Background: The 1st interim analysis of the CATNON trial showed benefit from adjuvant (adj) temozolomide (TMZ) on overall survival (OS) but remained inconclusive about concurrent (conc) TMZ. A 2nd interim analysis was planned after 356 events. 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 (doi: 10.1016/S0140-6736(17)31442-3). MGMT promoter methylation (MGMTmeth) status was re-assessed with the Infinium Methylation EPIC Beadchip using the MGMT_STP27 model. Isocitrate dehydrogenase 1 and 2 (IDH) mutation (mt) status was assessed with glioma targeted Agilent SureSelect baits sequence using an Illumina HiSeq2500 Rapid PE100. Results: With a median follow-up of 56 months and 356 events, the hazard ratio (HR) for OS adjusted for stratification factors after concTMZ was 0.968 (99.1% CI 0.73, 1.28). 5-year OS was 50.2% with and 52.7% without concTMZ (95% CI [44.4, 55.7] and [46.9, 58.1]). An IDHmt was found in 335 of 480 assessed cases (70%). Median OS was 19 mo (95% CI 16.3, 22.3) in IDHwt tumors and 116 mo (95% CI 82.0, 116.6) in IDHmt tumors. HR for OS after concTMZ in patients with known IDH status. Clinical trial information: NCT00626990. IDHmt was predictive of benefit from adjTMZ (IDHmt HR: 0.41, 95% CI 0.27, 0.64; IDHwt: HR 1.05, 95% CI 0.73, 1.52; interaction test p = 0.001). In IDHmt patients that received adjTMZ, the HR for OS after concTMZ was 0.71 (95% CI 0.35, 1.42, p = 0.32). MGMTmeth was found in 288 of 410 assessed cases (70%), interaction test for concTMZ (p = 0.092) and adjTMZ (p = 0.166) did not reach statistical significance. Conclusions: In the entire study cohort, concTMZ did not increase OS. However, in IDHmt tumors a trend towards benefit of concTMZ is present. AdjTMZ increased OS in IDHmt but not in IDHwt tumors. The ongoing molecular analyses and further follow-up will allow full assessment of efficacy in the molecular subgroups.

<table>
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<tr>
<th>Patients</th>
<th>n</th>
<th>events</th>
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<td>wt</td>
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<td>92</td>
<td>0.67 (0.44, 1.03)</td>
<td>p = 0.06</td>
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</table>

Randomized phase IIb clinical trial of continuation or non-continuation with six cycles of temozolomide after the first six cycles of standard first-line treatment in patients with glioblastoma: A Spanish research group in neuro-oncology (GEINO) trial.

Carmen Balana, Carlos Mesia Barroso, Sonia Del Barco Berron, Estela Pineda Losada, José Muñoz-Langa, Anna Estival, Ramon De las Peñas, Jose Fuster, Miguel J. Gil Gil, L Miguel Navarro, Miriam Alonso, Ana Herrero, María Ángeles Vaz Salgado, Sergi Peralta, Clara Olier, Pedro Pérez-Segura, Marta Covela Rúa, Cristina Carrato, Carolina Sanz, Juan Manuel Sepulveda-Sanchez; Institut Català d’Oncologia Badalona, Hospital Germans Trias i Pujol, Badalona/Barcelona, Spain; Institut Català d’Oncologia Hospital Duran i Reynals, Barcelona, Spain; Institut Català d’Oncologia, Hospital Universitari Josep Trueta, Girona, Spain; Medical Oncology, Hospital Clinic de Barcelona, Barcelona, Spain; Hospital Universitario La Fé, València, Spain; Medical Oncology Department. Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain; Oncology Service. Hospital Provincial de Castellon, Castellon, Spain; Hospital Son Espases, Palma De Mallorca, Spain; Breast Cancer Unit & Medical Oncology Department, Institut Català d’Oncologia, IDIBELL, Barcelona, Spain; Department of Medical Oncology, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain; Instituto de Biomedicina de Sevilla, IBIS/Hospital Universitario Virgen del Rocio/CSIC/Universidad de Sevilla, Seville, Spain; Hospital Miguel Servet, Zaragoza, Spain; Medical Oncology Department, Ramon y Cajal University Hospital, Madrid, Spain; Hospital Sant Joan de Reus, Reus/Tarragona, Spain; H Universitario Fundación Alcorcón, Alcorcón, Spain; Medical Oncology Department, Hospital Universitario Clínico San Carlos, Madrid, Spain; Hospital Universitario Lucus Augusti, Lugo, Spain; Hospital Germans Trias i Pujol, Barcelona, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain

Background: The GEINO-14-01 trial (NCT02209948) investigated the role of extending temozolomide (TMZ) for 6 cycles after the standard 6 cycles to improve 6m-PFS, SLP and OS in newly diagnosed glioblastoma (GBM) patients (p). Methods: Between 08/2014 and 11/2018, 166 p were screened and 159 randomized to extend (80p) or not (79p) TMZ treatment for 6 cycles after proving stable disease in the MRI performed before inclusion. Centralized review of histology and determination of MGMT status, if not previously available, were performed before randomizing patients. Two criteria of stratification were used: MGMT status and presence/absence of residual disease on the basal MRI (defined as a residual enhancement larger than 1cm in one). The primary endpoint was differences in 6mPFS, secondary endpoints were differences in PFS, OS, toxicity, between arms and per stratification factors. Results: Median age was 60.3 (range 29-83), 97p (61%) were methylated, basal MRI showed residual disease in 57p (35.8%). After a median follow up of 14.0 months, with 121 p(76.1%) already progressed and 81p (50.9%) already dead, median PFS is presented. Median (m) PFS is 8.0 months (95%CI: 5.7-10.2). There is no difference in mPFS between arms (adjusted HR = 0.98, 95% CI: 0.82-1.18, P = 0.907). Methylated tumors had longer mPFS (HR=0.57, 95% CI: 0.39-0.83, P=0.004) irrespectively to the study treatment. Conclusions: There is not apparent benefit of continuing TMZ treatment for more than 6 cycles. Data will be actualized for the congress. Supported by a Grant of the ISCIII: PI13/01751. Clinical trial information: NCT02209948.
Updated predictive analysis of the WHO-defined molecular subgroups of low-grade gliomas within the high-risk treatment arms of NRG Oncology/RTOG 9802.

Erica Hlavin Bell, Minhee Won, Jessica L. Fleming, Aline P. Becker, Joseph P. McElroy, Edward G. Shaw, Minesh P. Mehta, David G. Brachman, Stanley Z. Gertler, Albert D. Murtha, Christopher J. Schultz, David B. Johnson, Nadia N. Laack, Grant Kirton Hunter, Ian R. Crocker, Arnab Chakravarti; The Ohio State University, Columbus, OH; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Wake Forest School of Medicine, Winston-Salem, NC; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Saint Joseph's Hospital and Medical Center, Phoenix, AZ; Ottawa Hospital and Cancer Center, Ottawa, ON; Canada; Cross Cancer Institute, Edmonton, AB, Canada; Medical College of Wisconsin, Milwaukee, WI; St. Francis Reg West Medc Ctr, Lagrange, WY; Mayo Clinic, Rochester, MN; Intermountain Healthcare, Murray, UT; Emory University Hospital/Winship Cancer Institute, Atlanta, GA

Background: This study sought to update the predictive significance of the three WHO-defined molecular glioma subgroups (IDHwt, IDHmut/non-codel, and IDHmut/codel) in the subset of specimens available for analysis in NRG Oncology/RTOG 9802, a phase III trial of high-risk low-grade gliomas (LGGs) treated with radiation (RT) with and without PCV after biopsy/surgical resection. Notably, this is the first phase III study to evaluate the predictive value of the WHO subgroups in LGGs using prospectively-collected, well-annotated long-term overall survival data, in a post-hoc analysis. Methods: IDH1/2 mutation status was determined by immunohistochemistry and/or next-generation sequencing. 1p/19q status was determined by Oncoscan and/or 450K methylation data. Treatment effects on overall survival (OS) and progression-free survival (PFS) by marker status were determined by the Cox proportional hazard model and tested using the log-rank test in a secondary and exploratory analysis. Results: Of all the randomized eligible high-risk G2 patients (N = 251) in NRG Oncology/RTOG 9802, 106(42%) patients had tissue available with sufficient quality DNA for profiling. Of these, 80(75%) were IDHmut; 43(41%) were IDHmut/non-co-deleted, 37(35%) were IDHmut/co-deleted, and 26(24%) were IDHwt. Upon univariate analyses, no significant difference in either PFS or OS was observed with the addition of PCV in the IDHwt subgroup. Both the IDHmut/non-co-deleted and IDHmut/co-deleted subgroups were significantly correlated with longer PFS (HR = 0.32; p = 0.003; HR = 0.13; p < 0.001) and OS (HR = 0.38; p = 0.013; HR = 0.21; p = 0.029) in the RT plus PCV arm, respectively. Conclusions: Our analyses suggest that both IDHmut/non-co-deleted and IDHmut/co-deleted subgroups received benefit from treatment with PCV although sample size is limited and analyses are post-hoc. Our results also support the notion that IDHwt high-risk LGG patients do not benefit from the addition of PCV to RT. Funding: U10CA180868, U10CA180822, and U24CA196067. Also, R01CA108633, R01CA169368, RC2CA148190, U10CA180850-01, BTFC, OSU-CCC (all to AC). Clinical trial information: NCT00003375.
A phase I, open label, perioperative study of AG-120 and AG-881 in recurrent IDH1 mutant, low-grade glioma: Results from cohort 1.

Ingo K. Mellinghoff, Timothy Francis Cloughesy, Patrick Y. Wen, Jennie Webster Taylor, Elizabeth A. Maher, Isabel Arrillaga, Katherine B. Peters, Changho Choi, Benjamin M. Ellingson, Alexander P. Lin, Sunitha B Thakur, Brandon Nicolay, Min Lu, Kha Le, Feng Yin, Feng Tai, Steven Schoenfeld, Lori Steelman, Shuchi Sumant Pandya, Jennifer Leigh Clarke; Memorial Sloan Kettering Cancer Center, New York, NY; University of California Los Angeles, Los Angeles, CA; Dana-Farber Cancer Center/Harvard, Boston, MA; University of California, San Francisco, San Francisco, CA; The University of Texas Southwestern Medical Center, Dallas, TX; Massachusetts General Hospital, Boston, MA; Duke University, Durham, NC; Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; Agios Pharmaceuticals, Inc., Cambridge, MA

Background: AG-120 (ivosidenib [IVO]) is a first-in-class oral inhibitor of mutant isocitrate dehydrogenase 1 (mIDH1) evaluated in 66 glioma patients (pts) in an ongoing phase 1 study. AG-881 (vorasidenib [VOR]) is an oral, potent, brain-penetrant inhibitor of mIDH1/2 evaluated in 52 glioma pts in an ongoing phase 1 study. In an orthotopic glioma model, IVO and VOR reduced 2-hydroxyglutarate (2-HG) by 85% and 98%, respectively, despite different brain:plasma ratios (<0.04 vs 1.33).

Methods: Primary endpoint: brain tumor 2-HG concentration with IVO or VOR treatment in mIDH1 low-grade glioma. Pts with recurrent non-enhancing WHO-2016 Grade (Gr) 2 or 3 mIDH1-R132H oligodendroglioma or astrocytoma undergoing craniotomy were randomized 2:2:1 to IVO 500mg QD, VOR 50mg QD, or no treatment for 4 wks preoperatively in Cohort 1. Post-operatively, pts continued to receive IVO or VOR and control pts were randomized 1:1 to IVO or VOR. Tumors were assessed for mIDH1 status, cellularity, 2-HG, and drug concentration. Treated samples were compared to control pts and mIDH1 and wild type (WT) banked reference (ref) samples. Plasma and CSF 2-HG were assessed. Pts with non-evaluable tissue were replaced. Results: As of 29 Nov 2018, 26 pts (17M, 9F; 25 Gr 2, 1 Gr 3) were randomized preoperatively (IVO 10, VOR 11, control 5), 25 received drug (IVO 12, VOR 13). At the data cut, 19 tumors were analyzed with 16 evaluable. Common (>10%) TEAEs (all grade 1/2): diarrhea (36%), hypocalcemia and constipation (each 20%), anemia, hyperglycemia, pruritus, headache and nausea (each 16%), and hypokalemia and fatigue (each 12%). Mean brain:plasma ratio: 0.16 for IVO, 2.4 for VOR. Tumor 2-HG results are shown in Table. Updated data from Cohort 1 will be presented. Conclusions: In Cohort 1 of this phase 1 perioperative study, IVO and VOR were CNS penetrant and lowered 2-HG compared to untreated samples. Cohort 2 is open and will evaluate IVO 250mg BID and VOR 10mg QD. Brain tumor 2-HG concentration. Clinical trial information: NCT03343197.
Phase I study of a brain penetrant mutant IDH1 inhibitor DS-1001b in patients with recurrent or progressive IDH1 mutant gliomas.

Atsushi Natsume, Toshihiko Wakabayashi, Yasuji Miyakita, Yoshitaka Narita, Yohei Mineharu, Yoshiki Arakawa, Fumiyuki Yamasaki, Kazuhiko Sugiyama, Nobuhiro Hata, Yoshihiro Muragaki, Ryo Nishikawa, Naoki Shinojima, Toshihiro Kumabe, Ryuta Saito, Kazumi Ito, Masaya Tachibana, Yasuyuki Kakurai, Soichiro Nishijima, Hiroshi Tsubouchi; Nagoya University School of Medicine, Nagoya, Japan; Department of Neurosurgery, Nagoya University School of Medicine, Nagoya, Japan; Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan; National Cancer Center Hospital, Chuo-ku, Tokyo, Japan; Kyoto University Graduate School of Medicine, Kyoto, Japan; Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan; Department of Clinical Oncology and Neuro-Oncology Program, Hiroshima University Hospital, Hiroshima, Japan; Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; Tokyo Women’s Medical University, Shinjuku-ku, Tokyo, Japan; Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Saitama, Japan; Kumamoto University Hospital, Kumamoto, Japan; Department of Neurosurgery, Kita-Sata University School of Medicine, Fukuoka, Japan; Department of Neurosurgery, Tohoku University Graduate School of Medicine, Sendai, Japan; Daiichi Sankyo Co., Ltd., Tokyo, Japan; Daiichi Sankyo, Co., Ltd., Tokyo, Japan

Background: WHO grade II/III gliomas frequently harbor isocitrate dehydrogenase 1 (IDH1) mutations, resulting in intratumoral accumulation of oncometabolite 2-hydroxyglutarate (2-HG) and subsequent clonal expansion. DS-1001b is an oral selective inhibitor of mutant IDH1 R132X that was designed to penetrate the blood-brain barrier. Methods: In this first-in-human, multicenter, phase I study (NCT03030066), eligible patients (pts) with recurrent/progressive IDH1 mutant glioma received DS-1001b twice daily (bid), continuous. A modified continual reassessment method was used for dose escalation. RANO and RANO-LGG criteria were used to assess tumor response. Pts who planned to undergo salvage surgery after developing progressive disease (PD) and who provided informed consent received DS-1001b treatment until surgery. Tumor samples were also obtained from those pts to measure the free form of DS-1001b and 2-HG levels. Results: Between Jan 2017 and Oct 2018, DS-1001b (125-1400 mg bid) had administered for 45 pts (median age 44 yrs, prior radiation therapy 100%, prior chemotherapy 82%), and 17 pts were continuing treatment. Maximum tolerated dose (MTD) was not reached. Most AEs were Gr 1-2. Gr 3 AEs were observed in 42.2% of pts. No Gr 4 or 5 AEs or serious drug-related AEs were reported. One dose limiting toxicity was Gr 3 white blood cell count decreased (1000 mg bid). Common AEs ( > 20%) were skin hyperpigmentation, diarrhea, pruritus, nausea, rash, and headache. Of 29 evaluable pts with contrast enhancing gliomas, one, three and 10 achieved complete response, partial response and stable disease (SD), respectively. Of evaluable nine pts with contrast non-enhancing gliomas, two achieved minor response and seven achieved SD. Peak plasma concentration (Cmax) and area under the curve (AUC) increased dose-dependently. The brain/plasma ratio of free form of DS-1001b ranged 0.19–0.77 in 3 pts. Conclusions: DS-1001b was well tolerated up to 1400 mg bid with favorable brain distribution, and MTD was not reached. Recurrent/progressive IDH1 mutant glioma pts responded to treatment. Investigation is ongoing to determine the recommended Phase II dose. Clinical trial information: NCT03030066.
Efficacy and safety of selinexor in recurrent glioblastoma.

Andrew B. Lassman, Patrick Y. Wen, Martin J. Van Den Bent, Scott Randall Plotkin, Anna Maria Elisabeth Walenkamp, Xiu Huang, Karla Rodriguez-Lopez, Michael G. Kauffman, Sharon Shacham, Morten Mau-Sørensen; Columbia University Irving Medical Center, New York, NY; Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA; Erasmus MC Cancer Center, Rotterdam, Netherlands; Massachusetts General Hospital Cancer Center, Boston, MA; Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; Karyopharm Therapeutics Inc, Newton, MA; Karyopharm Therapeutics Inc., Newton, MA; Rigshospitalet, Copenhagen, Denmark

Background: New treatment modalities are needed for recurrent glioblastoma (rGBM). Selinexor (SEL) is a novel, oral selective inhibitor of nuclear export which forces nuclear retention of tumor suppressor proteins including p53 and p27, leading to apoptosis. We previously reported interim results showing tolerability, preliminary efficacy, and blood-brain barrier penetration in a surgical cohort (N = 8). We now report updated results following completion of accrual to non-surgical cohorts (N = 68). Methods: This is an open-label, multicenter, phase 2 study of SEL monotherapy. Patients (pts) not undergoing surgery for measurable rGBM (per RANO) were enrolled in one of 3 arms encompassing different dosing schedules. Treatment was continuous, although cycles were defined as 28 days and response was assessed every other cycle by MRI. Prior treatment with radiotherapy and temozolomide was required and prior bevacizumab was exclusionary. The primary endpoint was 6-month progression free survival (6mPFS) rate, calculated by the Kaplan Meier method. Results: A total of 76 pts were enrolled. Median age was 56 years (range 21-78). Median number of prior treatments was 2 (range 1-7). At the end of the 6 cycles, 30.2% patients on 80 mg QW were free from progression. The 6mPFS rate on 80 mg QW was 15.1%. Best RANO-defined responses (assessed locally) among 26 evaluable pts on 80 mg QW included 1 complete response, 2 partial responses, 7 stable disease, and 16 with progressive disease. Median duration of response was 10.8 months. The most common related adverse events in pts on ~85 mg BIW/60 mg BIW/80 mg QW were nausea (42%/64%/60%), leukopenia (38%/7%/43%), fatigue (71%/71%/43%), neutropenia (29%/14%/33%), decreased appetite (46%/71%/27%), and thrombocytopenia (67%/29%/23%). Conclusions: SEL demonstrated efficacy, with durable responses and disease stabilization in rGBM. Based on the favorable efficacy and safety profile, SEL at a dose of 80 mg QW is recommended for further development in rGBM. Clinical trial information: NCT01986348.

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<th>Parameter</th>
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<th>60 mg BIW (N = 14)</th>
<th>80 mg QW (N = 30)</th>
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<tr>
<td>6mPFS rate (%)</td>
<td>9.7 (2.7, 35.4)</td>
<td>11.4 (1.9, 67.9)</td>
<td>15.1 (6.1, 37.1)</td>
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<td>Overall Response Rate (%)</td>
<td>8.3 (1.0, 27.0)</td>
<td>7.1 (0.2, 33.9)</td>
<td>10.0 (2.1, 26.5)</td>
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<tr>
<td>Median Overall Survival (months)</td>
<td>9.0 (4.9, 16.4)</td>
<td>8.5 (7.8, NE)</td>
<td>9.4 (7.0, NE)</td>
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</table>
Activity of larotrectinib in TRK fusion cancer patients with brain metastases or primary central nervous system tumors.

Alexander E. Drilon, Steven G. DuBois, Anna F. Farago, Juneko E. Grilley-Olson, David S. Hong, Davendra Sohal, Cornelis Martinus van Tilburg, David Simon Ziegler, Nora Ku, Michael Craig Cox, Shivani Nanda, Barrett H. Childs, Francois P. Doz; Memorial Sloan Kettering Cancer Center; Weill Cornell Medical College, New York, NY; Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; Cancer Center, Massachusetts General Hospital, Boston, MA; Institut Gustave Roussy, Villejuif, France; University of North Carolina Hospitals, Chapel Hill, NC; The University of Texas MD Anderson Cancer Center, Houston, TX; Cleveland Clinic, Cleveland, OH; Hopp Children’s Cancer Center Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany; Kids Cancer Centre, Sydney Children’s Hospital, Randwick, Australia; Loxo Oncology, Inc., South San Francisco, CA; Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ; Institut Curie, Paris, France

Background: TRK fusions are oncogenic drivers of a variety of cancers, many of which can involve the central nervous system (CNS). Larotrectinib is an FDA-approved selective TRK inhibitor for the treatment of TRK fusion cancer (Drilon et al, NEJM 2018). While larotrectinib has been shown to cross the blood–brain barrier (Ziegler et al, Br J Cancer 2018), its clinical activity in a series of TRK fusion cancers with primary or metastatic intracranial disease has not been described. Methods: Patients (pts) with non-primary CNS solid tumors with brain metastases, or primary CNS tumors harboring a TRK fusion treated with larotrectinib in 2 clinical trials (NCT02637687, NCT02576431) were identified. Larotrectinib was administered until disease progression (PD), withdrawal, or unacceptable toxicity. Disease status was investigator-assessed (RANO and RECIST). Data cutoff: July 30, 2018. Results: 14 pts were identified: 5 non-primary CNS solid tumors (3 lung cancer, 2 thyroid cancer; fusion type: 2 ETV6-NTRK3, 3 SQSTM1-NTRK3, 1 EPS15-NTRK1; age range 25–79 y) and 9 primary CNS tumors (3 glioma, 2 glioblastoma, 1 astrocytoma, 3 NOS; fusion type: 3 BCR-NTRK2, 2 KANK-NTRK2, 1 each of AFAP1-NTRK1, AGTPBP1-NTRK2, ETV6-NTRK3, SPECC1L-NTRK2; age range 2–79 y). In the 5 pts with non-primary CNS tumors, the best objective response to therapy was PR in 3 (60%, 1 pending confirmation), SD in 1 (20%), and not evaluable (NE) in 1 (20%). Duration of response ranged from 9+ to 13 mo. In the 9 pts with primary CNS tumors, the best objective response to therapy was PR in 3 (60%, 1 pending confirmation), SD in 1 (20%), and not evaluable (NE) in 1 (20%). Duration of treatment ranged from 2.8–9.2+ mo. Conclusions: Larotrectinib is active in pts with TRK fusion cancers with intracranial disease. Confirmed responses and durable disease control were seen in metastatic disease and primary CNS tumors of various histologies. These results further support expanded testing for TRK fusions across all cancers, including primary CNS tumors. Clinical trial information: NCT02637687 and NCT02576431.
Trabectedin for recurrent WHO grade II or III meningioma: A randomized phase II study of the EORTC Brain Tumor Group (EORTC-1320-BTG).

Matthias Preusser, Antonio Silvani, Emilie Le Rhun, Riccardo Soffietti, Giuseppe Lombardi, Juan M. Sepúlveda, Petter Brandal, Ronald Philip Beaney, Alice Bonneville-Levard, Veronique Lorgis, Elodie Vauleon, Jacqueline Bromberg, Sara Erridge, Alison Cameron, Christine Marosi, Vassilis Goltzinopoulos, Thierry Gorlia, Michael Weller, Wolfgang Wick; Medical University of Vienna, Comprehensive Cancer Center, Vienna, Austria; Dept of Neuro-Oncology, Neurologic Institute Carlo Besta, Milan, Italy; Lille University Hospital, Lille, France; Department of Neuro-Oncology, University of Turin and City of Health and Science, Turin, Italy; Department of Clinical and Experimental Oncology, Medical Oncology 1, Veneto Institute of Oncology, IOV-IRCCS, Padua, Italy; Hospital Universitario 12 de Octubre, Madrid, Spain; Oslo University Hospital, Oslo, Norway; St Thomas Hospital, London, United Kingdom; Centre Léon-Bérard, Lyon, France; Centre Georges-François Leclerc, Dijon, France; Centre Eugène Marquis, Rennes, France; Erasmus MC University Medical Center Cancer, Rotterdam, Netherlands; University of Edinburgh, Edinburgh, United Kingdom; Bristol Haematology and Oncology Centre, Bristol, United Kingdom; University of Vienna, Wien, Austria; EORTC Headquarters, Brussels, Belgium; Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Center Zurich, University Hospital and University of Zurich, Zurich, Switzerland; National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany

Background: EORTC-1320-BTG investigated the activity, safety and quality of life of therapy with the tetrahydroisoquinoline alkaloid trabectedin (Yondelis) in patients with recurrent higher-grade meningiomas. Trabectedin was originally derived from the Caribbean sea squirt, *Ecteinascidia turbinata*, and currently is manufactured by total synthesis. Methods: Adult patients with histological diagnosis of WHO grade II or III meningioma and radiologically documented progression after maximal feasible surgery and radiotherapy were randomly assigned in a 2:1 ratio to receive intravenous trabectedin (1.5 mg/m² every three weeks) or local standard of care (LOC). The primary endpoint was progression-free survival (PFS). Results: Within 22.1 months, we randomized a total of 90 patients (n=29 in LOC arm, n=61 in trabectedin arm) in 35 institutions and nine countries. In the LOC arm, the following treatments were administered: hydroxyurea (n=11), bevacizumab (n=9), none (n=4), chemotherapy (n=3), somatostatin analogue (n=1), combined chemotherapy and somatostatin analogue (n=1). With 71 PFS events, median PFS was 4.17 months in the LOC and 2.43 months in the trabectedin arm (hazard ratio [HR] for progression, 1.42; 80% CI, 1.00-2.03; *p*=0.204) with a PFS-6 rate of 29.1% (95% CI, 11.9%-48.8%) in the LOC and 21.1% (95% CI, 11.3%-32.9%) in the trabectedin arm. Median OS was 10.61 months in the LOC and 11.37 months in the trabectedin arm (HR for death, 0.98; 95% CI, 0.54-1.76; *p*=0.94). Grade 3 to 5 adverse events occurred in 44.4% (18.5% related, 4 serious adverse events, 0 lethal events) of the patients in the trabectedin arm. Conclusions: In this first prospective randomized trial performed in recurrent grade II or III meningioma, trabectedin did not improve PFS and OS and was associated with significantly higher toxicity as compared to LOC treatment. The data collected in this study may serve as benchmark for future clinical trials in this setting. Clinical trial information: NCT02234050.

