2022 and October 2023. We recorded demographics, diagnostic and RT planning scans, and therapy received. All images were reviewed by a neuroradiologist, with RT changes classified as major (affecting cure or disease control) or minor (affecting target volumes or organs at risk). Summary statistics were calculated, and Pearson chi-squared tests assessed whether changes in RT plans varied by tumour type, time since diagnosis, and neuroradiologist findings. Data were analyzed using STATA SE v.17. **Results:** Of 205 patients, 81 (40%) had gliomas, 77 (38%) had brain metastases, 23 (11%) had meningiomas, 17 (8%) had schwannomas, and 7 (3%) had pituitary tumours. The mean age was 60 years (SD 14), 56% were male, and 36% were treatment-naïve. All but one had MRI scans, 128 (62%) had CT scans, and 9 (4.4%) had PET scans. The median number of diagnostic scans per patient was 2 (IQR 2-3), and all had two planning scans. The median interval between diagnosis and RT planning scans was 35 days (IQR 21-61). Disease progression was observed in 67 (33%) patients. Major and minor changes to RT plans were reported in 35 (17%) and 78 (38%) patients, respectively. A higher proportion of RT plans changed for brain metastasis (26% & 40%) and glioma (11% & 43%). Changes were not associated with tumour type ($p = 0.07$) or time since diagnosis ($p = 0.12$), but were significantly associated with neuroradiologist findings ($p < 0.0001$). **Conclusions:** Neuroradiologists' assessments led to major and minor changes in RT plans, regardless of tumour classification or interval since diagnosis. This expertise can enhance RT plan accuracy, improving patient outcomes. Research Sponsor: None.

Changes to radiotherapy treatments as per RCR categories and by tumour type, time interval, and neuroradiologist findings.

	Changes to radiotherapy plan			
	Major change (N= 35)	Minor change (N= 78)	No change (N=92)	P value*
Total	17 %	38%	45%	
Tumour classification				0.07
Glioma	9 (11.1)	35 (43.2)	37 (45.7)	
Meningioma	3 (13.0)	7 (30.4)	13 (56.5)	
Schwannoma	2 (11.8)	3 (17.7)	4 (57.1)	
Pituitary tumour	1 (14.3)	2 (28.6)	4 (70.6)	
Metastasis	20 (26.0)	31 (40.3)	26 (33.8)	
Time interval, weeks				0.12
Less than 8	27 (77.2)	61 (78.2)	59 (64.1)	
8-	4 (11.4)	10 (12.8)	20 (21.7)	
16-	1 (2.9)	3 (3.9)	7 (7.6)	
24-	-	2 (2.6)	1 (1.1)	
30-	-	2 (2.6)	3 (3.3)	
38-	3 (8.6)	-	2 (2.2)	
Neuroradiologist findings				<0.0001
Stable disease	17 (48.6)	35 (44.9)	71 (77.2)	
Residual disease	3 (8.6)	6 (7.7)	6 (6.5)	
Disease progression	15 (42.8)	37 (47.4)	15 (16.3)	

**Pearson chi-squared test.*

Identification and validation of potential diagnostic plasma biomarkers for diffuse gliomas by multiplex immunoassays.

Miyo K. Chatanaka, Lisa Avery, Mingyue Wang, Catherine Demos, Jermaine Brown, Taron Gorham, Salvia Misaghian, Nikhil Padmanabhan, Hans Layman, Daniel Romero, Martin Stengelin, Anu Mathew, George Sigal, Jacob Wohlstadter, Craig Horbinski, Kathleen McCortney, Eleftherios P. Diamandis, Ioannis Prassas; University of Toronto, Toronto, ON, Canada; Department of Biostatistics, University Health Network, University of Toronto, Toronto, ON, Canada; Meso Scale Diagnostics, LLC., Rockville, MD; Meso Scale Discovery, Rockville, MD; Department of Pathology, Northwestern University, Chicago, IL; Department of Neurological Surgery, Lou and Jean Malnati Brain Tumor Institute of the Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL; Sinai Health System, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada

Background: Diffuse gliomas are aggressive malignant tumors with poor prognosis. The current standard of care includes measurement of molecular biomarkers in biopsy samples. One unmet clinical need is to identify non-invasive biomarkers that may be used for differential diagnosis of gliomas from other brain tumors. Pre-clinical and clinical validation of such biomarkers could eliminate the need for biopsy, and support the implementation of more personalized and/or emerging treatments and the earlier enrolment of patients into clinical trials. Our objective is to use multidimensional proteomics to identify and validate potential plasma biomarkers for glioma management. **Methods:** We used the proximity extension assay from Olink Proteomics to analyze 3,000 proteins in plasma of patients with diffuse gliomas and meningiomas (as controls). By data visualization, we identified several plasma proteins that were increased or decreased in gliomas in comparison to meningiomas. Several candidate markers were selected for validation with an independent set of retrospectively collected samples by using quantitative research-use-only electrochemiluminescence assays available from Meso Scale Discovery. In the validation set, which included longitudinal data from patients, patient information included biopsy-requiring molecular tumor abnormalities such as IDH1 status, ATRX expression, MGMT promoter methylation, CDKN2A/B/p16 status, V1p 19q co-deletion and NF1 status. In the validation stage, we focused on diffuse gliomas. **Results:** In the discovery phase, associations between proteins were plotted to determine potential predictive ability for discriminating diffuse gliomas vs. meningiomas. A partitioning algorithm was fit to determine the optimal combination of GFAP (the strongest biochemical marker), age and sex, as well as with other candidate proteins. Differential expression was seen for a few other proteins such as NEFL, PROK1, FABP4, MMP3 and LMOD1. In the cross-sectional validation phase, we verified strong associations between GFAP and FABP4 plasma concentration and GBM, astrocytomas, oligodendrogliomas and meningiomas, where these markers could differentiate between the groups. Within diffuse gliomas, NEFL, GFAP, FABP4 and IL13 were significantly different. **Conclusions:** This study highlights the potential of plasma biomarkers to revolutionize glioma patient management through liquid biopsy applications. The strong associations observed between plasma protein concentrations and glioma subtypes support a diagnostic power that addresses a critical unmet need in neuro-oncology. More specifically, these biomarkers can help with patient differential diagnosis at initial presentation, with future aims to investigate the prognostic value and the possibility of acting as surrogates of molecular changes that are currently used for optimizing therapy. Research Sponsor: Canadian Institutes for Health Research, The Canadian Brain Foundation, Canadian Cancer Society Research Institute; CCS707057; National Cancer Institute; P50CA221747.

Association of plasma biomarkers with diagnostic molecular markers for potential diagnosis and prognosis of diffuse gliomas.

Leonardo Macedo Filho, Miyo K. Chatanaka, Andrew Ajisebutu, Lisa Avery, Mingyue Wang, Catherine Demos, Jermaine Brown, Taron Gorham, Salvia Misaghian, Nikhil Padmanabhan, Hans Layman, Daniel Romero, Martin Stengelin, Anu Mathew, George Sigal, Jacob Wohlstadter, Gelareh Zadeh, Alireza Mansouri, Eleftherios P. Diamandis; Penn State College of Medicine, Hershey, PA; University of Toronto, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada; Department of Biostatistics, University Health Network, University of Toronto, Toronto, ON, Canada; Meso Scale Diagnostics, LLC., Rockville, MD; Meso Scale Discovery, Rockville, MD; Penn State Health, Hershey, PA; Sinai Health System, Toronto, ON, Canada

Background: Diffuse gliomas were recently reclassified based on the 2021 WHO Classification criteria. Several molecular changes which carry diagnostic and prognostic power have been added to the classification parameters, including IDH1 mutation and MGMT promotor methylation. To characterize these molecular changes, however, an invasive biopsy is required. Our goal was to examine the relationship between seven plasma biomarkers for diffuse glioma and the established molecular changes and delineate if these markers can be used as surrogates of these molecular changes. **Methods:** Seven candidate markers, namely glial fibrillary acidic protein (GFAP), neurofilament light (NEFL), matrix metalloproteinase 1, 3, 9 (MMP1, MMP3, MMP9), total Tau (tTau) and fatty acid binding protein 4 (FABP4) were evaluated by quantitative research-use-only electrochemiluminescence assays available from Meso Scale Discovery by comparing the protein concentration distribution with non-parametric Wilcoxon rank sum tests and multiple testing adjustment. The molecular markers tested were IDH1, MGMT promotor and ATRX. The discovery cohort consisted of 49 IDH1 mutant (39%) and 77 IDH1 wildtype (61%) gliomas. Among this retrospective cohort were 103 primary samples (collected at diagnosis) and 23 recurrent samples (collected at time of recurrence). The retrospective validation cohort consisted of 36 IDH1 mutant (22%) and 129 IDH1 wildtype (78%), with 64 primary samples and 76 recurrent samples. **Results:** Several of the proteomic markers showed significant associations with genetic markers at an adjusted significance level of $P < 0.05$. For IDH1 status, the strongest association was with NEFL, with IDH1 wildtype samples showing higher levels of the protein. For ATRX expression, high FABP4 was correlated with ATRX retention. As expected, survival analysis based on molecular markers yielded that IDH1 status was most predictive of survival both in primary tumors and recurrent tumors. MGMT promotor methylation was predictive of survival in primary cases but not recurrent cases. When combining the genetic markers with protein concentrations, we were able to see some improvement in survival prediction. **Conclusions:** We demonstrate that some plasma biomarkers, particularly NEFL and FABP4, show significant associations with key molecular changes in diffuse gliomas, including IDH1 status and ATRX retention/loss. Future research will determine whether these proteomic markers can serve as surrogates for molecular alterations and assist in potentially improved diagnosis and monitoring of diffuse gliomas. Research Sponsor: None.

A multicenter randomized phase III study for recurrent glioblastoma comparing bevacizumab alone with dose-dense temozolomide followed by bevacizumab: JCOG1308C.

Motoo Nagane, Keiichi Kobayashi, Riku Kajikawa, Yoshiki Arakawa, Noriyuki Kijima, Shigeru Yamaguchi, Yoshiko Okita, Yoshiteru Shimoda, Hirokazu Takami, Yukihiko Sonoda, Kazuhiko Mishima, Ichiyo Shibahara, Takaaki Beppu, Ryo Nishikawa, Fumiyuki Yamasaki, Koichi Ichimura, Takashi Komori, Keita Sasaki, Haruhiko Fukuda, Yoshitaka Narita; Department of Neurosurgery, Kyorin University Faculty of Medicine, Tokyo, Japan; JCOG Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan; Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan; Department of Neurosurgery Osaka University Graduate School of Medicine, Osaka, Japan; Department of Neurosurgery, Faculty of Medicine, Hokkaido University, Hokkaido, Japan; Department of Neurosurgery, Osaka International Cancer Institute, Osaka, Japan; Department of Neurosurgery, Tohoku University Graduate School of Medicine, Miyagi, Japan; Department of Neurosurgery, The University of Tokyo Hospital, Tokyo, Japan; Department of Neurosurgery, Yamagata University Faculty of Medicine, Yamagata, Japan; Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Saitama, Japan; Department of Neurosurgery, Kitasato University School of Medicine, Kanagawa, Japan; Department of Neurosurgery, Iwate Medical University, Iwate, Japan; Department of Neurosurgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; Department of Pathology Kyorin University Faculty of Medicine, Tokyo, Japan; Department of Laboratory Medicine and Pathology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan; Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Temozolomide (TMZ) is an alkylating agent commonly used as the standard therapy for newly diagnosed glioblastoma (GBM), with the DNA repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT) serving as a key prognostic and predictive factor. Despite treatment, GBM almost always recurs with limited therapeutic options, leading to poor prognosis. Since MGMT is consumed during the repair of TMZ-induced O^6-methylguanine lesions in DNA, dose-intensified TMZ regimens are designed to deplete MGMT, thereby enhancing tumor sensitivity to TMZ. Bevacizumab (BEV), an anti-VEGF agent, has shown efficacy in recurrent GBM (re-GBM), but no effective therapies exist after BEV failure. Introducing an active agent before BEV may improve outcomes. To test this, we conducted a multicenter, phase III study comparing BEV monotherapy with dose-dense TMZ (ddTMZ) followed by BEV in re-GBM. **Methods:** Patients (pts) aged 20-75 years with KPS ≥60 and histologically confirmed GBM at first recurrence were enrolled from 31 Japanese hospitals. Participants were randomized to BEV monotherapy (10 mg/kg every 2 weeks; arm A) or ddTMZ (120-150 mg/m^2, 7 days on/7 days off) followed by BEV at progression (arm B). Treatment continued until progression or unacceptable toxicity. The primary endpoint was overall survival (OS). A planned sample size of 146 pts provided 70% power to detect a hazard ratio (HR) of 0.73 (median OS (mOS): 8 vs. 11 months) at a one-sided alpha of 10%. *MGMT* promoter methylation and *IDH* mutation status were analyzed. **Results:** From July 2016 to April 2022, 146 pts (73 per arm) were randomized. *MGMT* promoter methylation was observed in 78 pts, while 49 were unmethylated. *IDH1* mutations were identified in 8 of 129 pts to be tested. The mOS was 11.0 months (95% CI: 9.0-12.8) in arm A and 10.8 months (95% CI: 8.6-12.5) in arm B, with no significant difference (HR 0.922, 95% CI: 0.655-1.297, one-sided p = 0.320). No significant OS difference was observed between arms based on *MGMT* methylation status. The median progression-free survival (PFS) was 4.0 months (95% CI: 3.8-5.7) in arm A and 2.0 months (95% CI: 1.9-2.1) in arm B (HR 1.632, 95% CI: 1.168-2.281). Most pts in arm B exhibited progression at their first MRI. From the start of BEV treatment, mOS was 10.8 months (95% CI: 8.8-12.6) in arm A, and 8.0 months (95% CI: 6.1-9.1) in arm B. Grade 3-4 adverse events included hypertension (19.4%) in arm A and lymphopenia (52.1%) and leukopenia (8.2%) during ddTMZ in arm B. Grade 4 toxicities were rare. **Conclusions:** While ddTMZ was well-tolerated, this study failed to demonstrate a survival benefit for ddTMZ followed by BEV in re-GBM. BEV remains the preferred treatment at first recurrence. Further research is needed to develop effective therapies beyond the current standard for re-GBM. Clinical trial information: NCT02761070. Research Sponsor: Japan Agency for Medical Research and Development; 17824890.

Use of brain protein I3 (BRI3) to predict disease fate in glioblastoma.

Ifeanyichukwu Ogobuiro, Scott M. Welford, Markus Bredel; The University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL; University of Miami Leonard M. Miller School of Medicine, Miami, FL

Background: Genome-wide characterization has illuminated the molecular complexity of human gliomas. Genetic alterations help predict the clinical behavior of gliomas, but variability persists. Accordingly, there is a need to expanding molecular signatures that refine prognostication. The Brain Protein I3 (BRI3) gene, localized on chromosome 7, is associated with high-grade glioma, yielding the highest hazard ratio among all high-risk genes in an in-silico glioma model. Given GBM's known chromosome 7 gain and BRI3's chromosomal location, we hypothesized that gene dosage gains and overexpression serve as prognostic biomarkers. **Methods:** We used the Rembrandt (n = 461 patients) and TCGA low-grade glioma (LGG) and GBM (n = 1,148 patients) databases for multi-omic analyses. RNA sequencing (Illumina HiSeq) and DNA methylation profiles (Illumina 450K) were analyzed in a combined LGG and GBM cohort, with high/low expression and hyper/hypomethylation defined by median values. CNV analysis (GISTIC 2.0) classified 2 copies as gene-copy neutral and > 2 as gene dosage gain. Somatic mutation data (SNPs/INDELs) were derived from whole-exome sequencing to decipher IDH-wt and IDH-mutant gliomas. Univariate and adjusted Cox models, Kaplan-Meier estimates, and receiver operating characteristic (ROC) curve analysis were performed. **Results:** Of 461 Rembrandt patients, 47.29% were GBM, 31.89% astrocytoma, 14.53% oligodendroglioma, and 6.29% normal brain. Among 1,148 TCGA LGG/GBM patients, 551 had complete molecular and clinical data, with 28% IDH-wt status, 49% MGMT hypermethylation, and 36.66% BRI3 gene dosage gains. BRI3 expression was significantly higher in GBM, grade IV tumors, IDH-wt, and mesenchymal subtypes. Among the IDH-wt cases, 75% showed BRI3 gene dosage gains with significantly elevated mRNA expression. EGFR, co-amplified in 80% of IDH-wt cases, did not affect survival (25.27 vs. 17.90 months, $p = 0.346$). Conversely, BRI3 gene dosage gain correlated with worse survival (79.3 vs. 17.93 mo, $p = 0.001$), as did BRI3 high vs. low expression (17.90 vs. 25.27 months, $p = 0.015$) and MGMT hypermethylation (25.27 vs. 18.63 mo, $p = 0.021$). Univariate analysis linked patient age (HR: 2.858 [1.781–4.586], $p < 0.001$), MGMT hypermethylation (HR: 2.632 [1.307–5.301], $p = 0.007$), BRI3 high expression (HR: 1.938 [1.131–3.320], $p = 0.016$) and BRI3 gene dosage gain (HR: 2.504 [1.425–4.398], $p = 0.001$) to worse OS. Adjusted multivariate Cox regression confirmed BRI3 gene dosage gain, age, and MGMT methylation as independent OS predictors in IDH-wt cases. ROC analysis revealed stronger prognostic performance for BRI3 gene dosage gain than MGMT hypermethylation (AUC: 0.737 vs. 0.616, $p < 0.001$) in IDH-wt cases. **Conclusions:** Elevated BRI3 gene dosage and expression portend poor prognosis and could be incorporated into models predicting disease fate in GBM. Research Sponsor: None.

Effect of armed oncolytic adenovirus on immunotherapy for primary and metastatic brain tumors.

Jiasen He, Akhila Parthasarathy, Dong Ho Shin, Marc Moure, Andres Lopez-Rivas, Andrew G. Gillard, Alejandra Duran, Xuejun Fan, Timothy Phoenix, Frederick F. Lang, Marta Alonso, Juan Fueyo, Candelaria Gomez-Manzano, Hong Jiang; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Cincinnati, Cincinnati, OH; CIMA-Universidad de Navarra, Pamplona, Spain

Background: Oncolytic viruses have shown promise in clinical trials for solid tumors, including glioma and melanoma, but only a subset of patients benefits. We previously showed that arming the oncolytic adenovirus Delta-24-RGD with OX40L can enhance antitumor immunity. To further boost efficacy, we developed Delta-24-RGDOX-IL15, co-expressing OX40L and IL-15, and tested it in preclinical models of primary and metastatic brain tumors. **Methods:** To evaluate IL-15 and its receptor (IL15RA) expression in patients with glioma and melanoma, we conducted gene expression and survival analysis using the GEPIA web server, integrating RNA sequencing data from TCGA and GTEx. Transgene expression in Delta-24-RGDOX-IL15 was assessed via flow cytometry and ELISA, while viral potency was evaluated using replication and cell viability assays. Anti-tumor activity was tested in syngeneic intracranial models derived from mouse diffuse midline (DMG) glioma and melanoma cell lines in C57BL/6 mice, both of which expressed GD2 and luciferase. Tumor growth was monitored with bioluminescent imaging, survival with Kaplan-Meier analysis, and immune profiling of the tumor microenvironment using flow cytometry. **Results:** GEPIA analysis showed that melanoma had higher expression of IL-15 and IL-15RA compared to glioma. In melanoma patients, higher expression of IL-15RA or IL-15 was linked to better overall survival ($P < 0.005$), while no survival difference was found in patients with glioma. Delta-24-RGDOX-IL15 infected and co-expressed OX40L and IL-15 effectively in mouse glioma and melanoma cells, and induced potent oncolysis. Delta-24-RGDOX-IL15-infected tumor cells significantly enhanced the oncolysis activity of GD2 CAR T cells in culture. Intratumoral injection of the virus also resulted in better tumor reduction and improved survival in C57BL6 mice with gliomas derived from mouse DMG cells while no significant toxicity was observed. Additionally, locoregional therapy with Delta-24-RGDOX-IL15 induced a systemic inflammatory response in the tumor microenvironment, characterized by increased frequency of T cells and reduced that of myeloid cells. **Conclusions:** Higher expression of IL-15/IL-15RA is associated with better survival in patients with melanoma. Delta-24-RGDOX-IL15 demonstrates potent oncolytic activity in both glioma and melanoma cell lines. In the intracranial brain tumor mouse model, it exhibited promising anti-tumor effects with enhanced T cell stimulation and minimal toxicity. Delta-24-RGDOX-IL15 is a promising candidate for combination with cellular therapies in both primary and metastatic brain tumors. Research Sponsor: ChadTough Defeat DIPG Foundation.

A phase I clinical trial on combined (neo-)adjuvant intravenous plus intracranial administration of ipilimumab and nivolumab in recurrent glioblastoma (NEO-GLITIPNI).

Iris Dirven, Louise Lescrauwaet, Cleo Bertels, Latoya Stevens, Xenia Geeraerts, Freya Vaeyens, Anne-Marie Vanbinst, Hendrik Everaert, Stefanie Brock, Sandra Tuyaerts, Mark Kockx, Johnny Duerinck, Bart Neyns; Department of Medical Oncology, Laboratory for Medical and Molecular Oncology (LMMO), Translational Oncology Research Center (TORC), Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium; Department of Neurosurgery, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Laboratory for Medical and Molecular Oncology (LMMO), Translational Oncology Research Center (TORC), Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium; Centre for Medical Genetics, Research Group Genetics, Reproduction and Development, Clinical Sciences, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Department of Radiology, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Department of Nuclear Medicine, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Department of Pathology, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; CellCarta, Antwerp, Belgium

Background: Intravenous (IV) administration of ipilimumab (IPI) and nivolumab (NIVO) has shown limited activity in recurrent glioblastoma (rGBM). Intracerebral (iCer; within the brain tissue lining the resection cavity) and intracavitary (iCav; through an Ommaya reservoir) administration (admin) of IPI and NIVO was proven to be safe and resulted in promising survival outcomes (Duerinck et al. Neuro-Oncol 2024). Adding a neoadjuvant (NEOADJ) treatment phase to iCer/iCav IPI/NIVO may further improve outcome. **Methods:** In the Neo-Glitipni trial (NCT06097975), a single center, phase I clinical trial, patients (pts) with resectable rGBM (WHO grade 4, IDH wild type) who progressed after radiotherapy and temozolomide, with a baseline ECOG performance status of 0-2 and ≤8 mg methylprednisolone daily, received 2 NEOADJ cycles of IV IPI 1 mg/kg + NIVO 3 mg/kg followed by maximal safe resection (MSR) in week 5 with iCer admin of IPI 5 mg + NIVO 10 mg and iCav admin of IPI 1 mg + NIVO 10 mg. The adjuvant phase consists of biweekly postoperative iCav admin of IPI 1 mg + NIVO 10 mg and IV NIVO 240 mg for 12 cycles, followed by monthly NIVO 480 mg IV maintenance for up to two years. **Results:** 5 pts (4 male, median age 57 years (44-65); 1st recurrence in 3 pts) were enrolled. All pts received the 1st and 4 pts also the 2nd NEOADJ dose of IV IPI/NIVO. Out of the 5 pts, 3 were not amenable to MSR with iCer/iCav IPI/NIVO admin according to the protocol because of disease progression during the NEOADJ treatment phase and required corticosteroids (1 pt in week 2, 2 pts in week 4). Two pts successfully underwent MSR with iCer/iCav admin of IPI/NIVO per protocol. One pt initiated adjuvant treatment with iCav IPI/NIVO and IV NIVO. There were no unexpected adverse events (AE). Two pts experienced an immune-related AE that required corticosteroids and interruption of study treatment (grade 4 hepatitis in 1 pt, onset 8 days after MSR and grade 2 colitis in 1 pt, onset 28 days after MSR). One pt developed a thyroiditis during the NEOADJ treatment phase and 2 pts experienced a grade 3 treatment related AE that was not immune-related (seizure and Ommaya reservoir infection). None of the rGBM were characterized by a high tumor mutational burden on next generation sequencing. Gene expression profiling, and pharmacokinetic analysis of NIVO and IPI in the cerebrospinal fluid and blood are ongoing. After a median follow-up of 15 weeks (9-35w) all pts are alive, one pt remains free of progression (median progression free survival: 4.3 weeks). **Conclusions:** Four weeks of NEOADJ IV IPI/NIVO (comprising 2 admin) is safe, but symptomatic disease progression was observed in 3 out of 5 rGBM pts prior to the planned MSR with iCer/iCav IPI/NIVO admin in week 5. Therefore, the trial is being amended by shortening the NEOADJ treatment phase to 2 weeks (1 admin) and planned MSR with iCer/iCav IPI/NIVO admin in week 3. Clinical trial information: NCT06097975. Research Sponsor: None.

Effect of 18F-DOPA-PET and advanced MRI on treatment response assessment in IDH1/2-mutant gliomas treated with IDH inhibitors.

