Bevacizumab, irinotecan, and radiotherapy versus standard temozolomide and radiotherapy in newly diagnosed, MGMT-non-methylated glioblastoma patients: First results from the randomized multicenter GLARIUS trial.

Ulrich Herrlinger, Niklas Schaefer, Joachim Peter Steinbach, Astrid Weyerbrock, Peter Hau, Roland Goldbrunner, Franziska Friedrich, Florian Stockhammer, Florian Ringel, Christian Braun, Ralf Kohnen, Barbara Leutzge, Claus Belka, Horst Urbach, Walter Stummer, Martin Glas; Division of Clinical Neurooncology, Department of Neurology and Center of Integrated Oncology Cologne/Bonn, University of Bonn, Bonn, Germany; Senckenberg Institute of Neurooncology, Frankfurt, Germany; Department of Neurosurgery, University of Freiburg, Freiburg, Germany; Department of Neurology and Wilhelm Sander NeuroOncology Unit, University Hospital Regensburg, Regensburg, Germany; Department of Neurosurgery, University of Cologne and Center of Integrated Oncology Cologne/Bonn, Cologne, Germany; Department of Radiation Oncology, University of Leipzig, Leipzig, Germany; Department of Neurosurgery, University of Goettingen, Goettingen, Germany; Department of Neurosurgery, Klinikum rechts der Isar Technical University of Munich, Munich, Germany; Department of General Neurology, University of Tuebingen, Tuebingen, Germany; Research Pharmaceutical Services, Inc., Nuremberg, Germany; Roche Pharma AG, Grenzach-Wyhlen, Germany; Department of Radiation Oncology, Ludwig Maximilians University Munich, Munich, Germany; Department of Radiology, Division of Neuroradiology, University of Bonn, Bonn, Germany; Department of Neurosurgery, University of Munster, Munster, Germany; Division of Clinical Neurooncology, Department of Neurology and Center of Integrated Oncology Cologne/Bonn and Stem Cell Pathologies Group, University of Bonn and Clinical Cooperation Unit Neurooncology, MediClin Robert Janker Clinic, Bonn, Germany

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A randomized phase II study of bevacizumab versus bevacizumab plus lomustine versus lomustine single agent in recurrent glioblastoma: The Dutch BELOB study.

Walter Taal, Hendrika M Oosterkamp, Annemiek M.E. Walenkamp, Laurens Victor Beerepoot, Monique Hanse, J. Buter, Aafke Honkoop, Dolf Boerman, Filip Yves Francine Leon De Vos, Rob L. Jansen, Franckette W.P.J. van den Berkmortel, Dieta Brandsma, Johan M Kros, Jacoline E Bromberg, Irene van Heuvel, Marion Smits, Bronno van der Holt, Rene Vernhout, Martin J. Van Den Bent, Landelijke Werkgroep voor NeuroOncologie; Erasmus MC, Rotterdam, Netherlands; Medisch Centrum Haaglanden, Den Haag, Netherlands; Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands; St Elisabeth Hospital, Tilburg, Netherlands; Catharina ziekenhuis, Eindhoven, Netherlands; VU University Medical Center, Amsterdam, Netherlands; Isala Kliniek, Zwolle, Netherlands; Rijnstate ziekenhuis, Arnhem, Netherlands; Utrecht University Medical Center, Utrecht, Netherlands; Department of Medical Oncology, Maastricht University Medical Center, Maastricht, Netherlands; Atrium Medical Center, Heerlen, Netherlands; Department of Neurology, the Netherlands Cancer Institute - Antoni van Leeuwenhoek, Amsterdam, Netherlands; Department of Neuropathology, Erasmus MC – Daniel den Hoed Cancer Center, Rotterdam, Netherlands