Mark M. Souweidane, Kim Kramer, Neeta Pandit-Taskar, Zhiping Zhou, Pat Zanzonico, Maria Donzelli, Serge K. Lyashchenko, Sofia Haque, Sunitha B Thakur, Nai-Kong V. Cheung, Steven M. Larson, Ira J. Dunkel; Memorial Sloan-Kettering Cancer Center, New York, NY; Memorial Sloan Kettering Cancer Center, New York, NY

Background: Diffuse intrinsic pontine glioma (DIPG) represents one of the most deadly central nervous system tumors of childhood with a median survival of less than 12 months. Convection-enhanced delivery (CED) has been recently hypothesized as a means for efficiently distributing therapeutic agents within the brain stem. We conducted this study to evaluate CED in children with DIPG. Methods: We performed a standard phase I dose escalation study in patients with non-progressive DIPG 4 to 14 weeks post-completion of radiation therapy. Seven dose levels of a single injection of $^{124}$I-8H9 (Omburtamab) (range 0.25 to 4.0 mCi) were studied. Results: 37 children were treated with 34 evaluable for primary and secondary endpoints. The median age at enrollment was 6.8 years old (range 3.2 - 17.9). There was no dose limiting toxicity (DLT). Among adverse events that were at least possibly related to the treatment, there were no grade 4 or 5 events, and only 4 reversible grade 3 events in 4 patients (2 hemiparesis, 1 skin infection and 1 anxiety). Estimations of distribution volumes based on T2-weighted imaging were dose dependent and ranged from 1.5 to 20.8 cm$^3$, and for dose level 7, 10.5 - 19.0 cm$^3$. The mean volume of distribution/volume of infusion ratio (Vd/Vi) was 3.4 ± 1.1, and for dose level 7, 3.5 ± 1.0. The mean lesion absorbed dose was 33.3 ± 25.9 Gy, and for dose level 7, 50.1 ± 22.9 Gy. The mean ratio of lesion-to-whole body absorbed dose was 910. The mean volume of distribution/tumor volume ratio on dose level 7 was 82.5%, but the mean tumor overlap was 40.5%. No death occurred as a result of the treatment. Median survival was 15.3 months (n = 29, 95% CI 12.7 - 17.4). Median follow-up time of the 5 surviving patients is 27.2 months (range 11.5 - 72.4). Overall survival rate at 12 months was 64.7% (22/34, 4 alive), and overall survival rate at 24 months 14.7% (5/34, 3 alive). Conclusions: CED in the brain stem of children with DIPG who were previously irradiated is a safe therapeutic strategy. An infusion volume of 4,000 mcl appears to be a reasonable single dose for a target distribution volume but enhanced tumor coverage is likely needed. There seems to be a survival benefit using this therapeutic strategy and outcomes might be dependent on dosimetry and distribution patterns. Clinical trial information: NCT01502917.
NRG Oncology CC001: A phase III trial of hippocampal avoidance (HA) in addition to whole-brain radiotherapy (WBRT) plus memantine to preserve neurocognitive function (NCF) in patients with brain metastases (BM).

Vinai Gondi, Snehal Deshmukh, Paul D. Brown, Jeffrey Scott Wefel, Wolfgang Tome, Terri Armstrong, Deborah Bruner, Joseph A Bovi, Cliff Grant Robinson, Deepak Khuntia, David R Grosshans, Andre A. Konski, David Roberge, Vijayananda Kundapur, Kiran Devisetty, Sunjay A Shah, Kenneth Usuki, Bethany Marie Anderson, Minesh P. Mehta, Lisa A. Kachnic; Northwestern Medicine Cancer Center Warrenville and Northwestern Medicine Proton Center, Warrenville, IL; NRG Oncology, Philadelphia, PA; Mayo Clinic, Rochester, MN; The University of Texas MD Anderson Cancer Center, Houston, TX; Montefiore Medical Center, Bronx, NY; National Cancer Institute, Bethesda, MD; Winship Cancer Institute at Emory University, Atlanta, GA; Froedttert and the Medical College of Wisconsin, Wauwatosa, WI; Washington University in St. Louis, St. Louis, MO; East Bay Radiation Oncology Center, Castro Valley, CA; University of Pittsburgh, Chester, PA; CHUM-Hotel Dieu de Montreal, Montreal, QC, Canada; Department of Radiation Oncology, Saskatoon Cancer Center, Saskatchewan Cancer Agency, University of Saskatchewan, Saskatoon, SK, Canada; McLaren Cancer Inst Flint, Grand Blanc, MI; Helen F. Graham Cancer Center & Research Institute, Christiana Care Health System, Newark, DE; University of Rochester Medical Center, Rochester, NY; Univ of Wisconsin, Madison, WI; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN

Background: NRG CC001, a phase III trial of WBRT plus memantine (WBRT+M) with or without HA, sought to evaluate the neuro-protective effects of lowering the hippocampal radiation dose. Methods: Patients (pts) with BM were stratified by RPA class and prior radiosurgery/surgery and randomized to WBRT+M or HA-WBRT+M (30Gy/10 fractions). Standardized NCF tests were performed at baseline, 2, 4, 6, and 12 months (mos). The primary endpoint was NCF failure, defined as decline using the reliable change index on Hopkins Verbal Learning Test-Revised, Trail Making Test, or Controlled Oral Word Association. Cumulative incidence estimated NCF failure (death without NCF failure was competing risk); between-arms differences tested using Gray's test. Deterioration at each collection time point was tested using a chi-square test. Patient-reported symptoms were assessed using the MD Anderson Symptom Inventory Brain Tumor module and analyzed using mixed effects models and t-tests. Results: From 7/2016 to 3/2018, 518 pts were randomized. Median follow-up was 7.9 mos. HA-WBRT+M was associated with lower NCF failure risk (adjusted hazard ratio (HR) = 0.74, p = 0.02) due to lower risk of deterioration in executive function at 4 mos (p = 0.01) and encoding (p = 0.049) and consolidation (p = 0.02) at 6 mos. Age=<61 predicted lower NCF failure risk (HR = 0.60, p = 0.0002); non-significant test for interaction indicated independent effects of HA and age. Patient-reported fatigue (p = 0.036), difficulty speaking (p = 0.049) and problems remembering things (p = 0.013) at 6 mos favored the HA-WBRT+M arm. Imputation models accounting for missing data also favored the HA-WBRT+M arm for patient-reported cognition (p = 0.011) and symptom interference (p = 0.008) at 6 mos. Treatment arms did not differ in toxicity, overall survival, or intracranial progression. Conclusions: HA during WBRT+M for BM better preserves NCF and patient-reported symptoms, while achieving similar intracranial control and survival. Supported by grants UG1CA189867 (NCORP), U10CA180868 (NRG Oncology Operations), DCP from the National Cancer Institute. Clinical trial information: NCT02360215.
A randomized phase II trial of veliparib (V), radiotherapy (RT) and temozolomide (TMZ) in patients (pts) with unmethylated MGMT (uMGMT) glioblastoma (GBM).

Mustafa Khasraw, Kerrie Leanne McDonald, Mark Rosenthal, Zarnie Lwin, David M. Ashley, Helen Wheeler, Elizabeth Barnes, Matthew C. Foote, Eng-Siew Koh, Erik P. Sulman, Michael Back, Michael Buckland, Hao-Wen Sim, Lauren Fisher, Robyn Leonard, Merryn Hall, Sonia Yip, John Simes; Royal North Shore Hospital/University of Sydney, St Leonards, Australia; University of NSW, Kensington, Australia; The Royal Melbourne Hospital, Parkville, Australia; Department of Medical Oncology, Brisbane, QLD, Australia; Andrew Love Cancer Centre, Geelong, Australia; Royal North Shore Hospital, Department of Oncology, St Leonards, Australia; NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, NSW, Australia; University of Queensland, Brisbane, Australia; Princess Alexandra Hospital, University of Queensland, Brisbane, Australia; Liverpool Hospital, Liverpool, Australia; The University of Texas MD Anderson Cancer Center, Houston, TX; Royal North Shore Hospital, St Leonards, Australia; Royal Prince Alfred Hospital, Camperdown, Sydney, Australia; The Kinghorn Cancer Centre, St Vincent’s Hospital Sydney, Sydney, Australia; NHMRC Clinical Trials Centre, Sydney, Australia; COGNO Consumer Advisory Panel, Sydney, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; Sydney Catalyst Translational Cancer Research Centre, Sydney, Australia

Background: TMZ offers minimal benefit in uMGMT GBM pts. V is synergistic with both RT and TMZ in preclinical models, safe when combined with either RT or TMZ clinically, but the triplet (V+RT+TMZ) is poorly tolerated. This study examined a novel approach to patients with uMGMT GBM. Methods: VERTU is a randomized Phase 2 trial comparing Arm A (Standard of care) = RT (60Gy/30 fractions) + TMZ (75mg/m2 daily) followed by TMZ (150–200mg/m2D 1–5) every 28 days for 6 cycles vs Arm B (experimental arm) = RT (60Gy/30 fractions) + V (200mg PO BID) followed by TMZ (150–200mg/m2D 1–5) + V (40mg bid, D 1–7) every 28 days for 6 cycles in pts with newly diagnosed centrally determined uMGMT GBM. The study aims to randomize 120 pts (2:1 to the experimental arm). The primary endpoint was 6 months progression free survival (6mPFS) with multiple secondary and tertiary endpoints. Evaluation of feasibility and safety was planned after completion of RT in the first 60 pts (Stage 1). (ANZCTR #ACTRN12615000407594). Tumor tissue and serial bloods were collected for translational research. Results: 125 pts were randomized (41 Arm A, 84 Arm B). Mean (range) age 58 (22–78) years, 70% male, 61% ECOG 0, 86% macroscopic resection, 14% biopsy. At the time of analysis (cut-off date: 04/Feb/2019), median follow up was 16.5 months, 76 pts had died. 6mPFS (95% CI, Kaplan-Meier estimate) was 37% (22–52) in Arm A and 53% (41–63) in Arm B, and median PFS was 4.4m (95% CI 4.0–6.0) for Arm A and 6.2m (95% CI 4.9–7.1) for Arm B (HR = 0.81, 95% CI 0.54–1.21). 50% of pts in Arm A and 53% in Arm B experienced ≥ G3 adverse events (AEs). The most common G 3/4 AEs were decreased platelets, seizures, hyperglycemia and diarrhea (each 5%) in Arm A and decreased platelets (13%) and seizures (11%) in Arm B. Conclusions: In this multicenter, randomized study, the experimental therapy was feasible and well tolerated. The observed 6mPFS appeared longer in Arm B, but at the time of submitting the abstract, this result did not meet the prespecified primary endpoint. More mature results will be presented at the annual meeting. QoL in VERTU is reported separately. Central MR review, biomarker analyses, including DNA repair and methylation signature analyses are ongoing. Clinical trial information: ACTRN12615000407594.
Glioblastoma evolution pattern under surgery and radio(chemo)therapy (RCHT) to identify novel methylome based glioma subtypes.

Maximilian Knoll, Juergen Debus, Jennifer Furkel, Rolf Warta, Nina Bougatf, Carmen Rapp, Benedikt Brors, Wolfgang Wick, Andreas Unterberg, Christel Herold-Mende, Amir Abdollahi; Departments of Radiation Oncology, Neurology, Neurosurgery, Heidelberg University Hospital, National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Core-Center Heidelberg, Heidelberg, Germany; Heidelberg Ion-Beam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital (UKHD), National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK) Core Center Heidelberg, Heidelberg, Germany; National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), Division of Applied Bioinformatics, German Cancer Consortium (DKTK), Core Center Heidelberg, Heidelberg, Germany; National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany; Departments of Radiation Oncology, Neurology, Neurosurgery, Heidelberg University Hospital, National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Core-Center Heidelberg, Heidelberg, Germany; National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg and German Cancer Consortium (DKTK), Core Center Heidelberg, Heidelberg, Germany.

Background: Identification of isocitrate dehydrogenase mutations (IDHm) and glioma CpG island methylator phenotype (G-CIMP) as well as methylation of O6-methylguanine DNA methyltransferase (MGMT) promoter has substantially improved stratification of glioma patients into prognostic subgroups. In extension of static pre-therapy diagnostic, we sought to investigate the impact of glioblastoma evolution under selection pressure of standard therapy on methylome level. Methods: For the training cohort (T), methylome (450k Illumina) data of paired samples from 50 patients with glioblastoma (GBM, 11 G-CIMP+) were analyzed, i.e., primary (P) and at the time point of recurrence (R, re-surgery) after standard therapy at NCT. For 39 pairs matching RNASeq data was analyzed. Validation cohorts consisted of Heidelberg (V1) total n = 650, GBM (n:585, 8 G-CIMP+), grade III (n: 65, CIMP+ 65), Austrian GBM (V2, n = 499, 36 IDHm, pyrosequencing data) and the TCGA (V3) Lower-grade-glioma cohort (LGG, n = 477, grade III n: 247, 178 G-CIMP+, grade II n: 228, 206 G-CIMP+).

Results: Limited number of consensus differentially methylated probes (DMP) were found across all P vs. R samples (nCpG = 411 CpGs, FDR < 0.05). In contrast, heterogeneity in GBM evolution was found by similarity analysis of delta-methylome data of 50 PR pairs resulting in two distinct clinical subgroups and one “intermediate” group. Intriguingly, n = 114,652 DMP (FDR < 0.05) was found by comparing the evolutionary “poor” (n = 15) vs. “good” (n = 13) GBM phenotypes. A random forest classifier was built to identify the evolutionary subgroups in P samples. The performance of “good” prognosis classifier was in T cohort HR: 0.54 [0.30-0.97], p = 0.04; V1: 0.57 [0.43-0.76], p < 0.001. V2: 0.62 [0.47-0.82], p < 0.001, LGG: 0.16 [0.08-0.32], p < 0.001. In “good” prognosis group (T), neither G-CIMP+ (n = 3) nor MGMT-TP27 (oddsratio, OR: 0.56, p = 0.47) was enriched. MGMT-TP27 OR was 0.47 (V1, p = 0.47) or 1.28 (V2, p = 0.45), respectively. The evolutionary subgroups remain prognostic independent of GCIMP status in LGG (V3). “Poor” glioma are enriched for RTKI/II methylome subtypes, and contain less frequently the mesenchymal subtype. Bevacizumab treatment showed a survival benefits only in “poor” subtype (V1+2). Conclusions: Discovery of a methylome based classifier of glioma evolution informs on “good” and “poor” prognosis subtypes and may have ramification for stratifying patients for therapy such as e.g., antiangiogenesis.
Impact of predictive impact of MGMT promoter methylation in malignant astrocytomas depends on the methylation subgroup.

Wolfgang Wick, Tobias Kessler, Michael Platten, Christoph Meisner, Michael Bamberg, Ulrich Herrlinger, Caroline Happold, Sarah Weisang, Hanna Boelting, Joachim Steinbach, Guido Reifenberger, Felix Sahm, Andreas von Deimling, Antje Wick, Michael Weller; National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany; Neurology Clinic, DFKZ, DTK, Heidelberg, Germany; Heidelberg University, Heidelberg, Germany; Institute for Medical Biometry, Tuebingen, Germany; Department of Radiation Oncology, University Hospital Tübingen, Tübingen, Germany; Department of Neurology, University of Bonn Medical Center, Bonn, Germany; Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Center Zurich, University Hospital and University of Zurich, Zurich, Switzerland; University of Heidelberg, Heidelberg, Germany; University of Frankfurt, Frankfurt, Germany; Department of Neuropathology, Heinrich Heine University Hospital, Düsseldorf, Germany; Heidelberg University Hospital, German Cancer Research Center (DKFZ), Heidelberg, Germany; Department of Neuropathology, Institute of Pathology, Heidelberg University Hospital (UKHD), National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK) Core Center Heidelberg, Germany; Heidelberg University Hospital, German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK) Core Center Heidelberg, Germany; Neurology Clinic, University of Heidelberg, National Center for Tumor Diseases, Heidelberg, Germany

Background: O6-methylguanine DNA-methyl transferase (MGMT) status is predictive for alkylating chemotherapy in most series, but there are non-benefitting subgroups. Despite multiple attempts, MGMT has not been unambiguously established as a predictive biomarker for patients with malignant gliomas. Further, these tumors are to be better classified according to global methylation profiles. Methods: Long-term efficacy data of the NOA-08 trial (NCT01502241) that compared efficacy and safety of radiotherapy (RT, n=176) to temozolomide (TMZ, n=193) in patients >65 years with anaplastic astrocytoma (AA) or GB as well as genome-wide DNA methylation patterns and copy number variations assessed by methylation arrays in a biomarker subset (n=104) and an independent cohort (n=380) have been used to assess the interaction between MGMT status and methylation subgroups. Results: In the long-term update of NOA-08 patients with MGMT methylated tumors had longer OS and EFS when treated with TMZ (18.4 [13.9-24.4] months and 8.5 [6.9-13.3] months) versus RT (9.6 [6.4-13.7] months and 4.8 [4.3-6.2] months, HR 0.44 [0.27-0.70], p<0.001 for OS and 0.46 [0.29-0.73], p=0.001 for EFS). These data compared favorably with recently published data from patients treated with chemoradiation (Perry et al. NEJM 2017). Importantly, only patients with glioblastomas of the methylation class receptor tyrosine kinase II (RTKII) and mesenchymal but not RTK I demonstrated the predictive impact of MGMT in the NOA and the independent validation cohort. Conclusions: MGMT promoter methylation as a strong but methylation subclass-dependent predictive biomarker for the use of alkylating chemotherapy in malignant gliomas. The data call for embedding of MGMT tests into global methylation analyses for all patients with malignant gliomas potentially treated with alkylating chemotherapy.
Genomic characterization of lung tumors and metastatic (Met) sites in advanced (Adv) NSCLC.

Melinda D Willard, Emily Nash Nash Smyth, Ramon Velasquez Tiu, Julie Beyrer, Yajun Emily Zhu, Lee Bowman, Kristin M Sheffield, Yimei Han, Priscilla Brastianos; Eli Lilly and Company, Indianapolis, IN; Massachusetts General Hospital, Boston, MA

Background: Molecular alterations (MA) found in brain (Br) mets of NSCLC pts can differ from primary and/or other met sites, which may explain why therapies targeting primary tumors are less effective at preventing and treating intracranial disease. We analyzed the frequency of known driver genes in adv NSCLC pts and the association with overall survival (OS). Methods: This retrospective observational study identified pts from the Flatiron- Foundation Medicine NSCLC Clinico-Genomic Database who were diagnosed with adv NSCLC from 1 Jan 2011 to 31 Oct 2017 and had tumor tissue analyzed at any time following initial diagnosis via targeted DNA sequencing by FoundationOne. Descriptive statistics summarized MA from lung and met sites (Br and non-brain [NB]). OS was measured from adv diagnosis to death or last activity date (censored). Multivariable Cox proportional hazard regression model was used for time-to-event analysis. Results: Of 3257 pts, data were available from lung (n = 1621), Br (n = 180), and NB sites (n = 377): liver (n = 167), bone (n = 124), adrenal (n = 63), and spine (n = 23). Median age at adv diagnosis was 66.2 yrs. TP53(63.3%), KRAS(28.8%), EGFR(15.6%),STK11(13.5%), and CDKN2A(8.5%) were frequently mutated genes in lung samples. Genes for Br vs NB sites included TP53(70.6%; 64.7%), KRAS(36.1%; 26.5%), EGFR(9.4%; 18.8%), STK11(18.9%;12.7%), and CDKN2A(6.1%; 10.1). KEAP1 alterations were also present in 10% (Br), 7.4% (NB), and 6% of lung samples. In treated pts, lack of alterations in select genes (STK11, TP53, KEAP1) was associated with longer OS, whereas lack of other alterations (ARID1A, EGFR, ALK, ROS1) was associated with a shorter OS (p < 0.05). Patients with select mutations co-occurring with KRAS had higher risk of death compared to those with KRAS only (p < 0.05). Conclusions: Based on pts with NSCLC whose tumor tissue underwent DNA sequencing, the most frequently altered genes in lung and Br samples included TP53, KRAS, EGFR, STK11, and CDKN2A, with some being significantly associated with OS. Prognosis of NSCLC pts depends on clinical, demographic, and genomic factors and should be carefully considered to optimize clinical outcome.
Circulating tumor DNA analysis (ctDNA) for genomic testing in NSCLC patients with isolated CNS progression.

Mihaela Aldea, Laura Mezquita, Lizza Hendriks, Edouard Auclin, Jordi Remon, David Planchard, Cecile Jovelet, Jose Carlos Benitez, Anas Gazzah, Pernelle Lavaud, Charles Naltet, Ludovic Lacroix, Clive D. Morris, Emma Green, Karen Howarth, Claudio Nicotra, Benjamin Besse; Medical Oncology Department, Gustave Roussy, Villejuif, France; MUMC, Maastricht, Netherlands; Gastrointestinal Oncology Department, European Georges Pompidou Hospital, Paris, France; CIOCC Barcelona-HM Delfos, Barcelona, Spain; Medical Oncology Department, Thoracic Group, Gustave Roussy, Villejuif, France; Translational Research Laboratory, Gustave Roussy, Villejuif, France; Hospital Universitari Mútua de Terrassa, Barcelona, YT, Spain; Drug Development Department (DITEP), Gustave Roussy, Villejuif, France; Translational Research, Gustave Roussy, Villejuif, France; Inivata, Cheshire, United Kingdom; Inivata Ltd., Cambridge, United Kingdom; Paris-Sud University, Orsay and Gustave Roussy, Villejuif, France

Background: Genomic DNA profiles are mandatory in advanced, treatment naive non-small cell lung cancer (NSCLC) patients (pts) and strongly recommended at progression (PD) on personalized treatment. In pts with PD limited to central nervous system (CNS), tissue biopsy is difficult and the performance of ctDNA is unknown. Methods: Clinical, molecular, imaging data of NSCLC pts included in 2 prospective studies from 01.2016 to 11.2018 at Gustave Roussy were collected. Inclusion criteria were: stage IV disease and any known tissue genomic alteration (GA) EGFR, ALK, BRAF, KRAS, HER2, ROS1, MET, PIK3CA, TP53. Plasma ctDNA collected at baseline/PD were analyzed by next-generation sequencing (NGS-InVisionFirst™-Lung) in 3 groups: pts with isolated CNS (iCNS), extra-CNS only (noCNS) or both combined (cCNS) disease. iCNS was defined as any PD to CNS, while stable/absent extra-CNS metastases (mts). ctDNA was considered positive if ≥1 GA was found. ctDNA in cerebrospinal fluid (CSF) were also collected. Results: Out of 245 pts with ≥1 ctDNA: 56 had iCNS (66 samples), 97 noCNS (127 samples) and 92 cCNS (107 samples). In this cohort, 60% were female, median age 60 years, 47% smokers; 92% had adenocarcinoma. The median number of mts sites was 3 in noCNS/cCNS groups. Proportions of tissue GA at baseline were (iCNS vs noCNS/cCNS): EGFR (50% vs 44%), ALK (30% vs 11%), BRAF (4% vs 12%), KRAS (5% vs 15%), HER2 (2% vs 5%), ROS1 (5% vs 4%). Tyrosine kinase inhibitors were used in 73% iCNS vs 61% noCNS/cCNS. Local brain treatments were performed in 43% (n = 24) vs 32% (n = 29) and leptomeningeal mts (LM) detected in 34% (n = 19) vs 8% (n = 9), in iCNS and cCNS, respectively. CtDNA was positive (+) in 52% in iCNS vs 84% in noCNS and 92% in cCNS (p < 0.0001). In iCNS, there was a non-significantly higher proportion of + ctDNA in pts with LM vs only brain disease (59 vs 48%, P = 0.44). 12/56 pts of iCNS group had serial ctDNA, being collected also at time of cCNS. In 25% of cases, a negative ctDNA at time of iCNS shifted to + at time of cCNS. In 12 iCNS pts, ctDNA was + in 6 (50%) plasma and in 10 (83%) paired CSF (p = 0.193). Conclusions: Detection of GA by plasma ctDNA is lower in NSCLC pts with isolated CNS PD. Alternative strategies (as CSF analysis) should be explored.
Background: SVN53-67/M57-KLH (SurVaxM) is a novel cancer vaccine designed to stimulate an immune response targeting the tumor-specific antigen survivin. A multi-center, single-arm phase 2 clinical trial of SurVaxM in survivin-positive newly diagnosed glioblastoma (nGBM, NCT02455557) is now fully enrolled and data updated. Methods: Patients (n = 63) with nGBM were enrolled at 5 US cancer centers and followed for safety, 6-month progression-free survival (PFS6), 12-month overall survival (OS12) and immunologic response. All patients underwent craniotomy with near-total resection (< 1 cm³ residual contrast enhancement), TMZ chemoradiation, adjuvant TMZ and SurVaxM. Patients received 4 doses of SurVaxM (500 mcg) in Montanide with sargramostim (100 mcg) biweekly, followed by maintenance SurVaxM with adjuvants every 12 weeks until tumor progression. Immunogenicity of SurVaxM was assessed by detection of survivin-specific antibody (IgG) and CD8+ T-cell levels. Results: Median age was 60 yrs (range, 20-82), 53% methylated MGMT, 46% unmethylated MGMT (1 N/A) and 60% were male. Survivin expression ranged from 1-40% (median 12%) by immunohistochemistry. Median time to first immunization was 3.0 mo (1.9-4.0 mo) from diagnosis. There have been no RLT or grade ≥ 3 SAE attributable to SurVaxM. The most common AE was grade 1-2 injection site reactions. OS12 was 86% from first immunization and 93.4% from diagnosis. OS12 for meMGMT was 93.1% and unMGMT was 78% from first immunization. Median time to tumor progression (mPFS) was 13.9 months from diagnosis. Median OS has not yet been reached. SurVaxM produced an increase in survivin-specific IgG titre from pre-vaccine baseline to ≥ 1:10,000 in 67% of pts and ≥ 1:100,000 in 27%. CD8+ T cell responses were observed. Anti-survivin IgG and OS were correlated. Conclusions: SurVaxM immunotherapy generated encouraging efficacy and immunogenicity in nGBM and has minimal toxicity. A randomized, prospective trial of SurVaxM in nGBM is planned. Clinical trial information: NCT024455557.
Background: Preclinical GBM data targeting the checkpoint molecules Lag-3 and CD137 have shown promising anti-tumor immune response with resultant improved survival when combined with anti-PD-1. Here we report our experience from a multi-arm safety study in patients with recurrent GBM treated with anti-Lag-3 and anti-CD137. 

Methods: The Adult Brain Tumor Consortium (ABTC) 1501 trial is a phase I, open label, multicenter, multi-arm dose-finding/safety study of anti-LAG-3 (BMS-986016) or anti-CD137 (BMS-663513) alone and in combination with anti-PD-1 in patients at first recurrence of GBM. The primary objective is to define MTD for the mono and combinational treatment. The major secondary objective is to explore for a signal in efficacy. The key inclusion criteria are adults, first recurrence of GBM following RT+TMZ, TLC $\geq 1000/ul$, KPS $\geq 60\%$, stable corticosteroid regimen, measurable disease, and written informed consent. Sequential allocation was used for the treatment assignment at starting dose of 80mg for anti-LAG-3 and 8mg for anti-CD137. Anti-PD-1 was given at a flat dose of 240 mg in the combination treatment arms. The 3+3 design is used for the dose finding with a target DLT rate, 33%.