Diego Martín Prost, Lucia Nichelli, Laura Rozenblum, Alice Laurenge, Caroline Dehais, Bertrand Mathon, Julian Jacob, Louisa Drouiche, Angel Escamilla-Ramirez, Caroline Houillier, Khe Hoang-Xuan, Marc Sanson, Ahmed Idbaih, Franck Bielle, Francesca Branzoli, Julien Savatovsky, Aurelie Kas, Mehdi Touat; Hopital La Pitié Salpetriere, Paris, France; Hôpital Universitaire Pitié Salpêtrière, Paris, France; Hôpital La Pitié Salpêtrière, Paris, France; Pitié-Salpétrière (AP-HP), Paris, France; Groupe hospitalier Piti Salp tri re, Paris, France; Paris Brain Institute, Paris, France; Service de Neuro-Oncologie, Hôpital Pitié-Salpêtrière, Paris, France; Hôpital Pitié Salpétrière, Paris, France; Fondation A. de Rothschild Hospital, Paris, France

Background: Small-molecule inhibitors targeting IDH1/2-mutant proteins (IDHi) have shown promise as treatments for *IDH1/2*-mutant gliomas. However, accurate assessment of response using morphological magnetic resonance imaging (MRI) measurements remains difficult, and the potential of PET imaging with radiolabeled amino acids in this context is yet to be explored. Here, we investigated 3,4-Dihydroxy-6-[18F]-fluoro-L-phenylalanine PET (^{18}F-DOPA-PET) and MRI responses in *IDH1/2*-mutant glioma patients receiving IDHi. **Methods:** *IDH1/2*-mutant glioma patients receiving IDHi as part of trials or expanded access programs were included. Patients had pre- and post-treatment MRI and ^{18}F-DOPA-PET. Centralized evaluations included 2D/3D measurements on T2-weighted FLAIR images, T1-post contrast, perfusion, and diffusion imaging for MRI, and metabolic tumor volume (MTV), total lesion glycolysis (TLG), and tumor-to-background ratios (TBRs) for ^{18}F-DOPA-PET. Disease response evaluation using volumetric assessments, RANO 2.0 and PET RANO 1.0 criteria were compared and confronted to outcomes. **Results:** From 2021 to 2024, 10 patients with *IDH1/2*-mutant glioma (3 astrocytoma, 7 oligodendroglioma) receiving IDHi (4 ivosidenib, 6 vorasidenib) were analyzed. Significant reductions in ^{18}F-DOPA-PET parameters including TBRmean, TBRmax, and MTV were observed in 8/10 patients, aligning with observed changes in perfusion and diffusion imaging. Seven partial responses and one complete response were identified using ^{18}F-DOPA-PET, while both volumetric and standard 2D morphological MRI assessments indicated stable disease as best response. PET response was correlated with prolonged tumor control. **Conclusions:** This study highlights the potential of ^{18}F-DOPA-PET and advanced MRI sequences as valuable complements to standard RANO 2.0 MRI evaluations for assessing treatment response in glioma patients undergoing IDHi therapy. Research Sponsor: None.

Phase I/II study of maintenance therapy with metformin and temozolomide for newly diagnosed glioblastoma.

Yoshitaka Narita, Makoto Ohno, Shota Tanaka, Yukihiko Sonoda, Kazuhiko Mishima, Eiichi Ishikawa, Ken Ohashi, Motoo Nagane, Chifumi Kitanaka; Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan; Department of Neurosurgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; Department of Neurosurgery, Yamagata University Faculty of Medicine, Yamagata, Japan; Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Saitama, Japan; Faculty of Medicine, University of Tsukuba, Tsukuba-Shi, Japan; Department of General Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; Department of Neurosurgery, Kyorin University Faculty of Medicine, Tokyo, Japan; Department of Molecular Cancer Science, Faculty of Medicine, Yamagata University, Yamagata, Japan

Background: Glioblastoma (GBM) is an aggressive primary brain tumor with poor prognosis. A potential strategy for overcoming therapeutic resistance involves the development of novel therapies that target cancer stem/initiating cells. Our previous research demonstrated that metformin (MF), an antidiabetic drug, induces the differentiation of stem-like glioma-initiating cells and suppresses tumor formation via AMPK-FOXO3 activation (Stem Cells Transl Med, 2012). We conducted a phase I/II study to evaluate the clinical efficacy of MF combined with standard maintenance temozolomide (TMZ). Our phase I findings indicated that MF at doses of up to 2,250 mg/day combined with maintenance TMZ was well tolerated (Cancers, 2022). Here, we present the complete results of the phase I/II study. **Methods:** Patients aged 20–74 years with supratentorial GBM, Karnofsky Performance Status ≥ 70, and a history of initial chemoradiotherapy with TMZ were eligible. During the phase II study, patients received MF monotherapy for 14 days, followed by six cycles of TMZ combined with daily MF (2,250 mg) for 365 days. The primary endpoint was the 1-year progression-free survival (PFS) rate from the initiation of chemoradiotherapy with TMZ (target; one-sided alpha 10%, power 70%, threshold 1-year PFS, 27%; expected 1-year PFS, 50%, based on the historical EORTC/NCIC study (Stupp et al, 2005)). **Results:** From 2021–2023, 22 patients were enrolled in 5 hospitals and 21 patients received TMZ combined with daily MF. The cohort included 12 men and nine women, with a median age of 50 years (32–69 years). According to the WHO 2016 classification, the initial histology revealed 18 IDH-wild-type and 3 IDH-mutant GBMs. The 1-year PFS was 47.6 % (90% CI; 29.2–64.0), achieving the primary endpoint. The 2-year overall survival rate was 54.5%. Grade ≥ 3 adverse events included lymphocytopenia (19%), thrombocytopenia (4.8%), appetite loss (4.8%), body weight loss (4.8%), nausea (4.8%), and seizures (4.8%). **Conclusions:** Maintenance therapy with 2,250 mg/day of MF combined with TMZ for newly diagnosed GBM is promising. A phase III study comparing MF combined with TMZ vs. TMZ alone for the treatment of GBM is planned. Clinical trial information: jRCTs031200326. Research Sponsor: Japan Agency for Medical Research and Development; AMED 21ck0106623h0002.

Modification of the novel RANO clinical risk score for low- and middle-income countries without access to MGMT methylation testing.

Imdat Eroglu, Sıla Soylu Koçoğlu, Eron Merovci, Gözde Savaş, Fatih Gürler, Ahmet Ozet, Nuriye Özdemir, Ozan Yazici; Gazi University School of Medicine, Department of Medical Oncology, Ankara, Yenimahalle, Turkey; Gazi University School of Medicine, Ankara, Yenimahalle, Turkey

Background: The RANO Resect Group developed a new risk score using simple variables, including age, Karnofsky performance scale (KPS), RANO resection class (RRC), and MGMT methylation (MGMTm), for patients with IDH-wildtype glioblastoma (GBM). Although this score is easy to apply and demonstrates high prognostic accuracy, routine testing for MGMTm remains inaccessible in many low- and middle-income countries. In this study, we aimed to modify the RANO risk score by excluding MGMTm. **Methods:** This is a single-center, retrospective analysis of IDH-wildtype GBM patients. We applied the same scoring system established by the RANO Resect Group, excluding MGMTm. The point (p) allocations were as follows: RRC1 = 0p, RRC2 = 1p, RRC3 = 2p, RRC4 = 5p; KPS $>$ 80 = 0p, KPS $<$ 80 = 3p; age $<$ 65 = 0p, and age $>$ 65 = 1p (age was not scored if RRC = 1p). The relationship between overall survival (OS) and the variables (age, KPS, and RRC) was evaluated using univariate and multivariate Cox regression analyses. Three risk classes were defined as numerical scores derived through ROC analysis. The primary endpoint was overall survival, and the secondary endpoint was progression-free survival (PFS). **Results:** A total of 119 patients were included in the study. Of these, 100 patients received chemoradiotherapy with temozolomide followed by adjuvant temozolomide (CRT-TMZ), while 13 received CRT only, 1 patient received temozolomide only, and 1 received radiotherapy only. Four patients were unable to undergo any treatment. RRC, age, and KPS classifications were all significantly associated with overall survival in both univariate and multivariate analyses ($p < 0.001$).Based on ROC curve analysis, three risk classes were identified: low risk (0–1 points, n:47, 39.5 %), intermediate risk (2–3 points, n:27, 22.7 %), and high risk ($\geq$4 points, n:45, 37.8 %). The median OS was 35.5 months (95% CI: 21.1–50) for the low-risk group, 16 months (95% CI: 9.9–22.1) for the intermediate-risk group, and 5 months (95% CI: 3.8–6.1) for the high-risk group ($p < 0.001$). Similarly, the median PFS was 16.3 months (95% CI: 12.3–20.2) for the low-risk group, 9.9 months (95% CI: 7.2–12.6) for the intermediate-risk group, and 4.1 months (95% CI: 3.4–4.8) for the high-risk group ($p < 0.001$). **Conclusions:** The modification of the novel RANO clinical risk score by omitting MGMTm remains highly prognostic for patients with IDH-wildtype GBM. Since it relies on very basic parameters and is easy to use, the modified RANO score can serve as a practical tool in countries where MGMTm testing is inaccessible. Research Sponsor: None.

The impact of IDH mutation and 1p/19q codeletion on immune-checkpoint inhibitor efficacy in recurrent gliomas.

Shameel Shafqat, Muhammad Asad Maqbool, Terence C Burns, Jian Li Campian, Shannon Patricia Fortin Ensign, Evanthia Galanis, Julie Elaine Hammack, Maciej Mrugala, Bryan Neth, Alyx B. Porter, Michael W. Ruff, Ugur Sener, Wendy Joyce Sherman, Joon H. Uhm, Sani Haider Kizilbash; Mayo Clinic Comprehensive Cancer Center, Rochester, MN; Mayo Clinic, Rochester, MN; Division of Medical Oncology, Mayo Clinic, Rochester, MN; Division of Medical Oncology, Mayo Clinic, Phoenix, AZ; Division of Oncology, Mayo Clinic, Rochester, MN; Division of Neurology, Mayo Clinic, Jacksonville, FL; Division of Neurology and Hematology-Oncology, Mayo Clinic, Phoenix, AZ; Division of Neurology, Mayo Clinic, Phoenix, AZ; Division of Neurology, Mayo Clinic, Rochester, MN

Background: Recurrent gliomas are highly aggressive brain tumors, often resistant to conventional treatments. Immune checkpoint inhibitors (ICI) have emerged as promising therapeutic agents by targeting tumor cells through immune modulation. However, clinical trials have demonstrated limited efficacy in recurrent gliomas. This study aimed to identify potential factors influencing treatment efficacy of ICIs in recurrent gliomas. **Methods:** This retrospective study, conducted across the Mayo Clinic following IRB approval, included patients $\geq$ 18 years diagnosed with adult-type diffuse gliomas. Eligible patients received treatment with at least 2 cycles of ICI for recurrent glioma between 2014 – 2024. Patients treated with ICIs as initial therapy were excluded. Clinical, radiographic, histological, and molecular data were analyzed, with missing information excluded. Responders to ICI were defined as patients who did not meet iRANO criteria for progressive disease based on first radiographic response assessment (and confirmatory follow up imaging as needed for possible pseudo-progression). Survival outcomes [Progression-Free Survival (PFS) and Overall Survival (OS)] and potential predictive variables were analyzed using the Kaplan-Meier method and Cox-Regression Analyses. **Results:** 67 patients met eligibility criteria (mean age: 45.1 $\pm$ 15.0 years; 64.2% male; 94% white). 64 (95.5%) patients received Pembrolizumab, 2 (3%) Nivolumab, and 1(1.5%) combined Ipilimumab/Nivolumab, with a median treatment duration of 2.77 (1.39 – 19.4) months. All had prior alkylating chemotherapy. The OS (from diagnosis) for IDH wildtype (IDH-WT, n = 36), IDH mutant, 1p/19q non-co-deleted (IDH-MUT, n = 17) and IDH mutant, 1p/19q co-deleted (OLIGO, n = 14) gliomas were 3.1, 9.2, and 18.6 years, respectively. The median PFS from time of ICI was 2.23 (0.69 – 27.3) months. 24 (36.9%) patients were identified as Responders. PFS was not significantly different between patients with IDH-MUT and IDH-WT gliomas (2.30 vs 2.07 months, p = 0.593). However, patients with OLIGO gliomas had a significantly higher PFS compared to IDH-WT gliomas (5.16 vs 2.07 months, p = 0.021). The proportion of responders was greatest in OLIGO gliomas, however, did not reach statistical significance (IDH-WT, 31.4%; IDH-MUT, 29.4%; OLIGO, 61.5%, p = 0.120). Overall PFS was not impacted by patient age, sex, and extent of initial resection. When analyses were limited to Responders, the PFS for IDH-WT, IDH-MUT and OLIGO gliomas were 5.75, 7.01 and 10.8 months, respectively (p = 0.434). **Conclusions:** Patients with recurrent OLIGO gliomas may have a longer PFS with ICI therapy compared with recurrent IDH-WT and IDH-MUT gliomas. However, there is significant variability in ICI treatment efficacy between patients. Further molecular profiling is in progress to evaluate additional predictive biomarkers of response. Research Sponsor: None.

Factors influencing clinical trial enrollment in glioblastoma patients: A retrospective study at the University of Vermont Medical Center.

Leena Ziane, Shrey Patel, Oluwatosin Akintola; Larner College of Medicine, Burlington, VT; University of Vermont Larner College of Medicine, Burlington, VT; University of Vermont Medical Center, Burlington, VT

Background: The standard of care for patients with glioblastoma (GBM) is a combination therapy of radiation and temozolomide. NCCN guidelines recommend clinical trials should be offered to glioblastoma patients when appropriate. This study aims to investigate the number of patients enrolled in clinical trials at the University of Vermont Medical Center (UVMMC) and/or referred to larger academic centers for trials. This study sought to identify and analyze characteristics of patients enrolled in trials at UVMMC and other outside academic centers. **Methods:** A retrospective review was undertaken of the electronic health records of ninety patients with GBM from 2021 to 2023 who were followed at UVMMC. Patient age, gender, and educational and employment status were collected. We assessed all comers who were offered a clinical trial, patients who proceeded to enroll in a clinical trial, and factors that influenced enrollment. We also assessed location where the trial was conducted (UVMMC vs Outside Center) and the trial interventions provided at the various centers. **Results:** We assessed 90 patients diagnosed with GBM at UVMMC from 2021-2023. 87% of all patients were offered the opportunity to enroll in a clinical trial. 17% of patients who were offered a trial successfully enrolled. Amongst enrolled patients, 62% completed their clinical trial at UVMMC while 38% were referred and treated at nearby academic centers in the New England Area including Mass General Hospital and Dana-Faber Cancer Institute (DFCI). Intrinsic barriers to enrollment included poor Karnofsky performance scale (KPS) scores, MGMT negative status, presence of leptomeningeal disease, and deep tumor locations precluding resection. Extrinsic factors included distance to academic centers, trial closure to accrual, and socioeconomic status. There was a correlation between socioeconomic status and trial enrollment. Of the thirty-eight patients identified with higher educational attainment (college or higher), 87% were offered a clinical trial and 18% eventually enrolled. Among the non-college educated group of thirty-six, 92% were offered a trial. However, only 14% enrolled. Further analysis on age, gender, and clinical trial intervention will be reported in future publications. **Conclusions:** Expanding access to clinical trials is critical to optimizing care for GBM patients. Our findings highlight access to academic centers is crucial to clinical trial enrollment. Further studies analyzing modifiable barriers to clinical trial accrual are needed. Research Sponsor: None.

Safety and tolerability of olaparib, temozolomide, and pembrolizumab in a phase 2 trial in patients with progressive glioblastoma.

Luis Nicolas Gonzalez Castro, Christine Sceppa, Catharina C. Westergaard, Rachel Fox, Ugonma Nnenna Chukwueke, Gilbert Youssef, Elisa Aquilanti, Eudocia Quant Lee, David A. Reardon, Omar Arnaout, Wenya Linda Bi, Pierpaolo Peruzzi, Alexandra J. Golby, Jiyoon Kim, Rafael Vega, Lauren Schaff, Isabel Arrillaga, Keith L. Ligon, Robert Michael Prins, Patrick Y. Wen; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Center for Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA; Brigham and Women's Hospital, Boston, MA; DFCI, BWH, Boston, MA; Department of Biostatistics, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA; Beth Israel Deaconess Medical Center, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital, Boston, MA; Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA; UCLA, Los Angeles, CA; Division of Neuro-Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA

Background: Glioblastoma is the most aggressive primary brain tumor of adults, with patients obtaining limited survival benefit from standard-of-care therapies. We are conducting a phase 2, surgical window-of-opportunity study evaluating the combination of pembrolizumab (anti-PD-1 immunotherapy), olaparib (PARP inhibitor), and temozolomide (alkylating chemotherapy) in patients with progressive glioblastoma. Olaparib and temozolomide have the potential of synergistically enhancing the tumor's susceptibility to immune checkpoint immunotherapy through DNA damage and activation of immune pathways, potentially amplifying the efficacy of pembrolizumab. We provide a preliminary report on the safety and tolerability of the olaparib, temozolomide, and pembrolizumab combination. **Methods:** We enrolled patients with radiographically progressive glioblastoma, IDH-wildtype, MGMT promoter unmethylated, on 2mg daily or less of dexamethasone. Patients participating in the safety lead-in (Cohort 1) did not require surgically-resectable disease, while those enrolled in the surgical arm (Cohort 2) did. Treatment is provided in consecutive 42-day cycles with olaparib 200mg BID and temozolomide 50mg QD given on days 1-7 and 22-29, and pembrolizumab 400mg IV given on day 1. Adverse events (AEs), dose-limiting toxicities (DLTs), and high-frequency toxicities ($\geq$50% occurrence) were assessed, along with dose modifications or delays required to manage treatment-related toxicities. AEs were graded according to CTCAE v5.0 criteria, with pre-specified measures to address reversible toxicities through dose adjustments. **Results:** Six patients were enrolled in the safety lead-in (Cohort 1), which followed a 3+3 design. Grade 1–2 leukopenia, lymphopenia, and neutropenia were observed in 3 patients and resolved without intervention. Grade 4 neutropenia was observed in two patients (starting in cycle 2 for one patient, and on cycle 5 for the other). This resolved with dose delays, reduction in temozolomide dose or discontinuation of temozolomide (1 patient). In Cohort 2, which is ongoing (25 patients currently enrolled), toxicity profiles remain consistent with those observed in Cohort 1 patients. Grade 4 neutropenia has been observed in 1 (6%) of the enrolled patients, improving with dose delays and temozolomide dose reduction. **Conclusions:** The combination of olaparib, temozolomide, and pembrolizumab demonstrates a tolerable safety profile in patients with progressive glioblastoma. Observed hematologic toxicities are reversible with appropriate management, supporting the ongoing evaluation of this regimen to assess its efficacy and therapeutic potential. Clinical trial information: NCT05463848. Research Sponsor: Merck & Co.

Efficacy and safety of bevacizumab in combination with radiotherapy and temozolomide in patients with glioblastoma: A meta-analysis and meta-regression of randomized controlled trials.

Ibrahim Khalil, Umme Kulsum, Samiha Zaman Akhter, Afsana Rahman Maliha, Irfat Islam Eva, Shaila Saaki, M. Rafiqul Islam, Arindam Das Joy, Sunjida Amin Promi, Md. Imran Hossain, Md Abu Sayed; Dhaka Medical College & Hospital, Dhaka, Bangladesh; Rangpur Medical College, Rangpur, Bangladesh; Dhaka Medical College Hospital, Dhaka, Bangladesh; Dhaka Medical College, Dhaka, Bangladesh; Comilla Medical College and Hospital, Comilla, Bangladesh; Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh; Dhaka Medical College and Hospital, Dhaka, Bangladesh; Chittagong Medical College Hospital, Chittagong, Bangladesh; Manikganj Medical College, Manikganj, Bangladesh

Background: Glioblastoma (GBM), the most common primary brain tumor in adults, has a poor prognosis despite standard treatment. This meta-analysis evaluates the efficacy and safety of Bevacizumab, a VEGF inhibitor, when combined with radiotherapy and Temozolomide in terms of progression-free survival (PFS), overall survival (OS), and treatment-related adverse events. **Methods:** A systematic search of PubMed, Cochrane Library, Embase, and ClinicalTrials.gov identified randomized controlled trials (RCTs) evaluating Bevacizumab with radiotherapy and Temozolomide. Ten RCTs involving 4,425 patients (2,249 in the Bevacizumab arm and 2,176 in the control arm) met the inclusion criteria. A random-effects model calculated mean differences (MD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes with 95% confidence intervals (CI). **Results:** Bevacizumab significantly improved PFS by a mean difference of 2.39 months (95% CI: 1.34 to 3.44; P = 0.0005), but no significant benefit was observed in OS (MD: 0.46 months, 95% CI: -0.53 to 1.45; P = 0.318). The therapy increased the risk of vascular adverse events (RR: 1.52, 95% CI: 1.10 to 2.11; P = 0.023). While trends towards increased hematologic adverse events (RR: 1.24, 95% CI: 0.95 to 1.60; P = 0.093) and hypertensive events (RR: 2.17, 95% CI: 0.91 to 5.16; P = 0.066) were observed, they did not reach statistical significance. Other adverse events, including serious adverse events (RR: 1.21, 95% CI: 0.84 to 1.76; P = 0.221), grade 3-4 thrombocytopenia (RR: 1.05, 95% CI: 0.44 to 2.52; P = 0.858), visceral perforation (RR: 1.92, 95% CI: 0.54 to 6.90; P = 0.202), and thromboembolic incidents (RR: 1.32, 95% CI: 0.88 to 2.00; P = 0.120), showed no significant increase. Meta-regression analysis indicated that study-level covariates, including patient age, sex distribution, and histologic differences did not significantly influence the primary outcomes. However, MGMT methylation status demonstrated borderline significance ($P < 0.1$), suggesting potential prognostic relevance. **Conclusions:** Bevacizumab modestly improves PFS but not OS, with an increased risk of vascular toxicities. Personalized treatment strategies and further research are essential to optimize its role in glioblastoma management. Research Sponsor: None.

Adverse event outcomes associated with bevacizumab in glioblastoma patients.

Adverse Event Outcomes	RR	95%CI	P value
Any Adverse events	1.18	[0.64,2.16]	0.364
Hematologic adverse events	1.24	[0.95,1.60]	0.093
Any serious adverse events	1.21	[0.84,1.76]	0.221
Any vascular adverse events	1.52	[1.10,2.11]	0.023
Any grade 3-4 thrombocytopenia	1.05	[0.44,2.52]	0.858
Visceral perforation	1.92	[0.54,6.90]	0.202
Any arterial or venous thromboembolic incidents	1.32	[0.88,2.00]	0.120
Any hypertensive events	2.17	[0.91,5.16]	0.066

Assessment of age in the clinical risk stratification of patients with IDH-mutant gliomas.

Michal Nisnboym Ziv, Negar Sadeghipour, Joanne Xiu, Theodore Nicolaides, Manmeet Singh Ahluwalia, Michael J. Glantz, Sonikpreet Aulakh, Katherine B. Peters; Duke University Medical Center, Durham, NC; Caris Life Sciences, Phoenix, AZ; Caris Life Sciences, Irving, TX; Miami Cancer Institute, Miami, FL; Penn State Milton S. Hershey Medical Center, Hershey, PA; West Virginia University, Morgantown, WV

Background: Prognosis for mutant isocitrate dehydrogenase (mIDH) gliomas is influenced by tumor type, size, neurologic deficits, and age. Traditionally, patients over 45 are considered high-risk, prompting consideration of early chemoradiation. Recent promising results with the mIDH inhibitor vorasidenib challenge traditional age-based risk stratification, sparking debate over its role in treatment decisions. We evaluated survival relative to age and molecular data obtained from next-generation sequencing (NGS). **Methods:** Tumor specimens from 598 mIDH gliomas were analyzed using NGS and WTS at Caris Life Sciences (Phoenix, AZ). Samples were stratified by age at diagnosis into four groups: 12-26y, 27-40y, 41-60y, and $>$ 60y. Real-world overall survival (calculated from initial diagnosis to last contact) was obtained from insurance claims data and analyzed using Kaplan-Meier and Cox proportional hazards models. Covariates in the multivariate regression analysis included radiation treatment, temozolomide treatment, and mutation status of different biomarkers. **Results:** In mIDH astrocytoma group, age distribution was 12-26y, n = 74 (12.4%); 27-40y, n = 271 (45.3%); 41-60y, n = 205 (34.3%); and $>$ 60y, n = 48 (8.0%). In mIDH oligodendroglioma group, age distribution was 12-26y, n = 18 (5.5%); 27-40y, n = 76 (23.2%); 41-60y, n = 137 (41.8%); and $>$ 60y, n = 57 (17.4%). For each subtype, comparisons in survival were made between patients 27-40y vs. 41-60y given larger sample size, and patients with temozolomide treatment before biopsy were excluded (about 10%). Univariate analysis showed that 27-40y patients had shorter survival in astrocytoma (HR = 1.63, 95% CI: 1.07 – 2.50, p = 0.022). However, after adjusting for confounding factors in multivariate analysis, age was not associated with survival. In contrast, TP53 (HR = 4.0, 95% CI: 1.43-11.24, p = 0.008 – mutation rate = 95.4%) and TERT-promoter (HR = 10.36, 95% CI: 4.05-26.45, p $<$ 0.0001 – mutation rate = 9.0%) mutations were independently associated with poorer survival in astrocytoma patients. Univariate analysis showed that age was not associated with survival in oligodendroglioma (HR = 1.07, 95% CI: 0.79-3.65, p = 0.168). KRAS mutations were independently associated with poorer survival in oligodendroglioma patients (HR = 4.36, 95% CI: 1.12-16.92, p = 0.033 - mutation rate = 3%). **Conclusions:** In this enriched dataset of mIDH low grade glioma patients, which included NGS, age did not contribute to survival differences when comparing patients between 27-40 years with those aged 41-60 years. Rather, selected genetic alterations such as KRAS for oligodendroglioma and TP53 and TERT mutations for astrocytoma were associated with poorer survival. The results suggest that NGS, rather than age, may drive prognosis for mIDH glioma patients. Research Sponsor: None.