Background: Bevacizumab (BEV) is widely used in recurrent glioblastoma, alone or in combination with other agents. There is however no well-controlled trial to support the use for this indication. Methods: In a three-arm Dutch multicenter randomized phase II study (NTR 1929) patients were assigned to either BEV 10 mg/kg iv every 2 weeks, BEV 10 mg/kg iv every 2 weeks and 110 mg/m² lomustine every 6 weeks, or lomustine 110 mg/m² every 6 weeks. Eligible were patients with histologically proven glioblastoma, with a first recurrence after chemo-irradiation with temozolomide, having concluded radiotherapy more than 3 months ago, with adequate bone marrow, renal and hepatic function, and WHO performance status (PS) 0-2. Primary endpoint was 9 months overall survival (OS); P₀ was set at 35% and P₁ at 55%. Progression was defined using RANO criteria. A safety review after the first 10 patients in the combination arm was preplanned. Results: Between December 2009 and November 2011, 153 patients were enrolled of whom 148 were considered eligible. Median age was 57 years (range, 24-77) and median WHO PS was 1. With respect to prognostic factors groups were well balanced. After review of the safety cohort the dosage lomustine in the combination arm was lowered to 90 mg/m² because of hematological toxicity (predominantly thrombocytopenia without symptoms). At this lower lomustine dose level the combination treatment was in general well tolerated. Outcome: see Table. Conclusions: In this first well-controlled study on BEV in recurrent glioblastoma with a primary OS endpoint, combination treatment with bevacizumab and lomustine met the prespecified criterion for further investigation in clinical trials, whereas both drugs given as single agent failed to meet this criterion. Clinical trial information: NTR1929.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>% 9 mo OS (95% CI)</th>
<th>Median PFS (mo)</th>
<th>% 6 mo PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEV</td>
<td>50</td>
<td>38% [25, 51]</td>
<td>3</td>
<td>18 [9, 30]</td>
</tr>
<tr>
<td>Lomustine</td>
<td>46</td>
<td>43% [29, 57]</td>
<td>2</td>
<td>11 [4, 22]</td>
</tr>
<tr>
<td>BEV/lomustine 90 mg/m²</td>
<td>44</td>
<td>59% [43, 72]</td>
<td>4</td>
<td>41 [26, 55]</td>
</tr>
<tr>
<td>BEV/lomustine 110 mg/m²</td>
<td>8</td>
<td>88% [39, 98]</td>
<td>11</td>
<td>60 [15, 77]</td>
</tr>
</tbody>
</table>

n: number of patients, PFS: progression free survival, CI: confidence interval, mo: months.
Tumor response based on adapted Macdonald criteria and assessment of pseudo-progression (PsPD) in the phase III AVAglio trial of bevacizumab (Bv) plus temozolomide (T) plus radiotherapy (RT) in newly diagnosed glioblastoma (GBM).

Wolfgang Wick, Timothy Francis Cloughesy, Ryo Nishikawa, Warren Mason, Frank Saran, Roger Henriksson, Magalie Hilton, Yannick Kerloeguen, Oliver L. Chinot; University of Heidelberg Medical Center, Heidelberg, Germany; University of California, Los Angeles, Los Angeles, CA; Saitama Medical University International Medical Center, Saitama, Japan; Princess Margaret Hospital, Toronto, ON, Canada; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Regional Cancer Center Stockholm; Umeå University Hospital, Stockholm/Umeå, Sweden; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France

Background: Until recently the primary criteria for assessing response to GBM therapy were those by Macdonald et al. (JCO 1990;8:1277–80). Advances in imaging technology/targeted therapies exposed limitations, addressed in 2010 by Response Assessment in Neuro-Oncology Working Group. Prior to this, the AVAglio study similarly adapted Macdonald criteria to address anti-angiogenic therapy/corticosteroid use by incorporating non-contrast-enhancing components and integrating a strict algorithm to standardize assessment of possible PsPD.