Results: to date 44 patients were enrolled into the trial with median age at 57, median KPS at 90. Median treatment cycle was 3 and 39% tumors were MGMT methylated. The highest safe dose for Anti-LAG-3 alone is 800 mg without a DLT. The safe dose for anti-CD137 alone arm is 8mg with 1 DLT, and 2 grade 3 elevated serum ALT at end of cycle 2. Combination arms of Anti-LAG-3 +anti-PD-1 (160 mg/240mg as the highest dose combination) had one DLT (hypertension) and no toxicities were seen in the combination arm of Anti-CD137+Anti-PD-1 (3 mg/240 mg). mOS was 14 months for anti-CD137 alone, 8 months for Anti-Lag-3, and 7 months for Anti-Lag-3 + Anti-PD-1. Correlative data will be discussed. Conclusions: The trial is ongoing. The RP2D is 800mg for anti-LAG-3 as a monotherapy and 8mg for anti-CD137. For the combination arms, 160 mg of Anti-LAG-3 and 240 mg of anti-PD-1 and 3 mg of anti-CD137 and 240 mg antiPD-1 were the RP2D. Clinical trial information: NCT02658981.
Quantitative radiographic analysis of phase II and III trials in recurrent glioblastoma treated with VB-111 with or without bevacizumab or bevacizumab monotherapy.

Benjamin M. Ellingson, Catalina Raymond, Jingwen Yao, Ararat Chakhoyan, Dallas Turley, Joseph Tsung, Jodi Goldman, Jacob Schlossman, Caleb Tan, Andrew Jacob Brenner, Nicholas A. Butowski, Patrick Y. Wen, Tamar Rachmilewitz Minei, Yael Chava Cohen, Dror Harats, Timothy Francis Cloughesy; University of California Los Angeles, Los Angeles, CA; University of California, Los Angeles, CA; The University of Texas Health Science Center, San Antonio, TX; University of California, San Francisco, CA; Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA; VBL Therapeutics, Israel, Israel; Tel Aviv Sourasky Medical Center and Sakler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; VBL Therapeutics, Modiin, Israel

Background: VB-111 is a non-replicating adenovirus carrying a pro-apoptotic transgene for TNFR1/Fas under the control of a modified murine promoter to pre-proendothelin 1. The transgene is expressed only in angiogenic endothelial cells, and therefore VB-111 results in targeted apoptosis of neovascular vessels. The current study characterizes the quantitative radiographic results and impact on OS in phase 2 and 3 trials of recurrent glioblastoma (GBM) patients treated with VB-111 with or without bevacizumab (BV) or BV monotherapy. Methods: MRI data from a phase 2 (NCT01260506) and randomized, double arm, controlled phase 3 (GLOBE; NCT02511405) trial of VB-111 in recurrent GBM were used in current study: Arm A) VB-111 monotherapy until progression followed by combination VB-111 and bevacizumab (BV) (“Primed Combination”; Phase 2; N = 24); Arm B) VB-111 in combination with BV (“Unprimed Combination”; Phase 3; N = 124) and Arm C) BV monotherapy (“Control”; Phase 3; N = 120). Contrast enhanced T1-weighted digital subtraction was used to quantify tumor volume at all time points. Results: Baseline tumor volume was not significantly different between patient cohorts (Kruskal-Wallis; P = 0.1482; median~20mL). Continuous measures of baseline tumor volume were prognostic for OS in all treatment groups when controlling for therapy and age (Cox, P < 0.001, HR = 1.02). In patients with small tumors (≤25mL), the “primed combination” cohort (Arm A) from the phase 2 trial had a significant OS advantage compared to both upfront combination of VB-111 and BV (Arm B; P = 0.0094, HR = 0.5328; median OS = 7mo vs. 15mo) as well as BV alone (Arm C; P = 0.0248, HR = 0.5776; median OS = 8.5mo vs. 15mo). Patients with a radiographic response (> 65% reduction) had a significant survival difference from non-responders when controlling for age, baseline tumor volume, and treatment arm (P = 0.0014, HR = 0.5822). Notably, in responders to VB-111 monotherapy or combination therapy after priming with VB-111 exhibited characteristic, expansive areas of necrosis in areas of initial disease. Conclusions: Small recurrent tumors have a significant OS advantage when “priming” with VB-111 monotherapy prior to combination VB-111 and BV at recurrence. Patients responding to VB-111 exhibit specific imaging characteristics related to the drug mechanism of action. Clinical trial information: NCT02511405; NCT01260506.
First-in-human phase I trial of the combination of two adenoviral vectors expressing HSV1-TK and FLT3L for the treatment of newly diagnosed resectable malignant glioma: Initial results from the therapeutic reprogramming of the brain immune system.

Pedro R. Lowenstein, Daniel A Orringer, Oren Sagher, Jason Heth, Shawn L. Hervey-Jumper, Aaron Gerald Mammoser, Larry Junck, Denise Leung, Yoshie Umemura, Theodore Steven Lawrence, Michelle Miran Kim, Daniel Richard Wahl, Paul McKeever, Sandra Ines Camelo-Piragua, Andrew Lieberman, Sriram Venneti, Andrea Comba, David Altshuler, Karin Muraszko, Maria Castro; Univ of Michigan Medical School, Ann Arbor, MI; Michigan Medicine, Department of Neurosurgery, Ann Arbor, MI; University of Michigan Medical School, Michigan Medicine, Ann Arbor, MI; University of Michigan, Ann Arbor, MI; University of California, San Francisco, San Francisco, CA; University of Michigan, Department of Neurology, Ann Arbor, MI; William Beaumont Hosp, Royal Oak, MI; University of Michigan Medical School, Ann Arbor, MI; Univ of Texas MD Anderson Cancer Ctr, Novi, MI; Department of Radiation Oncology, University of Michigan Health System, Ann Arbor, MI; University of Michigan School of Medicine, Ann Arbor, MI; University of Michigan Health System, Ann Arbor, MI

Background: This is the initial report on a first in human Phase I dose escalation trial of the combination of two adenoviral vectors expressing HSV1-TK or FLT3L for the treatment of newly diagnosed, resectable malignant gliomas. The absence of functional dendritic cells from the brain precludes anti-brain tumor immune responses. We combined tumor cytotoxicity (Ad-HSV1TK) with recruitment of dendritic cells to the brain (Ad-FLT3L) to induce an effective anti-tumor immune response. This strategy induced an efficacious, cytotoxic CD8 and CD4 T-dependent immune response in many animal models of glioma. This immune response also generated anti-tumor memory, and the capacity for neoantigen recognition.

Methods: The trial was approved by FDA and all institutional cttees. Treatment was administered intraoperatively following complete glioma resection in newly diagnosed tumors. The trial consisted of vector dose escalation, starting at 1x10^9 i.u., and increasing to 1x10^11 i.u. of each vector. Dose escalation proceeded by increasing the vector dose through a total of 6 combinations administered to 6 cohorts of 3 patients each. Two cycles of 14 days each of valacyclovir were administered to activate HSV1-TK cytotoxicity. Cycle 1 starts on Day 1-3 post surgery for 14 days, and Cycle 2 on Week 8-12. Standard radiation, i.e., 60 Gy in 2 Gy fractions over 6 weeks, with concurrent temozolomide, was followed by cyclic temozolomide. Results: Examination of tumor samples at primary resection and first recurrence show an increase in the infiltration of inflammatory cells. The experimental treatment was well tolerated. At this time the MTD has not been reached. There were approx. 248 AEs, and 26 SAEs; these have not been linked to treatment. At this time the MTD has not been reached. A secondary outcome is overall survival. Preliminary analysis of partial data may suggest that the combined viral vector therapy may provide a clinically significant survival. Conclusions: Our results show for the first time that reprogramming of the host’s brain immune system to recognize gliomas reveals a new approach for the treatment of highly malignant brain tumors. Clinical trial information: NCT01811992.
Evaluation of controlled IL-12 in combination with a PD-1 inhibitor in subjects with recurrent glioblastoma.

E. Antonio Chiocca, Rimas Vincas Lukas, Ganesh Rao, John A. Barrett, Jill Y. Buck, Nathan Demars, Amy Smith, John Miao, Qiang (John) Zhou, Arnold Bruce Gelb, Laurence Cooper; Brigham and Women’s Hospital, Boston, MA; Northwestern University, Chicago, IL; The University of Texas MD Anderson Cancer Center, Houston, TX; Ziopharm Oncology, Inc., Boston, MA

Background: Ad-RTS-hIL-12 (Ad) is a novel gene therapy candidate conditionally expressing IL-12 under the control of veledimex (V) acting via the proprietary RheoSwitch Therapeutic System (RTS) gene switch with a therapeutic window. Intratumoral Ad + oral V monotherapy (Phase 1 study, NCT02026271) resulted in a new sustained intra-tumor influx of activated cytotoxic T cells, consistent with an immune-mediated anti-tumor effect improving median overall survival (mOS) of subjects with recurrent glioblastoma (rGBM). This correlated with an increased circulating CD8+/FoxP3+ T cell ratio (“cytoindex”), an emerging biomarker for mOS. PD-1 expression on infiltrating T cells at biopsy after Ad+V, supports combining controlled IL-12 with a PD-1 inhibitor to further augment T-cell-mediated anti-tumor effects. The rationale is also supported by increased OS (100% combo vs 63% for Ad+V vs 40% for anti-PD-1) in mice bearing GL-261 glioma. Methods: An ongoing open label, dose-escalation Phase 1 trial (NCT03636477) is evaluating safety and tolerability of local, controlled IL-12 with nivolumab (nivo) in adult subjects with rGBM. Ad was administered by single intratumoral injection (2 x 10^11 viral particles, Day 0) plus V (10-20 mg) PO QD x 15 with nivo (1-3mg/kg) IV on Days -7, 15, then Q2W. Results: Safety data revealed a similar profile as Ad +V monotherapy. Adverse reactions (ARs) during follow-on nivo dosing were consistent with anti-PD-1 reports. ARs were manageable and reversible with no synergistic toxicities. Nivo alone did not alter peripheral IL-12 levels (median baseline (before anti-PD-1) 0.9 pg/mL; Day 0 1 pg/mL) increasing to 5.5 pg/mL on Day 3. Nivo alone increased peripheral T cells (CD3+CD8+ median baseline 23%; Day 0 26%) and Ad+V elevated peripheral CD3+CD8+ to 31% at Day 14. Nivo alone decreased regulatory T cells (FoxP3 baseline 1.5% vs Day 0 0.8%). Ad+V decreased these to 0.3% (Day 14). Combination therapy improved the cytoindex (baseline 15; Day 0 29; Day 14 80). Conclusions: Controlled IL-12 production using Ad + V with nivo is a rational combination with initial data consistent with immune-mediated anti-tumor effects with a favorable safety profile, warranting continued investigation in rGBM. Clinical trial information: NCT03636477.
Background: Proteasome inhibition sensitizes glioma cells to TMZ and RT, providing a novel therapeutic strategy for GBM. MRZ, an irreversible, brain-penetrant, pan-proteasome inhibitor with anti-glioma activity was combined with standard TMZ/RT → TMZ in newly diagnosed GBM (NCT02903069), to determine the recommended dose (RD). The primary endpoint of this expanded phase 1 trial was toxicity, with secondary endpoint of OS.

Methods: Patients were enrolled in separate cohorts (TMZ/RT+MRZ → TMZ+MRZ, N=15; TMZ/RT → TMZ+MRZ, N=18) in dose-escalation (3+3 design), followed by dose-expansion (N=20) with TMZ/RT+MRZ at RD → TMZ+MRZ at RD. A separate cohort received TMZ/RT → TMZ+MRZ at RD with Tumor Treating Fields (Optune, N=13). MRZ was infused IV (10 min at 0.55, 0.7, 0.8, and 1.0 mg/m^2) on Days 1, 8, 15, 29, 36 (42-day TMZ/RT+MRZ cycle) and Days 1, 8, 15 (28-day TMZ+MRZ cycle).

Results: 66 patients treated; median age 58 years, 68% male, 50% receiving corticosteroid at baseline, 52% unmethylated MGMT. Dose-limiting toxicities (DLTs) in dose-escalation cohorts: 1 (fatigue) at 0.7 mg/m^2, 5 (ataxia/diarrhea; ataxia/confusion; myocardial infarction, delirium/ataxia; ataxia/fatigue) in 1.0 mg/m^2 cohorts. MRZ demonstrated a steep dose-response with treatment-emergent adverse events (TEAEs)/DLTs predominately CNS AEs (Grade ≥3 TEAEs in 12 of 12 patients at 1.0 mg/m^2 vs 22 of 41 patients at ≤0.8 mg/m^2); the RD for MRZ was determined to be 0.8 mg/m^2. Most common TEAEs (all grades): fatigue, nausea (both 70%), hallucination (54%), vomiting (53%), headache (47%), confusional state (33%), ataxia, constipation, muscular weakness (all 29%).

Conclusions: CNS TEAEs were short-lasting, reversible and ameliorated by early dose reductions (29% patients dose-reduced), allowing patients to remain on treatment. For patients receiving MRZ with TMZ/RT → TMZ (N=35), the median OS was 14.8 months (17 deaths, median follow-up 14.3 months), and 7 patients remain active (Cycles 11-23). The MRZ RD + TMZ/Optune combination was tolerated, with 4 of 13 patients treated on this arm remaining active. An international Phase 3 trial (EORTC 1709-BTG/CCTG CE.8, NCT03345095) is ongoing. Clinical trial information: NCT02903069.
Longitudinal analysis of quality of life following treatment with asunercept plus reirradiation versus reirradiation in progressive glioblastoma patients.

Wolfgang Wick, Andriy Kendryukov, Klaus Junge, Thomas Höger, Claudia Kunz, Harald Fricke; National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany; Apogenix AG, Heidelberg, Germany; Scope International AG, Mannheim, Germany

Background: Palliation of symptoms and the maintenance of quality of life (QoL) are important goals in cancer treatment.1,2 Beyond progression free survival (PFS) and overall survival (OS), health related QoL was one of the secondary endpoints in the asunercept plus irradiation Phase II trial (NCT01071837) in recurrent glioblastoma.3 Current analysis presents time to deterioration (TtD) of QoL using data from this study. Methods: Data from patients (pts) with a baseline and ≥1 post-baseline QoL assessment were included in this analysis. TtD was defined as the time from randomization to the first deterioration in the EORTC QLQ-C15, PAL EORTC QLQ-BN20 and Medical Research Council (MRC)-Neurological status. Deterioration was defined as a decrease of ≥10 points from baseline in the QLQ-C15 PAL overall QoL and functioning scales, an increase of ≥10 points from baseline in the QLQ-C15 PAL fatigue scale and the QLQ-BN20 total sum of score, and a rating of “Worse” in the MRC-Neurological status. Pts without a deterioration were censored at the last QoL assessment. Kaplan-Meier estimates were used to describe TtD and both treatment groups compared using the logrank test. The relationship between progression of disease (PD) and QoL deterioration has been investigated. Results: Compared to reirradiation alone, treatment with asunercept + reirradiation was associated with significant improvement of TtD (P<0.01; Table). PD was a key driver for QoL deterioration and the median TtD was comparable with PFS in favour of the asunercept treatment arm. Conclusions: Treatment with asunercept plus irradiation significantly prolongs TtD and maintains QoL, versus reirradiation alone in progressive glioblastoma patients. Clinical trial information: NCT01071837. References: 1. NCCN. Central Nervous System Cancers. Version 2018.2; 2. Stupp R et al. Ann Oncol 2014;25(S3):iii93-iii101; 3. Wick et al. Clin Cancer Res 2014;20:6304–13.

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<tr>
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<td>MRC Neurological status</td>
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* = Not reached
DGM1 may serve as a novel genetic biomarker of response to enzastaurin in glioblastoma.

Nicholas A. Butowski, Ronald L. Shazer, Hong Sun, Isabel Han, Manoj A. Jivani, Wen Luo; University of California, San Francisco, CA; Denovo Biopharma LLC, San Diego, CA

Background: Despite countless clinical trials being conducted, little has changed over the last decade in the chemotherapies available for glioblastoma (GBM) with survival remaining poor. Meaningful advances in treating this deadly malignancy may rely on precision medicine. We discovered a novel pharmaco-genomic biomarker for enzastaurin (enz) in treating lymphoma (lymph). We evaluated if this biomarker can be used to predict enz response in GBM. Methods: Biomarker discovery was performed by a genome-wide screen using DNA extracted from blood samples from a ph 3 enz lymph trial and confirmed in an independent ph 2 enz lymph trial. The biomarker was then evaluated for its predictability in GBM using the archived DNA samples from a prior ph 1/2 enz GBM trial. Results: A novel biomarker, Denovo Genomic Marker 1 (DGM1), a germline polymorphism on chromosome 8, was found to be highly correlated with response to enz in the two lymph trials. Using DNA extracted from blood of pts from the single-arm ph 1/2 study of newly diagnosed GBM receiving enz added to radiation and temozolomide (tmz), we found median OS for DGM1+ pts treated with enz was 18 mon vs 12.8 mon for DGM1- pts, HR (95% CI) 0.68 (0.25, 1.81), p = 0.12. In addition, we found pts in the GBM study receiving a mean daily dose of enz ≥ 245 mg had an OS of 19.8 mon vs 14.9 mon for pts receiving a mean daily dose of < 245 mg [HR (95% CI) 0.55 (0.34, 0.90)]; enz 500 mg/day was used in the lymph studies. Conclusions: These data are supportive of DGM1 as a potentially predictive biomarker for enz response in both lymph and GBM. There is an ongoing biomarker-driven pivotal ph 3 study in lymph at 500 mg/day, and DGM1 in GBM will be further evaluated in a planned randomized ph 2b study in newly diagnosed GBM with 500 mg/day of enz in combination with tmz.
Barriers to accrual and enrollment in brain tumor trials.

Eudocia Quant Lee, Ugonma Nnenna Chukwueke, Shawn L. Hervey-Jumper, John Frederick De Groot, Jose Pablo Leone, Terri S. Armstrong, Susan Marina Chang, David Arons, Kathy Rose Oliver, Evanthia Galanis, Bret Edward Buckley Friday, Nancy U. Lin, Minesh P. Mehta, Marta Penas-Prado, Michael A. Vogelbaum, Solmaz Sahebjam, Martin J. Van Den Bent, Michael Weller, David A. Reardon, Patrick Y. Wen; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; University of California, San Francisco, San Francisco, CA; The University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas Health Science Center School of Nursing, Houston, TX; National Brain Tumor Society, Newton, MA; International Brain Tumor Alliance, Surrey, United Kingdom; Mayo Clinic, Rochester, MN; SMD, Duluth, MN; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX; Cleveland Clinic, Cleveland, OH; Moffitt Cancer Center & Research Institute, University of South Florida, Tampa, FL; Erasmus MC Cancer Centre, Rotterdam, Netherlands; Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Center Zurich, University Hospital and University of Zurich, Zurich, Switzerland; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA

Background: A major impediment to improving neuro-oncology outcomes is poor clinical trial accrual. Methods: We convened a multi-stakeholder group including Society for Neuro-Oncology, Response Assessment in Neuro-Oncology, patient advocacy groups, clinical trial cooperative groups, and other partners to determine how we can improve trial accrual. Results: We describe selected factors contributing to poor trial accrual and possible solutions. Conclusions: We will implement strategies with the intent to double trial accrual over the next 5 years.

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<th>Challenges</th>
<th>Potential solutions</th>
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<td>Patient and Community Factors</td>
<td>Engagement with patient advocacy groups. Improved online search tools, smart phone apps, or patient navigators. Unconscious bias training. Strengthen pipeline of underrepresented minority candidates. Reinforce routine discussion of clinical trials in addition to existing standard therapies. Enhance incentives for patient enrollment in clinical trials or referrals to centers for trials; make most trials available more widely. Minimize clinic visits. Limit inclusion/exclusion to criteria critically relevant to study primary endpoint. Include patients with primary and metastatic brain tumors in early phase oncology clinical trials. Weighted or center-based randomization. Effective leadership of multidisciplinary team and organization culture to promote accrual. Greater partnership between academic and community oncology centers. Better support for trial patients and availability of trials in patients’ geographic region.</td>
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<tr>
<td>Limited patient awareness of trial opportunities. Patient misconceptions about research study involvement. Disparities Unconscious bias. Lack of diversity in oncology workforce. Physician and Provider Factors Failure to discuss clinical trials as an option with patients. Failure to refer to trials outside one’s own institution. Clinical Trial Factors Patient/caregiver hardships due to frequent study center visits. Excessively stringent eligibility criteria. Trial arms with limited equipoise. Site and Organizational Factors Requirement for specialized personnel, training, infrastructure, resources. Limited support resources at centers. Travelling distances.</td>
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Phase 1/2a study of once daily oral BAL101553, a novel tumor checkpoint controller (TCC), in adult patients with progressive or recurrent glioblastoma (GBM) or high-grade glioma.

Juanita Suzanne Lopez, Rebecca Sophie Kristeleit, Robert Rulach, Noor Md Haris, Mariana Scaranti, Paul James Mulholland, Donna Crawford, Saira Bashir, Caterina Aversa, Alison L. Hannah, Stephanie Anderson, Marc Engelhardt, Thomas Kaindl, Patrice Larger, Phil McKeran, TR Jeffry Evans, Elizabeth Plummer; Drug Development Unit-The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; University College London Hospitals, London, United Kingdom; Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom; The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom; The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, United Kingdom; Consultant, Sebastopol, CA; Basilea Pharmaceutica International Ltd, Basel, Switzerland; Basilea Pharmaceutica International Ltd., Basel, Switzerland; Freeman Hospital Newcastle, Newcastle, United Kingdom

Background: BAL101553 (prodrug of BAL27862) is a novel TCC that promotes tumor cell death by modulating the spindle assembly checkpoint. BAL27862 is a lipophilic, small molecule shown in rodents to penetrate the brain (brain/plasma ratio around unity), with promising antitumor activity in orthotopic preclinical GBM models as monotherapy or in combination with radiotherapy (RT) with or without temozolomide. In this ongoing study (NCT02490800, CDI-CS-002), daily oral BAL101553 was initially examined in solid-tumor patients, with an MTD of 16 mg/d and DLTs of G4 hyponatremia and G2 hallucinations (Lopez 2018, JCO 36, 2018, suppl. A2530). Subsequently the study was expanded by including a separate cohort of patients with progressive or recurrent GBM or high-grade glioma (Ingles Garces 2017, JCO 35, 2018, suppl. TPS2601).

Methods: Patients with histologically-confirmed GBM or high-grade glioma, with progressive or recurrent disease after prior RT with/without chemotherapy, received once-daily oral BAL101553 (28-day cycles) in a 3+3 dose-escalation design to determine the maximum tolerated dose (MTD). Adverse events were assessed by CTCAE v4.03 grade (G), and tumor response by RANO every two cycles. Pharmacokinetics (PK) were evaluated on Day 1 of Cycles 1 and 2. Results: In the ongoing study, 23 pts (13M/10F; median age 50 y), median (min–max) number of prior regimens = 2 (1–5), received doses of 8, 15, 20, 25 or 30 mg oral BAL101553 once daily. One DLT of reversible G2 depression and fatigue occurred at 20 mg. Both mean Cmax and AUC increased with dose between 8 and 30 mg. The PK exposure in GBM patients was lower than for solid tumor patients, in particular at 20 and 25 mg. At 25 mg/d (n = 3), one patient with IDH-mutated GBM had a partial response (63% area reduction per RANO) and continues on study > 8 months, and another patient had stable disease for 5 months. At 15–20 mg/d, stable disease was observed in 3/10 patients.

Conclusions: The current data in patients with GBM or high-grade glioma suggest that BAL101553 is well tolerated at dose levels above the MTD established in patients with advanced solid tumors, and shows indications of clinical activity. Clinical trial information: 02490800.
Plasma cell-free circulating tumor DNA (ctDNA) detection in longitudinally followed glioblastoma patients using TERT promoter mutation-specific droplet digital PCR assays.

Christine Cordova, Mahrukh M. Syeda, Broderick Corless, Jennifer M. Wiggins, Amie Patel, Sylvia Christine Kurz, Malcolm Delara, Zacharia Sawaged, Minerva Utate, Dimitris Placantonakis, John Golfinos, Jessica Schafrick, Joshua Seth Silverman, Rajan Jain, Matija Snuderl, David Zagzag, Yongzhao Shao, George Alan Karlin-Neumann, David Polsky, Andrew S. Chi; National Institutes of Health, Bethesda, MD; NYU Langone Medical Center, New York, NY; Weill-Cornell Graduate School of Medical Sciences, New York, NY; NYU School of Medicine, New York, NY; NYU Langone Health, New York, NY; NYU Langone Medical Center and School of Medicine, New York, NY; NYU Perlmutter Cancer Center, New York, NY; New York University School of Medicine, New York, NY; Department of Population Health, New York University School of Medicine, New York, NY; BioRad, Hercules, CA; Neon Therapeutics, Boston, MA

Background: There is a critical need for more specific and less invasive diagnostic and pharmacodynamic biomarkers in glioblastoma (GBM) patients (pts). Previously, we detected TERT promoter hotspot mutations (C228T and C250T) in the ctDNA of IDH wildtype (IDHwt) TERT promoter mutant GBM pts with 100% specificity using mutation-specific droplet digital PCR (ddPCR) assays. Here, we explored the dynamics and clinical associations of mutant TERT ctDNA levels in GBM pts undergoing therapy. Methods: We examined 14 pts with suspected IDHwt GBM based on preoperative MRI. Plasma was isolated and frozen from ~15 mL whole blood samples collected pre- and post-op, at end of radiation (RT), and 1, 3, and 6 m after end of RT. TERT promoter mutations were identified in FFPE tumor samples using ddPCR assays for C228T/C250T. Plasma samples were analyzed using ddPCR assays specific for the corresponding tumor mutation. The validated thresholds for positive detection were 1.5 (C228T) and 1.7 copies/mL (C250T). Results: 13/14 (92.9%) IDHwt tumors had TERT mutations (7 C228T and 6 C250T). Six of these 13 (46%) pts had positive plasma TERT ctDNA preop (4 C228T, 2 C250T). The mean cross sectional area of enhancing disease at presentation for positive or negative preop mutant ctDNA was similar. All 4 pts with multiple contrast enhancing lesions had positive preop mutant ctDNA. 2 pts who were negative initially developed detectable mutant ctDNA preceding progression. 3/4 pts with equivocal radiographic pseudoprogression had ctDNA dynamics that correlated with eventual clinical outcome. One patient with unresectable GBM had declining mutant ctDNA in later collections during clinical stability. Conclusions: We detected plasma TERT ctDNA in 46% of TERT mutant GBM pts before surgery, and in 100% of pts with multiple contrast enhancing lesions. TERT mutant ctDNA levels correlated with pseudoprogression or true disease progression and predicted progression before MRI. These data suggest that larger studies to test circulating cell-free TERT mutation as a diagnostic and pharmacodynamic biomarker in GBM are warranted.
Safety and activity of a first-in-class oral HIF2-alpha inhibitor, PT2385, in patients with first recurrent glioblastoma (GBM).