The tumoral molecular landscape of long-term survivors with isocitrate dehydrogenase wildtype glioblastoma: Lessons from ETERNITY (EORTC 1419).

Michael Weller, Dennis Friedel, Joerg Felsberg, Dorothee Gramatzki, Abigail k. Suwala, Jennifer Leigh Clarke, Oliver Schnell, Giuseppe Lombardi, Wolfgang Wick, Dietmar Krex, Martin Sill, Thierry Gorlia, Matthias Preusser, Patrick Y. Wen, Emilie Le Rhun, Andreas von Deimling, Guido Reifenberger, David Reuss, Roberta Rudà, Caroline Hertler, for the EORTC 1419 ETERNITY Study Group; Department of Neurology, University Hospital Zurich, and Brain Tumor Centre, University Hospital and University of Zurich, University Hospital Zurich, Zurich, Switzerland; University Hospital Heidelberg, Heidelberg, Germany; Institute of Neuropathology, Medical Faculty, Heinrich Heine University and University Hospital Düsseldorf, Düsseldorf, Germany; Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland; Department of Neuropathology, University Hospital Heidelberg, Heidelberg, Germany; University of California, San Francisco, San Francisco, CA; Department of Neurosurgery, Uniklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany; Veneto Institute of Oncology IOV, IRCCS, Padua, Italy; University of Heidelberg, Heidelberg, Germany; Department of Neurosurgery, Carl Gustav Carus University Hospital Dresden, Dresden, Germany; KiTZ, Heidelberg, Germany; EORTC Headquarters, Brussels, Belgium; Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; Division of Neuro-Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; University Hospital Zurich, Zurich, Switzerland; Division of Neuro-Oncology, Department of Neuroscience, City of Health and Science Hospital and University of Turin, Turin, Italy; University Hospital Zurich, Department of Neurology, Zurich, Switzerland

Background: Predictors of long-term survival in patients with isocitrate dehydrogenase (IDH)-wildtype glioblastoma remain incompletely understood. ETERNITY (EORTC 1419) is the largest registry study of glioblastoma patients surviving for 5 years or more worldwide. **Methods:** Here we characterized the DNA methylation and mutational landscapes of 142 tumors from ETERNITY patients and compared the findings with different reference cohorts. **Results:** The majority of tumors of the ETERNITY cohort showed molecular profiles corresponding to established methylation subclasses of IDH-wildtype glioblastoma. ETERNITY tumors were enriched for the mesenchymal subclass, depleted of the receptor tyrosine kinase 1 subclass, and showed a high frequency of *MGMT* promoter methylation. While large chromosomal alterations were remarkably similar in all cohorts, circumscribed homozygous deletions on chromosome 10q including the *MGMT* gene were enriched in ETERNITY tumors. Gene panel sequencing showed similar types and frequencies of gene alterations as in the reference cohorts with a trend towards more frequent *RB1* mutations. Deconvolution analyses of global DNA methylation data revealed fewer monocytes in the MES methylation class in ETERNITY compared with the reference cohort. ETERNITY tumors from patients without documented relapse showed no specific molecular profile. Small subgroups of tumors corresponded to rare incompletely defined tumor entities. **Conclusions:** The present study illustrates the profound association of *MGMT* gene alterations with outcome, but also suggests as yet unidentified clinical or molecular pathways and potential host-dependent features in long-term survival with glioblastoma. Clinical trial information: NCT03770468. Research Sponsor: Brain Tumor Funders' Collaborative Consortium.

Efficacy and safety of depatuxizumab mafodotin (ABT-414) in EGFR-amplified glioblastoma: A systematic review and Bayesian network meta-analysis.

Sunjida Amin Promi, Ibrahim Khalil, Umme Kulsum, M. Rafiqul Islam, Irfat Islam Eva, Md Abu Sayed, Anika Chowdhury, Shaila Saaki, Manisha Das, Shara Haque, Md. Ahsanul Hoque, Zahin Zeima, Sajjad Ghanim Al-Badri, Arindam Das Joy, Md. Imran Hossain; Chittagong Medical College Hospital, Chittagong, Bangladesh; Dhaka Medical College & Hospital, Dhaka, Bangladesh; Rangpur Medical College, Rangpur, Bangladesh; Shaheed Suhrawardy Medical College and Hospital, Dhaka, Bangladesh; Comilla Medical College and Hospital, Comilla, Bangladesh; Shaheed Suhrawardy Medical College & Hospital, Dhaka, Bangladesh; Dhaka Medical College Hospital, Dhaka, Bangladesh; Dhaka Medical College, Dhaka, Bangladesh; Shaheed Tajuddin Ahmad Medical College Hospital, Dhaka, Bangladesh; Dhaka Medical College and Hospital, Dhaka, Bangladesh; University of Baghdad, College of Medicine, Baghdad, Iraq; Manikganj Medical College, Manikganj, Bangladesh

Background: Glioblastoma (GBM) is a highly aggressive brain tumor with a poor prognosis, typically resulting in a median survival of 12–15 months. Epidermal growth factor receptor (EGFR) alterations, present in half of GBM cases, are key therapeutic targets. Depatuxizumab mafodotin (Depatux-M, ABT-414), an EGFR-targeting antibody-drug conjugate, represents a novel therapeutic option. This Bayesian network meta-analysis assessed the efficacy and safety of Depatux-M in EGFR-amplified GBM. **Methods:** Eight randomized controlled trials (RCTs) involving 1,183 patients were analyzed. Trials evaluating Depatux-M as monotherapy or combined with temozolomide (TMZ) and/or radiotherapy (RT) were included. Outcomes included overall survival (OS), progression-free survival (PFS), and safety (grade 3/4 adverse events and keratitis). Bayesian models estimated mean differences (MDs) and relative risks (RRs) with 95% credible intervals (CrI), while SUCRA values ranked treatments. **Results:** Depatux-M plus TMZ showed modest OS improvement over TMZ alone (MD: 0.91 months; 95% CrI: -11.83 to 13.86; SUCRA: 62.09%). Depatux-M monotherapy showed minimal OS benefit (MD: 0.07 months; 95% CrI: -12.69 to 12.95; SUCRA: 51.2%), and the combination of Depatux-M, TMZ, and RT had the lowest OS benefit (MD: -2.17 months; 95% CrI: -19.83 to 15.74; SUCRA: 35.48%). For PFS, Depatux-M monotherapy performed best (MD: 1.46 months; 95% CrI: -4.92 to 7.78; SUCRA: 81.00%), while Depatux-M plus TMZ (MD: -0.45 months; 95% CrI: -6.85 to 5.89; SUCRA: 40.03%) and Depatux-M, TMZ, and RT (MD: -1.54 months; 95% CrI: -10.34 to 7.24; SUCRA: 28.32%) were less effective. Depatux-M monotherapy had a lower RR for grade 3/4 adverse events (RR: 1.38; 95% CrI: 0.23 to 8.07) and keratitis (RR: 2.62; 95% CrI: 0.43 to 15.63) compared to combination regimens, with the highest keratitis risks observed in Depatux-M, TMZ, and RT. **Conclusions:** Depatuxizumab mafodotin offers limited survival benefits in EGFR-amplified GBM, with monotherapy showing the most favorable PFS. However, significant safety concerns, particularly keratitis, warrant further research to optimize its therapeutic potential and identify more tolerable regimens. Research Sponsor: None.

Efficacy and safety outcomes of depatuxizumab mafodotin in EGFR-amplified glioblastoma.

Regimen	Overall Survival (OS)	Progression-Free Survival (PFS)	Grade 3/4 Adverse Events (RR)	Keratitis (RR)
Depatux-M + TMZ	0.91 (-11.83 to 13.86); SUCRA 62.09	-0.45 (-6.85 to 5.89); SUCRA 40.03	1.54 (0.20 to 13.53); SUCRA 41.75	4.40 (0.51 to 31.10); SUCRA 33.07
Depatux-M	0.07 (-12.69 to 12.95); SUCRA 51.20	1.46 (-4.92 to 7.78); SUCRA 81.00	1.38 (0.23 to 8.07); SUCRA 49.06	2.62 (0.43 to 15.63); SUCRA 62.34
Depatux-M + TMZ + RT	-2.17 (-19.83 to 15.74); SUCRA 35.48	-1.54 (-10.34 to 7.24); SUCRA 28.32	0.98 (0.09 to 9.65); SUCRA 68.37	6.63 (0.62 to 66.40); SUCRA 12.73

Relationship between aperiodic dynamics and transcriptomic alterations and a neural signature of glioma-induced excitation-inhibition dysregulation.

Youssef Sibih, Niels Olshausen, Abraham Dada, Jasleen Kaur, Emily Cunningham, Sanjeev Herr, Vardhaan Ambati, Andy Daniel, Saritha Krishna, Alexander A. Aabedi, Kanish Mirchia, David Brang, Shawn L. Hervey-Jumper; University of California, San Francisco, San Francisco, CA; University of Michigan, Ann Arbor, MI

Background: Diffuse gliomas disrupt neuronal dynamics, leading to excitation-inhibition (E/I) imbalance and associated functional impairments. The aperiodic component of the power spectral density (1/f slope) has emerged as a proxy for estimating E/I balance, offering a novel framework for understanding glioma-induced neural dysregulation. This study is the first to validate the relationship between 1/f slope and E/I dysregulation in glioma by integrating electrophysiological, genomic, and behavioral data. **Methods:** Resting-state intraoperative subdural electrocorticography (ECoG) data were recorded from 13 glioma patients. Power spectral analysis at a frequency of 70–150Hz (high-gamma) computed 1/f slopes, and electrodes were classified as glioma-infiltrated or normal-appearing based on preoperative MRI T2-FLAIR. Linear mixed-effects models assessed E/I balance across tissue and glioma subtypes. Single-nucleus RNA sequencing (snRNA-seq) was performed on 14 spatially annotated glioma tissue samples from regions classified as inhibitory or excitatory by 1/f slope. Behavioral analysis of language tasks examined functional correlates of E/I imbalance. **Results:** The cohort included 23.0% WHO grade 2 IDH-mutant oligodendrogliomas, 38.5% WHO grade 2-3 IDH-mutant astrocytoma, and 38.5% glioblastoma (GBM). Glioma-infiltrated electrodes (n=142) exhibited significantly lower 1/f slopes than normal-appearing electrodes (n=518;$p < 0.0001$), reflecting an excitation-dominant state. Subtype analysis revealed hierarchical E/I imbalance, with GBM showing the steepest reductions in 1/f slope compared to astrocytoma and oligodendroglioma (glioma-infiltrated: $p<0.0001$; normal-appearing: GBM vs. oligodendroglioma, p=0.012; GBM vs. astrocytoma, p=0.019). SnRNA-seq revealed elevated excitatory and reduced inhibitory signaling gene expression in glutamatergic and GABAergic neuronal populations across glioma-infiltrated (n=12; n=4 per subtype) and normal cortex (n=2) samples. Excitatory module scores were significantly higher in excitatory 1/f samples compared to inhibitory 1/f samples, validating the 1/f slope as a genomic correlate of E/I imbalance in human cortical tissue. Behavioral analysis of language tasks demonstrated error-related reductions in 1/f slope ($e > i$), emphasizing the functional impact of glioma-induced dysregulation. **Conclusions:** Diffuse gliomas are associated with a profound shift toward excitation dominance in both glioma-infiltrated and normal-appearing cortex. For the first time, the 1/f slope is validated as a robust measure of E/I imbalance through electrophysiological, genomic, and behavioral analyses. These findings position the 1/f slope as a physiologically relevant biomarker of glioma-induced neural dysregulation, offering significant potential to inform therapeutic strategies. Research Sponsor: None.

Comparing ERK signaling and tumor microenvironment in BRAF-altered gliomas.

Lucy Chen, Negar Sadeghipour, Joanne Xiu, Sharon Wu, Alireza Mansouri, Calixto-Hope C. Lucas, Theodore Nicolaides, Sonikpreet Aulakh, Karisa C. Schreck; Johns Hopkins School of Medicine, Baltimore, MD; Caris Life Sciences, Phoenix, AZ; Penn State Milton S. Hershey Medical Center, Hershey, PA; Caris Life Sciences, Irving, TX; West Virginia University, Morgantown, WV

Background: Many patients with BRAF-altered glioma (V600E mutations, fusions) respond to BRAF inhibitors (BRAFi), but some—particularly those with high-grade gliomas (HGG)—progress on treatment. Here, we aim to assess MAPK/ERK activation associated with various BRAF alterations in a large dataset of adult and pediatric patients with low-grade (LGG) and HGG using previously validated transcriptomic signatures. **Methods:** Samples underwent next-generation sequencing and whole transcriptome sequencing at Caris Life Sciences (Phoenix, AZ). The MAPK Pathway Activity Score (MPAS, Wagle 2018, NPJPO) and two MEK inhibitor sensitivity signatures (Dry 2019, Cancer Res & Pratilas 2009, PNAS) were calculated from RNA-seq data. Tumor immune microenvironment was assessed using immune deconvolution (quanTIseq) and the Tumor Inflammation Signature (TIS). Results were compared for HGG in two age groups (AYA: 0-39y; adult: $>$ 39y) in V600E mutation, fusions, or controls (BRAF-WT/IDH-WT/NF1-WT). For LGG 0-39y, V600E were compared to fusion, but not to BRAF-WT due to near-universal enrichment of MAPK alterations in LGG. There were insufficient LGG $>$ 39y for analysis. Mann-Whiney U tests were used at $\alpha = 0.05$. **Results:** In adult HGG (V600E: n = 35, fusions: n = 11, WT: n = 3235), both V600E and fusions showed significantly higher MAPK/ERK signatures than WT (all $p < 0.01$), with no significant difference between V600E and fusions. In AYA HGG (V600E: n = 32, fusions: n = 11, WT: n = 235), all three MAPK/ERK signatures were significantly higher in V600E compared to WT (all $p < 0.01$), while fusions fell in between BRAF V600E and WT ($p > 0.05$). In both AYA and adult HGG, B cells were higher in WT compared to V600E, while among infiltrated cells only M1 and M2 macrophages were elevated in fusions compared to WT ($p < 0.05$). Comparison of MAPK/ERK signatures in LGG (V600E: n = 28, fusions: n = 54) revealed no significant difference between V600E and fusions. TIS did not differ among BRAF alterations in any groups. Pathway analysis revealed RAS signaling and inflammation were enriched in BRAF V600E compared to WT in both HGG and LGG (NES $>$ 2; FDR $<$ 0.005), regardless of age. When comparing all V600E HGG patients (0-90y) previously treated with BRAFi (n = 21) to those who were not (n = 46), no difference in MAPK/ERK signatures were seen. Pathway analysis revealed samples with prior BRAFi had upregulated complement activation, B-cell activation, and opsonization (NES $>$ 3.5; FDR $<$ 10e-5), while treatment-naïve samples had higher BRAF/MAPK signaling (NES $>$ 2, FDR $<$ 0.03). **Conclusions:** These data confirm higher MAPK/ERK dependence signatures and RAS signaling in BRAF-altered HGG (V600E, fusion) compared to BRAF-WT controls. Differences in immune cell infiltration were observed between BRAF alteration classes. Changes in humoral immunity may be correlated with acquired resistance to BRAFi, in line with previous reports of increased B-cell infiltration in BRAFi-resistant melanomas. Research Sponsor: None.

Phase II propensity-matched controlled trial evaluating metformin as an adjunct to neo-adjuvant, concomitant, and adjuvant temozolomide and hypofractionated-accelerated radiotherapy (M-HART) in glioblastoma patients (NCT02780024).

George Shenouda, Roberto Diaz, Bassam Abdulkarim, Kevin Petrecca, Scott Peter Owen, Valerie Panet-Raymond, Amro Mohammad, Miguel Barrera, William Davalan, Antoneta Baciu, Tationa Carvalho, Melissa Charbonneau, Marianna Perna, Tanya Kozel, Jeffery Hall, Marie-christine Guiot, Luis Souhami; McGill University Health Centre, Montréal, QC, Canada; McGill University, Montreal, QC, Canada; McGill University Health Centre, Montreal, QC, Canada; Montreal Neurological Institute, Montreal, QC, Canada; Juan N. Corpas University, Bogota, Colombia; The Montreal Children's Hospital, Montreal, QC, Canada; The Montreal Neurological Hospital, Montreal, QC, Canada

Background: Phase II, propensity-matched trial, to assess feasibility and toxicity of adding Metformin (MTF) to neo-adjuvant, concomitant and adjuvant Temozolomide (TMZ) and hypofractionated accelerated radiotherapy (M-HART), for patients with Glioblastoma (GBM). We compared median survival time (MST), and progression-free-survival (PFS) of M-HART versus a contemporaneous cohort of propensity-score matched controls (PSMC) who received standard of care (SOC). **Methods:** Eligible patients were ≥ 18 years with newly diagnosed GBM, ECOG score ≤ 2, with known MGMT status, gross total or partial resection, and residual surgical cavity > 15 mm from brainstem, or optic apparatus. Four weeks from surgery, M-HART patients started 2 weeks of neo-adjuvant MTF/TMZ followed by concomitant MTF/TMZ + HART 60 Gy/20 daily fractions, and 6 cycles of adjuvant MTF/TMZ. The PSMC patients received Stupp's regimen. We used a nearest neighbor matching with a caliper width of 0.2 SD and compared patients' characteristics using chi-square test (Table). Propensity scores were estimated using logistic regression model, with probability of M-HART treatment as dependent variable. **Results:** From April 2015 to November 2020, 50 patients participated in the M-HART trial and matched with 50 PSMC cohort treated during the same period, with a median follow up of 24.1 (M-HART) vs 17.6 months PSMC, respectively. M-HART patients had significantly longer MST of 24.1 (95% CI, 15.2- 30.3) vs. 17.7 months for PSMC patients (95% CI, 12-20) (HR, 0.62 [95% CI, 0.40-0.93]; P = 0.02), and significantly longer PFS of 13.7 (95% CI, 11.7 to 18.8) vs. 11.0 months (95% CI, 9-12) (HR, 0.63 [95% CI, 0.42-0.95]; P = 0.02). M-HART treatment was an independent predictor of survival. M-HART patients with methylated-MGMT and gross total resection had significant longer MST of 41.9 vs. 17.8 months for PSMC (95% CI, 15.1-20.5 months) (HR 0.21 [95% CI, 0.09-0.49]; P = 0.001). **Conclusions:** M-HART protocol is novel, feasible, and well-tolerated approach with significantly longer MST and PFS as compared to propensity-matched SOC controls. These results add to growing evidence for the use of Metformin as an adjunct to HART and TMZ especially in M-MGMT GBM. Clinical trial information: NCT02780024. Research Sponsor: No funding was received.

Characteristics of M-HART versus propensity-matched standard of care control patients.

	M-HART N=50 (%)	CONTROLS N=50 (%)	P-value
Age (years)			
≤ 60	34 (68)	27 (54)	0.218
> 60	16 (32)	23 (46)	
Sex			
Male	22 (44)	30 (60)	0.161
Female	28 (56)	20 (40)	
ECOG-score			
0-1	43 (84)	47 (94)	0.318
2	7 (14)	3 (6)	
Surgery			
Gross Total	41 (82)	39 (78)	0.803
Subtotal	9 (18)	11 (22)	
MGMT status			
Unmethylated	34 (68)	29 (58)	0.015
Methylated	16 (32)	21 (42)	
Re-operation			
Yes	24 (84)	18 (36)	0.077
No	26 (52)	32 (64)	
Chemotherapy at recurrence			
Yes	14 (28)	27 (54)	<0.001
No	36 (74)	23 (46)	

Association of MGMT status with survival in low and high-grade IDH-mutant astrocytomas.

Katherine E. Schwetye, Omar H. Butt, Manmeet Singh Ahluwalia, Sonikpreet Aulakh, Gilbert Youssef, Joanne Xiu, Theodore Nicolaides, Negar Sadeghipour, Patricia Pittman, Christian Davidson; Washington University, St. Louis, MO; Washington University in St. Louis, St. Louis, MO; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; West Virginia University, Morgantown, WV; Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; Caris Life Sciences, Phoenix, AZ; Caris Life Sciences, Irving, TX; CARIS Life Sciences, Phoenix, AZ

Background: The role of MGMT promoter methylation status on survival for IDH-mutant astrocytomas is less known than for glioblastoma, IDH-wildtype (GBM). Further, different laboratories utilize a variety of techniques to measure methylation of the MGMT gene promoter region, including pyrosequencing, methylation-specific polymerase chain reaction (PCR), and direct Sanger sequencing; these techniques are limited by low quantitative accuracy, short read length, and low sample throughput. In the current study, we used a large database of next-generation sequencing (NGS) and whole-transcriptome sequencing (WTS) performed in a single laboratory to determine the role of MGMT status on survival in IDH-mutant astrocytomas (CNS WHO grades 2-3 and 4), as well as in GBM. **Methods:** 10,181 glioma samples were analyzed by NGS (592, NextSeq, or WES, NovaSeq) and WTS (NovaSeq) at Caris Life Sciences (Phoenix, AZ), including determination of methylation status of the MGMT promoter region by pyrosequencing. Real-world overall survival was obtained from insurance claims data and calculated from initial diagnosis to last contact, while TMZ-OS was calculated from first dose of temozolomide to last of treatment. Hazard ratios (HRs) were analyzed using Cox proportional hazards model and p values (log-rank test). Multivariate regression analysis was performed on age, gender, radiation treatment, temozolomide treatment, and mutations in different biomarkers. Fisher's exact tests was used at a significance level of 0.05. **Results:** 693 IDH-mutant astrocytomas CNS WHO grades 2 or 3 ("g2/3"), 251 IDH-mutant astrocytoma CNS WHO grade 4 ("g4"), and 4469 glioblastoma ("GBM") met inclusion criteria. Univariate and multivariate survival analysis showed that MGMT promoter methylation (mMGMT vs. unmethylated, uMGMT) was associated with improved OS only in GBM (HR = 0.62, 95% CI: 0.57 – 0.67, $p < 0.0001$), but not in astrocytoma-g2/3 and g4. Similarly, TMZ-OS was only significantly longer in mMGMT vs. uMGMT in GBM (HR = 0.53, 95% CI: 0.48 – 0.58, $p < 0.0001$). In astrocytoma-g2/3, ATRX mutation was more prevalent in mMGMT than uMGMT (73.9% vs. 62.6%, $p < 0.05$), and SETD2 was more prevalent in uMGMT than mMGMT (4% vs. 1.1%, $p < 0.05$). Tumor mutational burden (TMB)-high was more prevalent in mMGMT than uMGMT in astrocytoma-g4 (14.8% vs. 2.7%, $p < 0.05$) and in GBM (5.4% vs. 1.9%, $p < 0.0001$). In GBM, many genes had different mutational rates between mMGMT and uMGMT groups, including MSH6 (2% vs. 0.7%, $p < 0.001$), ATRX (3.1% vs. 1.6%, $p < 0.01$), and CDKN2A (4.3% vs. 2.5%, $p < 0.01$). **Conclusions:** mMGMT was not associated with better survival in IDH-mutant astrocytoma-g2/3 or g4with respect to OS or TMZ-OS, whereas mMGMT conferred improved survival in GBM. These results, derived from a large database using same platform (next-generation sequencing at a single laboratory), support similar findings from recent, smaller cohort studies. Research Sponsor: None.

Prognostic impact of DDR mutations (mt) in IDH mutant high-grade gliomas (HGG).

John L. Villano, Joanne Xiu, Stephanie Rock, Ninad Kulkarni, Negar Sadeghipour, Jill M. Kolesar, Janna Neltner, Trevor Morris, Catherine R. Garcia, Clyde Coleman, David Spetzler, Emil Lou, Sonikpreet Aulakh, Michael J. Glantz, Eric T. Wong; University of Kentucky Markey Cancer Center, Lexington, KY; Caris Life Sciences, Phoenix, AZ; CARIS Life Sciences, Irving, TX; University of Kentucky, Lexington, KY; The University of Texas MD Anderson Cancer Center, Houston, TX; Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN; West Virginia University, Morgantown, WV; Penn State Milton S. Hershey Medical Center, Hershey, PA; Rhode Island Hospital, Providence, RI

Background: The oncometabolite 2-hydroxyglutarate (2HG) produced by *IDH1/2* mt in HGG has profound effects on numerous pathways including DNA damage repair (DDR). We investigated the prognostic effect of DDR mt in *IDH* mutant vs. wild type (wt) tumors in a large cohort using a real-world database. **Methods:** A total of 4894 HGG tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen sequencing of DNA (592-gene panel or whole exome sequencing) were included in the study. DDR alteration was defined as a pathogenic mutation in one of > 20 DDR genes. Patient survival was obtained by insurance claims data and calculated from the initiation of tissue collection (rwOS). Cox proportional hazards model was used to calculate hazard ratios (HR) and log-rank tests to calculate p values, which were adjusted for multiple comparisons. Significance was set at $p<0.05$. **Results:** In the 1121 HGG carrying either *IDH1* or 2 mutations, 100 carried a DDR mutation (8.9%) . When comparing DDR mutant (mt) vs. wild type (wt), no difference was seen in patient age (median 39 vs. 38 yrs; p = 0.8); gender (female 45% vs. 42%, p = 0.9), race or ethnicity ($p > 0.1$). The most frequent mutations were seen in *MSH6* (24% of the DDR mt), *ATM* (18%), *MLH1* (15%), *MSH2* (13%), *MSH3* (10%) and *BRCA2* (10%). When comparing the rwOS of DDR mt vs. wt, a significantly shorter survival was seen (24m vs. 51m, HR = 1.87, 95% CI [1.41-2.48], $p < 0.001$); the effect persisted in the subset of tumors collected prior to temozolomide treatment (26m vs. 64m, HR = 1.92 [1.35-2.74], $p < 0.001$). In contrast, in IDH wt tumors, patients with (N = 223) or without DDR mutation (N = 3550) showed similar survival (17.5m vs. 20.6m, p = 0.1). In the *IDH* mutant cohort, DDR mt was associated with an increased tumor mutational burden (TMB) compared to DDR wt tumors (median = 6 vs. 4 mutations/mb, by Wilcoxon). Multivariate analysis within the IDH mutant tumors indicated that both TMB and DDR status were independently associated with poorer rwOS, with TMB showing an adjusted HR of 1.01 per unit increase (p = 0.005) and DDR status with an adjusted HR of 1.59 (p = 0.028). **Conclusions:** In a large real-world database, we demonstrate IDH mt HGG with a DDR mutation exhibit significantly poorer survival compared to DDR wt. This is not seen in IDH wt, where survivals of the two groups are similar. These results stand in sharp contrast to reported prognostic effect of DDR mutation in many other solid tumors. The data suggest that DDR mutations in the context of 2HG accumulation in IDH mt HGG may be an indicator of profound genomic instability that confers severe negative impact on patient survival. Clinicians managing high-grade gliomas should consider the presence of DDR mutations in IDH mutant patients as a poor prognostic category in this overall favorable prognostic group and consider therapeutic approaches accordingly. Research Sponsor: None.

Prognostic value of inflammatory markers in glioblastoma: A meta-analysis of NLR and PLR stratified by cutoff values.

Abril Carrillo, Yenny Viviana Pinzón, Arantza Lizbeth Garcia Loera, Natalia Michel Carrillo, Omar A. Borges-Sosa, Diego Pichardo Rojas, Pavel Pichardo-Rojas; UT Southwestern Medical Center, Dallas, TX; Universidad Pedagógica Y. Tecnológica De Colombia, Tunja, Colombia; Instituto Politécnico Nacional, Ciudad De México, Mexico; Universidad Nacional Autónoma de México, Ciudad De México, Mexico; Indiana University, Bloomington, IN; Universidad Autonoma de Baja California, Tijuana, BJ, Mexico; The University of Texas Health Science Center at Houston, Houston, TX

Background: Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, with an unfavorable prognosis. Identifying prognostic markers is crucial to stratify patients and tailor therapeutic approaches. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory markers that have gained attention as outcome predictors in various cancers. While numerous studies have demonstrated associations between elevated NLR, PLR, and poor GBM outcomes, consensus on standardized cutoff values remains elusive, limiting their clinical application. In this meta-analysis, we stratified the data based on preoperative NLR and PLR cutoff values, aiming to identify the most accurate cutoff thresholds to predict overall survival (OS) outcomes. **Methods:** We performed a systematic search on PubMed, Medline, OVID, Embase, and Cochrane in November 2024 to identify cohort studies reporting hazard ratios (HR) for OS associated with preoperative NLR and/or PLR in patients with histopathologically confirmed GBM. Two reviewers screened articles; discrepancies were resolved by consensus. Data analysis was conducted using a random-effects model. Pooled HRs with 95% confidence intervals (CI) were calculated and subgroup analysis were performed. **Results:** From 227 studies initially identified, 22 studies met our inclusion criteria, encompassing a total population of 3,423 patients with GBM. In our general cohort, when compared to lower PLR, a higher PLR yielded a pooled HR of 1.30 (95% CI: 1.12-1.50, $p < 0.001$). Specific cutoff subgroup analysis revealed that, the < 135 cutoff group had a HR of 1.09 (95% CI: 0.62-1.93, $p = 0.60$), in the > 135 cutoff group, the HR was 1.42 (95% CI: 1.19-1.70, $p = 0.0001$). Regarding the NLR analysis, cutoff subgroup analysis showed that for NLR with a cutoff of < 3, the HR was 1.39 (95% CI: 0.96–2.02, $p = 0.08$), for NLR with a cutoff between 3 and 4.9, the HR was 1.56 (95% CI: 0.98–2.51, $p = 0.06$). For studies with a NLR cutoff of 4, the HR was 1.40 (95% CI: 1.23–1.58, $p = 0.01$). For studies with a NLR cutoff > 4.9, the HR was 1.85 (95% CI: 1.37–2.50, $p < 0.0001$). The overall pooled HR for elevated NLR regardless of cutoff value was 1.40 (95% CI: 1.23–1.58, $p < 0.00001$). **Conclusions:** Elevated preoperative NLR and PLR are significant prognostic markers for worse OS in GBM patients. Stratifying data by cutoff values revealed that PLR > 135 and NLR > 4.9 were more consistently correlated with poor survival outcomes. These findings suggest that higher cutoff values for these markers may better predict OS, particularly for NLR where values > 4.9 demonstrated a stronger association than the commonly used cutoff of 4. The results highlight the potential utility of NLR and PLR as accessible, cost-effective prognostic tools. Future prospective studies are warranted to validate these findings, refine optimal cutoff thresholds, and explore their applicability. Research Sponsor: None.

A phase 1, first-in-human study of regorafenib plus temozolomide with or without radiotherapy in patients with newly diagnosed MGMT methylated, IDHwt glioblastoma: The REGOMA-2 trial.

Marta Padovan, Matteo Simonelli, Amedeo De Nicolò, Paola Del Bianco, Giulia Cerretti, Mario Caccese, Pasquale Persico, Giorgia Menegatti, Alberto Bosio, Angelo Dipasquale, Marta Maccari, Agnese Losurdo, Marina Coppola, Marco Krengli, Sara Lonardi, Antonio D'Avolio, Gian Luca De Salvo, Giuseppe Lombardi; University of Padua, Padua, Italy; IRCCS Humanitas Research Hospital and Humanitas University, Rozzano, Italy; Department of Medical Sciences; University of Turin - ASL "Città di Torino", Torino, Italy; Clinical Research Unit, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy; Veneto Institute of Oncology IOV, IRCCS, Padua, Italy; Humanitas Research Hospital - IRCCS, Rozzano, Italy; Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Rozzano (Milano), Italy; IRCCS Humanitas Research Hospital, Department of Biomedical Sciences, Humanitas University, Rozzano (Milano), Italy; Hospital Pharmacy Unit, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy; Radiotherapy Unit, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy; Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy; Laboratory of Clinical Pharmacology and Pharmacogenetics, Amedeo di Savoia Hospital, University of Turin, Torino, Italy; Clinical Research Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: Regorafenib (REG) is an oral multikinase inhibitor and in vivo studies demonstrated a synergistic antitumor effect when combined with radiotherapy (RT) and temozolomide (TMZ) against glioblastoma (GBM). We conducted a phase 1 study to evaluate the safety, dose limiting toxicity (DLT), maximum tolerated dose (MTD) of REG, pharmacokinetics (PK), preliminary activity of this combination. **Methods:** This phase 1 multicenter academic study used a "3 + 3" design to evaluate REG doses of 80mg (Level 1), 120mg (Level 2), 160mg (Level 3) in 2 different cohorts of pts with histologic diagnosis of MGMT-methylated, IDHwt GBM (WHO 2021) and ECOG PS 0-1. In cohort A, pts who completed the concurrent chemoradiotherapy (CT-RT) regimen received REG in combination with standard maintenance TMZ; cohort B received REG concurrently with standard CT-RT and continued REG with maintenance TMZ. REG was administered according to the standard schedule of 3 weeks on/1 week off. The DLT evaluation period for cohort A was during the first two maintenance cycles and for cohort B during the concurrent CT-RT phase. During the DLT period, blood and clinical assessments were performed weekly. Toxicity was assessed by CTCAE v 5.0. RANO criteria were used for neuroradiologic assessment. Pharmacokinetics (PK) was also evaluated. **Results:** In cohort A, none of the 9 pts enrolled (median age 52ys) had a DLT at any dose; 1 pt in Level 2 had REG delayed and TMZ dose reduced due to grade (G) 2 thrombocytopenia. At Level 1 and 2, 1 G3 haematological toxicity, respectively. At Level 3, 1 pt had a G3 gastrointestinal toxicity. In cohort B, 12 pts were enrolled (median age 53ys); at Level 3, 2 of 6 pts reported a DLT (n=1 G3 hypertransaminasemia with a dose reduction of REG (51%) and TMZ (50%) and n=1 G4 thrombocytopenia at the last day of RT). One case of G3 hypertension and 1 case of G3 hypertransaminasemia were also reported. REG was reduced in another pt due to G2 pain (no DLT); at Level 2 there was 1 case of G3 hyperbilirubinemia. There were no G3-4 AEs at Level 1. PK analysis of REG alone or in combination with TMZ showed a significant reduction (P=0.038) in the AUC, with a geometric mean ratio (GMR) of 80% (CI_{90} 64 – 98%) when given together with TMZ. PK analysis of TMZ showed a slight but significant reduction in the Cmax and AUC (P = 0.003 and 0.015, respectively) when given with REG, with GMR of 72% (CI_{90} 57 – 91%) and 86% (CI_{90} 79 – 92%), respectively. These results suggest a weak PK interaction between the two drugs. **Conclusions:** The MTD of REG for cohort A was 160mg, for cohort B 120mg with a weak PK interaction between the two drugs. The MTD of 120mg can be considered the recommended dose of REG in combination with standard Stupp therapy for the phase 2 study. Preliminary activity analyses are ongoing. Clinical trial information: NCT06095375. Research Sponsor: None.

Azeliragon, a RAGE inhibitor, in combination with temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Preliminary results of phase Ib/II CAN-201 NDG trial.

Juan Manuel Sepulveda, Manuel Valiente, María Martínez-García, Estela Pineda, Maria Ángeles Vaz-Salgado, María Ruiz Vico, Gabriel Velilla, Manuel Mazariegos-Rubi, Izaskun Valduvieco, Maria Castro Henriques, Laia Cano, Stephen Garrett Marcus; Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; Spanish National Cancer Research Centre (CNIO), Madrid, Spain; Hospital del Mar, Barcelona, Spain; Medical Oncology Department, Hospital Clínic de Barcelona, Barcelona, Spain; Medical Oncology Department. Hospital Universitario Ramón y Cajal, Madrid, Spain; Radiation Oncology Department, Hospital Clínic de Barcelona, Barcelona, Spain; Cantex Pharmaceuticals, Inc., Weston, FL

Background: Azeliragon is an orally available inhibitor of the receptor for advanced glycation end-products (RAGE). RAGE pathway promotes cell proliferation and angiogenesis, contributing to glioblastoma (GBM) progression and resistance to temozolomide (TMZ) and radiation (RT). Azeliragon has extensive clinical safety data in patients (pts) with Alzheimer's disease. Our hypothesis was that azeliragon may enhance the efficacy of Stupp regimen in newly diagnosed GBM. **Methods:** CAN-201 NDG is an open-label, single arm, phase Ib/II trial in Spain. Newly diagnosed IDH wild-type pts with GBM, MGMT methylation locally available and with tumor resection were recruited. Pts received azeliragon in combination with standard radiotherapy and TMZ followed by maintenance with azeliragon. The trial consists of an initial dose finding phase in a 6 dose escalation strategy with a subsequent expansion phase (up to 14 additional pts) at the recommended phase 2 dose (RP2D). The dose levels were: 5 mg/day (L1), 10 mg/day (L2) and 20 mg/day (L3). The primary objective is to determine the RP2D, defined as the dose for which $<$ 33% pts experience a dose limiting toxicity (DLT) within 28 days from initiation of dosing. Main secondary endpoints include progression-free survival (PFS), overall survival (OS) and changes in corticosteroid requirements. **Results:** From Oct 2023 to Jul 2024, 20 pts were included, 6 in L1, 8 in L2 and 6 in L3. The median age was 52 years (range: 40-69). Most pts were male (65%), ECOG 0-1 (95%) and MGMT unmethylated (60%). No DLTs were observed. Serious adverse events, all considered unrelated to azeliragon, were reported in 4 pts (20%), being hemiplegia, pyrexia, infectious meningoencephalitis, epilepsy and neurological decompensation. Non-serious Grade 3-4 adverse events (AE), also considered unrelated, were G3 hematological AEs in 33.3% in L1 and 37.5% in L2. G1-2 azeliragon-related AEs were reported in 33.3%, 25% and 66.7% of pts in L1, L2 and L3, respectively. Azeliragon treatment was ended due to progression in 83.3% and 62.5% of pts in L1 and L2, respectively. All pts on L3 are still on treatment. With a median follow-up time of 8.4 months, pts in L1 showed a median PFS of 5.2 months (95% CI, 4.4-Not Reached [NR]) and 9.8 months (95% CI, 6.2-NR) in L2. No progression of disease was observed in L3 with a range of follow-up of 4.9-7.0 months. Median OS in L1 was 11.1 months (95% CI, 9.4-NR). Data was not mature enough to calculate OS in L2 and L3. **Conclusions:** Azeliragon in combination with standard RT and TMZ is safe, with no dose-limiting toxicities reported so far at the initial three dose levels. To further explore the safety and efficacy profile of azeliragon, we are now expanding the study to include two additional dose levels of 30 mg/day (L4) and 50 mg/day (L5). Enrollment is currently open for level L4. Clinical trial information: NCT05635734. Research Sponsor: CANTEX Pharmaceuticals, Inc.

From retrospective analysis to real-world impact: Mismatch repair deficiency detection in gliomas by tissue and liquid ctDNA NGS in glioma management.

Suman Suryanarayana Karanth, Nitesh Rohatgi, Anil Anand, Rakesh Gupta, Rana Patir, Ankur Bahl; FMRI, Gurugram, India; Fortis Memorial Research Institute, Gurugram, India; Fortis Memorial Research Institute Gurugram, Gurugram, India

Background: Tissue biopsy remains the gold standard for Microsatellite Instability and MMR (mismatch repair) gene alteration assessment. The regulatory approval of immune checkpoint inhibitors is for mismatch repair-deficient cancers, regardless of tumor type. Surgical resection or biopsy is challenging when the glioma is located deep in the brain or brainstem. Circulating tumor DNA (ctDNA) next-generation sequencing (NGS) offers a non-invasive alternative, garnering attention in extracranial cancers, however not so in gliomas due to the lower concentrations of tumor-derived biomarkers. While Cerebrospinal fluid (CSF) provides superior sensitivity and specificity for gliomas, it is not a standard test in gliomas with its own technical issues. **Methods:** A retrospective analysis was conducted using databases to evaluate the prevalence of pathogenic inactivating alterations in MMR genes in glioma tissue samples. Data were queried from the MSK, Clin Cancer Res 2019 database for targeted sequencing on MSK-IMPACT and FMI panels, comprising 1004 tissue samples (837 with matched normal) from 923 glioma patients through the cBioPortal platform. Frequencies of MMR gene alterations were assessed. **Results:** A total of 850 patients (out of 923) were retrospectively analyzed for MMR gene alterations, with 40.3% (343) being female and 59.6% (507) male. Primary samples constituted 79.8% (679), and recurrent samples 20.2% (172). OncoKb level alterations were categorized as Level 1 (0.5%), Level 2B (16.6%), Level 3B (13.6%), Level 4 (32.8%), and none (36.4%). MMR gene alterations were found in 35 samples (4%), with MSH2 and MSH6 each detected in 2%, MLH1 in 1%, and PMS1, PMS2, and MSH3 in less than 1% of samples. In a specific case, ctDNA NGS was performed on a 9-year-old boy diagnosed with diffuse intrinsic pontine glioma as tissue biopsy was not feasible. Survivals are 9 to 11 months despite multimodality treatment. ctDNA NGS identified a truncating MSH6 alteration at 100% Variant Allele Frequency, suggesting biallelic inactivation of MSH6. Additionally, an IDH R132C activating mutation, a TP53 splice site SNV and high tumor mutational burden (bTMB) at 132.33 Mut/Mb were detected. Post radiation resulted in no change in tumor size. Injection pembrolizumab 3 weekly was initiated. Follow up MRI revealed further reduction in size and tumor has remained stable with ongoing therapy. **Conclusions:** Identifying MMR alterations potentially broadens the therapeutic options for glioma. The compelling case of the 9-year-old boy highlights the clinical utility of ctDNA NGS in identifying actionable MMR gene alterations, leading to successful immunotherapy with pembrolizumab and continued stable disease beyond 13 months. While few studies exist on utility of ctDNA in gliomas, it is time for bigger studies in both primary and recurrent gliomas where biopsy is not feasible. Research Sponsor: None.

Immunohistochemical and gene expression profiles as predictors of survival in recurrent high-grade glioma treated with intracranial nivolumab, ipilimumab, and autologous CD1c(BDCA-1)$^+$/CD141(BDCA-3)$^+$ myeloid dendritic cells (myDC).

Cleo Bertels, Iris Dirven, Latoya Stevens, Xenia Geeraerts, Louise Lescrauwaet, Wietse Geens, Jacomi Del'haye, Stefanie Brock, Anne-Marie Vanbinst, Hendrik Everaert, Freya Vaeyens, Sandra Tuyaerts, Mark Kockx, Johnny Duerinck, Bart Neyns; Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium; Laboratory for Medical and Molecular Oncology (LMMO), Translational Oncology Research Center (TORC), Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium; Department of Neurosurgery, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Department of Neurosurgery, Vrije Universiteit Brussel (VUB)/ Universitair Ziekenhuis Brussel (UZ Brussel), Brussels, Belgium; Department of Pathology, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Department of Radiology, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Department of Nuclear Medicine, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; Centre for Medical Genetics, Research Group Genetics, Reproduction and Development, Clinical Sciences, Universitair Ziekenhuis Brussel (UZ Brussel), Vrije Universiteit Brussel (VUB), Brussels, Belgium; CellCarta, Antwerp, Belgium; Universitair Ziekenhuis Brussel, Brussels, Belgium

Background: Innovative treatments are needed for recurrent high-grade glioma (rHGG) patients (pts) as current salvage therapies fail to improve overall survival (OS). Immune checkpoint inhibitors lack efficacy in rHGG when administered IV. This single center, multi-cohort phase I trial (Glitipni, NCT03233152) investigated intracerebral (iCer) administration of ipilimumab (IPI) +/- nivolumab (NIVO) +/- myDC after maximal safe resection (MSR), followed by adjuvant intracavitary (iCav) IPI/NIVO through an Ommaya reservoir. **Methods:** Eligible pts (ECOG $\leq$ 2, $\leq$ 8mg/day methylprednisolone) with rHGG (WHO 2021 grade 3/4, IDH-1/2 wild type (wt) or mutant) after standard postoperative radiotherapy (RT) and temozolomide (TMZ) were included. Pts underwent MSR or stereotactic biopsy (if unresectable) $<$ 24h after receiving NIVO IV (10mg), followed by iCer injection of varying doses of IPI +/- NIVO +/- myDC and Ommaya catheter placement depending on the cohort (C). NIVO was administered IV (all cohorts) +/- iCav (C3-7) bi-weekly up to 12 cycles. Baseline tumor microenvironment characteristics were assessed by immunohistochemical (IHC) analysis and gene expression profiling (GEP). **Results:** Between 2016 and 2023, 110 pts (68% male, median age 57, 92% ECOG 0/1) were enrolled. At primary diagnosis, the majority (85%) were glioblastoma pts (WHO grade 4, IDH-wt), treated with the standard of care (MSR + RT + TMZ) (71%). All pts received 10mg NIVO IV preoperatively. Ninety percent of the pts who underwent the neurosurgical procedure started the postoperative treatment. Early discontinuation of study treatment occurred in 76% of pts, mainly due to tumor progression (86%). Treatment-related adverse events (TRAE) were mild (CTCAE grade 1/2), no grade 5 TRAE occurred. Most frequent TRAE were fatigue, headache and fever. At database lock (Jan 1st, '25), 9 pts remained progression-free. When including durable benefit from bevacizumab at first progression (13 pts), PFS and OS were significantly higher in C5/6 (+myDC) compared to other cohorts (-myDC) of our trial with resectable rHGG, and to a historical control group treated with VEGF(R)-inhibitors (descriptive $p < 0.05$ for each pairwise comparison). Absence of B7H3 on resected tumor tissues as demonstrated by IHC (C4, 5, 7) showed longer median OS, which was consistent with GEP. PD-L1 expression and density of CD8, Granzyme B or FOXP3 positive cells/mm^2 did not correlate with survival. A proliferative gene signature on GEP was significantly correlated with shorter PFS and OS. **Conclusions:** Intracranial administration of IPI/NIVO co-administered with myDC was feasible and safe, resulting in encouraging survival in pts with resectable rHGG. Baseline B7H3 levels and a proliferative gene signature correlated with survival. Clinical trial information: NCT03233152. Research Sponsor: None.

Development and validation of a droplet digital PCR (ddPCR) assay to detect MGMT promoter methylation in FFPE tumors of glioblastoma (GBM) patients.

Mahrukh M. Syeda, Miranda Ortega, Christine Cordova, Alexandra Michelle Miller, David Polsky; NYU Langone Medical Center, New York, NY; NYU Langone Health, New York, NY; Mayo Clinic Florida, Jacksonville, FL; New York University Langone Health, Brain and Spine Tumor Center, New York, NY

Background: Methylation of the MGMT gene promoter (MGMTp) is a critical biomarker to inform GBM prognosis and guide treatment decisions, including clinical trial eligibility. Rapid reporting of MGMTp methylation can help stratify patients early and facilitate clinical trial referral during the crucial post-operative period where treatment options are being considered by patients and physicians alike. **Methods:** We developed a probe-based ddPCR method to detect and quantify MGMTp methylation. Assay specificity was assessed using bisulfite-converted, unmethylated DNA. Assay linearity and Limit of Detection (LoD) were determined using MGMTp methylated cell line DNA samples of decreasing fractional abundances (35%, 5%, and 0.5%) and decreasing DNA inputs (30ng, 10ng, 3ng,1ng and 0.5ng). The limit of Blank (LoB) was calculated using 16 replicates of unmethylated bisulfite-converted PBMC DNA, and DNA from tonsil FFPE samples (n = 9). Reproducibility studies were conducted on two different days with two different operators. Accuracy and concordance were assessed using an in-house MGMTp methylation pyrosequencing assay as an orthogonal method to analyze11 melanoma and one glioblastoma cell line. Preliminary clinical validation was conducted via analysis of FFPE tumor DNA from 34 GBM patients with clinical MGMTp methylation pyrosequencing results. **Results:** The MGMTp methylation ddPCR assay demonstrated 100% specificity to detect promoter methylation. The method linearly quantified both total DNA and methylated DNA along a range of input DNAs with conserved fractional abundances. The LoB was 0.036% and 0.034% using PBMC and tonsil FFPE DNA, respectively. The LoD was 0.075%. The bisulfite conversion and assay were highly reproducible, with a coefficient of variation $< 20\%$. Among the 12 cell lines analyzed by both pyrosequencing and ddPCR the concordance was 100%. Ten of 11 GBM tumor samples identified as MGMTp methylated by the clinical pyrosequencing assay were also identified as methylated by the ddPCR assay. Five of 23 clinically unmethylated tumors were positive in the ddPCR assay with generally very low fractional abundances (0.08%, 0.12% 0.3%, 0.97% and 10.11%). **Conclusions:** We report preliminary validation of a highly sensitive and specific ddPCR assay to detect MGMTp methylation. Given the minimal sample requirements and rapid turnaround time for ddPCR assays, this test could eventually be utilized in clinical laboratories to quickly report MGMTp methylation status for GBM patient management. Research Sponsor: None.

Combining abemaciclib, temozolomide, and radiation in DIPG PDOX models: Insights from single-cell RNA-seq on cellular subtypes and genes critical for responsiveness and resistance.