Roy E. Strowd, Benjamin M. Ellingson, Patrick Y. Wen, Manmeet Singh Ahluwalia, Anna F. Piotrowski, Arati Suvas Desai, Jennifer Leigh Clarke, Frank S. Lieberman, Serena Desideri, Louis B. Nabor, Xiaobu Ye, Stuart A. Grossman; Wake Forest School of Medicine, Winston-Salem, NC; University of California Los Angeles, Los Angeles, CA; Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA; Burkhardt Brain Tumor NeuroOncology Center, Neurological Institute, Taussig Center Institute, Cleveland Clinic, Cleveland, OH; Memorial Sloan Kettering Cancer Center, New York, NY; Hospital of the University of Pennsylvania, Philadelphia, PA; University of California, San Francisco, San Francisco, CA; University of Pittsburgh Medical Center, Pittsburgh, PA; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; University of Alabama at Birmingham, Birmingham, AL; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD; Johns Hopkins Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Hypoxia inducible factor 2-alpha (HIF2a) mediates cellular responses to hypoxia and is overexpressed in GBM. PT2385 is an oral HIF2a inhibitor with in vivo activity against GBM. Methods: A two-stage single-arm open-label phase II study of adults with first recurrent GBM following chemoradiation with measurable disease was conducted through the Adult Brain Tumor Consortium. PT2385 was administered at the phase II dose (800 mg b.i.d.). The primary outcome was objective radiographic response (CR+PR); secondary outcomes were safety and survival. Exploratory objectives included PK (day 15 Cmin), PD, and pH-weighted amine-CEST MRI to quantify tumor acidity at baseline and explore associations with drug response. Stage 1 enrolled 24 patients with early stoppage for ≤1 response. Results: Of the 24 patients, mean age was 61 ± 11 years, median KPS 80, MGMT promoter methylated in 46%. PT2385 was well tolerated. Grade $\geq$3 drug-related AEs were hypoxia (n = 2), anemia (1), hyperglycemia (1), hypotension (2) and lymphopenia (2). No objective radiographic responses were observed; median PFS was 1.8 months (95%CI 1.6-3.1). Drug exposure varied widely (Table) and did not differ by corticosteroid use (p = 0.12), antiepileptics (p = 0.09), or sex (p = 0.37). Patients with high systemic exposure had significantly longer PFS (6.7 vs 1.8 months, 0.009). Non-enhancing infiltrative disease with high acidity gave rise to recurrence. Baseline acidity correlated significantly with treatment duration (R² = 0.49, p = 0.017). Conclusions: Drug exposure to PT2385 was variable. Signals of activity were observed in GBM patients with high systemic exposure and acidic (e.g. hypoxic) lesions on baseline imaging. A second-generation HIF2a inhibitor is being studied. Clinical trial information: NCT03216499.

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<th>Day 15 Cmin (ng/mL)</th>
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<td>≥ 1000</td>
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Survival outcomes in glioma patients with noncanonical IDH mutations: Beyond diagnostic improvements.

Enrico Franceschi, Dario De Biase, Annalisa Pession, Alicia Tosoni, Alexandre Paccapelo, Michela Visani, Giovanni Tallini, Chiara Maria Argento, Benedetta Urbini, Stefania Bartolini, Alba Ariela Brandes; Department of Medical Oncology, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy; Department of Pharmacy and Biotechnology (Dipartimento di Farmacia e Biotecnologie) - Molecular Diagnostic Unit, Azienda USL di Bologna, University of Bologna, Bologna, Italy; Bellaria Maggiore Hospital, Bologna, Italy; Department of Pathology Bellaria Hospital, Bologna, Italy; Department of Medicine (Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale) - Molecular Diagnostic Unit, Azienda USL di Bologna, University of Bologna, School of Medicine, Bologna, Italy; Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL di Bologna, Bologna, Italy; Clinical Oncology Unit, St. Anna University Hospital, Ferrara, Italy; Department of Medical Oncology, Azienda USL- IRCCS Institute of Neurological Science, Bologna, Italy; Medical Oncology, Bellaria Hospital, Bologna, Italy

Background: According to the 2016 WHO classification of Central Nervous System tumors, the assessment of exon 4 mutations in IDH1 or IDH2 genes is an essential step in the characterization of gliomas. The R132H mutation is the most frequent alteration in IDH1 gene, however other non-canonical IDH mutations have been identified. The aim of this study was to evaluate the prognostic role of IDH non-canonical mutations.

Methods: We analyzed our institutional data warehouse for all consecutive patients (pts) with newly diagnosed, histologically proven grade II – IV IDH mutant gliomas. IDH sequencing was performed using the 454 GS-Junior next generation sequencer (NGS) (Roche Diagnostic, Mannheim, Germany). All analyses were performed on DNA from formalin fixed and paraffin embedded (FFPE) specimens.

Results: The analysis included 493 pts with IDH mutations. We found 279 (56.6%) grade 2, 173 grade 3 (35.1%) gliomas, and 41 (8.3%) IDH mutant glioblastoma. Canonical IDH1 R132H mutation was found in 428 pts (86.8%). The remaining pts showed IDH2 (3.9%) or IDH 1 non-canonical mutations (mainly R132C, R132G, R132S – 9.3%). Median follow-up time was 80.5 months. Pts with non-canonical mutations showed a younger median age (32 vs 39 years, p = 0.001). Other clinical characteristics and treatments were similar across IDH groups. Median survival was 145 months (95%CI: 137.7 - 152.9) and 198.6 (95%CI 155.2 – 242.1) in patients with IDH R132H and non-canonical mutations, respectively (p = 0.013). In multivariate analysis grading (p < 0.001), extent of surgery (p < 0.001), 1p19q codeletion (p = 0.003) and presence of non-canonical mutations (p = 0.022) showed a significant role for improved survival.

Conclusions: Detecting non-canonical IDH1 mutations is essential for diagnosis and for prognosis in patients with gliomas. Differential enzymatic activity of non-canonical IDH1 mutations, resulting in different levels 2-hydroxyglutarate could be the reason of improved survival.
Glioblastoma gene expression subtypes and correlation with clinical, molecular and immunohistochemical characteristics in a homogenously treated cohort: GLIOCAT project.

Estela Pineda, Anna Esteve-Codina, Maria Martinez-Garcia, Francesc Alameda, Cristina Carrato, Oriol Arpi, Iban Aldecoa, Silvia Menendez, Teresa Ribalta, Noemi Vidal Sarro, Sonia Del Barco Berron, Anna Estival, Oscar Gallego, Miguel J. Gil Gil, Carlos Mesia Barroso, Jordi Craven, Salvador Villa, Rafel Fuentes, Núria de la Iglesia, Carmen Balana; Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; CNAG-CRG, Centre for Genomic Regulation, Barcelona, Spain; Medical Oncology, Hospital del Mar, Barcelona, Spain; Hospital del Mar, Barcelona, Spain; Hospital Germans Trias i Pujol, Barcelona, Spain; Cancer Research Program, IMIM (Hospital del Mar Research Institute), Medical Oncology Department, Hospital del Mar, Barcelona, Spain; Hospital Clinic de Barcelona, Barcelona, Spain; Pathology, Hospital Clinic de Barcelona, Barcelona, Spain; Pathology Department, Bellvitge University Hospital, Hospitalet De Llobregat, Spain; Institut Català d’Oncologia, Hospital Universitari Josep Trueta, Girona, Spain; Medical Oncology Department. Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain; Hospital De Sant Pau, Barcelona, Spain; Breast Cancer Unit & Medical Oncology Department, Institut Català d’Oncologia, IDIBELL, Barcelona, Spain; Institut Català d’Oncologia Hospital Duran i Reynals, Barcelona, Spain; Hospital Sant Pau, Barcelona, Spain; Catalan Institute of Oncology, Germans Trias, Barcelona, Spain; Institut Catalá de Oncologia, Girona, Spain; Translational Genomics and Targeted Therapeutics in Solid Tumors Lab (IDIBAPS), Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain; Institut Català Oncologia Badalona, Hospital Germans Trias I Pujol, Badalona/Barcelona, Spain

Background: Glioblastoma (GBM) gene expression subtypes have been described in last years, data in homogeneously treated patients is lacking. **Methods:** Clinical, molecular and immunohistochemistry (IHC) analysis from patients with newly diagnosed GBM homogeneously treated with standard radiochemotherapy were studied. Samples were classified based on the expression profiles into three different subtypes (classical, mesenchymal, proneural) using Support Vector Machine (SVM), the K-nearest neighbor (K-NN) and the single sample Gene Set Enrichment Analysis (ssGSEA) classification algorithms provided by GlioVis web application. **Results:** GLIOCAT Project recruited 432 patients from 6 catalan institutions, all of whom received standard first-line treatment (2004 - 2015). Best paraffin tissue samples were selected for RNAseq and reliable data were obtained from 124. 82 cases (66%) were classified into the same subtype by all three classification algorithms. SVM and ssGSEA algorithms obtain more similar results (87%). No differences in clinical variables were found between the 3 GBM subtypes. Proneural subtype was enriched with IDH1 mutated and G-CIMP positive tumors. Mesenchymal subtype (SVM) was enriched in unmethylated MGMT tumors (p = 0.008), and classical (SVM) in methylated MGMT tumors (p = 0.008). Long survivors ( > 30 months) were rarely classified as mesenchymal (0-7.5%) and were more frequently classified as Proneural (23.1-26%). Clinical (age, resection, KPS) and molecular (IDH1, MGMT) known prognostic factors were confirmed in this serie. Overall, no differences in prognosis were observed between 3 subtypes, but a trend to worse survival in mesenchymal was observed in K-NN (9.6 vs 15. ). Mesenchymal subtype presented less expression of Olig2 (p < 0.001) and SOX2 (p = 0.003) by IHC, but more YLK-40 expression (p = 0.023, SVM). On the other hand, classical subtype expressed more Nestin (p = 0.004) compared to the other subtypes (K-NN). **Conclusions:** In our study we have not found correlation between glioblastoma expression subtype and outcome. This large serie provides reproducible data regarding clinical-molecular-immunohistochemistry features of glioblastoma genetic subtypes.
Study of tumor infiltrating immune CELLS and vasculature in human gliomas: Differences in IDH1/2 mutant versus IDH1/2WT tumors.

Maria Cruz Martin Soberón, Juan Manuel Manuel Sepulveda Sanchez, Ricardo Gargini, Berta Segura, Jacqueline Gutierrez, Yolanda Ruano, Diana Cantero, Aurelio Hernandez-Lain, Pilar Sanchez-Gomez, Angel Perez-Núñez, Luis Jimenez Roldan, Patricia Marin, Daniel E. Castellano, Guillermo De Velasco, Teresa Cejalvo; Hospital Universitario 12 de Octubre, Madrid, Spain; University Hospital 12 Octubre, Madrid, Spain; 12 de Octubre University Hospital, Madrid, Spain; Instituto de Salud Carlos III, Majadahonda, Spain; Neurooncology Unit, 12 de Octubre University Hospital, Madrid, Spain; Medical Oncology Service, Hospital Universitario 12 de Octubre, Madrid, Spain; Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Doce de Octubre, Madrid, Spain

Background: Gliomas harboring mutations in IDH1/2 show a higher overall survival time than “wild type” (wt) tumors. Although the clinical aspects are well described, little is known about the underlying mechanisms by which these mutations generate such a difference in the clinical course. Our group has recently described that IDH1/2 mutations induce a distinct vascular phenotype in the tumors, with less blood-brain barrier (BBB) leakage than the IDH1/2 wt gliomas (In Press, DOI:10.1101/541326).

Methods: Prospective study analyzing a cohort of 20 patients with primary gliomas resected in one institution. Samples were obtained in the first surgery and 12 IDHmut and 8 IDHwt gliomas were included. Immune infiltration was analysed by flow cytometry and vasculature by immunohistochemistry. For molecular biology studies, western blots were performed with Mini-PROTEAN system. Proteins were visible by enhanced chemoluminescence.

Results: We show that the immune component also differentiates these two pathologies. There is significantly less immune infiltration in IDH1/2 mutant gliomas. Within the CD45 subset, IDH1/2 mutant gliomas have a reduced proportion of T lymphocytes with a different T cell exhaustion profile and an increased proportion of CD11b+ cells in comparison to IDH1/2 wt cases. Myeloid compartment distribution is also different in these two types of tumors, showing an augmented proportion of the M2 (CD206+) and the neutrophil subsets in IDH1/2 wt gliomas. Moreover, a higher proportion of CD45 PDL1+ was present in the IDH1/2 wt tumors samples. The analysis of the vasculature showed an increase density and the lumen size of the vessels of the IDH1/2 wt compared to the IDH1/2 mutant gliomas which correlate with changes in the immune profile. The biochemical analysis showed that there is an increment in EGFR and PDGFR activity in the IDH wt gliomas that is related with more vascular aberrations and higher CD45 infiltrate. This suggests that EGFR and PDGFR are the key regulators of the tumor microenvironment.

Conclusions: To understand the matching between the immune infiltration and vasculogenesis is relevant for interpreting data coming from the clinical trials with checkpoints inhibitors. At the time abstract submission survival analysis is not yet available due to the short time of follow-up but in May 2019, the number of expected events for analysis will be reached.
Phase I trial of TG02 plus dose-dense or metronomic temozolomide for recurrent anaplastic astrocytoma and glioblastoma in adults.

Jing Wu, Ying Yuan, Christine Cordova, Orwa Aboud, Marta Penas-Prado, Brett James Theeler, Christine Bryla, Yu-Ting Su, Ewa Grajkowska, Ann McCoy, Lisa Boris, Christine Siegel, Ramya Antony, Nancy Garren, Tracy Lawhon, Terri Armstrong, Mark R. Gilbert; NCI, Bethesda, MD; University of Texas MD Anderson Cancer Center, Houston, TX; National Institutes of Health, Bethesda, MD; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX; Walter Reed National Military Medical Center, Gaithersburg, MD; Medical Oncology Branch, National Cancer Institute at the National Institutes of Health, Bethesda, MD; National Cancer Institute, Bethesda, MD; Leidos Biomedical Research, Inc., Frederick, MD; Adastra Pharmaceuticals, Inc, San Diego, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Therapies targeting multiple survival pathways simultaneously may be more effective for high-grade gliomas, a disease highly resistant to treatment. Our preclinical studies have shown potent anti-glioma effects of TG02 and synergy with temozolomide (TMZ) through modulation of transcription and cellular metabolism. A phase I/II trial was launched to test the combination of TG02 and TMZ in recurrent malignant gliomas and herein we report the phase I results. Methods: Adults with recurrent high-grade astrocytoma, KPS $\geq 60$, normal organ function, $\leq 2$ prior relapses were enrolled. The primary endpoint was dose limiting toxicity (DLT) from the start of the combined treatment to 4 weeks after in each arm. Bayesian optimal interval (BOIN) design was employed to determine the maximum tolerated dose (MTD) with the target DLT rate of 35% and the toxicity profile of the combination of TG02 (starting dose 200mg orally on days 1, 12, 15, and 26) and TMZ, either as a dose-dense (DD; 125mg/m²/d, 7on/7off, Arm 1) or metronomic (MN; 50mg/m²/d, Arm 2) dosing schedule on a 28-day cycle. Results: Forty patients were enrolled; 38 were evaluable; 70% male; overall median age 50.7; median KPS 90. Of 18 evaluable patients in Arm 1 (DD TMZ), at TG02 dose level 200mg, 1/6 had a DLT: Gr3 diarrhea. At TG02 dose level 250mg, 3/12 had DLTs: Gr4 neutropenia for over 5 days, Gr3 elevated ALT, and Gr3 fatigue. Of 20 evaluable patients in Arm 2 (MN TMZ), at TG02 dose level 200mg, 1/6 had a DLT: recurrent Gr3 neutropenia. At TG02 dose level 250mg, 5/12 had a DLT: Gr3 elevated ALT, Gr3 fatigue, and Gr4 neutropenia. At TG02 dose level 300mg, 1 out of 2 had a DLT: Gr4 febrile neutropenia, Gr4 elevated ALT, Gr4 elevated AST, which resulted in hospitalization. Therefore, the TG02 dose level of 250mg was declared as the MTD in both Arm 1 and Arm 2. Conclusions: The combination of TG02 at the MTD of 250mg with DD or MN TMZ has a tolerable toxicity profile. Cohort expansion continues at the MTD in both arms to conduct pharmacokinetics and pharmacogenetics to better elucidate the toxicity profile. Objective responses have been observed, suggesting activity of this regimen and supporting continued investigation with the phase II randomized component. Clinical trial information: NCT02942264.
Phase II study to evaluate safety and efficacy of MEDI4736 (durvalumab) + radiotherapy in patients with newly diagnosed unmethylated MGMT glioblastoma (new unmeth GBM).

David A. Reardon, Thomas Joseph Kaley, Jorg Dietrich, Jennifer Leigh Clarke, Gavin Dunn, Michael Lim, Timothy Francis Cloughesy, Hui Kong Gan, Andrew J. Park, Paul Schwarzenberger, Toni Ricciardi, Mary J. Macri, Aileen Ryan, Ralph Rudolph Venhaus; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Memorial Sloan Kettering Cancer Center, New York, NY; Massachusetts General Hospital, Boston, MA; University of California, San Francisco, San Francisco, CA; Washington University School of Medicine, Saint Louis, MO; The Johns Hopkins Hospital, Baltimore, MD; University of California Los Angeles, Los Angeles, CA; Olivia Newton-John Cancer Research Institute, Melbourne, Australia; Ludwig Institute for Cancer Research, New York, NY; Ludwig Cancer Research, New York, NY; Ludwig Institute for Cancer Research, Ltd., New York, NY

Background: Durvalumab (durva), a human IgG1 monoclonal Ab against PD-L1, is FDA-approved for selected patients with bladder and non-small cell lung cancers. PD-L1 is expressed by some GBM tumors, while GBM infiltrating T lymphocytes often express PD-1. Radiation induced cell death releases tumor antigens and could potentiate anti-PD-(L)1 therapy. Methods: This ongoing Phase 2 open-label study (NCT02336165) evaluates the safety and efficacy of durva (10 mg/kg every 2 weeks) in 5 GBM cohorts. Results are presented for Cohort A, which evaluates durva + standard radiotherapy (RT, 60 Gy over 30 fractions) followed by durva monotherapy in patients with new unmeth GBM after maximum safe resection. The primary efficacy endpoint for Cohort A is overall survival at 12 months (OS12); secondary endpoints include safety/tolerability, tumor response rate, and progression-free survival (PFS). Historical benchmarks of median OS and OS12 for patients with new unmeth GBM following standard therapy are 12.7 months and 50%, respectively (EORTC 26981-22981/NCIC CE.3). Results: Median follow-up of 40 enrolled patients is 24.5 months (data cutoff = 05 Nov 2018). Baseline characteristics: male, 70%; median age, 57.0 [22 to 77] years; ECOG PS0, 60.0%; ECOG PS1, 40.0%; measurable disease, 80.0%; and dexamethasone use, 32.5%. Treatment-related adverse events with maximum CTCAE grade ≥ 3 occurred in 14 (35.0%) patients; the most common were asymptomatic increased lipase (n = 6) and increased amylase (n = 2). Twenty-four of 40 patients were alive at 12 months (Kaplan-Meier for OS12, 60.0% [90% CI: 46.1, 71.4]). Median OS was 15.1 (95% CI: 12.0, 18.4) months. As of 05 Nov 2018, 8 (20%) patients remain alive, with ongoing survival ranging from 15.7 to 34.9 months. Tumor immunocorrelative and systemic studies are pending. Conclusions: This is the first study report of anti-PD-L1 for new GBM. Durva was well tolerated when combined with RT and seemed to have efficacy among patients with new unmeth GBM. Further studies may be warranted. Clinical trial information: NCT02336165.
A TITE-CRM phase I/II study of disulfiram and copper with concurrent radiation therapy and temozolomide for newly diagnosed glioblastoma.

Jiayi Huang, Todd DeWees, Jian Li Campian, Milan G Chheda, George Ansstas, Christina Tsien, Gregory J. Zipfel, Gavin P. Dunn, Jospeh E Ippolito, J. Gregory Cairncross, Jacob C. Easaw, Josh Rubin, Albert H Kim; Washington University School of Medicine in St. Louis, St. Louis, MO; Washington University School of Medicine in St Louis, St Louis, MO; Washington University School of Medicine, St. Louis, MO; Charbonneau Cancer Institute at the University of Calgary, Calgary, AB, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada

Background: Disulfiram (DSF) has shown promising activity against glioblastoma in preclinical studies and is more effective when combined with copper (Cu). Our previous phase I study established the maximum tolerated dose (MTD) of DSF when combined with adjuvant temozolomide (TMZ). This phase I/II study aims to establish the MTD when disulfiram and copper are combined with concurrent radiation therapy (RT) and TMZ for newly diagnosed glioblastoma and to explore preliminary efficacy.

Methods: Eligible patients were treated with standard RT and TMZ plus escalating doses of DSF (250 mg - 375 mg PO QD) and Cu (2 mg PO TID), followed by adjuvant TMZ plus DSF (500 mg/day) and Cu. The time-to-event continual reassessment method (TITE-CRM) was used to continuously estimate the probability of dose-limiting toxicity (DLT) and to assign patients to doses with an estimated DLT probability of approximately 20% with a margin of 5%. Tumor mutations were evaluated with next-generation sequencing for all patients.

Results: Eighteen glioblastoma patients were treated with the study therapy: 8 with DSF of 250 mg/day and 10 with 375 mg/day. Three DLTs were observed: 1 with 250 mg/day (grade 2 urinary incontinence and ataxia), and 2 with 375 mg/day (both grade 3 elevated liver enzymes). DSF had an estimated DLT probability of 10% (95% CI: 3-29%) at 250 mg/day, and 21% (95% CI: 7-42%) at 375 mg/day. After a median follow-up of 12.3 months, 1-year progression-free survival (PFS) was 57%, and 1-year overall survival (OS) was 69%. There was no significant difference in PFS/OS when stratified by DSF doses, surgical extent, or MGMT methylation status. However, glioblastomas with IDH1 (n = 6), BRAF (n = 2), and NF1 (n = 1) mutations had significantly better PFS and OS than those without the mutations: 1-year PFS: 100% vs 22%, respectively, p = 0.001; 1-year OS: 100% vs 42%, respectively, p = 0.006. Conclusions: The MTD of DSF with RT/TMZ/Cu for glioblastoma is 375 mg/day, and the recommended phase II dose is 250 mg/day. Although confirmation with larger sample size is needed, the combination demonstrates promising preliminary efficacy for the subset of glioblastoma with IDH1, BRAF, and NF1 mutations. Clinical trial information: NCT02715609.
GLIAX: A stratified phase II clinical trial of avelumab and axitinib in patients with recurrent glioblastoma.

Bart Neyns, Laila Ben Salama, Gil Awada, Jennifer De Cremer, Julia Katharina Schwarze, Laura Seynaeve, Stephanie Du Four, Lydia Fischbuch, Anne-Marie Vanbinst, Hendrik Everaert, Alex Michotte, Anne Rogiers, Peter Theuns, Johnny Duerinck; Universitair Ziekenhuis Brussel, Brussels, Belgium; Vrije Universiteit Brussel, Brussels, Belgium; UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium; Universitair Ziekenhuis Brussel, Brussels, Belgium; Centre Hospitalier Universitaire Brugmann, Brussels, Belgium

Background: Patients (pts) with recurrent glioblastoma (rGB) have a poor prognosis, and no treatment option demonstrated to improve survival in a randomized trial. Axitinib (AXI), an oral VEGFR 1-3 inhibitor has demonstrated single agent activity in rGB and reduces the need for corticosteroids (CS). Avelumab (AVE) is a fully human anti-PD-L1 IgG1 antibody with clinical activity in various tumor types. Combination of AXI and AVE may improve the outcome of pts with rGB. Methods: This open-label, dual-strata, single-center phase 2 clinical trial investigated the activity of AXI plus AVE in adult pts with rGB following prior surgery, RT and temozolomide. Pts were stratified according to their baseline use of CS. Pts without baseline need for CS initiated treatment with AXI (5 mg oral BID) plus AVE (10 mg/kg IV Q2W) (cohort-1). Pts in need of CS initiated AXI as a monotherapy; AVE could be added to AXI after 6 wks if the CS dose could be tapered to a physiologic dose level or less (cohort-2). Six-month-PFS served as the primary endpoint (with a prespecified threshold of ≥ 50% for cohort-1) according to Fleming one-stage design. Results: Between Jun 2017 and Aug 2018, 54 pts (27 per cohort) were enrolled (med age 55 y [range 19-75]; 63% male; 91% WHO PS 0-1). All pts in cohort-1 and 16 pts (59%) in cohort-2 received at least 1 dose of AVE. The 6-month-PFS was 18% (95% CI 4-33) in both cohorts. At the time of analysis, 2 pts were progression-free and continuing study treatment. Median OS in cohort-1 and -2 was respectively 26 wks (95% CI 21-32) and 18 wks (95% CI 14-22). No clear relation was found between baseline cognitive functioning (Cogstate subtests) and PFS/OS. The best overall response rate (iRANO) was 41% and 26% respectively for pts in cohort-1 and -2. The most frequent all-grade treatment-related adverse events (TRAE) were dysphonia (67%), lymphopenia (50%), diarrhea (48%), hypertension (48%), and fatigue (46%). The incidence of grade 3-4 TRAE was 30%; there were no grade 5 AE. Conclusions: The combination of AVE plus AXI is sufficiently well tolerated but did not meet the threshold for activity justifying further investigation in an unselected population of patients with rGB. Clinical trial information: NCT03291314.
Clinical characteristics, treatment (Tx) patterns, and overall survival (OS) in advanced (Adv) NSCLC patients (Pts) with and without brain metastases (BM).

Emily Nash Nash Smyth, Ramon Velasquez Tiu, Melinda D Willard, Julie Beyrer, Yajun Emily Zhu, Lee Bowman, Kristin M Sheffield, Yimei Han, Priscilla Brastianos; Eli Lilly and Company, Indianapolis, IN; Massachusetts General Hospital, Boston, MA

Background: BM in NSCLC pts are associated with significant morbidity and mortality. This analysis describes the frequency and timing of BM development, pt characteristics, systemic txs, and OS in NSCLC pts with and without BM.

Methods: This retrospective observational study identified pts from the Flatiron-Foundation Medicine NSCLC Clinico-Genomic Database diagnosed from 1 Jan 2011 to 31 Oct 2017 with adv NSCLC and a tumor sample analyzed via FoundationOne. Tx pattern data were summarized by period (1 Jan 2011-1 Mar 2015; 2 Mar 2015-31 Dec 2017), therapy class (eg, anti-VEGF and EGFR, platinum-based), and BM occurrence. Descriptive statistics were used to summarize data; Chi-square and t-tests assessed statistically significant differences. OS was measured by site of met (BM only vs no-BM only vs BM and no-BM) via K-M methods from adv diagnosis until death or last activity date (censored).