Zilu Huang, Tongchao Jiang, Milagros Melanie Suarez Palacios, Brian Wray, Tommy Ouyang, Tsz-Kwong Man, Aalaa Abdallah, Long Niu, Jinnan Chen, Xin Zhai, Emily Ciolak, Wenan Qiang, Runxin Wu, Shi-Yuan Cheng, Matthew John Schipma, Xinkun Wang, Yunfei Xia, Yuchen Du, Xiao-Nan Li, John A. Kalapurakal; Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL; NUSeq Core Facility, Center for Genetic Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; Texas Children's Cancer Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX; Chemistry of Life Processes Institute, Evanston, IL; The Ken & Ruth Devee Department of Neurology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL; Department of Cell and Developmental Biology, Northwestern University Feinberg School of Medicine, Chicago, IL; State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China; Northwestern University Feinberg School of Medicine, Chicago, IL; Ann & Robert H. Lurie Children's Hospital, Chicago, IL; Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

Background: Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive pediatric brain tumor, with two-year survival less than 10%. Radiation therapy (XRT) offers limited survival benefits, and effective therapies are urgently needed. This study investigates the FDA-approved CDK4/6 inhibitors-Abemaciclib, XRT, and temozolomide (TMZ) as a therapeutic regimen for DIPG using organoids and patient-derived orthotopic xenograft (PDOX) models, aiming to improve survival outcomes and gain insights into the underlying cellular and molecular mechanisms of DIPG treatment responsiveness and resistance to support rapid translation into clinical trials. **Methods:** The efficacy of Abemaciclib, XRT, TMZ, and their combinations was evaluated in DIPG organoids and PDOX models (IBs-A0317DIPG and IBs-9119DIPG, H3.3K27M mutation). In vitro, PDOX organoids were treated with Abemaciclib, TMZ, with/without XRT. Synergy was assessed using the Bliss Independence model. In vivo, six treatment arms were tested: (1) control, (2) XRT (2 Gy/day $\times$ 5), (3) Abemaciclib (75 mg/kg, p.o., 14 days), (4) Abemaciclib + XRT, (5) TMZ (50 mg/kg, p.o., 5 days) + XRT, (6) Abemaciclib + TMZ + XRT. Single-cell RNA sequencing and IHC were used to assess cellular subtypes responses, gene expression changes, and resistance mechanisms. **Results:** In DIPG organoids, the combination treatment yielded Over Bliss values > 0 (0.25 and 0.58 in A0317DIPG and 9119DIPG models, respectively) demonstrating synergistic activities. In PDOX models, the triple therapy showed improved median survival compared to other treatment arms and significant survival advantage over control ($p = 0.0157$) and Abemaciclib alone ($p = 0.0461$) in A0317DIPG, and control ($p < 0.0001$), XRT alone ($p = 0.0032$), Abemaciclib alone ($p = 0.0006$), Abemaciclib + XRT ($p = 0.0046$), and TMZ + XRT ($p = 0.0001$) in 9119DIPG models. Single-cell RNA sequencing revealed six tumor subtypes: AC-like, NPC-like, OPC-like, MES-like, mitotic, and radiation-resistant cells. The triple therapy increased NPC-like and mitotic cell populations while decreasing AC-like and OPC-like cells in both models. Additionally, we identified a novel radiation-resistant subpopulation that expanded after XRT treatment. Dynamic gene expression analysis in different cell types identified key target genes and cell-type specific pathways that mediate therapy responsiveness and resistance. **Conclusions:** Our study demonstrates that the combination of Abemaciclib, TMZ, and XRT offers a novel, synergistic approach for DIPG, significantly improving survival in preclinical PDOX models. Single-cell RNA sequencing reveals the roles of different cell types and molecular changes underlying resistance, highlighting potential targets for future anti-resistance strategies in DIPG management. Research Sponsor: The Lou and Jean Malnati Brain Tumor Institute (MBTI).

MRI-based radiomics for prediction of isocitrate dehydrogenase subtype in glioblastoma multiforme through artificial intelligence models: A systematic review and meta analysis.

Sonali Belankar, Sravani Bhavanam, Ananya Prasad, Advaith N. Rao, Hitha Chitlur, Vinay C. Bellur, Priyanka Oza, Shruthi Raghunandan, Kushal Prasad, Shakirat Gold-Olufadi, Dosbai Saparov; M. S. Ramaiah Medical College, Bangalore, India; Brookdale University Hospital and Medical Center, New York, NY; Ramaiah Medical College, Bangalore, India; M. S. Ramaiah Medical College, Bengaluru, India; Ramaiah Medical College and Hospital, Bangalore, India; Vydehi Institute of Medical Sciences & Research, Bangalore, India; Bangalore Medical College and Research Institute, Bengaluru, India; Brookdale University Hospital, New York, Brooklyn, NY; Brookdale Hospital Center Housing Company, Inc., Brooklyn, NY

Background: Gliomas are aggressive tumours with poor prognosis. Isocitrate Dehydrogenase (IDH) mutations are present in approximately 12% of all Glioma tumours and are considered biomarkers for prognosis and response to chemotherapeutic agents. IDH mutant gliomas have better prognosis in comparison to IDH wild type Gliomas. IDH mutant Gliomas exhibit features like T2-Flair mismatch sign, reduced blood flow seen on perfusion-weighted images and reduced enhancement on MRI, which aid in identification of IDH mutation. Radiomic imaging techniques extract quantitative features from medical images like MRI and CT scans with the help of advanced algorithms and the extracted data can be utilized in the development of specific artificial intelligence (AI) models like Neural Networks for the prediction of IDH mutation. Thus, MRI based Radiomics is an emerging non invasive technique in comparison to conventional biopsy, for the determination of IDH mutation. The meta-analysis conducted aims to analyse the diagnostic potential of Radiomic imaging in predicting IDH mutations in Gliomas. **Methods:** A systematic search was conducted in PubMed, Google Scholar and Scopus. PRISMA guidelines were followed. A boolean expression was constructed to retrieve and select articles from major medical databases. The R Studio package was used to evaluate the potential of the diagnostic test. The Meta, Metadata and Mada packages were utilised to evaluate Pooled accuracy, sensitivity and specificity. **Results:** A total of 35 studies and 7522 radiomic features were assessed through this meta analysis. The Pooled Sensitivity and Specificity were estimated to be 86.70% ([74.85; 87.51], 95% CI, $p< 0.0001$, I^2 = 92.7% [90.9%; 94.1%]) and 82.75% ([0.7912; 0.8587], 95% CI, $p<0.0001$, I^2 = 82.8% [77.4%; 86.9%]) utilising the random effects model. The pooled Accuracy was found to be 81.28% ([0.6037; 0.9253], 95% CI, $p>0.01$, I^2 = 0.0% [0.0%; 45.4%]). **Conclusions:** Through the compilation of previously conducted studies, MRI based Radiomics show High Pooled Sensitivity of 86.70% and High Pooled Specificity of 82.75% in the detection of Isocitrate Dehydrogenase mutations in Gliomas. Pooled Accuracy rate of 81.8% indicates steady reliability of Radiomics in the prediction of IDH mutations. MRI based Radiomics is a dependable and consistent non invasive technique in the detection of IDH mutations in GBM and can be utilized for the generation of predictive models, enhancing clinical diagnosis and tailored management based on IDH mutation. Research Sponsor: None.

Correlative and spatial transcriptomic analysis of olaparib and durvalumab in patients with recurrent/refractory *IDH*-mutant gliomas.

Xin Wang, Yosef Ellenbogen, Gurveer Gill, Vikas Patil, Thiago Pimentel Muniz, Mary Jane Lim-Fat, Andrew Gao, Ben X. Wang, Sorana Morrissy, Warren P. Mason, Gelareh Zadeh, Eric Xueyu Chen; Department of Medical Oncology, University of Toronto, Sunnybrook HealthSciences Centre, Toronto, ON, Canada; University Health Network, Toronto, ON, Canada; Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; Princess Margaret Cancer Centre, Toronto, ON, Canada; Sunnybrook Health Sciences Center, Toronto, ON, Canada; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Combination of immune checkpoint and PARP inhibition has potential synergistic effects in *IDH*mt gliomas in pre-clinical models. Durvalumab and olaparib demonstrated objective responses in a subset of patients (pts) with *IDH*mt gliomas (NCT03991832). We report mutational, transcriptomic, and spatial correlative analysis of pts samples from baseline and at time of progression. **Methods:** Pts with recurrent/refractory *IDH*mt gliomas received olaparib 300 mg twice daily and durvalumab 1500 mg IV every 4 weeks until disease progression as determined by RANO 2.0 criteria. Whole exome sequencing (WES, n = 28) and total RNA sequencing (RNA-seq, n = 21) were performed on baseline archival formalin-fixed, paraffin-embedded tumor samples. Baseline tumor microenvironment was characterized with multiplex-immunohistochemistry (n = 29). Matched responders (n = 4) and non-responders (n = 6) were further profiled using 10X Visium HD for spatial transcriptomics. An unsupervised deconvolution method was applied using consensus non-negative matrix factorization for *de novo* discovery of expression programs corresponding to cell types and cell states. Associations with objective response (OR) to therapy were determined using either Fisher's exact test or rank-sum test. **Results:** In the 29 pts enrolled between January 2020–February 2023, median age was 40.5 (range 23–66) and 41% were female. The initial tumor grade was 2 (n = 9), 3 (n = 8), and 4 (n = 12). The OR rate was 14% (95% CI 3.9–32%), 1 complete response and 3 partial responses. All cases were mismatch repair proficient. The median tumor mutation burden (TMB) was 16.5, with TMB > 10 in 21 pts (75%). Baseline TMB was not associated with response. The most common co-mutations were *TP53* (n = 21, 75%), *ATRX* (n = 20, 71%), *ARID1A* (n = 7, 25%), *CIC* (n = 4, 14%), and *NF1* (n = 3, 11%), none were associated with response. There were no canonical mutations in *BRCA1*, *BRCA2*, or *PALB2*. Pathway analysis on differentially expressed genes between responders and non-responders showed convergence on interferon signaling and inflammation among responders ($p < 0.001$). Lower pre-existing M2-polarized tumor associated macrophages/microglia (high expression of CD68, PDL1, CD163) was associated with response ($p < 0.01$). These findings were supported by metaprograms in the HD spatial data, which showed higher levels of CD8+ cytotoxic T-cells at baseline in responders. Conversely, M2-polarized macrophage/microglia were enriched in non-responders. Paired progression samples will additionally be presented. **Conclusions:** Responders to olaparib and durvalumab had decreased baseline M2-polarized macrophages/microglia and increased pre-existing immunogenicity (interferon signaling). Several spatially conserved expression metaprograms targeting baseline immune infiltration were associated with response. Clinical trial information: NCT03991832. Research Sponsor: None.

The utilization of palliative care services by patients with glioblastoma: A cross-sectional study with care partners of patients with GBM recruited from Facebook support groups.

Lauren Robbins, Anna Vreeling, Elizabeth A. James, Alaina B. Doss, Barbara J. Lutz, Laurie A. Minns, Samantha K. Ennis; UNC Wilmington, Wilmington, NC

Background: Glioblastoma(GBM) is a terminal brain cancer that has a rapid onset and results in symptoms such as headaches, vomiting, seizures, anxiety, depression, agitation, speech impairment, memory impairment, infections, brain bleeds, mobility changes, changes in sleep patterns and cognitive changes. Palliative care helps patients diagnosed with an incurable or chronic disease manage physical, social and psychological symptoms while undergoing treatment, and has been shown to increase survival for patients with cancer. Previous data of former care partners of patients with GBM indicated only 30% of patients used palliative care during the disease trajectory, whereas 90% engaged hospice during the end of life stage. **Methods:** To better understand the reasons for underutilization of palliative care, primary caregivers of patients with GBM recruited from a Facebook support group in February 2024 completed a 38-question survey about where care was received, who was on their care team, and whether they had discussions around palliative care. Inclusion criteria: current primary care partner of a patient with GBM over the age of 18, and willing to participate (IRB exempt;H24-0393). The care partner was excluded if their patient was no longer living. **Results:** Of the 77 care partners who participated in the study, the median age of the caregivers was 56 years (98% female) and the median age of the patients with GBM was 60 years (87% female). Patients with GBM were initially diagnosed in community hospitals, major medical centers, university medical centers, brain tumor centers, and as part of incidental findings. Approximately $^{1}/_{4}$ of patients pursued second opinions. Of the 21 patients initially diagnosed in community medical centers, over half received treatment in other facilities. Medical care team members differed by facility type with a marked difference in palliative care utilization. Only 27% of care partners reported palliative care was part of the care team. Notably,when care team members discussed palliative care with patients and their care partners (n = 21), 71% of the dyads utilized palliative care. In contrast, when palliative care was not discussed (n = 56), only 7% of the care partners used these services ($p < 001$). Participants reported they would have benefited from additional supportive services provided by patient navigation and palliative care. **Conclusions:** This data highlights the value of discussions about palliative care in its utilization among GBM patients and their care partners. These conversations should take place early in the disease's progression to ensure that care partners receive the necessary education and resources in a timely manner. Research Sponsor: None.

Identification of novel electrophysiologic biomarkers of cognition in glioma-infiltrated cortex.

Vardhaan Ambati, Sanjeev Herr, Jasleen Kaur, Paul M. McMillan Villalobos, Emily Cunningham, Youssef Sibih, Sena Oten, Alexander A. Aabedi, David Brang, Shawn L. Hervey-Jumper; University of California, San Francisco, San Francisco, CA; Drexel University College of Medicine, Philadelphia, PA; UCSF Department of Neurological Surgery, San Francisco, CA; University of Michigan, Ann Arbor, MI

Background: Diffuse gliomas, the most common primary brain cancers, often invade speech-critical areas. Maximal resection improves survival, but damage to functional cortex may cause permanent impairments. Direct cortical stimulation (DCS) differentiates functional (DCS+) from nonfunctional (DCS-) cortex by temporarily disrupting neuronal activity, yet it remains unknown how DCS+ sites elicit transient impairments. DCS is technically challenging and resource-intensive. As a result, fewer than 50% of glioma patients receive optimal surgical care. This translational study aims to identify electrophysiologic biomarkers of DCS+ cortex to 1) aid in safe resection by avoiding functional cortex and 2) to elucidate causal relations behind these transient impairments. **Methods:** Local field potentials of subdural array data from glioma infiltrated cortex was annotated as DCS+ or DCS- prospectively. We compared spectral electrophysiologic variations (mean Theta [4-8 Hz], Alpha [8-13 Hz], Beta [13-30 Hz], and Full Gamma [30-150 Hz] ranges) at resting state between DCS+ and DCS- sites using linear mixed-effects models (to account for patient-level differences). **Results:** 1421 cortical sites of language were studied in 91 patients including 21 Oligodendroglioma WHO grade 2-3, 19 Astrocytoma WHO 2-3, 3 Astrocytoma WHO 4, 48 IDHwt glioblastoma [GBM] WHO 4). 115 (8.0%) were DCS+. After alignment to ECoG electrode arrays, 512 cortical sites (49 DCS+) were assigned to electrodes. In oligodendrogliomas, DCS+ (N=16) vs DCS- (N=132) sites had higher alpha (77.7 ± 111.9 vs 38.6 ± 39.8, p=0.018), beta (23.1 ± 18.1 vs 11.9 ± 17.9, p=0.033), and full gamma (0.6 ± 0.6 vs 0.3 ± 0.3, $p<0.001$) power. Similarly, in astrocytoma, DCS+ (N=13) vs DCS- (N=147) sites had significantly higher theta (98.5 ± 94.9 vs 57.1 ± 67.2, p=0.020), alpha (83.5 ± 76.3 vs 39.9 ± 42.4, p=0.003), beta (55.9 ± 58.4 vs 16.3 ± 17.8, $p<0.001$), and gamma (0.9 ± 0.9 vs 0.4 ± 0.4, p=0.006) power. Interestingly, when comparing DCS+ (N=20) and DCS- (N=237) sites in GBM patients, no significant differences were found in any studied ranges (all $p>0.05$). **Conclusions:** This study is the first of its kind to identify unique electrophysiological biomarker differences (at resting state) for oligodendroglioma and astrocytoma speech cortex. It has two key implications. First, clinically, the identification of electrophysiologic biomarkers may improve direct cortical stimulation (DCS) mapping: It can make surgeries faster by identifying cortex critical for cognition (speech) based on these biomarkers, safer by helping neurosurgeons avoid resecting critical regions, and more accessible. Second, this research suggests that different tumor types (low-grade gliomas vs. GBM) remodel speech areas differently, prompting further investigation into tumor-specific effects on neural circuits. Research Sponsor: None.

A single-institution retrospective study of multicentric gliomas stratified by *IDH* mutational status.

Chuyin Yang, Ryan Mostafavi, Collin Le, Addison Fisher, Blaine S.C. Eldred, Terry J. Prins, Linda M. Liau, Richard G. Everson, Robert A. Chong, Phioanh Leia Nghiemphu, Benjamin M. Ellingson, Albert Lai; University of California, Los Angeles, Los Angeles, CA; Department of Neurology, University of California, Los Angeles, California, Los Angeles, CA; Department of Neurosurgery, University of California, Los Angeles, California, Los Angeles, CA; Department of Radiology, Brain Research Institute, University of California, Los Angeles, Los Angeles, CA

Background: Multicentric glioma (MCG) is a subset of diffuse glioma that can be synchronous or metachronous and is defined as the occurrence of two or more tumor foci, with separation of FLAIR (Fluid-attenuated Inversion Recovery) hyperintensity on MRI. MCG has not been extensively studied in studies stratifying *IDH* wild-type and mutant gliomas. This large single-institution study investigates the prevalence of MCG, examines the prognostic implications of MCG, and characterizes metachronous MCG (mMCG) in a cohort that has been stratified by *IDH* mutational status. **Methods:** In this IRB approved UCLA study, we identified diffuse glioma patients with known *IDH* mutational status and adequate MRI studies. Patients with multiple lesions on the MRI study pre-surgery or up to 3 months post-surgery were considered synchronous MCG (sMCG). Patients who developed a new independent lesion at least 6 months after initial surgery were considered mMCG. To qualify as MCG, we identified additional tumors on MRI that had no overlapping FLAIR borders and met one or more of the following: pathologically confirmed with biopsy, exhibited growth and thickening over time, and developed or increased in enhancement. Difference in prevalence was compared using Student's t-test. Kaplan-Meier and Cox-multivariate analyses were used to analyze OS and time to metachronous (TtM) appearance. **Results:** We identified 911 consecutive *IDH* wild-type, high-grade diffuse glioma patients from 2013-2023 and 515 consecutive *IDH* mutant patients from 2007-2024 with pre-surgical MRI or MRI within three months of initial surgery. From the examined cohort, we found 39 *IDH* mutants with 21 sMCG and 18 mMCG and 153 *IDH* wild types with 95 sMCG and 63 mMCG. In eight *IDH* wild-type cases but no *IDH* mutant cases, mMCG arose from sMCG patients. We found that MCG had higher prevalence in *IDH* wild-types than in mutants (WT = 16%, Mut = 7%, $p < 0.0001$), and *IDH* mutant MCG showed more male predominance than *IDH* wild-type MCG (Mut = 73%, WT = 58%, $p < 0.0001$). In *IDH* mutant patients, mMCG, but not sMCG, was associated with lower OS (mMCG: HR = 2.476, p = 0.0115; sMCG: HR = 0.6437, p = 0.5027). However, in *IDH* wild types both sMCG and mMCG and were associated with lower OS (mMCG: HR = 1.589, p = 0.0025; sMCG: HR = 1.347, p = 0.0332). There was no difference in TtM between the two groups (HR = 0.5738, p = 0.5318). Amongst patients with multiple biopsied lesions, *IDH* wild types had consistent pathologies between lesions in all examined patients (29/29), but 71% of *IDH* mutants exhibited different pathologies between lesions (5/7). **Conclusions:** Our study examined a cohort of adult diffuse gliomas stratified by *IDH* mutational status and shows MCG is less common in *IDH* mutant gliomas and sMCG is not associated with worse prognosis. Further studies to identify molecular features underlying MCG will be valuable. Notes: For mMCG, FLAIR overlap might have occurred had the new lesion been observed synchronously. Research Sponsor: Bradley Zankel Foundation; NIH/NCI P50 CA211015-01A1 (UCLA SPORE in Brain Cancer).

Diagnostic accuracy of machine learning models in glioma classification: A meta-analysis.

Maya Gowda, Zouina Sarfraz, Khalis Mustafayev, Logan Spencer Spiegelman, Fatma Nihan Akkoc Mustafayev, Mohammad Arfat Ganiyani, Michael W. McDermott, Arun Maharaj, Rupesh Kotecha, Yazmin Odia, Manmeet Singh Ahluwalia; Cornell University, New York, NY; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Baptist Health South Florida, Miami Cancer Institute, Miami, FL; Miami Neuroscience Institute, Baptist Health South Florida, Miami, FL; Miami Cancer Institute, Miami, FL

Background: Machine learning (ML) is promising in IDH-based glioma classification using magnetic resonance imaging (MRI), but variability in methods and algorithms necessitates a comprehensive evaluation. This meta-analysis assesses the pooled diagnostic performance of ML-based approaches. **Methods:** A literature search was conducted in January 2025 across PubMed, MEDLINE, and Cochrane. MICCAI, RSNA, and SNO meeting abstracts were additionally reviewed. Eligible studies evaluating ML models for IDH-based glioma classification using MRI were included. Data were pooled using a random-effects model, analyzing sensitivity, specificity, heterogeneity, and publication bias via Egger's test and funnel plots. Leave-one-out analysis was conducted. **Results:** A total of 5982 cases were analyzed. Gliomas were classified as WHO Grades II (11.5%), III (23.1%), and IV (65.4%). Histopathology-based reference standards, including genetic and molecular testing, were used in 73.1% of studies, while immunohistochemistry, pathology, biopsy-proven markers, and immunohistopathologic diagnosis were each used in 3.8–7.7%. Deep learning models, including CNNs and ResNet, were the most used classifiers (30.8%), followed by Support Vector Machines (26.9%). Ensemble methods, such as Random Forest accounted for 19.2%, regression-based approaches (LASSO, logistic regression) for 15.3%, and other techniques like multilayer perceptron and AdaBoost for 7.7%. This meta-analysis included 25 studies for sensitivity and 26 for specificity, using a random-effects model with DerSimonian-Laird estimation. Pooled sensitivity was 83.0% (95% CI: 79.5–86.5%) and specificity was 78.6% (95% CI: 73.7-83.4%), both statistically significant ($p < 0.0001$). Substantial heterogeneity was found ($I^2 = 100\%$ for both), with Cochran's Q values of 1.9e+06 for sensitivity and 4.2e+06 for specificity ($p < 0.001$). Leave-one-out analysis showed minimal variation in pooled estimates (sensitivity: 82.6–83.8%, specificity: 77.6–79.4%). Egger's test revealed significant small-study effects ($p = 0.0001$ for both), suggesting potential publication bias. **Conclusions:** ML models demonstrated moderate diagnostic performance in IDH-based glioma classification, achieving a sensitivity of 83.1% and specificity of 78.6%. However, substantial heterogeneity and potential biases pose significant challenges to their clinical implementation. To enhance the reliability and broader applicability of ML models in IDH-based glioma diagnosis, standardization of imaging protocols and external validation are imperative. Research Sponsor: None.

Meta-analytical findings.

Metric	Sensitivity (%)	Specificity (%)
Pooled Estimate	83.0 (79.5–86.6)	78.6 (73.7–83.4)
Z-Value	46.4	31.76
P-Value	<0.0001	<0.0001
I^2 (%)	100	100
T^2	80.0	159.0
Cochran's Q	1.9e+06 (df=24, p<0.001)	4.2e+06 (df=25, p<0.001)
Leave-One-Out Range	82.6–83.8	77.6–79.4
Egger's Test (P-value)	0.001	0.001

Identifying key molecular drivers of survival and therapeutic targets in glioblastoma through integrated transcriptomic analysis.

Mohammad Kashkooli, Seyed Reza Salarikia, Ali Nabavizadeh, Mohammad Javad Taghipour, Hossein Darabi, Mahdi Malekpour, Farzad Midjani, Bita Behrouzi; Harvard-MIT Health Sciences and Technology, Boston, MA; Shiraz University of Medical Sciences, Shiraz, Iran; Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Background: Glioblastoma multiforme (GBM) remains one of the most aggressive brain tumors, characterized by poor survival rates and limited therapeutic success. Advancing treatment requires identifying molecular drivers of tumor progression and therapy resistance. Integrated transcriptomic analyses offer a powerful means to uncover pathogenic pathways, therapeutic targets, and refine prognostic tools. This study aimed to explore GBM's molecular landscape to identify survival-relevant genes and actionable pathways, ultimately paving the way for precision therapies to improve outcomes. **Methods:** RNA-sequencing data from TCGA, CGGA, CPTAC, GLASS, GSE121720, and GSE147352 datasets, encompassing 783 samples, were analyzed. Only primary, untreated GBM tumors with survival data were included. Data normalization was performed using the voom function in limma, and batch effects were corrected using ComBat while preserving survival-related and gender-specific variations. Differential expression analysis (DEA) was used with thresholds of $|\log FC| > 1$ (two-fold expression change) and adjusted $p < 0.001$, accounting for age, gender, race, and IDH1 mutation. Protein–protein interaction (PPI) networks were constructed using STRING, and Cox regression identified survival-related genes. DrugBank was used to link survival-associated genes to potential therapeutics. **Results:** Of the 783 samples, 488 met inclusion criteria (473 tumor, 15 non-tumor). DEA identified 1,453 differentially expressed genes (DEGs) with significant differences between tumor and non-tumor samples. PPI analysis highlighted 270 hub genes, of which 47 were significantly associated with survival. Notably, CDK1, RRM2, and BIRC5 showed negative prognostic effects (hazard ratio [HR] > 1.7, adjusted $p < 0.05$), while RPL3L, RPL21, and RPL9 exhibited protective effects ($HR < 0.5$, adjusted $p < 0.001$). DrugBank analysis identified gallium nitrate (targeting RRM2) and Alsterpaullone (inhibiting CDK1) as promising therapeutic candidates. **Conclusions:** This study provides a comprehensive bioinformatics analysis of GBM, integrating multiple transcriptomic datasets to identify critical survival-related genes, including CDK1, RRM2, and BIRC5, as key therapeutic targets. Notably, it highlights the protective roles of ribosomal proteins (RPL7, RPL9, RPL21), challenging the traditional view that ribosomal upregulation solely drives tumorigenesis. These findings emphasize the dual nature of ribosomal dysfunction, which has been implicated in both oncogenic and tumor-suppressive pathways. Through rigorous data normalization, batch correction, and PPI analysis, the findings offer robust insights into GBM biology and its molecular drivers. These results lay a strong foundation for future studies to validate their clinical relevance, refine prognostic models, and advance precision therapy strategies for GBM patients. Research Sponsor: None.

Effect of ivosidenib and vorasidenib on 2-hydroxyglutarate levels in low grade glioma: An in vivo MR spectroscopy study.

Max Saint-Germain, Dunja Simicic, Seyma Alcicek, Lindsay Blair, Helge Zollner, Christopher Davies-Jenkins, Matthias Holdhoff, John Laterra, Chetan Bettegowda, Karisa C. Schreck, Doris D. Lin, Peter B. Barker, David Olayinka Kamson, Georg Oeltzschner; Johns Hopkins University School of Medicine, Baltimore, MD; The Johns Hopkins University School of Medicine, Baltimore, MD; Kennedy Krieger Institute, Baltimore, MD; Johns Hopkins University, Baltimore, MD; Johns Hopkins Medical Center, Baltimore, MD; Johns Hopkins School of Medicine, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: IDH-mutant gliomas are slow-growing infiltrating tumors of astrocytic (AS) or oligodendroglial (OG) origin (WHO grade 2/3). The mutations occur in genes that encode the metabolic enzyme IDH1 or, more rarely, IDH2 and lead to production of 2-hydroxyglutarate (2-HG) that can be measured with optimized in-vivo MRS. Small-molecule IDH inhibitors (IDHi) ivosidenib (inhibits mIDH1 enzyme) and vorasidenib (inhibits mIDH1 and mIDH2 enzymes) showed good tumor penetrance and ~95% 2-HG reduction measured in tumor biopsies. Both ivosidenib and vorasidenib have evidence of responses in tumor growth rate. As volume reductions are often observed, but after a delay of several months, thus an early response biomarker highly desired. The aim of this study was to explore whether MRS measurements of 2-HG can be used to non-invasively monitor response to treatment with IDHmut-inhibiting drugs and compare this response to changes in tumor volume. **Methods:** 14 patients (Age ≥18y) with a histomolecularly confirmed IDH1 mutated diffuse glioma (AS or OG) received ivosidenib (n = 12) or vorasidenib (n = 2) therapy as part of their routine clinical care. MRI was performed before treatment (*baseline*) and repeated (*follow-up*) with a median on-drug follow-up of 6 months [4, 12 IQR]. Tumors were segmented from FLAIR images in 3D Slicer and volumes were calculated in cm^3. All MRS data were processed in Osprey with the built-in LCModel fitting module. Comparisons between baseline and follow-up measured metabolite levels were conducted using paired t-tests or (in cases where the normality assumption was not met) non-parametric Wilcoxon tests. **Results:** We analyzed spectra from 11 patients with both baseline and follow-up sessions. All spectra exhibited characteristic tumor features: reduced total N-acetylaspartate (tNAA) and elevated levels of total choline (tCho), lactate (Lac), and myo-inositol (mI), along with a 2-HG peak at 2.25 ppm that is visibly smaller after treatment. The decrease in 2-HG levels was highly significant ($p < 0.001$) across all included patients undergoing ivosidenib/vorasidenib therapy, regardless of reference standard. Volumetric assessment revealed tumor growth arrest and a subtle reduction in tumor growth in some individuals. **Conclusions:** This is the first in-vivo evidence using MRS that ivosidenib/vorasidenib reduces 2-HG. We found that 2-HG levels respond specifically and rapidly to treatment, while volumetric changes manifest slowly and more gradually, consistent with previous studies. This preliminary study suggests that in vivo MRS-derived 2-HG estimates could serve as sensitive and specific biomarkers for monitoring low grade gliomas in vivo in response to small-molecule IDH inhibitor therapy after initiation of treatment. Longitudinal volumetric and radiomic analyses are underway. Research Sponsor: None.

Vault proteins as prognostic biomarkers and therapeutic targets in lower-grade gliomas.

Sebawe Syaj, Jaber H. Jaradat, Jehad A. Yassin, Leen Alkuttob, Anwaar Saeed; Division of Hematology and Oncology, Department of Medicine, University of Pittsburg Medical Center, and UPMC Hillman Cancer Center, Pittsburgh, PA; University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA; School of Medicine, University of Jordan, Amman, Jordan; Division of Malignant Hematology and Medical Oncology, Department of Medicine, University of Pittsburgh School of Medicine, and UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Vault proteins, including MVP, VPARP, and TEP1, are components of the vault complex, and are involved in drug resistance, DNA repair, and cell survival. However, their role in low-grade gliomas (LGG) remains unclear. This study explored the expression and prognostic significance of LGG with the aim of uncovering their potential as biomarkers. **Methods:** Using the TCGA-LGG cohort, Kaplan Meier (KM) and uni/multivariate Cox proportional hazards regression (CPH) analyses were performed using R 4.3.3, and hazard ratios (HR) with 95% confidence intervals (CI) were reported. MVP, TEP1, and VPARP (PARP4) expression levels were further stratified according to the LGG subtype. Multi-gene KM plots were generated to stratify overall survival (OS), progression-free survival (PFS), and disease-specific survival (DSS) using gene set variation analysis (GSVA) scores. "ImmuCellAI" algorithm was utilized for immune infiltration analysis. The GDSC and CTRP databases were used for drug sensitivity analyses. **Results:** As indicated by KM and univariate CPH analyses, MVP (hazard ratio [HR] = 1.5, 95% CI: 1.3-1.8), TEP1 (HR = 1.7, 95% CI: 1.4-2.0), and VPARP (HR = 1.6, 95% CI: 1.3-1.9) predicted poor OS. MVP, in multivariate CPH model adjusted to tumor grade and histology, remained significant (HR = 1.37, 95% CI: 1.14-1.70). The expression of MVP, TEP1, and VPARP was the highest in astrocytomas and the lowest in oligodendrogliomas ($p < 0.05$), with oligoastrocytomas in between. 3-gene KM signature analysis revealed a negative association between higher GSVA scores and OS, PFS, and DSS (log-rank $p < 0.01$) (Table). Immune infiltration analysis indicated positive macrophage, Th1, Th2, and dendritic cell infiltration with higher GSVA (derived from MVP, TEP1, and VPARP) ($r > 0.40$, FDR < 0.05) and negative infiltration of naive CD8+ and neutrophils ($r < -0.30$, FDR < 0.05). Drug analysis revealed vincristine resistance with higher MVP expression ($r = 0.44$, FDR < 0.001). **Conclusions:** MVP, TEP1, and VPARP were associated with poor survival outcomes and distinct immune infiltration patterns in LGG. These findings highlight the potential of vault proteins as biomarkers and therapeutic targets for LGG. Research Sponsor: None.

Univariate Cox proportional hazards ratios for the different survival types for GSVA scores of the three major proteins of the vault (MVP, TEP1, and VPARP).

Survival type	Hazard Ratio	Cox P value	Logrank P value	Higher risk of death
OS	1.7	<0.001	24E-2.03	Higher GSVA
PFS	1.43	0.01	9.09E-03	Higher GSVA
DSS	1.75	<0.001	2.18E-03	Higher GSVA

Accelerator-based boron neutron capture therapy, a randomized controlled trial for refractory recurrent high-grade meningiomas.

Shin-Ichi Miyatake, Masahiko Wanibuchi, Keiji Nihei, Koji Ono, Motomasa Furuse, Naosuke Nonoguchi, Shinji Kawabata, Naokado Ikeda, Hideki Kashiwagi, Kazuhiko Akita, Naonori Hu; Kansai BNCT Medical Center, Osaka Medical and Pharmaceutical University, Takatsuki, Japan; Department of Neurosurgery, Osaka Medical and Pharmaceutical University, Takatsuki, Japan; Kansai BNCT Medical Center, Osaka Medical and Phamaceutical University, Takatsuki, Japan; Osaka Mdical and Phamaceuticcal University, Takatsuki, Japan

Background: High-grade meningiomas (HGMs) recurred after X-ray treatment showed pessimistic prognosis. We conducted "A phase II investigator-lead RCT using accelerator-based BNCT system for refractory recurrent high-grade meningioma". **Methods:** We prepared 2 study arms, BNCT test treatment arm (12 subjects) and control best supportive care arm (6 subjects) in RCT fashion. PFS judged by the third-party committee was primary endpoint and PFS judged by investigators themselves and OS of BNCT arm and so on were secondary endpoints. Rescue BNCT was permitted for control group patients, if they were judged as PD by investigators. First patient-in and last patient-in were August 2019 and August 2021, respectively. Last patient visit was February 2024 and final OS survey and final observation for effectiveness and safety in BNCT arm were performed in July 2024. These results were compared to EORTC's RCT of trabectedin. **Results:** Three and 2 grade 3 subjects were included in BNCT and control arm, respectively. Others were grade 2 subjects. All cases were confirmed relapse after some radiotherapy in follow-up images. One subject allocated in BNCT arms was excluded after enrollment due to protocol violation. At the end of the observation, as primary endpoint, PFS of each arm judged by committees showed statistical significance (p=0.0157, Log-rank). As one of the secondary endpoints, PFS of each arm judged by investigators also showed statistical significance (p=0.0002). Median PFS judged by committees were 14.4 (95% CI:7.9-26.4) and 1.4 (1.0-9.0) months for BNCT and control arm, respectively. Median PFS judged by investigators showed 14.7 (7.6-22.8) and 1.5 (1.0-9.0) months, respectively. Five out of 6 cases in control arm received rescue BNCT after PD assessments. Other endpoints are listed in the table. **Conclusions:** As primary endpoint, PFS judged by committee showed statistical significance between treatment and control arms. Recently, the results of RCT of "Trabectedin" for recurrent HGMs, organized by EORTC, (EORTC-1320-BTG) was reported. Unfortunately, there was no effect of Trabectedin not only in PFS but in OS. Therefore, EORTC's report seems to be natural course of recurrent refractory HGMs. Our current BNCT shows extremely excellent results in comparison with EORTC's RCT in mPFS, PFS-6 months, mOS, OS-1 year and ORR (Table). Clinical trial information: 2051190044. Research Sponsor: AMED.

Comparison of both RCT (current study and EORTC trabectedin).

	Current study (n=18)		EORTC trabectedin (n=90)	
	BNCT	Control	Trabectedin	Control
mPFS (months)	14.4	1.4	2.43	4.17
PFS-6 months (%)	100	44.4	21.1	29.1
mOS (months)	46.9	-	11.4	10.6
OS-1 year (%)	100.0	-	48.1	43.0
OS-2 year (%)	90.9	-	-	-
ORR (CR+PR) (%)	27.3	0	1.6	0

Phase 2 study of nivolumab for patients with meningiomas refractory to surgery and radiotherapy with immune-related response criteria.

Hikaru Sasaki, Tetsuya Takimoto, Ryo Takemura, Kohei Nakamura, Ryutaro Kawano, Shigeru Yamaguchi, Kazuhide Adachi, Masayuki Kanamori, Daisuke Kuga, Dai Kamamoto, Masato Nakaya, Utaro Hino, Hirokazu Fujiwara, Tomoru Miwa, Hiroshi Nishihara, Hideyuki Saya, Yutaka Kawakami; Tokyo Dental College Ichikawa General Hospital, Ichikawa, Japan; Oncology Innovation Center, Fujita Health University, Toyoake, Japan; Biostatistics Unit, Clinical and Translational Research Center, Keio University Hospital, Tokyo, Japan; Center for Cancer Genomics, Keio University School of Medicine, Shinjuku-Ku, Japan; Department of Neurosurgery, Faculty of Medicine, Hokkaido University, Hokkaido, Japan; Department of Neurosurgery, Fujita Health University, Toyoake, Japan; Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan; Department of Neurosurgery, Kyushu University School of Medicine, Fukuoka, Japan; National Hospital Organization Tochigi Medical Center, Utsunomiya City, Tochigi Prefecture, Japan; Department of Neurosurgery, Saiseikai Yokohamashi Tobu Hospital, Yokohama, Japan; Keio University School of Medicine, Shinjuku-Ku, Japan; Center for Cancer Genomics, Keio University Hospital, Shinjuku-Ku, Japan; Department of Immunology, School of Medicine, International University of Health and Welfare, Narita, Japan

Background: The majority of meningiomas, which are the most common central nervous system (CNS) tumors, are benign and often cured by surgical resection alone. However, 20%–30% of meningiomas can be malignant tumors of CNS WHO grade II or III that are refractory to repetitive resection and radiotherapy. Moreover, a proportion of grade I meningiomas is associated with an aggressive clinical course reminiscent of grade II tumors. Reports of effective medical therapy for those tumors are extremely rare. **Methods:** A single-arm, open-label, phase 2 study was conducted to evaluate the efficacy and safety of nivolumab for meningiomas refractory to surgery and radiotherapy. Nivolumab (480 mg) was administered intravenously every 4 weeks and continued until tumor progression or unacceptable toxicity for up to 365 days. The primary endpoint was the objective response rate (ORR) determined by a central independent review committee. With a one-sided significance level of 5%, a power of 80%, a threshold response rate of 5%, and an expected response rate of 20%, the required sample size was calculated to be 27 patients using the exact binomial test. Considering a 10% attrition rate, the target sample size was set at 29. To avoid premature discontinuation of potentially effective immunotherapy, response was evaluated based on the iRANO (meningioma) criteria, which is based on the RANO (meningioma) criteria (Neuro Oncol 21(1):26-36, 2019) with the integration of the immune-related response criteria outlined previously (Lancet Oncol 16(15):e534-e542, 2015). Archival tumor specimens from all 29 cases were obtained for biomarker analyses. **Results:** A total of 29 patients started the study therapy. Response assessment by the central review committee was performed for 28 patients: grade I meningioma in 5, grade II in 19, and grade III in 4 by definition of the 2016 WHO criteria. The best overall response was PR in 1, SD in 13, and uPD/cPD in 14. The ORR was 3.6% and progression-free survival at 6 months was 23.9%. Biallelic inactivation of the *NF2* gene was detected in 20/27 cases (74%), whereas biallelic inactivation of the *CDKN2A* gene was identified in 7/27 cases (26%). One patient who had multiple grade I meningiomas with biopsy-proven lung metastases showed near CR following initial radiological progression. The TMB of the tumor was 8.1/MB. Next-generation sequencing found that none of the tumors had mutations of the DNA mismatch repair genes. Nivolumab was well tolerated. **Conclusions:** Although nivolumab monotherapy failed to meet the prespecified primary endpoint, our study demonstrated that a subset of patients could benefit from the therapy and that immune-related response criteria are necessary to evaluate immunotherapy for meningiomas. Clinical trial information: jRCT2031190074. Research Sponsor: Ono pharmaceuticals.

Analysis of genetic mutation profile and CNS pharmacokinetics in relapsed/refractory primary CNS lymphoma patients responding to novel emavusertib (IRAK4i) and BTKi combination.

Christian Grommes, Anna P. Dabrowska-Iwanicka, Han W. Tun, Christopher D'Angelo, Adolfo De La Fuente, Itai Levi, Lakshmi Nayak, David Lavie, Alessia Castellino, Michal Taszner, Praveen Ramakrishnan, Laurence Schenone, Andrés José María Ferreri, Teresa Calimeri, Luca Nassi, Caroline Houillier, Anna Schmitt, Gaurav S. Choudhary, Wanying Zhao, Grzegorz S. Nowakowski; Department of Neuro-oncology, Memorial Sloan Kettering Cancer Center, New York, NY; Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Częstochowa, Poland; Hematology Oncology Division, Mayo Clinic-Florida, Jacksonville, FL; Division of Hematology and Oncology, University of Nebraska Medical Center, Omaha, NE; Department of Hematology, MD Anderson Cancer Center Madrid, Madrid, Spain; Soroka Medical Center, Be`Er Sheva, Israel; Dana-Farber Cancer Institute, Boston, MA; Hematology department, Hadassah Medical Center, Jerusalem, Israel; Santa Croce e Carle Hospital, Cuneo, Italy; Department of Haematology, Medical University of Gdańsk, Gdańsk, Poland; UT Southwestern Medical Center, Dallas, TX; Department of Hematology, CHRU de Nancy, Hôpitaux de Brabois, Vandœuvre-Lès-Nancy, France; IRCCS San Raffaele Scientific Institute, Milano, Italy; Careggi Hospital, University of Florence, Florence, Italy; Service de Neuro-Oncologie, Hôpital Pitié-Salpêtrière, Paris, France; Bergonié Institute, Bordeaux, France; Curis Inc, Lexington, MA; Division of Hematology, Mayo Clinic, Rochester, MN

Background: Primary Central Nervous System Lymphoma (PCNSL) is a rare and aggressive non-Hodgkin lymphoma with no approved treatments for relapsed/refractory (R/R) patients, representing a critical unmet need. MyD88 mutations in ~70% of PCNSL patients drive Interleukin-1 receptor associated kinase 4 (IRAK4) activation, promoting NF-κB signaling, inflammation, and tumor progression. Emavusertib, a potent oral IRAK4 inhibitor, crosses the blood-brain barrier and shows preclinical synergy with Bruton tyrosine kinase inhibitors (BTKi), re-sensitizing BTKi-resistant cell lines. This study evaluates the molecular and pharmacokinetic (PK) data associated with responses to emavusertib + ibrutinib combination therapy in R/R PCNSL patients. **Methods:** The safety, clinical activity, and potential biomarkers of emavusertib in R/R PCNSL are being investigated in the ongoing open-label, Phase 1/2 TakeAim Lymphoma trial (NCT03328078). Pre-dose and 1.5-hour post-dose plasma samples were collected on Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1. Cerebrospinal fluid (CSF) samples were obtained via a lumbar puncture within 1.5 hrs of collection of the post-dose plasma PK sample on Cycle 3 Day 1. Mutation analysis was based on patients' molecular pathology reports provided by trial sites. Sequencing of archival tissues, CSF and plasma are in progress. **Results:** As of 06 December 2024, CSF concentration data were available for 7 PCNSL patients. The mean emavusertib concentration in CSF was 81.3 ng/ml (54.7-104.0) in patients receiving 100 mg emavusertib BID (n = 4). In patients receiving 200 mg emavusertib BID (n = 3), the mean emavusertib concentration in CSF was higher at 175.7 ng/ml (114.8-209.4), which is 2.2X the mean value in patients who received 100 mg emavusertib BID (p-value = 0.02). All 7 patients received 560 mg ibrutinib QD, and the ibrutinib concentrations in the CSF were consistent with findings from previously published clinical studies. MyD88 mutation status was available for 7 patients of which all had prior exposure to BTKi regimens. Among these, 6 patients had MyD88 mutation of which 4 patients had responded (3 complete responses and 1 partial response) to emavusertib + ibrutinib combination with duration of response (DOR) up to 18.9 months with data collection ongoing. **Conclusions:** Preliminary CNS pharmacokinetic data demonstrates that emavusertib concentration in CSF increases with increasing emavusertib dose. Patients with MyD88 mutations showed expected promising preliminary efficacy to emavusertib + ibrutinib combination and may overcome BTKi resistance. Enrollment in this trial is ongoing. Clinical trial information: NCT03328078. Research Sponsor: None.

Unraveling survival disparities in primary central nervous system (CNS) lymphoma: An analysis of race, socioeconomic factors, and treatment outcomes using the Surveillance, Epidemiology, and End Results program (2000–2021).

Imran Khan, Abat Khan, Shahzaib Maqbool, Pouyan Gohari, Mohammad Ebad Ur Rehman, Arham Ihtesham, Abdur Rehman, Zaheer Qureshi, Jose David Sandoval-Sus; NYC Health and Hospitals/Woodhull, Brooklyn, NY; Memorial Cancer Institute, Pembroke Pines, FL; Rawalpindi Medical University, Rawalpindi, Pakistan; The Frank H. Netter M.D. School of Medicine at Quinnipiac University, Bridgeport, CT; H. Lee Moffitt Cancer Center and Research Institute, Pembroke Pines, FL

Background: Primary central nervous system lymphoma (PCNSL) is a rare B-cell non-Hodgkin lymphoma with survival outcomes influenced by treatment, demographic, and socioeconomic factors (Villano JL et al., Br J Cancer, 2011). This study evaluated survival disparities associated with race, socioeconomic status (SES), and treatment modalities in PCNSL patients using a large U.S. population database. **Methods:** This retrospective cohort study used the SEER-17 database to analyze data from 7,068 patients diagnosed with PCNSL between 2000 and 2021. Demographic, socioeconomic, and treatment data were collected. Kaplan-Meier analysis was used to compare survival across groups, and Cox proportional hazards models identified independent prognostic factors. **Results:** The cohort included 7,068 patients (52.3% male; mean age: 63 years, SD ± 15). Racial distribution was 63.9% Caucasians, 16.0% Hispanics, 12.2% Asian/Pacific Islanders, 7.3% African Americans, and 0.4% American Indian/Alaskan Natives. Among these, 27.3% received radiation, and 64.3% received chemotherapy. During the study period, 73.5% of patients died from PCNSL. Survival analysis revealed that Asian/Pacific Islanders had the longest median overall survival (OS) at 22 months (95% CI: 16.5–27.5), followed by Hispanics (16 months; 95% CI: 11.8–20.2), Caucasians (11 months; 95% CI: 9.8–12.2), and American Indian/Alaskan Natives with the shortest survival at 5 months (95% CI: 0–11.2) ($p<0.001$). Socioeconomic analysis showed a direct association between higher income and improved OS: patients with household incomes ≥75k had a median OS of 13 months (95% CI: 11.2–14.8), compared to 6 months (95% CI: 4.2–7.8) in those earning <50k ($p<0.001$). Multivariable Cox regression identified male sex (HR 1.21, $p<0.001$) and older age (HR 1.027, $p<0.001$) as adverse prognostic factors, while chemotherapy significantly improved survival (HR 0.43, $p<0.001$). Radiation provided a modest benefit (HR 0.913, $p=0.005$). **Conclusions:** This large study demonstrates that lower income levels and racial disparities are associated with reduced survival in PCNSL. Findings underscore the need for equitable healthcare access and tailored therapeutic strategies to address these inequities. Keywords: CNS lymphoma, survival disparities, socioeconomic status, race, treatment outcomes, public health oncology. Research Sponsor: None.

Predicting survival in malignant meningiomas: A machine learning approach.

Mustafa Alshwayyat, Sakhr Alshwayyat, Noor Almasri, Salsabeel Aljawabrah, Kholoud Alqasem, Tala Abdulsalam Alshwayyat, Abdalwahab M. Z. M. Alenezy; Jordan University of Science and Technology, Irbid, Jordan; University of Jordan, Amman, Jordan; King Hussein Cancer Center, Amman, Jordan

Background: Intracerebral meningiomas account for over 90% of all meningioma cases, with only 1–3% classified as malignant. Malignant meningiomas remain understudied compared with other brain tumors. This study is the first to apply machine learning (ML) to identify prognostic factors and improve outcomes of malignant intracerebral meningiomas. **Methods:** Data were obtained from the SEER database (2004-2021). Patients who met any of the following criteria were excluded: diagnosis not confirmed by histology; previous history of cancer or other concurrent malignancies; or unknown data. To identify prognostic variables, we conducted Cox regression analysis and constructed prognostic models using ML algorithms to predict the 5-year survival. Patient records were randomly divided into training (70%) and validation (30%) sets. A validation method incorporating the area under the curve (AUC) of the receiver operating characteristic curve was used to validate the accuracy and reliability of the ML models. We also investigated the role of multiple therapeutic options using Kaplan-Meier survival analysis. **Results:** A total of 1,363 patients were included. Most patients were White (71.8%) or female (56.7%). The median patient age was 62 years, and the median tumor size was 4.8 cm. Most of the tumors were localized (67.8%). Adjuvant radiation therapy was administered to 50.2% of the patients. Patients aged < 62 years exhibited better 5-year survival rates, with an overall survival (OS) of 79.4% and cancer-specific survival (CSS) of 82%, compared to those aged ≥ 62 years, who had an OS of 40.9% and CSS of 50.6%. Tumors smaller than 4.5 cm were associated with higher survival rates (OS: 67.7%, CSS: 72.4%) than larger tumors (OS: 53.6%, CSS: 61.9%). The impact of adjuvant radiation therapy showed an OS of 59.9% and 64.5%, respectively, compared with those who did not receive radiation, with an OS of 59.5% and CSS of 68.7%. Multivariate Cox regression analysis identified older age (HR: 3.6, 95% CI: 3.03–4.4) and large tumor size (HR: 1.4, 95% CI: 1.22–1.7) as poor prognostic factors. The Random Forest and MLP classifiers were the most accurate models. The ML models identified age as the most significant prognostic factor. The performance metrics for all the ML algorithms are summarized in Table. **Conclusions:** This study underscores the transformative potential of ML in enhancing personalized medical approaches for malignant intracerebral meningiomas. Furthermore, whether the benefits of adjuvant radiotherapy outweigh the risks remains unclear, indicating the need for further targeted research to investigate its therapeutic impact on these rare tumors. Research Sponsor: None.