Results: Of 3257 pts, 1018/3257 (31.3%) had BM during follow-up; 726/1018 (71.3%) presented with BM within 30 days of adv diagnosis. The median age at adv diagnosis was 66.2 yrs. Relative to pts without BM, BM pts were younger, more likely to be female, of Asian descent, have stage IV disease, ≥2 met sites (including BM) at initial presentation, ≥3 met sites (including BM) during follow-up, and non-squamous histology (all p < 0.01). Approximately 78% (n = 2534) were treated with ≥1 systemic tx; platinum-based chemo-combinations were the most common 1st line tx, regardless of BM status. Increased use of PD-1/L1 tx was seen in 1st, 2nd, and 3rd line during the latter vs earlier period. No statistically significant difference in OS was observed in pts with BM only (17.1 mos; 95% CI 12.5-29.9), no-BM only (21 mos; 95% CI 19.4-22.8), or BM and no-BM (20.4 mos; 95% CI 18.9-23.3) (log rank p = 0.3027).

Conclusions: In met NSCLC pts with a tumor sample that was molecularly profiled, OS was comparable, regardless of site(s) of disease; additional multivariate analyses including molecular profiles are needed. BM screening at initial diagnosis is important given the frequency in NSCLC. Future studies should assess whether the shift in systemic tx patterns impact the development and clinical outcomes.
Effect of grade on survival in IDH-mutant grade II and grade III gliomas.

Giuseppe Lamberti, Enrico Franceschi, Alicia Tosoni, Antonella Mura, Alessandro Paccapelo, Maria Pia Foschini, Sofia Asioli, Dario De Biasi, Annalisa Pession, Giovanni Tallini, Stefania Bartolini, Felice Giangaspero, Alba Ariela Brandes; Department of Medical Oncology S.Orsola Malpighi Hospital Bologna, Bologna, Italy; Department of Medical Oncology, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy; Bellaria Maggiore Hospital, Bologna, Italy; Unit of Anatomic Pathology at Bellaria Hospital, Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; Department of Biomedical and Neuromotor Sciences (DIBINEM)-Surgical Pathology Section- Alma Mater Studiorum - University of Bologna, Universita degli Studi di Bologna Scuola di Medicina e Chirurgia, Bologna, Italy; Department of Pharmacy and Biotechnology (Dipartimento di Farmacia e Biotecnologie) - Molecular Diagnostic Unit, Azienda USL di Bologna, University of Bologna, Bologna, Italy; Department of Medicine (Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale) - Molecular Diagnostic Unit, Azienda USL di Bologna, University of Bologna, School of Medicine, Bologna, Italy; Department of Medical Oncology, Azienda USL– IRCCS Institute of Neurological Science, Bologna, Italy; Università La Sapienza - Rome & IRCCS Neuromed - Pozzilli, Rome & Pozzilli, Italy; AUSL-IRCCS Institute of Neurological Sciences, Bologna, Italy

Background: The 2016 WHO classification dramatically changed the diagnosis of gliomas. Diffuse gliomas are classified according to the presence of IDH-mutation (IDH-mut) and the deletion of both 1p and 19q chromosome arms (1p/19q codel). Now debate is whether grade still has an independent prognostic value. The aim of this study was to find out if grade is a prognostic factor independently of molecular status. Methods: We analyzed our institutional data warehouse for all consecutive patients (pts) with newly diagnosed, histologically proven Grade II or Grade III IDH-mut gliomas. IDH 1/2 assessment by polymerase chain reaction (PCR) or immunohistochemistry (IHC) was accepted. Next Generation Sequencing (NGS) for IDH1(exon 4) and IDH2(exon 4) was performed on all specimens wild-type for the IDH. Results: The analysis included all the 399 pts who had a grade II (n = 250, 62.7%) or grade III (n = 149, 37.3%). Median follow-up time was 105.3 months. After surgery, 72 pts (18.0%) received RT alone, 44 (11.0%) received CT alone, 135 (33.8%) received both RT and CT, and 142 (35.6%) follow-up without any treatment. Median survival was 148.1 months. In multivariate analysis Grade (HR = 0.342, 95% CI: 0.221 – 0.531; P < 0.001) and 1p/19q codeletion (HR = 0.440, 95%CI: 0.290 – 0.668; P < 0.001) were independently associated with a lower risk for death. The difference in survival remained when adjusted for histological subtype. Residual disease after surgery or biopsy negatively affected survival (HR 2.151, 95%CI 1.375 – 3.367, P = 0.001). Post-surgical treatment with RT + adjuvant CT improves survival in respect to follow-up and other treatments (HR: 0.316, 95%CI 0.156 – 0.641, P = 0.001). Conclusions: Grade still affects survival in IDH mutant Grade II and III gliomas. This effect was independent onmolecular features, surgical extension and post-surgical treatments. Clinical management of gliomas should continue to take into account grade as well as molecular characteristics.
Adjuvant chemotherapy to improve survival in average-risk adult medulloblastoma patients: Long-term results.

Giuseppe Lamberti, Enrico Franceschi, Alicia Tosoni, Santino Minichillo, Monica Di Battista, Alexandre Pacapelo, Carmelo Sturiale, Maurizio Mascarin, Barbara Masotto, Lorenzo Volpin, Stefania Bartolini, Felice Giangaspero, Alba Ariela Brandes; Department of Medical Oncology S.Orsola Malpighi Hospital Bologna, Bologna, Italy; Department of Medical Oncology, Bellaria Hospital, Azienda USL - IRCCS Institute of Neurological Sciences, Bologna, Italy; Bellaria Maggiore Hospital, Bologna, Italy; Department of Medical Oncology, Azienda USL– IRCCS Institute of Neurological Science, Bologna, Italy; Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna - IRCCS Institute of Neurological Sciences, Bologna, Italy; Department of Neurosurgery Azienda USL– IRCCS Institute of Neurological Science, Bologna, Italy; Department of Radiotherapy Unit, CRO, Aviano, Italy; Department of Neurosurgery, Azienda Ospedaliera-Universitaria of Verona, Verona, Italy; Department of Neuroscience and Neurosurgery, San Bortolo Hospital, Vicenza, Italy; Università La Sapienza - Rome & IRCCS Neuromed - Pozzilli, Rome & Pozzilli, Italy; AUSL-IRCCS Institute of Neurological Sciences, Bologna, Italy

Background: Medulloblastoma is extremely rare in adults and, therefore, it is difficult to accrual patients in clinical trials. Radical surgery and radiotherapy (RT) provide a significant control of disease. Nevertheless, about 25% of average-risk patients have a relapse and die because of disease progression. The role of chemotherapy (CT) after standard RT for average-risk adult patients remains controversial. Methods: We analyzed 48 average-risk patients according to Chang classification diagnosed from 1988 to 2016. Median age was 29 years (range 16-61), M/F ratio was 26 (54.2%)/22 (45.8%). Fifteen patients had classic medulloblastoma (31.3%), 15 patients had desmoplastic medulloblastoma (31.3%), 5 patients had extensive nodularity (10.4%) and 2 patients had large cells/anaplastic histology (4.2%). The patients were homogeneously distributed in the two groups: 24 (50%) received adjuvant RT alone and 24 (50%) received RT + CT that consisted in a platinum-etoposide based combination. Results: After a median follow-up of 12.5 years, CT increases progression-free survival rate at 15 years (PFS-15 82.3 ± 8.0% in RT-CT group vs. 38.5% ± 13.0% in RT group p = 0.05) and overall survival rate at 15 years (OS-15 89.3% 7.2% vs. 52.0% 13.1%, p = 0.02). Among patients receiving CT, the reported grade ≥ 3 adverse events were: 9 cases of neutropenia; 6 cases of G3 neutropenia (25%) and 3 cases of G4 neutropenia (13%), 1 case of G3 thrombocytopenia (4%) and 2 cases of G3 nausea (8%). Conclusions: Our study with a long follow up period suggests that adding adjuvant chemotherapy to RT might improve PFS and OS in average-risk adult medulloblastoma patients.
Phase II trial of palbociclib in recurrent RB-positive anaplastic oligodendroglioma: A Spanish group for research in neurooncology (GEINO) trial.

Juan Manuel Sepulveda-Sanchez, Miguel J. Gil Gil, Miriam Alonso, María Ángeles Vaz Salgado, Elena Vicente, Carlos Mesia Barroso, Angel Rodriguez Sanchez, Gema Durán, Ramon De Las Penas, José Muñoz-Langa, Guillermo de Velasco, Aurelio Hernandez-Lain, Amaya Hilarion, Miguel Navarro, Manuel Benavides, Laura Oleaga, Diana Cantero, Yolanda Ruano, Pilar Sanchez-Gomez, Estela Pineda; Hospital Universitario 12 de Octubre, Madrid, Spain; Breast Cancer Unit & Medical Oncology Department, Institut Català d’Oncologia, IDIBELL, Barcelona, Spain; Hospital Universitario Virgen del Rocio, Seville, Spain; Medical Oncology Department, Ramon y Cajal University Hospital, Madrid, Spain; Complejo Hospitalario Insular, Las Palmas de Gran Canaria, Spain; Institut Català d’Oncologia Hospital Duran i Reynals, Barcelona, Spain; Hospital of Leon, Leon, Spain; Complejo Hospitalario Regional de Málaga, Malaga, Spain; Oncology Service Hospital Provincial of Castellón, Castellón, Spain; Hospital Universitario La Fé, Valencia, Spain; Department of Medical Oncology, University Hospital 12 de Octubre, i + 12, Madrid, Spain, Madrid, Spain; 12 de Octubre University Hospital, Madrid, Spain; Department of Medical Oncology, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain; Hospital Regional Universitario y Virgen de la Victoria, Málaga, Spain; Hospital Clinic Barcelona, Barcelona, Spain; Instituto de Salud Carlos III, Majadahonda, Spain; Medical Oncology, Hospital Clinic Barcelona, Barcelona, Spain

Background: The pRB-dependent cell cycle checkpoint is altered in the vast majority of anaplastic oligodendrogliomas (AO), either by homozygous deletion or by hypermethylation of CDKN2A and/or CDKN2B, or by amplification and/or overexpression of CDK4. Palbociclib is an oral inhibitor of CDK4 and 6 that has already been shown to be highly active in breast cancer.

Methods: We conducted a multicenter, open-label, phase II trial evaluating efficacy and safety of Palbociclib in patients with AO that progressed to radiotherapy and more than one chemotherapy regimen containing Temozolomide and/or Lomustine. Inclusion criteria included: histologically and molecularly confirmed grade III oligodendroglioma (WHO 2016 classification, IDH1/2 mutation and 1p/19 codeletion were mandatory), recurrence after radiotherapy and 1 or 2 chemotherapy regimens and conserved RB protein expression by immunohistochemistry (IHC). Patients were treated with Palbociclib 125 mg/daily 3 weeks on/1off. The primary objective of the study was progression-free survival at 6 months (6M-PFS).

Results: Between October 2015 and September 2018, 34 patients were enrolled across ten hospitals. The study was stopped early secondary to lack of efficacy, with 74% of evaluable patients progressing within 6 months. Number of patients alive and free from progression at 6 months after the enrollment was 9 (26%) out of the first 34 patients, below the minimum number required (18 out of 40) to consider Palbociclib as an active drug in this population. With a median follow-up of 11.2 months, the median PFS was 3 months (95% CI: 2.5-3.5 months). Median overall survival (OS) was 23.1 months (95% CI: 17.2-25 months). There were no partial or complete responses and only 11 patients (32%) achieved stable disease as best response. Palbociclib was well tolerated with neutropenia (Grade 3 or 4: 40%) and thrombocytopenia (Grade 3 or 4: 15%) as the most common adverse effects (AEs). Both AEs had no significant impact since there were no episodes of febrile neutropenia or bleeding. Conclusions: Despite the good tolerance and drug exposure, Palbociclib monotherapy did not show favorable activity in recurrent AO. Clinical trial information: NCT02530320.
MDNA55: A locally administered IL4 guided toxin as a targeted treatment for recurrent glioblastoma.

Dina Randazzo, Achal Achrol, Manish K. Aghi, Martin Bexon, Steven Brem, Andrew Jacob Brenner, Nicholas A. Butowski, Chandtip Chandhasin, Sajeel A. Chowdhary, Melissa Coello, John Floyd, Santosh Kesari, Fahar Merchant, Nina Merchant, Michael A. Vogelbaum, Frank D Vrionis, Miroslaw Zabek, John H. Sampson; Duke University Medical Center, Durham, NC; Pacific Neuroscience Institute and John Wayne Cancer Institute at Providence, Saint John’s Health Center, Santa Monica, CA; UC San Francisco, San Francisco, CA; Medicenna Biopharma, Houston, TX; University of Pennsylvania, Philadelphia, PA; The University of Texas Health Science Center, San Antonio, TX; University of California, San Francisco, CA; Florida Hosp Cancer Inst, Orlando, FL; The University of Texas Health Science Center at San Antonio, San Antonio, TX; University of California, San Diego, La Jolla, CA; Cleveland Clinic, Cleveland, OH; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Mazovian Brodnovski Hospital, Warsaw, Poland

Background: IL4 receptor (IL4R) is frequently and intensely expressed on a variety of human cancers and is associated with poor survival outcomes. Determining the role of the IL4R biomarker in glioblastoma (GBM) will be important for treatment with targeted therapies such as the IL4 fusion toxin MDNA55. Methods: A classification for IL4Rα expression in GBM tissues by H-Score was developed using a validated immunohistochemistry-based approach. MDNA55-05 is an open-label study of MDNA55 administered intratumorally via convection enhanced delivery in recurrent GBM. Levels of IL4Rα expression were assessed retrospectively in 24 subjects in the clinical trial and were correlated with GBM history, imaging responses and survival outcomes following treatment with MDNA55 to explore clinical validation.

Results: Range, linearity, specificity and sensitivity testing using a rabbit polyclonal antibody to IL4Rα were performed using normal cortex (negative control) and a panel of normal human tissues and GBM cases from tissue banks. A total of 41 GBM samples were screened and grouped by reactivity thresholds: H-Scores ≥50 were observed in 95% of cases (39/41), H-Scores ≥200 were observed in 51% of cases (21/41), and H-Scores ≥250 were observed in 24% of cases (10/41). GBM tissues obtained at initial diagnosis from subjects enrolled in the trial show that moderate/high IL4R expression (H-Score ≥75) was associated with shorter time to first relapse when compared to subjects with low IL4R expression (H-Score ≤75) (10.3 mos vs. 16.7 mos, respectively) after upfront standard-of-care treatment, consistent with published findings that IL4R expression is associated with more aggressive disease. Remarkable decreases in tumor size seen in some subjects following MDNA55 treatment were associated only with moderate/high IL4R expression and survival rate at 12 months in this group was also improved (OS12 = 55%) compared to subjects with low IL4R expression (OS12 = 30%). Conclusions: Treatment options for patients with recurrent GBM are very limited and positive outcomes remain rare. Targeting therapies such as MDNA55 by IL4R status may improve patient outcomes and help guide patient selection strategies for future clinical studies. Clinical trial information: NCT02858895.
Cancer differentiation analysis technology as a novel technology for cerebral cancer screening.

Hongmei Tao, Xing Tang, Yue Lin, Chris Chang Yu, Xuedong Du; AnPac Bio-Medical Science and Technology Co., LTD, Shanghai, China; Anpac Bio-Medical Science Co Ltd, Shanghai, China; Anpac Bio-Medical Science Co. Ltd., Shanghai, China

Background: While the current cancer screening methods mostly failed to detect cerebral cancer, a novel, promising technology named cancer differentiation analysis (CDA) technology has been developed to measure novel bio-physical properties to obtain valuable multi-level and multi-parameter information including protein, cellular and molecular level information. Initial results showed that CDA technology is capable of detecting cerebral cancer with a high degree of sensitivity and specificity.

Methods: In this study, samples from 78 cerebral cancer patients and 321 healthy individuals were measured. Peripheral blood of each individual was drawn in EDTA tubes. One class of bio-physical property in blood samples was utilized for CDA tests. CDA data were conducted using SPSS, and the results were shown in table.

Results: The average CDA values of cerebral cancer and control groups were 52.30 and 33.38 (rel. units) respectively. The results indicated that cerebral cancer could be significantly distinguished from the control (p < 0.001). Area under ROC curve (AUC) was 0.980, and sensitivity and specificity was 92.3% and 96.6% respectively.

Conclusions: Initial results showed that CDA technology could effectively distinguish cerebral cancer from healthy individuals. As a novel bio-physical based cancer detection approach with multi-level and multi-parameter expressions, CDA could be a potential candidate for cerebral cancer screening. Results from Statistical Analysis of CDA.

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A gene signature of response to radiotherapy in patients with grade II-III oligodendrogliomas.

Elizabeth Moyal, Julia Gilhodes, Guillaume Peyraga, Emmanuelle Uro-Coste, Damien Pouessel, Delphine Larrieu-Ciron, Catherine Carpentier, Francois Ducray, Caroline Dehais, POLA Network; Institut Claudius Regaud, IUCT-O, Toulouse, France; ICR-Institut Universitaire du Cancer, Toulouse, France; Institut Universitaire du Cancer, Toulouse, France; CHU-Institut Universitaire du Cancer, Toulouse, France; Institut Universitaire du Cancer, París, France; IUCT-O, Toulouse, France; Institut Du Cerveau et de La Moelle-Groupe Hospitalier Pitié Salpêtrière, París, France; Service de Neuro-oncologie, Hôpital Neurologique, Hospices Civils de Lyon, Lyon, France; Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires La Pitié-Salpêtrière, Department of Neuro-oncology, París, France

Background: Grade II and III Oligodendroglioma associate mutations of isocitrate deshydrogenase 1 or 2 genes and the whole-arm chromosomal loss of 1p and 19q and have a better prognosis than other gliomas. However, even if the preferred treatment consists of a combination of radiotherapy (RT) and chemotherapy, some patients will less respond to this treatment and will relapse faster, in part because of an heterogeneity in the response to RT. In the aim to identify factors of response to RT, we analyzed clinical and molecular data of patients with grade II-III oligodendroglioma exclusively treated with RT in the POLA cohort. Methods: Gene expression profiles on Affymetrix expression arrays of patients from the POLA cohort with co-deleted 1p/19q grade II/II gliomas treated by exclusive RT were used to identify a gene expression set predictive of radiation sensitivity. The primary endpoint was the progression free survival (PFS), defined as the time from treatment start until progression or death. A supervised approach with penalized regression was applied to select most informative predictors, and then a risk score was created based on the linear predictor given by the multivariable model. Results: Forty-five patients corresponded to the study criteria, with a median age at diagnosis of 45 (range 23-64). The supervised approach allowed identifying a three-gene prognostic set including Semaphorin -3C (SEMA3C), Neuronal Pentraxin 2 (NPTX2 ) and the Metabotropic Glutamate Receptor 5 (GRM5), involved in proliferation, migration and inflammation. The risk score associated to these three genes was statistically associated to PFS (HR = 2.72, p = 0.00005) and remains significant when adjusted on clinical covariates age at diagnosis, necrosis, endothelial proliferation and type of surgery (complete, partial or subtotal surgery) (HRadj = 2.36, p = 0.001). Conclusions: We report an independent three genes SEMA3C-NPTX2-GRM5 risk score signature of response to radiotherapy in patients with oligodendroglioma, which highlights the heterogeneous response in this reputed good prognosis population. This signature could help in determining the adapted treatment as well as potential new targets to address.
Health-related quality of life (HRQL) in VERTU: A randomized phase II trial of veliparib (V), radiotherapy (RT), and temozolomide (TMZ) for newly diagnosed MGMT unmethylated (uMGMT) glioblastoma (GBM).

Hao-Wen Sim, Elizabeth Barnes, Zarnie Lwin, Mark Rosenthal, Helen Wheeler, Eng-Siew Koh, Matthew C. Foote, Lauren Fisher, Robyn Leonard, Merryn Hall, John Simes, Mustafa Khasraw; The Kinghorn Cancer Centre, St Vincent’s Hospital Sydney, Sydney, Australia; NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, NSW, Australia; Department of Medical Oncology, Brisbane, QLD, Australia; The Royal Melbourne Hospital, Parkville, Australia; Royal North Shore Hospital, Department of Oncology, St Leonards, Australia; Liverpool Hospital, Liverpool, Australia; Princess Alexandra Hospital, University of Queensland, Brisbane, Australia; NHMRC Clinical Trials Centre, Sydney, Australia; COGNO Consumer Advisory Panel, Sydney, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; Royal North Shore Hospital/ University of Sydney, St Leonards, Australia

Background: The VERTU trial (ANZCTR #ACTRN12615000407594) compared Arm A (standard of care) = RT (60Gy/30 fractions) + TMZ (75mg/m² daily) followed by TMZ (150–200mg/m² D1–5) every 28 days for 6 cycles vs Arm B (experimental arm) = RT (60Gy/30 fractions) + V (200mg PO BID) followed by TMZ (150–200mg/m² D1–5) + V (40mg PO BID, D1–7) every 28 days for 6 cycles in pts with newly diagnosed centrally determined uMGMT GBM. To ensure that veliparib was not associated with clinical detriment, serial HRQL assessments were performed for comparison as a secondary objective.

Methods: Pts completed the EORTC quality of life core questionnaire (QLQ-C30) and brain cancer module (BN20) every 4 weeks (w) (baseline: w0; concurrent: w4,8; adjuvant: w10,14,18,22,26,30). Based on relevance to GBM patients, 5 HRQL scales (global health [GH], physical functioning [PF], social functioning [SF], motor dysfunction [MD] and communication deficit [CD]) were pre-selected for primary analysis. Maximum change from baseline score (clinically relevant deterioration/improvement defined as ≥10-point change) during the progression-free period, and deterioration-free survival (time to deterioration/progression/death) were evaluated. Results: Patient characteristics were well-matched (Arm A: N = 41, median age = 62, male = 68%, ECOG 0 = 66%, macroscopic resection = 88%; Arm B: N = 84, median age = 60, male = 70%, ECOG 0 = 65%, macroscopic resection = 86%). Almost all completed at least one HRQL assessment (98%). HRQL assessments during the progression-free period were completed in 87% (Arm A) and 90% (Arm B) of cases. For Arm A vs B, the proportion of patients who experienced a deterioration in GH (59% vs 64%, p = 0.69), PF (53% vs 53%, p > 0.99), SF (46% vs 53%, p = 0.56), MD (63% vs 58%, p = 0.70) and CD (45% vs 46%, p > 0.99) were similar. Deterioration-free survival was not statistically different for any HRQL item. Conclusions: The addition of veliparib to standard of care for newly diagnosed uMGMT GBM does not appear to compromise HRQL. This would support the primary efficacy analysis of the VERTU trial. Clinical trial information: ACTRN12615000407594.
Pembrolizumab (Pem) in recurrent high-grade glioma (HGG) patients (PTS) with mismatch repair deficiency (MMRd): An observational study.

Giuseppe Lombardi, Mario Caccese, Matteo Simonelli, Matteo Fassan, Marta Padovan, Pasquale Persico, Luisa Bellu, Angelo Dipasquale, Marina Paola Gardiman, Stefano Indraccolo, Vittorina Zagone; Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Humanitas University, Humanitas Clinical and Research Hospital-IRCCS, Pieve Emanuele, Italy; Department of Medicine (DIMED), Pathology Unit, University of Padua, Padova, Italy; Padova, Italy; Humanitas Clinical and Research Hospital-IRCCS, Rozzano, Italy; Radiotherapy Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Unità Anatomia Patologica, Azienda-Università di Padova, Padua, Italy; Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: Pem, an immune checkpoint inhibitor, demonstrated to be active in various neoplasms with MMRd. No data exists about its efficacy in MMRd glioma PTS. Methods: MMRd HGG relapsed after receiving RT and CT were treated with Pem. MMR status was analyzed by immunohistochemistry, including the MLH1, MSH2, MSH6, and PMS2 markers. MMRd was defined as presence of a weak (wMMRd) or absent (aMMRd) signal for at least one MMR protein. Other inclusion criteria were: ECOG PS 0-2, histologically confirmed glioma, dexamethasone #4 mg. Pem was administrated at 200 mg every 3 weeks until disease progression or unacceptable toxicity. Tumor response was evaluated by brain MRI every 10 weeks according to the RANO criteria. OS and PFS were evaluated by Kaplan-Meier curves. Results: among 167 glioma PTS, we found 22 MMRd gliomas. 12 PTS were treated with Pem: 8 wMMRd and 4 aMMRd. According to Bethesda criteria, all PTS had microsatellite stability. Tumor histologies included 5 anaplastic astrocytoma, 1 anaplastic oligodendroglioma, 6 glioblastoma (GBM). MSH2 deficiency was found in 6 cases, MSH6 deficiency in 9 cases, PMS2 and MLH1 deficiency in 2 cases. Median number of prior lines of chemotherapy was 1 (range 1-5). Stable disease (SD) was reported in 4 PTS (33%); 8 PTS showed progressive disease (PD). PTS with anaplastic gliomas showed a statistically significant association with SD (p=0.03, OR=3); all GBM PTS reported PD; status of MMRd (weak/absent), IDH (mutated/wild-type), MSH2 and MLH6 (deficient/proficient) were not associated with SD. Median follow up was 14.7 ms. OS was 5.6 ms (95% CI 1.0-13.8), PFS 2.4 ms (95% CI 1.8-2.9). OS was 2.8 ms and 5.6 ms (p=0.9), PFS was 1.8 ms and 3.1 ms (p=0.5) in PTS with wMMRd and aMMRd, respectively. PTS reporting SD and PD had PFS of 7.4 ms (95% CI 4.6-10.2) and 1.8 ms (95% CI 0.2-3.4), p=0.002; OS was “not reached” and 2.8 ms in PTS having SD vs PD (p=0.04), respectively. Grade 3 adverse events were reported in 8% of PTS. Conclusions: a subgroup of recurrent MMRd HGG might benefit from Pem, especially anaplastic gliomas. There was a trend for a longer PFS and OS in PTS with aMMRd. The enrollment and analyses for identifying additional molecular predictive factors are ongoing.

Denise Fabian, Erica Hlavin Bell, Joseph P. McElroy, Tiantian Cui, Jessica L. Fleming, Aline P. Becker, Marjolein Geurts, Jahar Haque, Pierre A. Robe, Arnab Chakravarti; Ohio State University, Columbus, OH; The Ohio State University, Columbus, OH; The Ohio State University Department of Radiation Oncology, Columbus, OH; University Medical Center Utrecht/Brain Center Rudolf Magnus, Utrecht, Netherlands; Ohio State Univ-Arthur G. James Cancer Ctr, Dublin, OH

Background: Glioblastoma (GBM) is the most aggressive and common primary brain tumor. Nomograms are prediction models that help form individualized risk scores for cancer patients, which are valuable for treatment decision-making. The aim of this study is to create a refined nomogram by including novel molecular variables beyond MGMT promoter methylation.

Methods: Clinical data and miRNA expression data were obtained from 226 newly diagnosed GBM patients. Clinical data included age at diagnosis, sex, Karnofsky performance status (KPS), extent of resection, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status, IDH mutation status and overall survival. Due to low representation of less than 13 cases each, IDH mutant glioblastomas and patients submitted to biopsy-only were excluded. Total RNA was isolated from formalin-fixed paraffin-embedded (FFPE) tissues; miRNA expression was subsequently measured using the NanoString human miRNA v3a assay. A Cox regression model was developed using glmnet R package with the elastic net penalty while adjusting for known prognostic factors. A dichotomized genomic score was created by finding the optimal cutpoint (maximum association with survival) of the linear combination of the selected. A nomogram was generated using known clinical prognostic factors, specifically age, sex, KPS, and MGMT status along with the dichotomized genomic score.

Results: Four novel miRNAs were found to significantly correlate with overall survival and were used to create the dichotomized miRNA genomic score (GS). This score split the cohort into a poor performing group (GS_high) and a better performing group (GS_low) (p = 0.0031). A final nomogram was created using the Cox proportional hazards model (Figure 1). Factors that correlated with improved survival included younger age, KPS > 70, MGMT methylation and a low genomic score.

Conclusions: This study is a proof of concept demonstrating that integration of molecular variables beyond MGMT methylation improve existing nomograms to provide individualized information about patient prognosis. Future directions include a more comprehensive analysis, including proteomic and methylation data, and subsequent validation in an external cohort. Finally, network analysis integrating molecular signatures of poor performers will help identify therapeutic targets.
Health-related quality of life (HRQoL) evaluation in the REGOMA trial: A randomized, phase II clinical trial analyzing regorafenib activity in relapsed glioblastoma patients.

Giuseppe Lombardi, Paola Del Bianco, Alba Ariela Brandes, Marica Eoli, Roberta Ruda, Toni Ibrahim, Ivan Lolli, Andrea Pace, Bruno Daniele, Francesco Pasqualetti, Simona Rizzato, Eleonora Bergo, Mario Caccese, Giovanna Magni, Riccardo Soffietti, Gian Luca De Salvo, Vittorina Zagonel; Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Clinical Trials and Biostatistics Unit, Veneto Institute of Oncology, IOV-IRCCS, Padua, Italy; AUSL-IRCCS Institute of Neurological Sciences, Bologna, Italy; Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Department of Neuro-Oncology, University of Turin and City of Health and Science, Turin, Italy; Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; Medical Oncology Unit, IRCCS Saverio de Bellis, Castellana Grotte, Italy; Neurooncology Unit, IRCCS Regina Elena Cancer Institute, Rome, Italy; G. Rummo Hospital, Benevento, Italy; Department of Radiotherapy, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; Department of Oncology, University Hospital Udine, Udine, Italy; Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy

Background: REGOMA trial showed that regorafenib (REG) significantly improved OS and PFS in relapsed glioblastoma (GBM) patients (pts) with respect to lomustine (LOM). REG showed a different toxicity profile compared to LOM. Here, we report final results of the HRQoL assessment, a secondary end point. Methods: HRQoL was measured using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (QLQ-C30) and brain module (QLQ-BN20) administered before any MRI assessments, every 8 weeks (+/- 2 weeks) until disease progression. To evaluate treatment impact on HRQoL, questionnaires at progression were excluded. Mixed-effect linear models were fitted for each of the HRQoL domain to examine the change over progression-free time within and between arms. The models included the time of questionnaire assessment, the treatment group and their interaction, as fixed effects, and a compound symmetry covariance structure for the random effects. Differences of at least 10 points were classified as a clinically meaningful change. To correct for multiple comparisons and to avoid type I error, the level of significance was set at P = 0.01 (2-sided).

Results: Of 119 randomized pts, 117 participated in the HRQoL evaluation, and 114 had a baseline assessment (n = 56 REG; n = 58 LOM). No statistically significant differences were observed in any generic or cancer specific domain during treatment in the REG and LOM arms, or between the two arms, except for the appetite loss scale which was significantly worse in PTS treated with REG (Global mean 14.7 (SD = 28.6) vs 7.6 (SD = 16.0); p = 0.0081). The proportion of pts with a clinically meaningful worsening for appetite loss was not statistically different between the two arms (9 out of 24 and 0 out of 13 in the REG and LOM arm, respectively; p = 0.0146). Conclusions: In the REGOMA trial, HRQoL did not change during REG treatment. Pts treated with REG and LOM reported no significant difference in HRQoL.

Clinical trial information: NCT02926222.

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Background: Recent clinical trials have shown that adding tumor treating fields (TTF) to the Stupp protocol (SP) has increased survival after glioblastoma (GBM) diagnosis. However, whether this regimen improves population-based survival for patients with GBM remains unknown. **Methods:** We retrospectively identified adult patients with newly diagnosed GBM treated at our institution from January 2000 to July 2017 (n = 438, median age: 63 years). We grouped patients into three time periods for comparison: 2000-2004 (group 1, prior to SP), 2005-2013 (group 2, SP) and 2014-2017 (group 3, adding TTF to SP). The Kaplan-Meier method was used to estimate survival. Statistical analysis included unadjusted group comparisons by Chi-square and Log-rank tests and adjusted group comparisons using logistic and Cox models. **Results:** Thirty-seven percent (43/117) of patients with GBM in group 3 received TTF with SP therapy; when compared to those who received SP only, these patients had significant improvements in 6-month and 1-year overall survival (OS) rates (100.0% vs. 82.4%, p < 0.01; 86.0% vs. 66.2%, p < 0.05, respectively) (unadjusted for prognostic factors including sex, age, KPS and extent of resection) and an increased trend of median OS (479.0 vs. 448 days, p = 0.269). However, after adjusting for those prognostic factors, we didn’t find a statistically better survival for patients treated with TTF (OR: 6.156, p = 0.097, OR: 2.102, p = 0.185, respectively). Furthermore, multivariate Cox proportion hazards model after adjusting for those prognostic factors showed no significant survival benefits for patients treated with TTF and SP compared to those treated with SP only (HR = 0.797, p = 0.648). In addition, we didn’t find significant increases of 6-month, 1-year survival rates and median OS for patients in group 3 when compared to those in group 2 who had seen increased trends of survival trends when compared to those in group 1. **Conclusions:** Although adding TTF to SP appeared to benefit patients with GBM, this effect might be due to selection bias, e.g., TTF was offered to those patients with better prognostic factors. Ascertaining the long-term benefits of TTF requires further investigation.
EGFR amplification predicted selective sensitivity to PARP inhibitors with high PARP-DNA trapping potential in human GBM.

W. K. Alfred Yung, Shaofang Wu, Feng Gao, Siyuan Zheng, Jie Ding, Chen Zhang, Xialong Li, Ravesanker Ezhilarasan, Ningping Feng, John Frederick De Groot, Erik P. Sulman, Timothy Heffernan, Dimpy Kou; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX; MD Anderson Cancer Center, Houston, TX; University of Texas at San Antonio, San Antonio, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; UT MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX

Background: Poly-ADP-ribose polymerase (PARP) is an enzyme critical for regulating a variety of DNA damage repair mechanisms such as BER/SSBR, and PARP inhibitors have been shown to have single agent activity in breast and ovarian cancer patients with BRCA\(^1\) mutations. However, PARP inhibitor such as veliparib has limited single agent activity in GBM and identifying markers predicting sensitivity is critical to select individuals or certain groups of patients for PARP inhibitor therapy. **Methods:** Potency and selectivity of PARP inhibitors were analyzed in a panel of glioma stem cells (GSCs) with varying genetic background. In vivo anti-tumor activity was evaluated in xenograft models. **Results:** In this study, we report that PARP inhibitor, talazoparib, showed strong single-agent cytotoxicity and remarkable selective activity in glioma stem cells (GSCs). This single agent activity was strongly correlated with EGFR amplification. GSCs with EGFR amplification (which occurs in about 45% of GBMs) showed higher oxidative base damage, DNA breaks, and genomic instability than non-amplified GSCs. To sustain the elevated basal oxidative stress, EGFR-amplified GSCs had increased basal expression of DNA repair proteins. As a result of blocked DNA damage repair by talazoparib treatment, DNA damage accumulated and lead to increased PARP-DNA complexes, which was then trapped by talazoparib and resulted in high toxicity. The PARP-DNA trapping function of PARPi is essential as olaparib and veliparib, two PARP inhibitors with weak DNA-PARP trapping potential did not show sensitivity in GSCs. In contrast, Pamiparib, another PARP inhibitor with similar PARP-DNA trapping ability to that of talazoparib, showed selective sensitivity in EGFR-amplified GSC. **Conclusions:** Our data showed that EGFR amplified GSCs with higher basal DNA damage exhibited therapeutic vulnerability to PARP inhibitors with high PARP-DNA trapping ability, and that EGFR amplification is a potential selection or predictive biomarker for PARP inhibitor therapy in GBM.
Interim results of a phase I/IIa trial of a therapeutic CMV vaccine against recurrent glioblastoma (GBM).

Andrew B. Lassman, David A. Reardon, Eudocia Quant Lee, Fabio Massaiti Iwamoto, Francisco Diaz-Mitoma, David E Anderson, Patrick Y. Wen; Columbia University Irving Medical Center, New York, NY; Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; VBI Vaccines, Cambridge, MA; VBI VACCINES, Cambridge, MA; Dana-Farber/Brigham and Women’s Cancer Center, Harvard Medical School, Boston, MA

Background: Cytomegalovirus (CMV) antigens have been reported in over 90% of GBM tumors. CD4+ and CD8+ T cells are most frequently directed against the gB and pp65 antigens, respectively, and are immunogenic targets in a CMV-based GBM vaccine. Methods: We have initiated a phase I/IIa clinical trial for patients with recurrent GBM using gB/pp65 enveloped virus-like particles (eVLPs) formulated with GM-CSF and administered intradermally. Subjects are vaccinated monthly until tumor progression, with immunomonitoring performed 2 weeks after each vaccination and MRI exams every 6 weeks. In phase I, eligible patients were age 18-70 with Karnofsky Performance Status at least 70, normal end-organ function, on stable or decreasing corticosteroids of at most 4mg dexamethasone (or equivalent), with recurrent GBM following any standard initial therapy and any number of recurrences. The primary endpoint was safety/tolerability and secondarily to assess immunogenicity. Three vaccine doses (0.4 μg, 2 μg, and 10 μg pp65) were evaluated with 6 subjects in each cohort and DSMB safety review of the first 3 subjects in each cohort prior to enrolling additional subjects. Results: The DSMB identified no DLTs or safety concerns with any of the doses. Grade 2, 3 or 4 AEs occurred in 66%, 22% and 11% of participants, respectively, but were not related to vaccine administration. Twelve men and 6 women were enrolled with a median age 54 (range 39-66). Prior therapies included radiotherapy, temozolomide, and nivolumab. Immunological analyses demonstrate robust boosting of CMV-specific antibody titers and T cell responses against both gB and pp65 antigens in some but not all subjects, across all dose cohorts. Boosting of IFN-g secreting T cells (measured by ELISPOT) exceeded the assay threshold for several subjects. Stable disease by MRI of 3 months or greater has been observed in 2 subjects in the high dose cohort and 1 subject in the low dose cohort and may correlate with vaccine response. Conclusions: The phase IIa extension phase of the trial planned to begin in Q2 2019 is designed to explore efficacy in an additional 10 subjects that will receive the optimal vaccine dose and includes the additional requirements of unifocal, measurable enhancing tumor 1-3 cm across at first recurrence and no prior immunotherapy. Clinical trial information: NCT03382977.
Evaluating the capacity of connectome analysis to predict survival in high-grade astrocytoma.

Rebecca A. Harrison, Rongjie Liu, Vikram Rao, Melissa Petersen, Hannah Dyson, Shiao-Pei S. Weathers, Kristin Alfaro-Munoz, John Frederick De Groot, Shelli Kesler; The University of Texas MD Anderson Cancer Center, Houston, TX; Rice University, Houston, TX; MD Anderson Cancer Center, Houston, TX; University of Texas MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX

Background: While factors such as age, histology and tumor molecular variants (e.g. IDH status) contribute to prognosis in patients with high grade astrocytoma (HGA), there remains a wide variability in patient survival outcomes. The connectome, or brain network organization, incorporates biologic, molecular and environmental processes providing a uniquely parsimonious summary of key prognostic factors. This study compared the capacity of machine learning (ML) models based on baseline connectomics and clinical variables to predict patient survival in HGA. Methods: Patients with a new diagnosis of HGA and a presurgical 3D, T1-weighted MRI available were retrospectively identified. Individual patient connectomes were derived from MRI with 90 cortical/subcortical features. Presurgical clinical features included age, gender, histology, tumor grade and IDH status. Three ML algorithms were implemented: extreme learning machine with Buckley–James estimator (ELMBJ), random survival forest (RSF) with logrank splitting and RSF with concordance index (CI) splitting. For each algorithm, we used a 60/40 training/testing split with 50 iterations and CI as the performance metric. We tested three models: 1) connectome only, 2) clinical only, and 3) connectome plus clinical variables. Results: Of patients identified (n = 105), 66 had glioblastoma and 39 had anaplastic astrocytoma. Thirty-eight harbored IDH mutation. Median overall survival was 27.43 months (SD 39.57). Connectome-only models showed better prediction performance compared to clinical-only models across all algorithms. ELMBJ showed the best performance (connectome median CI = 0.522, clinical CI = 0.201). Connectome models also performed as well as combined models (e.g. median CI = 0.523 for ELMBJ). Conclusions: This study demonstrates the potential of a connectome model to predict survival of patients with HGA. Replication in a larger sample is required to validate these results and refine ML models including examination of additional clinical features. If successful, use of a simple T1 MRI could provide additional variables to augment existing prognostic prediction, especially in scenarios where tumor genotyping is not available.
Stratified monotherapy approach according to MGMT methylation status in elderly patients with glioblastoma.

Mitsuaki Shirahata, Junichi Adachi, Keiichi Kobayashi, Fumiyuki Yamasaki, Kaoru Tamura, Tomonari Suzuki, Kazuhiko Mishima, Motoo Nagane, Koichi Ichimura, Ryo Nishikawa; Saitama Medical University International Medical Center, Saitama, Japan; Kyorin University Faculty of Medicine, Tokyo, Japan; Hiroshima University Hospital, Hiroshima, Japan; Tokyo Medical and Dental University, Department of Neurosurgery, Tokyo, Japan; Saitama Medical University International Medical Center, Hidaka-shi, Saitama, Japan; Department of Neuro-Oncology/Neurosurgery, Saitama Medical University International Medical Center, Saitama, Japan

Background: The elderly patients with glioblastoma have an extremely poor prognosis. As they often have some degree of age-related vulnerability, it is especially important to minimize a risk of treatment-related adverse events by optimizing treatment intensity for this population. We conducted phase II clinical trial to investigate the efficacy of stratified monotherapy approach according to O6-methylguanine-DNA methyltransferase (MGMT) methylation status in elderly patients with glioblastoma.

Methods: Patients aged 70 years or older with Karnofsky performance status (KPS) of at least 60 were eligible for this study. MGMT methylation status was quantitatively assessed by pyrosequencing based on the average methylation ratio of 16 CpG sites in the MGMT gene promoter. The patients with highly methylated MGMT promoter defined as an average methylation ratio with 30% or higher were treated with temozolomide (TMZ) monotherapy (standard 5/28 regimen), while the others with low or intermediate levels of MGMT promoter methylation were treated with radiation therapy (40Gy/15fr) alone.

Results: Between April 2013 and December 2017, 70 patients were enrolled in this study. Median age was 78 years (70-91) and median KPS was 60 (60-100). Of 70 patients, 19 patients with highly methylated MGMT promoter received TMZ monotherapy, while the remaining 51 patients were treated with radiation therapy. Median progression-free survival (PFS) and median overall survival (OS) were 7.5 and 17.4 months in the TMZ group, respectively. Median PFS and median OS were 4.6 and 10.4 months in the radiotherapy group, respectively. Conclusions: For elderly glioblastoma patients with highly methylated MGMT promoter, TMZ monotherapy could be a treatment option. Clinical trial information: UMIN000012172.
The timing of chemoradiotherapy after surgical resection and its impact on overall survival in glioblastoma.

Robert H. Press, Sarah L. Shafer, Renjian Jiang, Zachary S. Buchwald, Mustafa Abugideiri, Sibo Tian, Tiffany Morgan, Madhusmita Behera, Soma Sengupta, Alfredo Daniel Voloschin, Jeffrey J. Olson, Walter John Curran, Jr., Bree Ruppert Eaton, Hui-Kuo George Shu, Jim Zhong; Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; Winship Research Informatics, Winship Cancer Institute of Emory University, Atlanta, GA; Department of Biostatistics and Bioinformatics, Winship Cancer Institute of Emory University, Atlanta, GA; Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, GA; Department of Neurosurgery, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Prior studies examining time to initiate chemoradiotherapy (CRT) after surgical resection (S) in glioblastoma (GBM) have not provided clear consensus on its clinical impact. We sought to evaluate the effect that differential timing of adjuvant therapy may have on overall survival (OS).

Methods: With the National Cancer Database (NCDB), patients (pts) with GBM who underwent S and adjuvant CRT from 2004-2013 were analyzed. Analysis was performed for the entire cohort as well as by Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classes (i.e. I, II, and III). Time from S to CRT was grouped weekly (i.e. 0-1, 1-2, 2-3, 3-4, 4-5, 5-6, 6-7, 7-8, and > 8 weeks). Pts were excluded if they died within the first 8 weeks to account for immortal time bias. Kaplan-Meier analysis, log-rank testing, and multivariate (MVA) Cox proportional hazards regression were performed with OS as the primary outcome.

Results: A total of 30,414 pts were included for analysis. RPA class I, II, and III contained 903, 4,347, and 25,164 pts, respectively. The most common time to initiate CRT was week 4-5 (n = 7389), and this group served as reference for survival analysis. On MVA, weeks 0-1 (hazard ratio [HR] 1.18, 95% confidence interval [CI] 1.02-1.35), 1-2 (HR 1.24, CI 1.17-1.32), and 2-3 (HR 1.11, CI 1.07-1.15) demonstrated worse OS (all p < 0.03). For RPA class I pts, week 1-2 (HR 2.07, CI 1.08-3.95) was associated with worse OS (p = 0.028). For RPA class II pts, weeks 1-2 (HR 1.34, CI 1.14-1.57), 2-3 (HR 1.18, CI 1.07-1.31), and 3-4 (HR 1.10, CI 1.01-1.21) were associated with worse OS (all p < 0.05). For RPA class III pts, weeks 0-1 (HR 1.18, CI 1.02-1.38), 1-2 (HR 1.22, CI 1.14-1.3), and 2-3 (HR 1.09, CI 1.05-1.14) were associated with worse OS (all p < 0.03). No time point after week 5 was associated with change in OS for the overall cohort or any RPA class subgroup.

Conclusions: These data provide insight into the optimal timing of CRT in GBM and describe RPA-class specific outcomes. In general, OS was negatively impacted if CRT started less than 3 weeks from S. Waiting up to 8 weeks, however, was not detrimental to OS and suggests delaying CRT beyond week 4-5 should be considered if clinically indicated without undue concern.
Correlation of systemic and local inflammation with survival prognosis in glioma patients.

Pegah Mir Seyed Nazari, Cihan Ay, Christine Marosi, Florian Moik, Julia Riedl, Gerda Ricken, Johannes A. Hainfellner, Matthias Preusser, Ingrid Pabinger, Anna Sophie Berghoff; Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; Clinical Division of Oncology, Department of Medicine I, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; Institute of Neurology, Medical University of Vienna, Vienna, Austria

Background: Immune modulating therapies have been a long withstanding treatment approach in glioma. However, gliomas are characterized by a particular absence of tumor infiltrating lymphocytes in the local tumor microenvironment. We aimed to gain insight on the distinct patterns of inflammation associated with survival prognosis in glioma.

Methods: Patients were recruited at time of glioma diagnosis or progression in the prospective observational Vienna Cancer and Thrombosis Study (CATS). A single blood draw was performed at study inclusion. PD-L1 expression in the tumor tissue was investigated via immunohistochemistry. Optimal cut-off according to ROC curve was used to assess cut off values for survival analysis. Results: 193 patients with glioma (75.6% glioblastoma (WHO grade IV), 19.7% anaplastic glioma (WHO grade III), and 4.7% diffuse glioma (WHO grade II)) were included. 40/193 (20.7%) glioma had an IDH1 mutation. Membranous PDL1 expression in the tumor tissue was observed in 20/193 (10.4%) patients. 1/20 patient presented with PD-L1 expression and IDH1 mutation (p = 0.082). PD-L1 significantly correlated with increased monocyte count (median: 0.657 vs. 0.450 [G/L], p = 0.008), higher C-reactive protein (CRP) (0.43 vs. 0.1 [mg/dL], p = 0.005) and higher fibrinogen (379 vs. 303 [mg/dL], p = 0.001). Presence of IDH1 mutation significantly correlated with increased monocyte count (median: 0.657 vs. 0.450 [G/L], p = 0.008), higher C-reactive protein (CRP) (0.43 vs. 0.1 [mg/dL], p = 0.005) and higher fibrinogen (379 vs. 303 [mg/dL], p = 0.001). Presence of IDH1 mutation significantly correlated with increased platelet count (303 vs. 232 [G/L], p = 0.001) and lower Neutrophil/Lymphocyte (N/L) ratio (3.34 vs. 5.13, p = 0.016). Higher lymphocyte count (> 1.484 [G/L], log-rank: p = 0.011), higher platelet count (> 245.5 [G/L], p = 0.0001), as well as decreased N/L ratio (< 5.13, p = 0.001) were significantly associated with increased survival prognosis. Conclusions: PD-L1 expression in tumor tissue was associated with markers of systemic inflammation in glioma patients. Systemic inflammation markers furthermore predicted improved survival. Immune modulating therapy approaches might be a promising approach in subgroups of glioma associated with increased baseline interaction of immune system and glioma.
**Evaluation of controlled IL-12 as monotherapy in subjects with recurrent GBM.**

**Rimas Vincas Lukas, E. Antonio Chiocca, Sylvia Christine Kurz, John Yu, Joseph C. Landolfi, Ganesh Rao, John A. Barrett, Jill Y. Buck, Nathan Demars, Amy Smith, John Miao, Qiang (John) Zhou, Arnold Bruce Gelb, Laurence Cooper; Northwestern University, Chicago, IL; Brigham and Women’s Hospital, Boston, MA; NYU Langone Medical Center and School of Medicine, New York, NY; Cedars-Sinai Medical Center, Los Angeles, CA; NJ Neuroscience Institute at JFK Medical Center, Edison, NJ; The University of Texas MD Anderson Cancer Center, Houston, TX; Ziopharm Oncology, Inc., Boston, MA**

**Background:** Interleukin-12 (IL-12), a master regulator of the immune system, results in anti-tumor responses in preclinical models, but safe use requires tightly controlled production. It was conditionally produced in Ph1 “main” study (NCT02026271) in subjects with recurrent glioblastoma (rGBM) using a replication-incompetent adenovirus modified to express IL-12 under transcriptional control of the proprietary RheoSwitch Therapeutic System (Ad-RTS-hIL-12, Ad) regulated by dose of veledimex (V). Monotherapy resulted in sustained intra-tumor influx of activated cytotoxic T cells, consistent with immune-mediated anti-tumor effect, improving overall survival (OS). This correlated with increased circulating CD8+/FoxP3+ T-cell ratio (“cytoindex”), an emerging biomarker of OS. While widely used with neurosurgery, dexamethasone (dex) blunts response to immunotherapies, nevertheless median mOS of subjects who received 20mg V of 12.7 mo (n=15) at 13.1 mo follow-up. However, subanalysis (n=6) showed low-dose dex (total ≤20 mg) during V dosing improved mOS (17.8 mo). We report a 36 subject substudy in rGBM with limited dex, total rGBM treated (n=70+).

**Methods:** Ongoing Phase 1 substudy (NCT03679754) assesses safety and tolerability of local, inducible IL-12 by single intra-tumoral injection of Ad (2 x 10^{11} viral particles) + V (20 mg PO QD x15 doses Days 0-14) in subjects not receiving dex 4 wks prior to Ad. **Results:** As of 03Jan19, the majority of new subjects received low-dose dex (total ≤20 mg Days 0-14). The initial impact of dex on mOS will be reported. As in the main study, Ad+V 20 mg respectively increased (median) serum IL-12 and downstream IFN-g from Days 0-3: 0.8 to 8.8 pg/mL and 0 to 8.6 pg/mL. Between Days 0-14, there was net increase in cytoindex (from 20 to 46). The safety profile was similar to the main study with the main adverse reaction (AR) being mild to moderate cytokine release syndrome (CRS) characterized by flu-like symptoms. No grade 4 CRS was noted; all ARs were manageable and reversible upon holding V. **Conclusions:** Local, controlled IL-12 production using the Ad + V platform in subjects with rGBM safely activates the immune system and when dex is limited, appears to further improve mOS, which warrants continued investigation. Clinical trial information: NCT03679754.
Decision making in surveillance of high-grade gliomas using perfusion MRI as adjunct to conventional MRI and artificial intelligence.

Sotirios Bisdas, Loizos Shakallis, Andy McEvoy, Anna Miserocchi, George Samandouras, Sebastian Brandner, Jeremy Rees, Naomi Ferscht, Jorge M Cardoso, Jasmina Panovska-Griffiths, Carole Sudre, Faiq Shaikh, Diana Roettger; University College London, London, United Kingdom; Department of Neuroradiology, University College London Hospitals, London, United Kingdom; Department of Neurosurgery, University College London Hospitals, London, United Kingdom; Department of Neurology, University College London Hospitals, London, United Kingdom; Department of Radiation Oncology, University College London Hospitals, London, United Kingdom; Imaging and Biomedical Engineering, King’s College London, London, United Kingdom; Department of Applied Health Research, University College London, London, United Kingdom; Imaging and Biomedical Engineering, King’s College London, London, United Kingdom; IAG, London, United Kingdom

Background: Surveillance of High-Grade Gliomas (HGGs) remains a major challenge in clinical neurooncology. Histopathological validation is not an option during the course of disease and imaging surveillance suffers from ambiguous features of both disease progression and treatment related changes. This study aimed to differentiate between Pseudoprogression (PsP) and Progressive Disease (PD) using an artificial intelligence (support vector machine - SVM) classification algorithm. Methods: Two groups of patients with histologically proven HGGs were analysed, a group with a single time point DSC perfusion MRI (45 patients) and a group with multiple time point DSC perfusion MRI (19 patients). Both groups included conventional MRI studies prior and after each perfusion MRI. This study design aimed to replicate decision making in clinical practice including multiple previous studies for each patient. SVM training was performed with all available MRI studies for each group and classification was based on different feature datasets from a single or multiple (subtracted features) time points. Classification accuracy comparisons were performed by calculating prediction error rates for different feature datasets and different time point analyses. Results: Our results indicate that the addition of multiple time point perfusion MRI combined with structural (conventional with gadolinium-enhanced sequences) MRI features results in optimal classification performance (median error rate: 0.016, lowest value dispersion). Subtracted feature datasets improved classification performance, more prominently when the final and first perfusion studies were included in the analysis. On the contrary, in the single time point group analysis, structural feature-based classification performed best (median error rate: 0.012). Conclusions: Validation of our results with a larger patient cohort may have significant clinical importance in optimising imaging surveillance and clinical decision making for patients with HGG.
Analysis of the EF-14 phase III trial reveals that tumor treating fields alter progression patterns in glioblastoma.