ML Model	Accuracy	Precision	Recall	F1 score	AUC
LR	63%	50.8%	61.2%	55.6%	0.696
KNN	63.3%	51.2%	45.1%	48%	0.660
RFC	69.1%	58.9%	60.2%	59.5%	0.743
GBC	66.2%	55.6%	52.6%	54.1%	0.723
MLP Classifier	67.48%	57.47%	53.76%	55.56%	0.716

TPS2088 **Poster Session**

Phase IIa study of αDC1 vaccines targeting HER2/HER3 combined with pembrolizumab in patients with asymptomatic brain metastasis from breast cancer.

Shipra Gandhi, Peter A. J. Forsyth, Mateusz Opyrchal, Audrey Rawleigh, Matthew Sydor, Kamran A. Ahmed, Kristopher Attwood, Patrick Michael Dillon, Camilo E. Fadul, Dheerendra Prasad, Sheheryar Kairas Kabraji, Ellis Glenn Levine, Kevin Kalinsky, Brian J. Czerniecki, Pawel Kalinski; Roswell Park Comprehensive Cancer Center, Buffalo, NY; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Indiana University, Indianapolis, IN; Roswell Park Comprehemsive Cancer Center, Buffalo, NY; University of Virginia, Charlottesville, VA; University of Virginia School of Medicine, Charlottesville, VA; Winship Cancer Institute at Emory University, Atlanta, GA

Background: Brain metastases develop in up to 50% of patients (pts) with metastatic breast cancer. Overexpression of HER3 in brain metastatic breast cancer (BMBC) is a resistance factor to HER2-targeted therapies and a driver of brain metastasis. Disease progression is associated with loss of anti-HER2 and anti-HER3 immunity. Previously, we have demonstrated that glioma-specific peptide-loaded αDC1 which produces CXCL9, CXCL10, CXCL11, and CCL5, the chemokines that attract CXCR3- and CCR5- expressing cytotoxic T-lymphocytes (CTLs) and T-helper 1 (Th1) cells, induce clinical responses and long-term disease stabilization in pts with aggressive recurrent primary brain tumors (Okada et al. JCO 2011. PMID: 21149657). We hypothesized that anti-HER2/3-loaded αDC1 combination with PD1 blockade will result in a strong Th1/CTL response against HER2/3 epitopes (Basu A et al. Cancer Immunol Res. 2022 PMID: 34785506) that will translate into anti-cancer benefit in the central nervous system (CNS) and systemically. **Methods:** This is a phase II single-arm, non-randomized multicenter study (NCT04348747). Eligibility includes pts with BMBC ≥18 years, ECOG PS ≤1, normal marrow and organ function with asymptomatic untreated brain metastases ≥ 5 mm. The study subjects receive αDC1 q3 weeks x 3 along with pembrolizumab every 3 weeks. Thereafter, αDC1 booster doses can be administered every 3 months until disease progression, intolerable side effects, or withdrawal from study, up to 24 months. Baseline and 9-week post-αDC1 peripheral biopsies (non-CNS) are required for six pts. The primary endpoint is CNS response rate (RR) by RANO-BM criteria. If no CNS response is observed after 12 pts, the study will be terminated. If ≥ 1 response is observed, then 9 more pts will be enrolled, for a total of 21 pts. If ≥ 3 CR are observed, the proposed therapy will be considered promising for further evaluation. Secondary endpoints include non-CNS RR per RECIST v1.1, median CNS, non-CNS and overall progression-free survival, overall survival, and safety. Exploratory endpoints include changes in intratumoral biomarkers (CTLs, PDL1, chemokines) in pre- and post-treatment peripheral tumor biopsies and immune changes in the blood. So far, 7 of the planned 21 pts have been enrolled. Clinical trial information: NCT04348747. Research Sponsor: U.S. Department of Defense.

TPS2089 **Poster Session**

A multicenter, randomized, controlled, pivotal trial of microbubble-enhanced transcranial focused ultrasound for patients with NSCLC brain metastases (LIMITLESS).

Manmeet Singh Ahluwalia, Ahmad Ozair, Kanwalcharan Singh Sahni, Nader Sanai, Arjun Sahgal, Michael W. McDermott, Kingsley Nwaogu, Lisa Dye, Gaganjot Sooch, Graeme Woodworth, Nir Lipsman, LIMITLESS Trial Investigators; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; University of Maryland School of Medicine, Baltimore, MD; Johnston-Willis Hospital, Richmond, VA; Ivy Brain Tumor Center at Barrow Neurological Institute, Phoenix, AZ; Sunnybrook Health Sciences Center, Toronto, ON, Canada; Miami Neuroscience Institute, Baptist Health South Florida, Miami, FL; Insightec Inc, Miami, FL

Background: The efficacy of systemic therapies for brain metastases (BM) is hindered by the blood-brain barrier (BBB) and brain-tumor barrier. Transcranial low-intensity focused ultrasound combined with IV microbubble oscillators (MB-FUS), allows for localized, controlled, non-invasive and temporary BBB opening, which has been shown to enhance tumor drug delivery of systemic therapies, as well as impro efficacy of immunotherapies. Non-small cell lung cancer (NSCLC) is the most common cause of BM, and this randomized controlled trial (RCT) aims to evaluate the safety and efficacy of MB-FUS-mediated BBB opening combined with standard of care (SOC) systemic therapy versus systemic therapy alone for patients with NSCLC BM. **Methods:** LIMITLESS is prospective, multicenter, parallel-arm, RCT, ongoing at up to 30 centers, that randomizes patients with NSCLC BM, in a 2:1 ratio to either: (i) Arm 1: MR-guided MB-FUS plus all FDA approved on-label use of immune checkpoint inhibitors (ICIs) with or without chemotherapy regimen (SOC systemic therapy), or (ii) Arm 2: SOC systemic therapy alone. Included patients are ≥18 years aged, with normal organ function, KPS ≥70, and have ≥0.5 cm size BM meeting measurable disease criteria as per RANO-BM. Patients on both arms receive standard-of-care therapy, while those on arm 1 also undergo MB-FUS. Patients undergo pre-treatment brain MRI, followed by IV administration of microbubbles for enhanced sonication effects. BBB opening is performed using a transcranial 220 kHz device with 1024-element phased array transducer with real-time acoustic feedback-based power control for maintaining effective microbubble activation. The primary study outcome is the overall objective response rate (ORR) at 6 months as assessed using RANO-BM criteria. Using a Bayesian design for power analysis, a superior ORR of 60% is assumed for MB-FUS arm versus 30% in the control arm for a total sample size of N = 96, 64 participants in MB-FUS and 32 in control arm, for 80% power using a two-sided chi-square test with an alpha of 0.05. For the upper-bound estimate, ORR of 45% in MB-FUS arm and 30% in the control arm, the study needs N = 369 participants: 246 in LIFU arm and 123 in control arm. The secondary outcomes are best objective response rate and median time-to-response per treatment arm. Exploratory outcomes are median progression-free survival (PFS), overall survival (OS), median intracranial PFS, median extracranial PFS, and quality of life. Patient enrollment commenced in 2022 and is ongoing (ClinicalTrials.Gov Registration: NCT05317858). Clinical trial information: NCT05317858. Research Sponsor: Insightec Inc.

TPS2090 **Poster Session**

Delayed or upfront brain radiotherapy in treatment-naïve lung cancer patients with asymptomatic or minimally symptomatic brain metastases and ALK rearrangements (DURABLE).

Joshua David Palmer, Nathaniel James Myall, Erin L. Schenk, Fawzi Abu Rous, Lai Wei, Carly Pilcher, Brian Spahnie, Charles David Tobin, Kimberly Cameron, Dwight Hall Owen; Department of Radiation Oncology, Ohio State University, Columbus, OH; Stanford Cancer Center, Stanford, CA; University of Colorado Anschutz Medical Campus, Aurora, CO; Henry Ford Hospital, Detroit, MI; Center for Biostatistics, Department of Biomedical Informatics, The Ohio State University, Columbus, OH; The Ohio State University, Columbus, OH; Ohio State University Comprehensive Cancer Center- The James Cancer Hospital and Solove Research Institute, Columbus, OH; HCRN, Indianapolis, IN

Background: Patients with non-small cell lung cancer (NSCLC) with ALK rearrangements have a high frequency of brain metastases. Alectinib was shown to be superior to crizotinib in the first-line treatment of patients with ALK-positive NSCLC in the ALEX trial, and the intracranial response rate (CNS ORR) was 85.7% with alectinib versus 71.4% with crizotinib in patients who received prior radiotherapy and 78.6% versus 40.0%, respectively, in those who had not. Alectinib has also shown benefit in earlier stages of NSCLC. Given the high intracranial efficacy rate demonstrated by alectinib, as well as the known toxicities of cranial irradiation, the role of early irradiation of CNS disease vs delaying radiation in favor of treatment with alectinib needs to be defined to inform clinical practice. **Methods:** NCT05987644 is a multi-center, multi-cohort study consisting of a Phase 1b and Phase 2 portion. The Phase 1b portion of the study is a single-arm, open label study of alectinib in patients with CNS disease. Twelve subjects will be enrolled in the Phase 1b portion of the study and treated with alectinib alone; patients with PD will come off study treatment and move on to standard of care treatment per national guidelines. The phase 2 portion will be a randomized, non-blinded, open-label study. Forty-four subjects will be enrolled and randomized 1:1 to either alectinib upfront (Arm A) or alectinib + SRS (arm B). A group sequential design will be implemented with one interim analysis for futility and, and one final analysis using the composite outcome. The primary objective of phase 1b is to determine the safety and feasibility of delayed brain radiation in patients with ALK fusion positive NSCLC and CNS metastases. The primary objective of the phase 2 study is to determine whether treatment with alectinib results in preserved neurological status and control of CNS disease at 12 months compared to alectinib plus SRS. Secondary endpoint will be intracranial progression free survival at 12 months (icPFS12), response rate and icPFS, OS, and safety and tolerability. The study is open and accruing at 4 sites. Clinical trial information: NCT05987644. Research Sponsor: Genentech.

TPS2091 **Poster Session**

FORTE: A phase 2 master protocol assessing plixorafenib for BRAF-altered cancers.

Karisa C. Schreck, Macarena Ines De La Fuente, Jessica Rine, Irina Kline, Stacie Peacock Shephard, Jordi Rodon Ahnert, Eric Jeffrey Sherman, Rona Yaeger; Johns Hopkins School of Medicine, Baltimore, MD; Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL; Fore Biotherapeutics, Philadelphia, PA; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Plixorafenib (FORE8394; PLX8394) is a novel, oral, small-molecule BRAF inhibitor highly selective for BRAF V600 monomers and BRAF-containing dimers. Plixorafenib binding disrupts RAF dimerization, targeting both BRAF V600 mutations and fusions, thereby preventing paradoxical activation and avoiding the need for combination with a MEK inhibitor. In a phase 1/2a study, plixorafenib demonstrated promising safety and clinical activity across a range of doses tested in tumors with BRAF V600 mutations or fusions. The most common adverse events (AEs) included predominantly low-grade liver function test changes and grade 1 fatigue, nausea, diarrhea, and vomiting. **Methods:** The FORTE Phase 2 basket study is currently enrolling patients ≥10 years of age into 4 sub-protocols. Study details are shown in theTable. Eligible patients have received prior therapy for advanced disease, have measurable disease, and have a Karnofsky (≥16 years) or Lansky (<16 years) Performance Score of ≥60 at study entry. All patients receive plixorafenib continuous dosing, in some cohorts coadministered with cobicistat, a pharmacokinetic (PK) booster. Prior MAPK inhibitor therapy is excluded unless otherwise specified below. As of January 2025, the trial is recruiting participants in 9 countries globally, with 54 sites activated. Clinical trial information: NCT05503797. Research Sponsor: Fore Biotherapeutics.

	Sub-Protocol A	Sub-Protocol B	Sub-Protocol C	Sub-Protocol D
Patient Population	Advanced solid and primary CNS tumors harboring BRAF fusions	BRAF V600-mutated recurrent primary CNS tumors	Rare[1] BRAF V600-mutated advanced solid tumors	BRAF V600-mutated melanoma[2] or thyroid cancer without anaplastic or undifferentiated components
Planned Enrollment	~100	~50	~75	~12
Design	Single-arm, open-label, Bayesian optimal phase 2 design			1:1 randomized, open-label crossover design to compare plixorafenib administered alone and with PK booster
Planned Efficacy Interim Analyses	N=25 N=50	N=25	N=25 N=50	None
Primary Endpoint	ORR[3]			Intra-patient PK
Key Secondary Endpoints	DOR, DCR, PFS, OS, PK, Safety			Safety, ORR, DOR, DCR, PFS, OS, Safety
Key Exploratory Endpoint	Longitudinal ctDNA assessments[4]			

[1]BRAF V600-mutated tumors occurring in ≤40,000 US patients annually (eg, ovarian/gynecologic cancers, cholangiocarcinoma, small intestinal/gastrointestinal cancers other than colorectal adenocarcinoma, neuroendocrine cancers).
[2]Patients with melanoma should have received and not tolerated a prior BRAF inhibitor.
[3]Response assessed by BICR using RECIST v1.1 for solid tumors or RANO HGG or LGG for primary CNS tumors. ORR for primary CNS tumors using RANO 2.0 is an exploratory endpoint. Tumors assessed at cycle 1 day 1, every 9 weeks for 48 weeks, then every 12 weeks.
[4]Plasma for all patients; plasma and CSF for patients with primary CNS tumors.

TPS2092 **Poster Session**

Retifanlimab with bevacizumab and hypofractionated radiotherapy to treat recurrent glioblastoma.

Nishika Karbhari, Angela Ulrich, Wendy Joyce Sherman, Susan Michelle Geyer, Shannon Patricia Fortin Ensign, Milan G. Chheda, Roy E. Strowd, Michael W. Ruff, Sani Haider Kizilbash, Ugur Sener, Joon H. Uhm, Bryan Neth, Evanthia Galanis, Eric J. Lehrer, William Breen, Elizabeth Yan, Anita Mahajan, Paul D. Brown, Jian Li Campian; Mayo Clinic, Rochester, MN; Division of Neurology, Mayo Clinic, Jacksonville, FL; Alliance Statistics and Data Management Center, Mayo Clinic, Rochester, MN; Division of Medical Oncology, Mayo Clinic, Phoenix, AZ; Washington University School of Medicine, St. Louis, MO; Atrium Health Wake Forest Baptist, Winston-Salem, NC; Division of Neurology, Mayo Clinic, Rochester, MN; Division of Oncology, Mayo Clinic, Rochester, MN; Department of Radiation Oncology, Mayo Clinic, Rochester, MN; Mayo Clinic Rochester, Rochester, MN

Background: Glioblastoma (GBM) is the most common primary brain malignancy in adults. GBM is universally recurrent and associated with dismal outcomes. Re-irradiation (reRT) is ideal for evaluating combination therapy for recurrent GBM (rGBM) due to its multifactorial mechanism of action, including downstream immunomodulatory activity. RT (especially multi-fraction) increases immunogenicity in preclinical models by promoting immune activation, immune migration, and antigen uptake. Additionally, a recent study demonstrated enhanced PD-L1 expression in the glioma tumor microenvironment (TME) following RT, and combining stereotactic RT with a PD-1 inhibitor improved survival in murine models. Retifanlimab is a humanized monoclonal anti-PD1 IgG4 antibody that received FDA approval for adults with metastatic or recurrent locally advanced Merkel cell carcinoma. Bevacizumab, an anti-VEGF antibody, is a treatment for radiation necrosis/cerebral edema with less immune suppression than corticosteroids. In a previous Phase 2 study, hypofractionated RT (HFRT), retifanlimab, and bevacizumab was associated with a 9-month overall survival (OS) rate of 71.4%. To demonstrate the efficacy of this regimen compared to HFRT and bevacizumab, we have designed a new randomized controlled Phase 2 trial. We hypothesize that combination reRT with retifanlimab will produce a more robust anti-tumor immune response and improve OS compared to reRT without retifanlimab. **Methods:** This is a multicenter, open-label, randomized, controlled Phase 2 study of retifanlimab, bevacizumab, and HFRT for adult patients with rGBM. Patients are randomized 1:1 to the experimental (bevacizumab + retifanlimab + HFRT) or control cohort (bevacizumab + HFRT). Key eligibility criteria include age ≥ 18 years, Karnofsky performance status ≥ 60, ≥ 4 months since administration of any prior bevacizumab, and dexamethasone dose ≤ 4 mg at the time of randomization. The primary endpoint is 9-month OS. Secondary endpoints include OS, progression-free survival, objective response rate, neurologic assessment by NANO criteria, and adverse events profile. Protocol treatment will continue up to two years, or until progression or intolerable toxicity. Survival follow up will continue every two months, up to four years. Seven of the planned 94 patients have been enrolled as of submission on 1/28/25. Clinical trial #: NCT06160206. Funding provided by Incyte. Clinical trial information: NCT06160206. Research Sponsor: Incyte Corporation.

TPS2093 **Poster Session**

PEAR-GLIO: Clinical evaluation of an AI-driven functional precision medicine platform for therapeutic efficacy in gliomas.

Matthew Williams, Eleonora Peerani, Elli Tham, Diana Visian, Thomas David Laurent Richardson, George Richard Tiger Bevan de Fraine, Keqian Nan, Duleek Nimantha Bandara Ranatunga, Waqar Saleem, Isaac Phang, Elizabeth Lim, Helen Benghiat; Ourotech Ltd t/a Pear Bio, London, United Kingdom; Ourotech (t/a Pear Bio), London, United Kingdom; Imperial College Healthcare NHS Trust, London, United Kingdom; Royal Preston Hospital, Preston, United Kingdom; University Hospitals Plymouth NHS Trust, London, United Kingdom; University Hospitals Birmingham, London, United Kingdom

Background: Gliomas and other primary brain tumors remain a leading cause of cancer-related mortality, with limited predictive biomarkers to guide therapy selection. The PEAR-GLIO trial investigates the use of Pear Bio's AI-driven ex vivo platform to assess the therapeutic sensitivity of FDA-approved and experimental treatments on patient-derived 3D immune-microtumors. This observational study seeks to validate whether this platform can provide actionable insights for patient stratification and treatment optimization in subsequent trials. The trial also incorporates patient and public involvement and engagement (PPIE) to understand perspectives and enhance study design and accessibility. **Methods:** PEAR-GLIO (NCT06038760) is a UK-based, observational study enrolling 50 patients diagnosed with operable primary brain tumors, including grades 2–4 gliomas. Inclusion criteria require histologically confirmed malignancy, the ability to provide ≥0.4g of tumor tissue and 40mL of whole blood, and consent for data and sample use. Exclusion criteria include pre-surgical chemotherapy or radiotherapy within 30 days and inoperable disease. Tumour-extracted and immune patient cells are cultured as physiologically-relevant 3D immune-microtumors and exposed to FDA-approved and experimental treatments. Phenotypic and molecular responses, including changes in tumour viability, cell death, migration, immune cell infiltration are assessed using live imaging and computer vision. The study uniquely integrates real-time confocal imaging and omics analyses to evaluate drug mechanisms of action. This includes correlation of ex vivo responses with biomarkers such as MGMT methylation, IDH mutation, and 1p/19q co-deletion, alongside exploratory analysis of experimental therapies. Recruitment began in October 2023, with 12 patients of the target 50 enrolled thus far. Data from the first cohort will inform platform optimization and scalability. All biological samples are anonymized, with outcomes tracked per RANO guidelines. Even at this early stage, PPIE has helped improve trial design. We are concurrently validating the platform in other high-unmet-need indications including early-stage breast cancer (NCT05435352), metastatic breast cancer (NCT06182306) and metastatic kidney cancer (NCT06264479) hoping to shift the paradigm in precision treatment selection. Clinical trial information: NCT06038760. Research Sponsor: Ourotech (t/a Pear Bio).

TPS2094 **Poster Session**

A multicenter, pivotal trial of microbubble-enhanced transcranial focused ultrasound (MB-FUS) for plasma-based liquid biopsy in patients with glioblastoma (LIBERATE).

Manmeet Singh Ahluwalia, Ahmad Ozair, Terence C. Burns, Michael W. McDermott, Alon Mogilner, Bhavya Shah, Toral R. Patel, Jordina Rincon-Torroella, Mark Vikas Mishra, Richard G. Everson, Justin Hilliard, Yarema Bezchlibnyk, Matthew Hibert, Julia Zhu, Jeffrey S. Weinberg, Christopher Paul Cifarelli, Ali Rezai, Vibhor Krishna, Nir Lipsman, Graeme Woodworth, LIBERATE Trial Investigators; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; University of Maryland School of Medicine, Baltimore, MD; Mayo Clinic, Rochester, MN; Miami Neuroscience Institute, Baptist Health South Florida, Miami, FL; NYU Langone Health, New York, NY; UT Southwestern Medical Center, Dallas, TX; Johns Hopkins Medicine Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; University of Maryland School of Medicine, Clarksville, MD; Department of Neurosurgery, University of California, Los Angeles, California, Los Angeles, CA; University of Florida Gainesville, Gainesville, FL; University of South Florida, Tampa, FL; Insightec Inc, Miami, FL; University of Texas MD Anderson Cancer Center, Houston, TX; West Virginia University Health Sciences Center, Morgantown, WV; West Virginia University, Morgantown, WV; The University of North Carolina at Chapel Hill, Chapel Hill, NC; Sunnybrook Health Sciences Center, Toronto, ON, Canada

Background: Liquid biopsy in glioblastoma (GBM) is hindered by a lack of requisite circulating tumor (ct) and cell-free (cf) DNA levels in blood due to the blood-brain barrier (BBB). This limits the identification of blood-based tumor biomarkers along with the development and use of biomarker-driven systemic therapies. Low intensity focused ultrasound combined with intravenously administered microbubble oscillators (MB-FUS), leads to non-invasive BBB opening. This trial aims to evaluate the utility of LIFU for bolstering blood ctDNA and cfDNA for enhance liquid biopsy in patients with GBM. **Methods:** LIBERATE is an ongoing, prospective, multi-center, self-controlled, pivotal trial evaluating safety and technical efficacy of transcranial MR-guided MB-FUS for increasing blood ctDNA and cfDNA levels in adults, aged 18-80 years with GBM. Patients with suspected GBM planned for tumor biopsy or resection at 17 centers in US and Canada are being enrolled. Patients with multifocal tumors or tumors arising from deep midline, thalamus, cerebellum, or brainstem are excluded. Patients are administered IV microbubbles for enhanced sonication, after which MR-guided BBB opening using a 220 kHz device, with 1024-element phased array transducer, is performed with real-time acoustic feedback control for effective cavitation. Pre- and post-procedure, phlebotomy and MRI brain are done. Patients are offered optional 2nd procedure during adjuvant chemotherapy phase if willing. Primary efficacy endpoint is correlation between biomarker patterns in tumor tissue collected during surgery/biopsy and blood collected following MB-FUS procedure. Confirmatory secondary efficacy endpoint is ratio between greatest yield of cfDNA in blood post-MB-FUS compared to cfDNA level in blood pre-MB-FUS. The primary study hypothesis is that agreement rate on biomarker pattern between resected/biopsied tumor tissue and blood is $> 70\%$. The secondary hypothesis is that MB-FUS BBBO leads to a $\geq$2-fold rise in blood cfDNA. Assuming the true agreement rate expected is 89%, a sample of N = 50 patients will provide 90% power to meet the primary endpoint (Exact test, Binomial Proportion, one-sided Alpha = 0.025). Exploratory endpoints include (1) sensitivity of detection of known specific somatic mutations in ctDNA from blood samples collected before and after MB-FUS, (2) estimation of ctDNA levels in samples collected at 30-minutes, 1-hour, 2-hour, and 3-hour post-MB-FUS to determine time of greatest yield, (3) correlation of MRI parameters related to grading of BBB opening and ctDNA-based biomarkers from post-MB-FUS blood samples, (4) biomarker correlation between plasma cfDNA sampled during adjuvant chemotherapy phase and tumor tissue harvested at surgery. Patient enrollment commenced in 2022 and is ongoing (NCT05383872). Clinical trial information: NCT05383872. Research Sponsor: Insightec Inc.

TPS2095 **Poster Session**

Liposomal curcumin and standard radiation and temozolomide for newly diagnosed high-grade gliomas: A phase 1/2 study.