Suriya A. Jeyapalan, Steven A Toms, Andreas Felix Hottinger, Lawrence Kleinberg, Erqi Pollom, Scott G. Softys, Martin Glas; Rhode Island Hospital, Brown University, Newton, MA; Warren Alpert Medical School of Brown University, Providence, RI; CHUV University Hospital, Lausanne, Switzerland; Johns Hopkins University School of Medicine, Baltimore, MD; Stanford University Cancer Center, Stanford, CA; Stanford Cancer Institute, Palo Alto, CA; University Hospital Essen, Essen, Germany

Background: The EF-14 [NCT00916409] trial showed that addition of alternating electric fields (Tumor Treating Fields, TTFields) to Temozolomide (TMZ) resulted in improved survival in newly diagnosed Glioblastoma (GBM) patients with supratentorial tumors treated compared to TMZ alone. TTFields delivery is planned to optimize dose at the tumor bed, leading to the hypothesis that TTFields treated patients are more likely to exhibit distal progressions, including progression to the infratentorial brain where TTFields dose is minimal when targeting the supratentorium. Here we present analysis of the EF-14 trial testing this hypothesis.

Methods: Patients on treatment for more than two months who had an MRI that exhibited progression were included in the study (treatment: N=280/466, control: N=122/229). Regions of enhancing tumor, necrosis and resection were contoured on T1 contrast MRIs acquired at baseline and at the date of first progression. New lesions at progression were classified as distal if they appeared outside of a Proximal Boundary Zone (PBZ) of 20 mm surrounding the lesions identified in the baseline MRI. The rate of occurrence of distal progressions in the TTFields-treated arm was compared to the rate observed in the control arm. Patients with (distal) infratentorial progression were identified.

Results: Distal progressions were more common in the treatment arm (49/280 (18%) vs. 10/122 (8%) P<0.02; chi-squared). Infratentorial progression were observed in 4% (10 patients) of the treatment arm vs. 0 patients in the control (P<0.002 t-test). Distal lesions at progression were more distant from the original lesion in the TTFields treated arm (58.57 + 28.12 mm vs 46.61 + 20.48 mm, P<0.02; Wilcoxon rank sum test. The relative tumor growth rates in TTFields treated patients were significantly slower than those observed in the control arm (0.036+ 0.126 ml/day vs. 0.036+ 0.183 ml/day P<0.03; t-test).

Conclusions: This analysis indicates that adding TTFields to TMZ could impact GBM growth patterns. The results suggest that TTFields increases local control of tumor growth, emphasizing the need for adaptive treatment after progression to control progressing disease. Clinical trial information: NCT00916409.
Molecular genetic, host-derived and clinical determinants of long-term survival in glioblastoma: First results from the ETERNITY study (EORTC 1419).

Background: Glioblastoma represents the most aggressive primary brain tumor in adults, and less than 5% of patients survive 5 years from diagnosis. Factors influencing this long-term survival are poorly understood. Methods: In cooperation with the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels, Belgium, more than 20 clinical sites in the US, Europe and Australia have registered patients with centrally confirmed glioblastoma who survived ≥ 5 years, collecting clinical data including therapy and quality of life-related factors, as well as biospecimens allowing to analyse molecular and immunological parameters. Results: At the cut-off of December 31, 2018, 392 patients were registered, of which 232 had glioblastoma confirmed by central pathology review; 59 dropped out due to histology other than glioblastoma. Glioblastomas were isocitrate dehydrogenase (IDH)-wildtype in 70.7% and had a positive O6-methylguanine DNA methyltransferase (MGMT) promotor methylation status in 75.9%. Median age at diagnosis was 52 years (range: 21-77 years). There was enrichment for patients with gross total resection. Further analyses are ongoing. Conclusions: In a comprehensive effort, the consortium funded by the US Brain Tumor Funders’ Collaborative characterizes factors modulating long-term survival in glioblastoma in a unique large patient cohort. Clinical trial information: NCT 03770468.
Efficacy of re-irradiation with carbon ions (RiCi) in patients with recurrent high-grade glioma (rHGG) compared to the standard re-irradiation with photons (RiP): The reference multicenter cohort of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG).

Maximilian Knoll, Maria Waltenberger, Nina Bougatf, Denise Bernhardt, Sebastian Adeberg, Volker Budach, Michael Baumann, Martin Stuschke, Emmanouil Fokas, Anca Grosu, Daniel Zips, Claus Belka, Stephanie E Combs, Andreas von Deimling, Martin Bendszus, Wolfgang Wick, Andreas Unterberg, Stefan Rieken, Juergen Debus, Amir Abdollahi; Departments of Radiation Oncology, Neurology, Neurosurgery, Heidelberg University Hospital, National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Core-Center Heidelberg, Heidelberg, Germany; Heidelberg Ion-Beam Therapy Center (HIT), Department of Radiation Oncology, Heidelberg University Hospital (UKHD), National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK) Core Center Heidelberg, Heidelberg, Germany; German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Berlin, Berlin, Germany; National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Essen, Essen, Germany; German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Frankfurt, Oxford, United Kingdom; German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Freiburg, Freiburg, Germany; German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Tübingen, Tübingen, Germany; German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Munich, Munich, Germany; German Cancer Consortium (DKTK) Core Center Heidelberg and DKTK Partner Site Munich (TUM), Munich, Germany; Department of Neuropathology, Institute of Pathology, Heidelberg University Hospital (UKHD), National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK) Core Center Heidelberg, Germany, Heidelberg, Germany; Department of Neuropathology, Institute of Pathology, Heidelberg University Hospital (UKHD), National Center for Tumor Diseases (NCT), UKHD and German Cancer Research Center (DKFZ), Heidelberg, Germany; Departments of Radiation Oncology, Neurology, Neurosurgery, Heidelberg University Hospital, National Center for Tumor Disease (NCT), UKHD and German Cancer Research Center (DKFZ), German Cancer Consortium (DKTK), Core-Center Heidelberg, Germany National Ce, Heidelberg, Germany

Background: Local recurrence after surgery and radio(chemo)therapy remains a major obstacle in curative treatment of patients with HGG. Eradication of radioresistant glioma subpopulations (hypoxic- and stem cell like cells) together with formation of an antiangiogenic and immuno-permissive glioma niche are among beneficial radiobiological effects recently attributed to carbon ion irradiation in preclinical models. The impact of this novel therapy in management of rHGG patients remains elusive.

Methods: 197 patients with rHGG (grade III: 71, IV: 126) received RiCi between Nov 2009 and Feb 2018 at HIT with a median dose of 42GyRBE in 14 fractions. In DKTK-ROG multicenter cohort n:565 rHGG patients (grade III: 63, IV: 479) underwent RiP between 1997-2016 with a median dose of 36 Gy in 14 fractions. Median follow up was 34.2 months (M) for RiCi and 7.1 M for RiP (DKTK) cohort. All three prognostic scores validated in DKTK-ROG cohort were evaluated and re-irradiation risk score (RRRS) considering initial grade, Karnofsky Performance Score and age at re-irradiation was utilized for stratification and matched comparisons.

Results: Median PFS was 5.08 [4.26-5.87] M (grade III: 6.79, grade IV: 3.64) after RiCi, data was not available for RiP. Median OS was 10.52 [9.28-12.66] M (grade III: 28.2, grade IV: 8.53) after RiCi compared to 7.93 [7.15-8.79] M (grade III: 10.89, grade IV: 7.93) after RiP. Among the three prognostic scores evaluated, RRRS most robustly correlated with OS. RiCi was associated with HR of 0.52 ([0.49-0.72], p = 0.0000002), and HR 0.66 ([0.51-0.85], p = 0.001) for RRRS matched analysis. Conclusions: Carbon ions demonstrated activity in rHGG. This effect is most prominent in grade III while grade IV patients may further benefit from innovative multimodal strategies. Based on these encouraging results prospective randomized trials utilizing RRRS for stratification are recommended.
Detection of targetable somatic alterations in glioblastoma (GBM) and clinical impact.

Michael Fusco, Robert J Macaulay, Peter A. J. Forsyth, Christine Marie Walko; Moffitt Cancer Center, Tampa, FL; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: In GBM, molecular markers are utilized to establish an integrated diagnosis as described in the WHO 2016 guidelines and identify patients (pts) with molecular targets amenable to therapeutic intervention. Herein we review our experience at Moffitt Cancer Center. Methods: A retrospective chart review between 4/1/2013 and 11/1/2018 was performed to collect demographic, clinical, disease, treatment and outcome variables on 163 unique pts with GBM whose tumors underwent comprehensive genomic profiling by FoundationOne or CDx testing. Genomic data was analyzed for recurrent alterations and tumor mutational burden (TMB). Results: Median age was 58 years (range 19 to 85). 13% were IDH1 or 2-mutated. Among the 141 IDH-wild type (wt) pts, TERT promoter mutations occurred in 83% and CDKN2A/B co-deletion in 65%. O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was seen in 33%. A median of 5 clinically relevant alterations were identified per tumor sample (range, 2 to 34) and a median of 2 mutations (range, 0 to 6) were found to be actionable after review by our molecular tumor board. The most commonly actionable alterations were found in EGFR, BRAF and genes associated with homologous recombination deficiency (HRD) (see table). Four pts were treated with EGFR-targeted therapy, one pt with an HRD alteration received a PARP inhibitor (progression free survival [PFS] of 34 weeks), and two pts with BRAF V600E received dabrafenib/trametinib combination therapy (treatment ongoing at 14 weeks and 38 months, respectively). Median TMB (n = 118) was 4 (range, 0 to 371 Muts/Mb). One pt who received 44 months of temozolomide exposure had a hypermutated tumor (371 Muts/Mb) and was treated on trial with pembrolizumab, but progressed after 2 months. Conclusions: Though limited in patients with GBM, clinically actionable alterations are found in a small subset and can translate into meaningful clinical benefit.

<table>
<thead>
<tr>
<th>Alterations</th>
<th>IDH-Mut n (%)</th>
<th>IDH-Wt n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3F3A (K27M, G35R)</td>
<td>0 (0%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>HHRD</td>
<td>6 (27%)</td>
<td>15 (11%)</td>
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<tr>
<td>Amp of chromosome 4q (e.g. Genes - KDR, KIT, PDGFRA)</td>
<td>2 (9%)</td>
<td>12 (9%)</td>
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<tr>
<td>EGFR amplification (Median copy #: 57, range 11 to 166)</td>
<td>1 (5%)</td>
<td>61 (43%)</td>
</tr>
<tr>
<td>EGFR vIII and other EGFR</td>
<td>1 (5%)</td>
<td>52 (37%)</td>
</tr>
<tr>
<td>BRAF</td>
<td>0 (0%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>FYN-ROS1 rearrangement</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td>NTRK1 (duplication exons 10-17)</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
</tr>
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Background: The prospective phase I/II CINDERELLA trial investigates toxicity and effectiveness of a dose escalated reirradiation with carbon ions in patients with recurrent gliomas. Methods: Following a dose escalating protocol, 52 patients with WHO°II-IV gliomas were irradiated with carbon ions with doses of 3 Gy (RBE) in 10 – 16 fractions in 7 dose levels. Median age was 42 years (range: 28 - 69) with 19 female and 33 male participants. Forty-one patients were diagnosed with WHO°III/IV gliomas and 11 patients with WHO°II gliomas. At the time of reirradiation, all patients showed contrast-enhancing recurrences. MRI-based treatment planning encompassed the contrast enhancing lesion (GTV) with additional safety margins of 5 mm (CTV) and 3 mm (PTV). Clinical follow-up visits including contrast-enhanced MRI were scheduled every two months. We used RANO-criteria for diagnosis of progression. Survival rates were analyzed with Kaplan-Meier estimator. Relevant prognostic factors were determined with log rank-test, and toxicity was classified according to CTCAE v4.0. Results: Median time between first irradiation and reirradiation was 9 months (range: 7 – 228). PTV size was 12 – 310 ml. During follow-up ≥°3 toxicities were not observed. Follow-up MRI suggested radiation necrosis in 4 patients. Median overall survival was 352 days and was not influenced by age, gender or radiation dose. A significant trend for improved survival rates was seen in patients with small target volumes (480 days [PTV < 75ml] vs. 322 days [PTV > 75ml], p = 0.06) and initial low grade histology (497 days [WHO°II] vs. 322 days [WHO°III/IV], p = 0.069). During follow-up, 45 patients had local progression, while clinical deterioration was not seen. Median local progression-free survival was 138 days. Twenty-eight patients received chemo-/immunotherapy after reirradiation. Of those, 14 patients were treated with bevacizumab. Progression after reirradiation did not influence overall survival significantly. Conclusions: Carbon ion reirradiation with 10-16 fractions of 3 Gy for patients with recurrent gliomas is safe; no dose limiting toxicities were observed. Median overall survival with approximately one year is high in comparison to other treatment options. It remains unclear if RANO-criteria is securing the diagnosis of therapy failure after carbon ion reirradiation. Further randomized controlled trials must be awaited to evaluate the effectiveness of reirradiation of carbon ions compared to other treatment options. Clinical trial information: NCT01166308.
Oncolytic polio/rhinovirus recombinant (PVSRIPO) against WHO grade IV malignant glioma (MG): Experience with retreatment of survivors from the phase I trial.

Annick Desjardins, Matthias Gromeier, James Emmett Herndon, Dina Randazzo, Stevie Threatt, Eric S. Lipp, Elizabeth S. Miller, Jennifer Jackman, Dani P. Bolognesi, Allan H. Friedman, Henry S. Friedman, Frances McSherry, Katherine B. Peters, Margaret O Johnson, John H. Sampson, David M. Ashley, Darell D. Bigner; Duke University Medical Center, Durham, NC

Background: We completed a study evaluating a single intratumoral delivery of PVSRIPO in recurrent WHO grade IV MG patients (N Engl J Med. 2018 Jul 12;379(2):150-161). Some patients who originally benefitted from the infusion of PVSRIPO demonstrated tumor recurrence, and we hypothesized that retreatment could trigger an immune recall effect, further extending their survival. We now report the impact of second and third intratumoral reinfusion of PVSRIPO in patients treated in the original dose finding study. Methods: Eligible patients were adults with recurrent supratentorial WHO grade IV MG who were experiencing disease recurrence after having benefitted from the first infusion of PVSRIPO. Additional eligibility criteria included: solitary tumor 1-5.5 cm in diameter; ≥4 weeks after chemotherapy, bevacizumab or study drug; adequate organ function; KPS ≥70%; and positive anti-polio titer. One patient each was retreated at 1 x 10^7 TCID50 and 1 x 10^10 TCID50, and three patients were retreated on the identified phase 2 dose of 5 x 10^7 TCID50. Results: As of 2/09/2019, five patients have received a second intratumoral dose of PVSRIPO on study, one of which received a total of 3 doses. The patients who received two infusions of PVSRIPO were retreated 72 months, 43 months, 34 months, and 6 months after the first infusion. One additional patient received a second infusion of PVSRIPO 60 months after the first infusion and a third infusion of PVSRIPO 78 months after the first infusion. All patients demonstrated soap bubble degeneration on imaging, and two patients demonstrated tumor contraction. No grade 3 or higher adverse events related to PVSRIPO were observed after retreatment. Three of these patients remain alive more than 81, 80 and 52 months following the first PVSRIPO infusion and more than 9, 20 and 18 months after the second infusion, respectively. Two patients died 63 months and 20 months after the first infusion of PVSRIPO and 19.6 and 14 months after the second, respectively. The patient treated 3 times received the third infusion more than 2 months ago. Conclusions: Intratumoral reinfusion of PVSRIPO via CED is safe, and encouraging efficacy results have been observed. Clinical trial information: NCT01491893.
Are patients with oligodendrogioma at higher risk for radiation neurotoxicity?

Haroon Ahmad, Sohil H. Patel, Joseph Donahue, M. Beatriz Lopes, Benjamin Purow, David Schiff, Camilo E. Fadul; University of Virginia, Charlottesville, VA; University Of Virginia, Charlottesville, VA

Background: Symptomatic radiation neurotoxicity (RN), manifesting on MRI as focal necrosis and/or T2 signal abnormality, is a dreaded complication of radiation therapy (RT). While RT is standard of care for anaplastic gliomas, the long-term benefit vs risk profile in low-grade gliomas is not well defined. Patients with oligodendrogioma carry a better overall survival than those with astrocytoma. Anecdotally, they are more prone to experience RN than astrocytomas, as suggested by Acharya et al in 2017. We hypothesized that, independent of grade, oligodendrogiomas have a higher incidence of RN as compared to astrocytomas. Methods: We reviewed the records of 628 patients with WHO grade II and III gliomas from our institution. Study population comprised 326 patients with: standard fractionated RT, pathology confirmation by a neuropathologist, and follow up of at least 2 years after diagnosis. RN was defined as either histologically confirmed by pathology or requiring intervention for clinically presumed RN (bevacizumab or high-dose steroids.) A separate category included patients with dramatic cognitive decline with increased T2 signal abnormality, in the absence or tumor progression. Results: There were 131 patients with oligodendrogioma, based upon 1p/19q co-deletion (105 cases) or histology in the absence of molecular testing (26 cases). The remaining 195 patients had astrocytoma with intact 1p/19q, isocitrate dehydrogenase (IDH) wild-type, or diagnosed histologically absent molecular testing. The incidence of RN were 18.3% and 8.2% for oligodendrogioma and astrocytoma, respectively (p = 0.0063). An additional four patients with oligodendrogioma and two with astrocytoma had significant cognitive deterioration with increased T2 signal abnormality, without tumor progression. Conclusions: The greater than two-fold increase in RN incidence for oligodendrogiomas is significant and suggests patients with oligodendrogiomas may be more at risk to develop RN. Therefore, in patients with oligodendrogioma, the consideration of fractionated RT needs to be weighed against the increased potential for RN. Analysis of baseline imaging and patient characteristics variables that correlate with development of RN are ongoing and will be presented at the meeting.
A phase I study of MGMT-P140K transfected hematopoetic progenitor cells (HPC) combined with TMZ/O6BG dose escalation for newly diagnosed, MGMT unmethylated glioblastoma: Tolerance and evidence of survival benefit.

Andrew E. Sloan, Lisa Roger, Chris Murphy, Jane Reese, Hillard M. Lazarus, Boro Dropulic, Stanton L. Gerson; University Hospital Case Medical Center, Cleveland, OH; University Hospitals, Cleveland, OH; Seidman Cancer Center, Cleveland, OH; Case Western Reserve University School of Medicine, Cleveland, OH; University Hospital of Cleveland, Cleveland, OH; Lentigen Technology Inc., A Miltenyi Biotec Company, Gaithersburg, MD; Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH

Background: GBM is the most common malignant brain tumor with a median survival of 15 months despite surgery and radio-chemotherapy. The most important mechanism of TMZ resistance is the O6-methylguanine-DNA methyltransferase (MGMT) gene which repairs temozolamide-induced DNA methylation. The MGMT inhibitor O6-benzylguanine (BG) demonstrated efficacy in depleting MGMT and maximizing tumor response in early phase clinical trials. However, MGMT expression is also low in hematopoietic cells, so this approach led to unacceptable bone marrow toxicity and thus has been abandoned. We hypothesized that chemoprotection of hematopoietic HPC with an MGMT mutant (MGMT-P140K) characterized by normal methyltransferase activity, coupled with low affinity for BG would maximize anti-tumor response while enabling patients to tolerate TMZ & BG dose escalation with minimal toxicity. A phase I trial was performed to test this hypothesis. Methods: 10 adults with newly diagnosed MGMT unmethylated, IDH-1 WT, GBM underwent standard surgery and radiation, followed by transplantation with autologous CD34+ HPC engineered to express MGMT-P140K using a lentiviral vector. We tested tolerance and efficacy of three different paradigms for conditioning bone marrow and re-infusion of HPC. To assess chemo-protection, patients’ blood counts and transgene marking were monitored during and after treatment, as was toxicity, response, and progression-free and overall survival. Results: Treatment was moderately toxic with 3/10 patients suffering grade 3-4 hematologic toxicity; no high grade non-hematologic toxicity was observed. Viral transduction rates ranged from 3-75% and were clearly improved in Arm III utilizing BCNU conditioning and intra-patient dose escalation of TMZ/O6GB. In patients tolerating 3 cycles or more, P140K-MGMT gene markings in peripheral blood and bone marrow cells increased 3-26-fold with only mild (Grade 2-3) myelosuppression consistent with chemo-protection as hypothesized. Median PFS and OS was 22 and 31 months respectfully, and three patients in Arm III are healthy and progression free at 36-39 months. OS exceeded RPA predicted survival by 3.3-fold suggesting clinical benefit. Viral insertion site analysis demonstrate lack of clonal dominance. Conclusions: P140K-MGMT transfected HPC enables TMZ/ BG dose escalation with acceptable toxicity and increased survival in a small cohort of selected patients. A phase II study is ongoing. Clinical trial information: NCT01269424.
Retrospective review for outcomes of IDH mutant, 1p/19q co-deleted gliomas based on initial treatment.

Christopher Ray Trevino, Shiao-Pei S. Weathers, Kristin Alfaro-Munoz, Gemma Hallatt, Garret L. Wiliford, Minjeong Park, Diane D. Liu, Tim Overeen, Jacob Joseph Mandel, John Frederick De Groot; MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Department of Neuro-Oncology, Houston, TX; Palantir Technologies, Palo Alto, CA; The UT MD Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX; Baylor College of Medicine, Houston, TX

Background: Treatment for oligodendroglioma in the molecular era is based on trials that used histologic criteria alone and has evolved over time to include observation and a combination of radiation (RT) and chemotherapy. In particular, treatment for high-risk patients is variable including sequential RT followed by temozolomide (TMZ) or procarbazine, lomustine, and vincristine (PCV) or chemoradiation with TMZ. This is a single institutional review of outcomes of molecular IDH mutant, 1p19q co-deleted oligodendroglialoma based on initial treatment.

Methods: Using both Palantir Foundry and direct record review, we stratified adult patients with grade II/III gliomas diagnosed from 1997-2017 harboring an IDH mutation and 1p/19q co-deletion based on initial treatment and excluded patients without molecular testing. Overall survival (OS) and progression free survival (PFS) were calculated by Kaplan-Meier analysis. Results: 187 patients were initially managed as: 55 (31%) observation, 16 (9%) RT alone, 51 (29%) chemotherapy alone, 39 (22%) sequential RT and chemotherapy, and 17 (10%) chemoradiation. For all patients, a subtotal (STR) or gross total resection (GTR) was associated with prolonged OS vs biopsy (NR vs 123 mos, p = 0.007). Age ≤ 40 did not correlate with OS (p = 0.87). In the chemotherapy group, although PCV demonstrated improved PFS vs TMZ (157 vs 45 mos, p = 0.004) there was no difference in OS, only 3 patients received PCV. For patients treated sequentially with RT and PCV or TMZ vs chemoradiation, there were no differences in OS (NR vs 140 mos; p = 0.87) or PFS (49 vs 45 mos, p = 0.52), though sequential treatment trended toward prolonged survival.

Conclusions: This data supports both STR and GTR as prognostic for overall survival. Despite the prolonged PFS observed with patients treated with PCV alone which did not translate to improved OS, the small PCV sample size limits the strength of this evidence. We did not find significant survival differences between sequential RT and chemotherapy vs concurrent, but interestingly, there was a trend toward improved OS in sequentially treated patients.
Prospective phase II trial in patients with first relapse of high-grade astrocytoma using TVB-2640 in combination with bevacizumab versus bevacizumab alone.

Brandon Konkel, Laura D Caflisch, Adolfo Enrique Diaz Duque, Joel Michalek, Qianqian Liu, Andrew Jacob Brenner; Cancer Therapy and Research Center at UT Health Science Center, San Antonio, TX; University of Texas Health Science Center San Antonio, San Antonio, TX; University of Texas Health San Antonio - MD Anderson Cancer Center, San Antonio, TX; UT Health San Antonio Cancer Center, San Antonio, TX; The University of Texas Health Science Center, San Antonio, TX

Background: Recurrent glioblastoma (rGBM) following chemoradiation is associated with a poor prognosis. While bevacizumab is the most common salvage therapy, responses remain brief and without an associated survival benefit. Resistance may involve overexpression of Fatty Acid Synthase (FASN). Our institution is conducting a phase 2 study of bevacizumab with FASN inhibitor TVB-2640 in patients with GBM in first relapse. Methods: This is a prospective, phase 2 study of bevacizumab with TVB-2640 in patients with GBM in first relapse. Primary end point is progression free survival (PFS). Inclusion criteria are: age ≥ 18, ECOG 0 to 2, GBM progression following standard combined modality treatment. Randomization into two arms for the first 28 days is included for exploratory biochemical analysis: patients in arm 1 receive bevacizumab every 2 weeks in combination with TVB-2640; those in arm 2 receive bevacizumab alone every 2 weeks. MR-Spectroscopy (MRS) and serum sampling for exosome analysis are obtained on patients at day 1 and 28 of first cycle. Starting on cycle 2 day 1, all patients converge to a single arm and continue to receive bevacizumab in combination with TVB-2640. Results: We have enrolled 24 patients to date; 23 have started treatment. Of those 23 patients, 10 have died, 4 have progressed but are still alive, 2 withdrew, and 7 are still active on trial. The PFS6 is and OS9 are both currently 50%, which compares favorably with historical controls. There have been no reports of grade 4 or 5 treatment-related AEs (of note, 2 deaths were thought definitely unrelated to treatment, including 1 case of intracerebral hemorrhage, and 1 case of sepsis). There have been two cases of grade 3 hand-foot syndrome thought definitely related to treatment. Updated results will include PFS, response, and biomarker analysis (exosome, MRS). Conclusions: The combination of TVB2640 with bevacizumab appears be well tolerated. PFS6 and OS9 are both currently 50%. The study has completed accrual with final data expected later in 2019. Clinical trial information: NCT03032484.
Phase I/II study of depatuxizumab mafodotin (ABT-414) monotherapy or combination with temozolomide in Japanese patients with/without EGFR-amplified recurrent glioblastoma.

Yoshitaka Narita, Yoshihiro Muragaki, Takashi Maruyama, Naoki Kagawa, Katsunori Asai, Junichiro Kuroda, Kazuhiro Kurozumi, Motoo Nagane, Masahid Matsuda, Keisuke Ueki, Christopher Joseph Ocampo, Ikiru Matsumoto, Reiko Odagawa, Yasuko Nishimura, Kazuhiro Mishima; National Cancer Center Hospital, Chuo-ku, Tokyo, Japan; Tokyo Women’s Medical University Hospital, Shinjyuku-ku, Tokyo, Japan; Tokyo Women’s Medical University Hospital, Shinjyuku-ku, Tokyo, Japan; Osaka University Hospital, Osaka, Japan; Osaka Inter. Cancer Institute, Osaka, Japan; Kumamoto University Hospital, Kumamoto, Japan; Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama-shi, Okayama, Japan; Department of Neurosurgery, Kyorin University Faculty of Medicine, Tokyo, Japan; Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan; Dokkyo Medical University Hospital, Tochigi, Japan; AbbVie Inc., Chicago, IL; AbbVie GK, Tokyo, Japan; Saitama Medical University International Medical Center, Hidaka-shi, Saitama, Japan

Background: The poor prognosis of glioblastoma (GBM; WHO grade IV) results from a high rate of disease recurrence and lack of effective treatment options. Depatuxizumab mafodotin (depatux-m, ABT-414) is comprised of an EGFR-directed antibody, depatuxizumab (depatux, ABT-806), conjugated to the microtubule toxin monomethyl auristatin F (MMAF, mafodotin). Once bounded with tumor cells, depatux-m is internalized and releases the cytotoxin, resulting in cell death. Here, we report safety, pharmacokinetic (PK) and efficacy in an ongoing phase 1/2 study of Japanese patients with/without EGFR-amplified recurrent GBM (rGBM). Methods: M13-714 (INTELLANCE-J, NCT02590263) is a non-randomized, phase 1/2 study in Japanese patients. Phase 1 assessed tolerability and PK where the dose escalation of depatux-m was from 0.5 to 1.25 mg/kg/Q2W at day 1 and 15 during 28-day cycle until progression disease (PD) or intolerable toxicity. Phase 2 assessed efficacy and safety of depatux-m in EGFR-amplified, rGBM and patients received 1.0 mg/kg of depatux-m on day 1 and 15 + 150 mg/m² temozolomide (TMZ) on days 1-5 during each 28-day cycle until PD or intolerable toxicity. Results: As of 10 Jan 2019, 38 patients (WHO grade ≥3) were enrolled (9 in phase 1, 29 in phase 2). There was no dose limiting toxicity in phase 1. The recommended phase 2 dose was 1.25 mg/kg where the most common adverse events (AEs) were punctate keratitis in 21 patients (72%); lymphopenia in 14 patients (45%), thrombocytopenia in 13 patients (41%). Grade 3/4 AEs included thrombocytopenia and lymphopenia in 20 patients (69%). Ocular AEs were reported in 27 patients (93%) including punctate keratitis (72%). PK results (31 patients) in both phases were similar to those of non-Japanese result. Progression Free Survival (PFS) of 27 patients in phase 2 for 12 and 6 months were 8% and 27.5% respectively. The median PFS was 4 months. The overall survival (OS) for 24, 12 and 6 months were 28%, 62.5% and 93% respectively. The median OS was 15.5 months. Conclusions: Preliminary safety, PK and efficacy in Japanese patients with/without EGFR-amplified, rGBM suggests depatux-m was tolerated and showed encouraging anti-GBM effects. Clinical trial information: NCT02590263.

Benjamin Y. Lu, Richa Gupta, Tyler Stewart, Harriet M. Kluger, Lucia Jilaveanu, Kurt A. Schalper, Sarah B. Goldberg; Yale School of Medicine, New Haven, CT; Yale New Haven Hospital, New Haven, CT; Yale School of Medicine and Smilow Cancer Center, Yale New Haven Hospital, New Haven, CT; Yale University School of Medicine, New Haven, CT

Background: Despite the biological and clinical implications, the immune composition and functional characteristics of adaptive immune cells in brain metastases (BrM) are poorly understood. Using multiplexed quantitative immunofluorescence (QIF), this study evaluates the level and functional profile of major T-cell subsets in primary lung tumors, BrM, and extracranial metastases (ECM) from lung cancers.

Methods: A tissue microarray was constructed from formalin-fixed, paraffin-embedded tumor samples of 94 lung cancer patients treated at Yale Cancer Center between 2002-2013. Multiplexed QIF was used to evaluate the cases with a panel containing phenotype markers for major T-cell subsets (CD3, CD4, CD8 and FOXP3), and cell-localized activation and proliferation (granzyme-B and Ki-67). Signal for each marker was measured in marker-selected tissue compartments using the Automated Quantitative Analysis (AQUA) platform. Associations between markers and major clinico-pathologic variables were studied.

Results: In total, 40 primary lung tumors, 63 BrM, and 15 ECM were analyzed, including paired samples from 22 patients. Lung cancer histology included adenocarcinoma 62.5%, squamous cell carcinoma 11.5%, small cell 9.4%, and other non-small cell 16.7%. BrM had both significantly lower levels of CD3+ T-cells (p<0.0001) and T-cell granzyme B (p=0.0188) compared with primary malignancies. FOXP3 measured in CD4+ T-cells were significantly lower in BrM compared with primary malignancies (p=0.0002) and ECM (p=0.0404). Among patients with BrM, higher levels of CD3+ T-cells in BrM were associated with longer overall survival.

Conclusions: Lung cancer-associated BrM have lower T-cell infiltration, cytolytic function, and regulatory T-cells than primary lesions. These results indicate lower adaptive anti-tumor responses in BrM and suggest the presence of a tolerogenic microenvironment in the brain. Overcoming this could be used to design optimal treatment strategies.
Stereotactic radiosurgery for resected brain metastases: Does the surgical corridor need to be treated?

Siyu Shi, Joseph Abi Jaoude, Navjot Sandhu, Elyn Wang, Kirsten Schofield, Michael C. Jin, Carrie Zhang, Elisa Liu, Erqi L. Pollom, Scott G. Soltys; Stanford Cancer Institute, Palo Alto, CA

Background: Post-operative stereotactic radiosurgery (SRS) is the standard of care for resected brain metastases, but SRS techniques are not standardized. Although expert consensus guidelines recommend that the surgical corridor leading to the resection cavity be included in the SRS plan, this statement is not based on data. We analyzed the patterns of failure and toxicity with post-resection SRS, with the hypothesis that the corridor needs not be targeted with SRS. Methods: In this IRB-approved retrospective review, from 428 lesions treated from 2005-2018 with post-resection SRS, 58 lesions (57 patients) had evaluable data and a ‘deep’ tumor with a surgical corridor defined as $\geq 1.0 \text{ cm}$ from the surface pre-operatively. SRS targeted the surgical corridor, defined as the surgical tract uninvolved by tumor on pre-operative imaging, in 33(57%). Brain failure was defined as local (LF) if within the surgical cavity involved with tumor pre-resection, corridor (CF) if within the surgical tract leading to the surgical cavity, distant (DF) if a new parenchymal tumor, or leptomeningeal (LMD) for new nodular/classical leptomeningeal enhancement. The cumulative incidences of failure and adverse radiation effect (ARE) were analyzed with death and whole brain radiation therapy as competing risks. Results: The median follow-up was 14 months. Not targeting surgical corridor was associated with prior SRS/resection for other brain metastases (23% vs. 0%, $p=0.01$), deeper tumors (median 2.1 cm vs. 1.4 cm, $p<0.01$), and systemic treatment within 3 months ($p=0.01$), but not other factors ($p>0.10$). The 12-month failure rates, if surgical corridor was not treated vs. treated, respectively, were: CF 8% (1-24%) vs. 0% ($p=0.12$), LF 4% (0-17%) vs. 13% (4-27%) ($p=0.32$), LMD 40% (19-61%) vs. 10% (2-23%) ($p=0.03$), DF 65% (43-81%) vs. 35% (19-52%) ($p=0.02$), and ARE 8% (1-22%) vs. 13% (4-28%) ($p=0.35$). After adjusting for systemic treatment, differences were not statistically significant ($p>0.05$). Conclusions: Omitting the surgical corridor in post-operative SRS for resected brain metastases was not associated with statistically significant differences in recurrences or adverse radiation effect. Surgical corridor does not need to be included in all post-resection SRS.
Insight into the brain metastasis journey: Initial survey results from patients and caregivers.

Nicole Willmarth, Scott Elder, Avery Fine, Manmeet Singh Ahluwalia, Jill Barnholtz-Sloan, Priscilla Kaliopi Brastianos, Daniel Brat, Minesh P. Mehta, Robin Page, Ralph DeVitto, Debbie Robins; American Brain Tumor Association, Chicago, IL; Penn Schoen Berland (PSB) Research, Washington, DC; Burkhardt Brain Tumor NeuroOncology Center, Neurological Institute, Taussig Center Institute, Cleveland Clinic, Cleveland, OH; Case Comprehensive Cancer Center and Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, OH; Departments of Medicine and Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA; Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, Chicago, IL; Miami Cancer Institute, Baptist Health South Florida, Miami, FL; Core Life Wellness, Libertyville, IL

Background: Brain metastases (BM) are the most common central nervous system tumors in the US. Though the exact incidence is unknown, BM are estimated to occur in up to 10-20% of all cancers. Despite the high frequency, there is little systematic knowledge about how BM are typically diagnosed and treated. The American Brain Tumor Association (ABTA) seeks to understand the BM journey: symptoms, diagnosis, treatment, and end of life, through a survey of BM patients and caregivers.

Methods: Two surveys were developed by the ABTA with vendor, PSB Research, after careful literature review. The surveys were reviewed by a panel of clinicians who treat BM patients. Online survey research was conducted between 8/13-9/16/18, with one survey for adults with BM (N = 237) and another for caregivers (N = 211). Respondents came from PSB’s panels and ABTA collaborators: LUNGevity, Melanoma Research Foundation and the Kidney Cancer Association. Results: Ninety percent of patients, and a similar number of caregivers, were surprised by the diagnosis, with only 20% of patients knowing about BM before diagnosis. Most caregivers were the adult child of a patient. The impact of the diagnosis was primarily emotional. Top concerns after diagnosis, for both patients and caregivers, were likelihood of treatment success and impact on quality of life. Although a majority of patients were happy with the quality of information given, they stated a need to receive a greater quantity of information about treatment success and options. Only 30% of patients were referred to a patient advocacy organization. When referred, information on treatment success rates and options was most sought. Conclusions: Direct patient and caregiver feedback provides valuable insight towards understanding the BM journey and resources needed to support patients and caregivers. A subsequent survey among oncologists and other clinicians, planned for spring of 2019, will add to these findings.
A phase II trial of bevacizumab in patients with recurrent solid tumor brain metastases who have failed whole brain radiation therapy (WBRT).

Priya Kumthekar, Karan Dixit, Sean Aaron Grimm, Rimas Vincas Lukas, Margaret A. Schwartz, Alfred Rademaker, Laura Sharp, Valerie Nelson, Jeffrey J. Raizer; Northwestern Memorial Hospital, Chicago, IL; Northwestern University, Chicago, IL; Cadence Brain and Spine Tumor Center, Warrenville, IL; University of Chicago, Chicago, IL; Northwestern University Feinberg School of Medicine, Chicago, IL; Robert H. Lurie Cancer Center of Northwestern University, Chicago, IL

Background: Brain metastases (BM) are the most common intracranial malignancy with overall a poor prognosis estimated at approximately 4 months from time of initial diagnosis for treated patients, and even lower after failing WBRT after which treatment options have been limited and outcomes poor.

Methods: This is an open label phase 2 study where patients who have previously failed WBRT received bevacizumab at a dose of 10 mg/kg intravenously every two weeks until CNS disease progression with one cycle being defined as 4 weeks. The primary endpoint was objective radiographic tumor response as defined by modified Response Assessment in Neuro-oncology (RANO) criteria. Secondary endpoints included progression free survival (PFS) at 6 months, time to progression, time to response, duration of response, overall survival (OS), quality of life (QOL) as measured by the FACT-G and FACT-Br and safety.

Results: A total of 27 patients were consented and registered to study of which 24 were evaluable for ORR (3 came off study prior to first follow up MRI brain). Median age was 53 (range 27-73), median number of cycles was 5.5 (range 1-20) with a median follow up of 8.7 months (range 2.4-47.9 mo). Of the 24 evaluable patients, there were 6 Partial response, 16 stable disease and 2 progressive disease. The 6 month PFS: 46% (95% CI: 25% - 67%) and median PFS was 5.3 months. Median OS was 9.5 months (95% confidence interval 6.3m – 15.0m). For the patients who completed sequential QOL assessments, there was no significant decline in QOL but there was a nonsignificant improvement in the FACT-Br scores. Overall, treatment was well tolerated with 3 grade 3 adverse events seen: hypertension (n = 3), headache (n = 1) and thrombotic event (n = 1).

Conclusions: For this WBRT failure BM population, we were able to show a 25% disease response to bevacizumab therapy along with good drug tolerability and no noted central nervous system bleeding. Improved survival as compared to historical controls was seen 9.5 m. Of the 24 evaluable patients, 81% (22/24) experienced clinical benefit defined as stable disease or better. Bevacizumab therapy could be a viable option for solid tumor BM patients who experience progression following WBRT, however a larger trial is required to confirm this data. Clinical trial information: NCT01898130.
Novel anti-EGFRvIII bispecific T cell engager (BiTE) antibody construct in glioblastoma (GBM): Trial in progress of AMG 596 in patients with recurrent or newly diagnosed disease.

Mark Rosenthal, Carmen Balana, Myra Ellen Van Linde, Cyrus Sayehli, Walter M. Fiedler, Martin Wermke, Christophe Massard, Agnes Ang, Johannes Kast, Sabine Stienen, Timothy Francis Cloughesy; Peter MacCallum Cancer Centre, Melbourne, Australia; Institut Catala Oncologia Badalona, Hospital Germans Trias I Pujol, Badalona/Barcelona, Spain; Amsterdam University Medical Center, Amsterdam, Netherlands; Universitätsklinikum Würzburg, Wuerzburg, Germany; University Medical Center Hamburg-Eppendorf, Hamburg, Germany; University Cancer Center Dresden, Dresden, Germany; Institut Gustave Roussy, Villejuif, France; Amgen Inc., Thousand Oaks, CA; Amgen, Inc., San Francisco, CA; Amgen Inc., Munich, Germany; Ronald Reagan UCLA Medical Center, Los Angeles, CA

Background: GBM is the most aggressive primary brain tumor in adults and is extremely difficult to treat. Patients with GBM tend to progress rapidly within weeks or months. Median overall survival is only 12–15 months despite aggressive treatment, and less than 5% of patients survive 5 years. GBM also severely impacts quality of life and cognitive function. Approximately 50% of GBM tumors test positive for amplification or mutation of the epidermal growth factor receptor (EGFR), the most common of which is the EGFRvIII gain-of-function mutation. AMG 596 is a bispecific T cell engager (BiTE®) antibody construct designed to crosslink and engage CD3-positive T cells to EGFRvIII-positive tumor cells, inducing tumor cell lysis and T cell proliferation. A clinical trial is being conducted for this novel immunotherapy agent in patients with EGFRvIII-positive GBM.

Methods: NCT03296696 is a phase 1, first-in-human, open-label, sequential dose-escalation and dose-expansion study evaluating the safety, tolerability, and pharmacokinetics and pharmacodynamics (PK/PD) of AMG 596 in patients with EGFRvIII-positive GBM. AMG 596 is administered via continuous intravenous infusion. The study is expected to enroll approximately 82 patients total and comprises two groups (Group 1: patients with recurrent GBM; Group 2: patients with newly diagnosed GBM in the maintenance treatment phase after standard of care). Key inclusion criteria include: male or female; $18$ years of age; with pathologically documented and diagnosed grade IV GBM; Eastern Cooperative Oncology Group performance status $\leq 1$; life expectancy $\geq 3$ months per study investigator; and acceptable renal, hematological, and hepatic function. The primary endpoint evaluates the safety and tolerability of AMG 596 via collection of treatment-emergent adverse events. Additional endpoints include objective response rate per modified Response Assessment in Neuro-Oncology Criteria and PK/PD analyses of AMG 596 in serum. The study began enrolling patients in April 2018 and enrollment is ongoing. For more information, please contact Amgen Medical Information: medinfo@amgen.com. Clinical trial information: NCT03296696.

Patrick Roth, Jaap C. Reijneveld, Thierry Gorlia, Frederic Dhermain, Filip Yves Francine Leon De Vos, Maureen Vanlancker, Christopher J. O’Callaghan, Emilie Le Rhun, Martin J. Van Den Bent, Warren P. Mason, Michael Weller; University Hospital Zurich, Zurich, Switzerland; Department of Neurology, VU University Medical Center, Amsterdam, Netherlands; EORTC Headquarters, Brussels, Belgium; Institut Gustave Roussy, Villejuif, France; University Medical Center Utrecht, Division of Medical Oncology, Utrecht, Netherlands; EORTC, Brussels, Belgium; Queen’s University, Canadian Cancer Trials Group, Kingston, ON, Canada; Lille University Hospital, Lille, France; Erasmus MC Cancer Centre, Rotterdam, Netherlands; Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; Laboratory of Molecular Neuro-Oncology, Department of Neurology, and Neuroscience Center Zurich, University Hospital and University of Zurich, Zurich, Switzerland

Background: The standard treatment for patients with newly diagnosed glioblastoma comprises maximum safe surgery, radiotherapy (RT), and concomitant and up to six cycles of maintenance temozolomide (TMZ) chemotherapy (TMZ/RT→TMZ). Despite this intense therapy, the prognosis remains poor and there is an urgent need to develop new therapeutic options. Marizomib is a novel, irreversible and brain-penetrant pan-proteasome inhibitor. Following its successful assessment in phase I trials in patients with newly diagnosed as well as recurrent glioblastoma, marizomib is now being investigated in a phase III trial. Methods: EORTC 1709/CCTG CE.8 is a multicenter, randomized, controlled, open label phase III superiority trial. Eligibility criteria include histologically confirmed newly diagnosed glioblastoma and a performance status ≥70. Approximately a total of 750 patients will be enrolled and randomized 1:1. Stratification factors include institution, age, Karnofsky performance status and extent of surgery. The primary objective of this study is to compare overall survival in patients receiving marizomib in addition to standard of care (TMZ/RT→TMZ) with patients receiving standard treatment only. The testing strategy specifies the determination of this objective in both the intent-to-treat population and the subgroup of patients with tumors harboring an unmethylated MGMT promoter. Secondary endpoints include progression-free survival, safety, neurocognitive function and quality of life. The study is accompanied by a translational research program. The study will be opened at 50 EORTC sites in Europe and done as an intergroup collaboration with the Canadian Cancer Trials Group (CCTG) with 25 sites in Canada and additional sites in the US. Patient enrolment started in June 2018 and as of January 29, 2019, a total of 85 patients have been randomized. An update on the enrolment status will be provided at the ASCO conference. Clinical trial information: NCT03345095.
A phase I/II study of nivolumab plus or minus ipilimumab in combination with multifraction stereotactic radiosurgery for recurrent high-grade radiation-relapsed meningioma.

Jiayi Huang, Jian Li Campian, Feng Gao, Tanner Michael Johanns, Annick Desjardins, Andrea Wang-Gillam, Josh Rubin; Washington University School of Medicine in St. Louis, St. Louis, MO; Washington University, Kirkwood, MO; Duke University Medical Center, Durham, NC; Washington University School of Medicine, St. Louis, MO

Background: There is currently lack of effective therapy for meningiomas that have relapsed despite surgery and radiation therapy (RT). Reirradiation have been used in selected cases, but the long-term clinical outcomes remained poor, especially for high-grade meningiomas. Preclinical data have suggested synergy between hypofractionated radiosurgery with immune checkpoint inhibitors such as PD1 and CTLA4 inhibitors. The purpose of this study is to evaluate feasibility and preliminary clinical efficacy of combining reirradiation using hypofractionated radiosurgery with concurrent nivolumab (PD1 inhibitor) plus or minus ipilimumab (CTLA4 inhibitor) for recurrent high-grade meningiomas.

Methods: During the phase I portion, eligible patients will be treated according to treatment-escalation schema following the modified 3+3 design (Table). The maximum tolerated combination (MTC) will be the regimen at which ≤1/6 patients experience dose-limiting toxicity within 8 weeks of the start of study therapy. During the phase II portion, a total of 24 evaluable patients will be enrolled at the MTC using Simon’s MinMax two-stage design. Key eligibility criteria include patients with recurrent grade II-III meningiomas after prior RT; age ≥ 18 years; ECOG score ≤ 2; measurable disease but ≤ 5 cm (or 20 cm³); prior radiation dose ≤ 70 Gy with at least 6 months interval; normal organ function; no active autoimmunity. The primary endpoints are to determine the MTC (phase I) and the objective response rate of the MTC (phase II). Secondary endpoints include safety, duration of response, progression-free survival, overall survival. Exploratory endpoints include developing an immune or molecular signature for predicting treatment response and resistance. The trial is actively enrolling and funded by the National Cancer Institute Experimental Therapeutics Clinical Trials Network (NCI-ETCTN). Treatment Escalation Schema. Clinical trial information: NCT03604978.
Phase I study of PD-L1 inhibition with avelumab and laser interstitial thermal therapy in patients with recurrent glioblastoma.

Adilia Hormigo, John Mandeli, Constantinos Hadjipanayis, Sacha Gnjatic, Seunghee Kim-Schulze, Saadi Ghatan; Icahn School of Medicine at Mount Sinai, New York, NY; Icahn Mount Sinai School of Medicine, New York, NY; Columbia Univ, New York, NY

Background: Glioblastoma (GBM) the most frequent malignant brain tumor in the adult has a dismal prognosis and limited treatment options. Current advances have highlighted how tumors and specifically GBM evade the immune system by exploiting the mechanisms of tolerance and inducing local and systemic immunosuppression. Another hurdle in the treatment of GBM is the blood-brain barrier (BBB). Recent work suggests that MRI-guided laser interstitial thermal therapy (LITT) can increase the permeability of the BBB and may have an abscopal effect. Therefore, utilizing MRI-guided LITT, a potential immunogenic cell death-inducing procedure that disrupts the BBB and makes Avelumab a PD-L1 monoclonal antibody being more accessible to GBM tumors, seem a valid approach for immunomodulation and successful implementation of a combined regimen to treat brain cancer.

Methods: This is a prospective non-randomized open label to characterize the tolerability and safety profile of Avelumab in combination with LITT in patients with recurrent glioblastoma who were treated with radiation therapy with concurrent Temozolomide chemotherapy at diagnosis, and whose tumor at recurrence measures less than 3 cm³. Avelumab is administered within a week after real-time MRI-guided LITT therapy and every 2 weeks thereafter. On part A patients are treated with intravenous Avelumab alone and on part B patients receive Avelumab in combination with MRI-guided LITT. Part A completed enrollment without DLT. Enrollment on part B began in October 2018. A Simon minimax two-stage design is being used for efficacy. Toxicity will be scored using the NCI-CTCAE 4.03 criteria. Blood samples and tumor tissue will be collected for correlative studies. Quantification of the changes in inflammatory and immunosuppressive profiles across time points for patients receiving treatment with Avelumab will be obtained. This information will instruct future immunotherapy approaches to treat GBM and the rational for those combinations. Clinical trial information: NCT03341806.
A phase Ib trial of CB-839 (telaglenastat) in combination with radiation therapy and temozolomide in patients with IDH-mutated diffuse astrocytoma and anaplastic astrocytoma (NCT03528642).

Sani Haider Kizilbash, Samuel McBrayer, John Port, Joel M. Reid, Ian Lanza, Jacob B Allred, Arnab Chakravarti, Charles Kunos, Alex A. Adjei; Mayo Clinic, Rochester, MN; Dana Farber Cancer Institute, Boston, MA; Department of Oncology, Mayo Clinic, Rochester, MN; Ohio State Univ-Arthur G. James Cancer Ctr, Dublin, OH; National Cancer Institute, Rockville, MD

Background: IDH mutant astrocytomas express high levels of 2-hydroxyglutarate (2-HG), an oncogenic metabolite which drives gliomagenesis. Excess 2-HG inhibits branched chain amino acid transaminase, which catalyzes glutamate synthesis from branched chain amino acids. This defect causes these tumors to become more reliant on glutaminase for glutamate biosynthesis from glutamine. CB-839 (telaglenastat) is a novel glutaminase inhibitor which is well tolerated in humans. McBrayer et al have recently demonstrated that CB-839 further depletes intracellular glutamate and glutathione in IDH mutant glioma cells, and enhances RT (radiation therapy) efficacy in an orthotopic glioma model. Methods: NCI #10218 is a CTEP supported phase I clinical trial investigating the safety and tolerability of CB-839 when combined with RT/TMZ (temozolomide) in patients with previously untreated IDH mutant grade II/III astrocytoma. Patients with grade II and III astrocytomas will be treated with 50.4 and 59.4 Gy of RT, respectively, with standard doses of concurrent TMZ. CB-839 will also be administered orally concurrently with RT, with doses escalated in cohorts based on a standard 3+3 design. After defining the maximum tolerated dose (MTD) of CB-839, an expansion cohort will evaluate the pre- and post-CB-839 therapy metabolome of patients with IDH mutant astrocytoma. Enrollment to this cohort will require measurable disease and patients will additionally be treated with a 7 day run-in of CB-839 at MTD prior to RT. The effect of CB-839 on the metabolome will be studied in both plasma (LC/MS/MS) and tumor (magnetic resonance spectroscopy), along with PK to confirm adequacy of systemic exposure. Preliminary data on neurocognitive endpoints will also be acquired. NCI #10218 is currently activated for enrollment to cohort 1. Clinical trial information: NCT03528642.
Oral DNA vaccination targeting VEGFR-2 combined with anti-PD-L1 avelumab in patients with progressive glioblastoma, a phase I/II study: NCT03750071.

Background: The vaccine (VXM01) is a VEGFR-2 coding DNA vaccine, using a Salmonella Ty21a carrier for oral application. VEGFR-2 is over-expressed in glioblastoma and serves as a promising target for VEGFR-2 primed T cells with the potential to alter tumor angiogenesis and/or eliminate VEGFR-2 expressing tumor cells. VXM01 was well tolerated in a previous phase I/II study involving 14 patients with progressive glioblastoma multiforme. Immunological correlates of vaccination and anti-tumor immunity in the blood and in the tumor were detected. At least one objective clinical response was attributed to vaccine monotherapy, with one more PR achieved in combination with nivolumab. Prolonged overall survival was associated with peripheral immune responses against VEGFR-2, J Clin Oncol 36, 2018 (suppl; abstr 2017). A combination study with the anti PD-L1 checkpoint inhibitor monoclonal antibody avelumab is currently underway.

Methods: A multicentre, open-label phase I/II study (EudraCT.gov no. 2017-003076-31), will enrol 30 patients with progressive glioblastoma, previously treated with temozolomide/radiotherapy. The primary objective is to evaluate safety and tolerability of the vaccine in combination with avelumab. In a 1+2 safety run in, two cohorts of non-reoperable patients will be vaccinated with one of 2 doses of the oral vaccine (10^6 or 10^7 CFU) with concurrent intravenous avelumab. Vaccinations for all patients will be on day 1, 3, 5, and 7, followed by 4-weekly boosts until progression. Avelumab 800 mg will be administered every two weeks until progression. The enrolment of cohort 1 started with inclusion of the 1st patient in November 2018. The end of study is week 60. Follow up visits will be on months 1, 3, 6, 12 and 24. Objective response rate (ORR), clinical response using iRano criteria, immunological correlates before and after treatment using ELISPOT, FACS, TCR-sequencing, IF, and IHC laboratory methods. Clinical trial information: NCT03750071.