Matthias Holdhoff, Solmaz Sahebjam, Peng Huang, David Olayinka Kamson, Michaella Iacoboni, Tamara Dobson-Brown, Karisa C. Schreck, Lawrence Kleinberg, Kristin Janson Redmond, Victoria J. Croog, Carmen Kut, Byram Ozer, Stuart A. Grossman, Michelle Comas, Jonathan Plehn, Joy D. Fisher, Peter P. Sordillo; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; SignPath Pharma, Sandy, UT

Background: Curcumin, derived from turmeric (Curcuma spp.), exhibits anti-inflammatory and antitumoral activity in preclinical studies, including inducing cell cycle arrest, apoptosis, autophagy and disrupting key cancer signaling pathways (e.g., STAT-3, AKT, VEGF, NF-κB, and IDO). Despite its promise, oral curcumin has limited bioavailability. Liposomal curcumin (LC), a novel intravenous formulation, achieves plasma curcumin levels over 1000 times higher than oral administration and preferentially accumulates in tumor cells. In preclinical glioma models, LC has antitumoral efficacy, particularly when combined with cytotoxic therapies. Previous trials in healthy volunteers and cancer patients demonstrated LC's safety, pharmacokinetics, and manageable adverse effects, with doses up to 300 mg/m^2 being well-tolerated. However, a case of hemolytic anemia was observed in a prior study at this dose in a patient who was also taking several known hemolytic drugs, suggesting the need for further safety evaluation at this and potentially higher doses. **Methods:** This Phase I/II open-label, study evaluates LC combined with standard radiation (RT) and concomitant and adjuvant temozolomide (TMZ) in newly diagnosed HGG patients (NCT05768919). The primary endpoints are MTD, RP2D and safety. Secondary endpoints include treatment feasibility (≥80% adherence to LC, RT, and ≥60% to TMZ), and exploratory efficacy measures (PFS, OS by RANO criteria). The study has two phases: (1) dose-escalation using the TITE-BOIN method to determine MTD, and (2) dose-extension to evaluate RP2D safety and feasibility. Up to 50 patients will be screened to enroll 30. LC is given weekly at 4 dose levels (240, 300, 350, and 400 mg/m^2) alongside standard adjuvant TMZ (150–200 mg/m^2 x 5 days every 28 days) and RT. Treatment continues for up to 6 TMZ cycles, with LC monotherapy possible afterward until progression or toxicity. MRI is done before and 4 weeks post-chemoradiation, then every 2 cycles of TMZ, as per standard of care. DLTs are evaluated over 10 weeks to determine the MTD which will be determined by TITE-BOIN dose escalation rule and Safety Review Committee's guidance. A separate exploratory protocol is offered to patients interested in additional imaging, which uses chemical exchange saturation transfer (CEST) MRI to visualize liposome accumulation in tumor tissue non-invasively. As of 1/24/2025, 14 patients have been enrolled in the dose-escalation part of this study. Clinical trial information: NCT05768919. Research Sponsor: SignPath Pharma.

TPS2096 **Poster Session**

A global phase 3, open-label, randomized 2-arm study comparing the clinical efficacy and safety of niraparib with temozolomide in adult participants with newly-diagnosed, MGMT unmethylated glioblastoma.

Nader Sanai, Shwetal Mehta, An-Chi Tien, Artak Tovmasyan, Jocelyn Harmon, William R. Kennedy, Amine Aziez, Anthony J. Chalmers, Mustafa Khasraw, Mary Jane Lim-Fat, Giuseppe Minniti, Juan M. Sepúlveda, Mehdi Touat, Yoshie Umemura; Ivy Brain Tumor Center at Barrow Neurological Institute, Phoenix, AZ; R&D, GSK, Zug, Switzerland; University of Glasgow, Glasgow, United Kingdom; Duke University Medical Center, Durham, NC; Sunnybrook Health Sciences Center, Toronto, ON, Canada; Sapienza University of Rome, Rome, Italy; Hospital Universitario 12 de Octobre, Madrid, Spain; Hôpital La Pitié Salpêtrière, Paris, France

Background: Glioblastoma (GBM) is associated with dismal prognosis and poor quality of life. In approximately 60% of tumors, the O6-methylguanine methyltransferase (MGMT) promoter is unmethylated and the prognosis is even more dire, with a median overall survival (OS) of 12.7 months following surgical resection, temozolomide (TMZ), and fractionated radiotherapy (RT). Poly (ADP-ribose) polymerase (PARP) mediates DNA damage response in GBM and niraparib is an investigational PARP1/2-selective inhibitor. At ASCO 2024, we reported on a Phase 0/2 study of niraparib plus radiotherapy in newly-diagnosed, MGMT-unmethylated glioblastoma (GBM), demonstrating superior tumor pharmacokinetic and pharmacodynamic performance compared to other studied PARP inhibitors and a median overall survival (OS) of 21.7 months. Based on the proof-of-concept data, a global registrational Phase 3 study (Gliofocus) was initiated. **Methods:** This Phase 3, open-label, randomized 2-arm study (NCT06388733) will compare niraparib versus TMZ in 450 adult participants with newly-diagnosed, MGMT-unmethylated GBM. Participants must have a biopsied or resected GBM, per 2021 World Health Organization classification. MGMT promoter methylation status is determined locally by validated pyrosequencing or quantitative methylation-specific polymerase chain reaction assays. Other key inclusion/exclusion criteria include: (1) Karnofsky performance status of ≥70, (2) no prior treatment for GBM (including brachytherapy or BCNU wafers), (3) no tumor-treating field therapy, and (4) suitability for RT of 60 Gy in 30 fractions using ESTRO-EANO ‘single phase’ targeting approach. Following 1:1 randomization, niraparib (Arm A) or TMZ (Arm B) is administered concomitantly with RT and then adjuvantly until disease progression by Blinded Independent Central Review (BICR) or until completion of 6 cycles of TMZ. . The primary endpoints of the study are progression-free survival (PFS) (per RANO 2.0; HR = 0.612, 90% power, 1-sided alpha = 0.001) and overall survival (OS) (HR = 0.698, 90% power, 1-sided alpha = 0.0239). Secondary endpoints include overall response rate, health-related quality of life, neurocognitive function, and the safety and tolerability of niraparib compared to TMZ. The first patient was accrued in June 2024 and an interim futility analysis is planned in 2025. This study, sponsored by the Ivy Brain Tumor Center and with drug and funding provided by GSK, is expected to enroll in a minimum of 115 clinical sites across 11 countries. Clinical trial information: NCT06388733. Research Sponsor: GSK.

TPS2097 **Poster Session**

Personalized targeted glioblastoma therapies by *ex vivo* drug screening: Advanced brain tumor therapy clinical trial (ATTRACT).

Anna Sophie Berghoff, Matthias Preusser, Maximilian Mair, Zoltan Spiro, Calvin Abdel Malak, Amin El Heliebi, Franziska Eckert, Julia Furtner, Franz König, Annette Leibetseder, Martha Nowosielski, Stefan Oberndorfer, Barbara Prietl, Josef Pichler, Thomas Pieber, Sabine Spiegl-Kreinecker, Adelheid Woehrer, Georg Widhalm, Tadeja Urbanic Purkart; Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria; Division of Oncology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria; Gottfried Schatz Research Center, Division of Cell Biology, Histology and Embryology, Medical University of Graz, Graz, Austria; Department of Radiation Oncology, Medical University of Vienna, Vienna, Austria; Research Center for Medical Image Analysis and Artificial Intelligence, Faculty of Medicine and Dentistry, Danube Private University, Krems an Der Donau, Austria; Center For Medical Data Sciences, Medical University of Vienna, Vienna, Austria; Department of Internal Medicine and Neurooncology, Kepler University Hospital Linz and Department of Neurology, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria; Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria; Clinical Division of Neurology, Karl Landsteiner University of Health Sciences, St. Pölten, Austria; Precision Medicine Technologies, CBmed GmbH, Graz, Austria; Department of Internal Medicine and Neurooncology, Kepler University Hospital Linz, Neuromed Campus, Linz, Austria; Department of Neurosurgery, Johannes Kepler University, Linz, Kepler University Hospital Linz and Clinical Research Institute for Neurosciences, Johannes Kepler University and Kepler University Hospital Linz, Linz, Austria; Department of Pathology, Neuropathology and Molecular Pathology, Medical University of Innsbruck, Innsbruck, Austria; Department of Neurosurgery, Medical University of Vienna, Vienna, Austria; Precision Medicine Technologies, CBmed GmbH and Department of Neurology and Division of Neuroradiology, Vascular and Interventional Radiology, Medical University of Graz, Graz, Austria

Background: Targeted therapies used in a personalized treatment concept have revolutionized the management of several solid cancers. So far, various clinical trials aiming to introduce the concept of personalized targeted therapies in glioblastoma have failed, as no clinically meaningful responses were observed. Importantly, most clinical trials investigating molecular targeted therapies included all-comers and concentrated on genetic biomarkers to predict treatment response. Given the biological complexity of glioblastoma, genetic biomarkers might give only an insufficient insight into the response of a given patient, and more personalized approaches are warranted. As novel approaches to guide personalized treatment in glioblastoma are urgently needed, we designed a prospective clinical trial to investigate the novel approach of cultivated patient-derived tumor cells (PDCs) for *ex vivo* drug screening. **Methods:** In this randomized phase 2 study, we are testing the ability of PDC-based *ex vivo* drug screening to formulate a personalized recommendation for maintenance treatment in patients with newly diagnosed glioblastoma with unmethylated MGMT promoter after neurosurgical resection followed by combined radio-chemotherapy. Based on overall survival as the primary endpoint, we plan to include 240 patients (120 per group) to show with a power of 80% that we can increase the median survival from 12 to 17 months (hazard ratio 0.7). Patients are randomized 1:1 to either the standard group (no drug screening) or the intervention group (drug screening and personalized recommendation for maintenance treatment). In the intervention group, automated drug screening is performed on PDCs with 28 drugs used for treatment of solid tumors and hematological malignancies. Based on the cytotoxic/cytostatic activity of these drugs, as quantified by relative viability based on adenosine triphosphate levels, a molecular tumor board recommends a personalized treatment regimen. The first patient was enrolled in July 2024. Interim analysis of the ATTRACT study (NCT06512311) is expected in late 2027, and final results in 2030. Moreover, the clinical trial is accompanied by a comprehensive translational research program to gain insights into the biological underpinnings of treatment response in glioblastoma. Clinical trial information: NCT06512311. Research Sponsor: Ludwig Boltzmann Society.

TPS2098 **Poster Session**

Trial in progress: Feasibility of CSF and plasma ctDNA in BRAF-altered glioma during treatment with plixorafenib.

Karisa C. Schreck, Grace Tobin, Peng Huang, Michaella Iacoboni, Joy D. Fisher, Chetan Bettegowda; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; National Institutes of Health, Bethesda, MD

Background: Gliomas with BRAF alterations are often difficult to treat in the recurrent setting due to emergent resistance to FDA-approved targeted therapies. Additionally, it can be difficult to assess response to treatment given the limitations of radiographic techniques and the infeasibility of serial tissue sampling. This protocol serves as a prototype for determining the feasibility of using CSF and plasma circulating tumor DNA (ctDNA) as biomarkers for response to a novel-BRAF inhibitor, plixorafenib. Plixorafenib is a small-molecule selective inhibitor of BRAF-V600E and BRAF-fusion alterations that does not induce paradoxical reactivation of MAPK signaling. **Methods:** This study is a single institution trial of plixorafenib in patients (18+ years of age) with BRAF-V600E mutant glioma following progression on prior BRAF-targeted therapy who are recommended for a clinically-indicated diagnostic or debulking surgery. Eligible patients have recurrent BRAF-V600E mutant glioma (any grade) with measurable disease (by RANO 2.0), have a Karnofsky performance status $>$ 70, and are able to undergo surgery. Leptomeningeal disease is allowed. A total of 12 evaluable patients will be enrolled. Enrolled patients undergo clinically-indicated resection or biopsy for confirmation of disease progression and characterization of putative resistance alterations. All patients have a ventricular reservoir placed at time of surgery with CSF and plasma sampling. Patients will initiate oral plixorafenib 900mg daily with cobicistat, a CYP3A inhibitor and PK enhancer, when clinically recovered from surgery. Patients will take the drug continuously under fasting conditions. MRI, CSF, and plasma assessments will occur approximately every two months to evaluate disease status. The primary endpoint is proportion of samples with detectable tumor ctDNA baseline and after one month of treatment with plixorafenib. Secondary endpoints include the correlation of ctDNA with disease status over time and response rate to plixorafenib. The trial is IRB approved and currently open to enrollment. Clinical trial identifier NCT06610682. Clinical trial information: NCT06610682. Research Sponsor: Ivy Brain Tumor Foundation; Fore Biotherapeutics.

TPS2099 **Poster Session**

Neuro-oncology anywhere 242: Pilot study evaluating telehealth and in-person assessments in patients with glioma receiving oral chemotherapy—Clinical trial in progress.

Ugur Sener, Taylor Galloway, Sydney Schultz, Heather Hughes, Sue Steinmetz, William Tauer, Charles Mason, Carey Huebert, Carolyn Mead-Harvey, Charles Van Der Walt, Susan Michelle Geyer, Joon H. Uhm, Jian Li Campian, Sani Haider Kizilbash, Bryan Neth, William Breen, Eric J. Lehrer, Terence C. Burns, Becky Kottschade, Tufia C. Haddad; Division of Neurology, Mayo Clinic, Rochester, MN; Mayo Clinic, Rochester, MN; Mayo Clinic, Scottsdale, AZ

Background: Gliomas are the most common primary central nervous system (CNS) malignancy in adults, accounting for 26.3% of all brain tumors. Care at high volume centers is associated with an overall survival benefit, but access to in-person evaluations can be challenging due to disease-related neurological disability and loss of income. Telehealth represents a convenient and efficient alternative to in-person evaluations, but acceptability and comparative safety of this care delivery modality has not been prospectively evaluated among glioma patients undergoing chemotherapy. **Methods:** This single-arm non-randomized pragmatic clinical trial evaluates patient satisfaction with, and safety of video-enabled telehealth assessments compared to in-person evaluations for patients with glioma undergoing temozolomide chemotherapy. The study includes adult patients with a diagnosis of glioma requiring adjuvant temozolomide chemotherapy. Participants act as their own controls, alternating between in-person and telehealth assessments while undergoing chemotherapy dosed per standard of care. Monitoring labs are completed locally and transmitted electronically. For participants without access to Wi-Fi or a device (e.g. mobile phone or computer), cellular-enabled tablet devices are provided to facilitate appointments and completion of electronic study components. All participants who travel to in-person appointments are reimbursed for travel expenses. The primary outcome measure is patient satisfaction with care delivered, as measured by institutional Press-Ganey survey scores obtained following telehealth and in-person assessments. A key secondary outcome measure is completion rate of planned oral chemotherapy, tracked using a digital pill diary incorporated into our institutional electronic health record. The digital diary allows real-time tracking of chemotherapy adherence and adverse events experienced by participants. Other secondary outcomes include acute care utilization days following telehealth and in-person visits (defined as emergency department evaluations and days of inpatient stay), neurologic disability as measured by the Neurologic Assessment in Neuro-Oncology (NANO) scale, and disease related quality of life measured by the EORTC QLQ-C30. All participant surveys are self-reported and completed electronically. This decentralized pragmatic clinical trial provides unprecedented, prospective real-world data on utilization of telehealth services compared to in-person visits for patients undergoing chemotherapy for glioma. We expect the data generated to inform the design and conduct of future decentralized interventional neuro-oncology trials. NCT06625047 opened for enrollment in October 2024, 16 of 30 intended participants were accrued as of January 2025. Clinical trial information: NCT06625047. Research Sponsor: Mayo Clinic.

TPS2100 **Poster Session**

Update on GBM AGILE: A global, phase 2/3 adaptive platform trial to evaluate multiple regimens in newly diagnosed and recurrent glioblastoma.

Emma Maria Viktoria Hyddmark, Donald A. Berry, Nicholas S. Berry, Howard Colman, John Frederick de Groot, Benjamin M. Ellingson, Hui Kong Gan, Adam Johnson, Andrew B. Lassman, Michael Lim, Ingo K. Mellinghoff, James R. Perry, Erik P. Sulman, Michael Weller, Patrick Y. Wen, Timothy Francis Cloughesy, GBM AGILE Trial Network; Global Coalition for Adaptive Research, Larkspur, CA; Berry Consultants LLC, Austin, TX; Berry Consultants, LLC, Austin, TX; Hunstman Cancer Institute at the University of Utah, Salt Lake City, UT; University of California, San Francisco, San Francisco, CA; University of California, Los Angeles, Los Angeles, CA; Olivia Newton-John Cancer Wellness & Research Centre, Victoria, NSW, Australia; Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York-Presbyterian Hospital, New York, NY; Stanford University Medical Center, Stanford, CA; Memorial Sloan Kettering Cancer Center, New York, NY; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Department of Radiation Oncology, NYU Grossman School of Medicine, New York, NY; Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland; Division of Neuro-Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Department of Neurology, University of California, Los Angeles, California, Los Angeles, CA

Background: GBM AGILE (Glioblastoma Adaptive, Global, Innovative Learning Environment) is a biomarker based, multi-arm, international, seamless Phase 2/3 response adaptive randomization platform trial designed to efficiently identify investigational therapies that improve overall survival and confirm efficacious therapies and associated biomarker signatures to support drug approvals and registration. GBM AGILE is a collaboration between academic investigators, patient organizations, and industry to support new drug applications for newly diagnosed and recurrent glioblastoma. **Methods:** The primary objective of GBM AGILE is to identify therapies that improve overall survival in patients with newly diagnosed or recurrent glioblastoma. Operating under a Master Protocol, GBM AGILE allows multiple drugs from different pharmaceutical/biotech companies to be evaluated simultaneously and/or over time against a common control. New investigational therapies are added as new information about promising drugs is identified, while other therapies are removed as they complete evaluation. Bayesian response adaptive randomization is used within subtypes of the disease to assign participants to investigational arms based on their performance. GBM AGILE has screened over 2300 patients and enrollment continues to be robust. An estimated 25% of all US glioblastoma patients enrolled in clinical trials participate in GBM AGILE. The trial is open at select sites in the United States, Canada, Switzerland, France, Germany, and Australia. In addition to the efficient evaluation of investigational arms, a primary goal of GBM AGILE is to expand knowledge of glioblastoma to support advancements in treatment using the data collected within the trial (learning environment). Over 7 million data points are currently available for inclusion in the development of a longitudinal model. Such a model may be able to inform randomization by providing earlier and continuous information regarding patient and arm performance. In addition, serial magnetic resonance imaging scans and biospecimens from baseline through patient progression are being collected for further analysis. An initial 500 baseline tissue samples are being characterized using whole genome sequencing and whole transcriptome analysis. Clinical trial information: NCT03970447. Research Sponsor: None.

TPS2101 Poster Session

Dual targeting of VEGF and PD-1: A phase I/II trial of ivonescimab, a novel bispecific antibody, in recurrent glioblastoma.

Anuj Dilip Patel, Ashley Aaroe, Carlos Kamiya-Matsuoka, Ruitao Lin, Nazanin Majd, Barbara Jane O'Brien, Chirag B. Patel, Shiao-Pei S. Weathers, Vinay K. Puduvalli; University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with recurrent glioblastoma have limited effective treatment options due to the highly immunosuppressive microenvironment and rapid proliferation fueled by neo-angiogenesis. Anti-angiogenic therapy, including targeting vascular endothelial growth factor (VEGF) with bevacizumab, and immune checkpoint inhibition with programmed cell death protein 1 (PD-1) inhibitors, have independently had limited efficacy in these tumors. Ivonescimab is a humanized tetravalent bispecific antibody against PD-1 and VEGF, which has demonstrated cooperative binding *in vitro* leading to increased binding of PD-1 in the presence of VEGF and vice-versa[1]. Ivonescimab has shown activity in multiple phase 3 trials conducted in China in non-small cell lung cancer, including one trial which demonstrated activity in patients with brain metastases, but has not yet been evaluated in patients with primary brain tumors. This trial evaluates ivonescimab in patients with recurrent glioblastoma. **Methods:** This investigator-initiated study consists of a phase I and II component; the primary objectives are safety and tolerability for phase I and determining progression-free survival for phase II. The phase I component evaluates 3 dose levels of ivonescimab (7.5, 10, and 20 mg/kg every 3 weeks), employing a Bayesian optimal interval (BOIN) design for assessing toxicity. Once the recommended phase II dose is determined, the phase II portion will follow a Bayesian optimal phase II (BOP2) design, with interim analyses at pre-specified enrollment points allowing for monitoring of efficacy as well as ongoing evaluation of toxicity. The maximum accumulative sample size at the target dose will be 30 patients. Radiographic assessment will utilize the Response Assessment in Neuro-Oncology 2.0 criteria. Key eligibility criteria include adults with recurrent glioblastoma, IDH-wildtype (by WHO CNS 2021 classification) at first or second recurrence with Karnofsky Performance Scale ≥60 and normal blood counts and organ function. Prior therapy with anti-angiogenic agents (including bevacizumab) or check-point inhibitors is excluded, as well as concurrent corticosteroids ≥ 2 mg/day dexamethasone or equivalent. Samples of archival tumor, blood and stool microbiome will be collected for correlative studies as an exploratory evaluation of predictive biomarkers of response or resistance to ivonescimab. The study has been approved by the institutional review board and accrual to phase I will commence in the first quarter of 2025. 1. Zhong T, Huang Z, Pang X, et al. 1194 Mechanism of action of ivonescimab (AK112/SMT112): a first-in-class tetravalent Fc-silent bispecific antibody with dual blockade of PD-1 and VEGF that promotes cooperative biological effects. Journal for ImmunoTherapy of Cancer 2023;11:doi: 10.1136/jitc-2023-SITC2023.1194. Clinical trial information: NCT06672575. Research Sponsor: Summit Therapeutics.

TPS2102 **Poster Session**

Regorafenib versus local standard of care in patients with grade 2-3 meningioma no longer eligible for loco-regional treatments: The MIRAGE trial.

Alberto Bosio, Giulia Cerretti, Marta Padovan, Paola Del Bianco, Maurizio Polano, Susanna Mandruzzato, Stefano Indraccolo, Renzo Manara, Giovanni Librizzi, Mario Caccese, Martina Corrà, Marta Maccari, Sara Lonardi, Gian Luca De Salvo, Giuseppe Lombardi; Veneto Institute of Oncology IOV, IRCCS, Padua, Italy; Clinical Research Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Experimental and Clinical Pharmacology Unit, National Cancer Institute C.R.O. - IRCCS, Aviano, Italy; Immunology and Molecular Oncology Diagnostics, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy; Basic and Translational Oncology Unit, Istituto Oncologico Veneto (IOV)-IRCCS, Padua, Italy; Neuroradiology Unit, Padova University Hospital, Padua, Italy

Background: Meningiomas are the most common intracranial tumors. Standard treatment involves surgical resection with curative intent. When gross total resection is not achievable, or in case of recurrence, RT is frequently utilized. On the other hand, the role of systemic treatments remains poorly supported by evidence.Regorafenib is an oral multi-tyrosine kinase (RTK) inhibitor. It exhibits high selectivity for VEGFR1/2/3, while also inhibiting PDGFRβ, FGFR1, and c-RAF/RAF1 and BRAF pathways, highly expressed in high-grade meningiomas. **Methods:** TheMIRAGE Trial (NCT06275919) is a multicenter, open-label, randomized phase 2 clinical trial evaluating grade 2/3 meningioma pts who have progressed following surgery and RT. A total of 94 pts are being randomized (1:1) to receive either Regorafenib (160 mg orally for 3 weeks on, 1 week off) or local standard-of-care therapies (e.g., bevacizumab, hydroxyurea, somatostatin analogues).Major inclusion criteria include histological confirmation of WHO 2021 grade 2-3 meningioma, radiologically documented progression at least 24 weeks from RT (estimated planar growth $>$ 25% in two dimensional tumor areas within the prior 12 months or development of a new lesion) with at least 1 measurable lesion (minimum 10 x 10 mm) on baseline MRI, ineligibility for further surgery and/or radiotherapy, absence of extracranial lesions and a WHO performance status of 0-1.The primary endpoint is 6-month PFS (6m-PFS). Assuming a 6m-PFS of 20% in the control arm and 40% in the regorafenib arm (corresponding to a HR = 0.57) with a = 5%, b = 85%, 104 patients are needed to assess the targeted efficacy. Response to treatment will be assessed by using RANO criteria. Secondary endpoints include OS, ORR, DCR, volumetric analysis of the target lesions, safety and health-related quality of life. Multi-omics exploratory analysis will also be performed to investigate possible prognostic and predictive biomarkers. Radiomics analysis will also be performed. MIRAGE, initiated in September 2024, is an academic trial promoted by the Istituto Oncologico Veneto, IOV-IRCCS and will recruit patients across 15 neuro-oncology Centers in Italy with an estimated study duration of 18 months. Discussion: MIRAGE is the first randomized phase 2 trial analyzing the role of a RTK inhibitor (regorafenib) in prolonging PFS in pts with grade 2-3 meningioma who are ineligible for further surgery and/or radiotherapy. Clinical trial information: NCT06275919. Research Sponsor: None.