Methods: Randomised pts (n=921) received: T/RT + Bv or placebo (P), 6 wks; 28-d break; maintenance T + Bv or P (6 cycles); monotherapy Bv or P until PD/unacceptable toxicity. Tumor response was investigator (inv)-assessed by MRI (adapted Macdonald criteria) at baseline (BL), end of break, every 2nd maintenance cycle, every 9 wks during monotherapy, at PD and 9 wks post-PD. PsPD was inv-assessed at the end of the break. A ≥25% increase in index lesions and/or unequivocal progression of existing non-index lesions relative to BL and in the absence of clinical deterioration was assessed as PsPD. Confirmatory PsPD assessment: end of the 2nd maintenance cycle. If progression was confirmed, PsPD was retrospectively designated as PD. If PsPD was confirmed, pts remained on treatment and the 1st post-RT MRI was used as a new BL. Best ORR was evaluated in pts with lesions at BL, excluding pts with confirmed PsPD.

Results: Co-primary endpoint of inv-assessed PFS was longer for pts receiving Bv/RT compared with P/RT (HR 0.64, 95% CI 0.55–0.74; p<0.0001). Best ORR and PsPD are shown (Table).

Conclusions: Addition of Bv to 1st-line T/RT significantly improves ORR. The rate of confirmed PsPD was low in both arms. Clinical trial information: NCT00943826.

| Best ORR |
|-----------------|-----------------|
| Bv+T/RT | P+T/RT |
| n | 375 | 366 |
| Responders, n (%) | 144 (38.4 (33.5–43.5) | 66 (18 (14.2–22.4)) |
| Difference, % (95% CI) | 20.4 (13.9–26.8) | p<0.0001 |

| Potential PsPD, n (%) | 458 | 463 |
| End of treatment break | 12 (2.6) | 84 (18.1) |
| Post-2nd maintenance cycle | 10 (2.2) | 43 (9.3) |
| Confirmed PsPD, n (%) | 1 (0.2) | 35 (7.6) |
| Rejected PsPD, n (%) | 1 (0.2) | 6 (1.3) |
| Missing, n (%) | 1 (0.2) | 6 (1.3) |
Comparative impact of treatment on patient reported outcomes (PROs) in patients with glioblastoma (GBM) enrolled in RTOG 0825.

Terri S. Armstrong, Minhee Won, Jeffrey Scott Wefel, Mark R. Gilbert, Stephanie L. Pugh, David Brachman, Ritsuko Komaki, Ian R. Crocker, H. Ian Robins, R. Jeffrey Lee, Minesh P. Mehta, Merideth M Wendland; University of Texas Health Science Center School of Nursing, Houston, TX; Radiation Therapy Oncology Group, Philadelphia, PA; The University of Texas M.D. Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Arizona Oncology Services Foundation, Phoenix, AZ; Department of Radiation Oncology, Emory University, Atlanta, GA; University of Wisconsin Hospitals and Clinics, Madison, WI; Intermtn Medcl Ctr, Salt Lake City, UT; University of Maryland, Baltimore, MD; Willamette Valley Cancer Institute, Eugene, OR

Background: RTOG 0825 tested if adding bevacizumab (BEV) to standard chemoradiation improves survival (OS) or progression free survival (PFS) in newly diagnosed GBM. While OS was equivalent, PFS was longer with Bev (Arm 2) than with placebo (Arm 1). Patients completed quality of life and symptom PROs to evaluate clinical benefit. Methods: The M.D. Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) and the EORTC core Quality of life Questionnaire and brain tumor module (EORTC QLQ-C30/BN20), were completed by pts at baseline (B) and longitudinally (wk 6, 10, 22, 34, and 46) while on study. The difference between treatment arms were compared from B with evaluation in subsequent weeks in those pts without disease progression; and early change (EC) (baseline to wk 10) between those with and without progression as predictors for OS and PFS. Results: 542 pts consented to participate on this trial, and 507 randomized pts participated, with completion of forms by 94% at baseline, 75% at wk 10, 61% at wk 22, and 58% at wk 34. There was a trend for all MDASI-BT symptom groupings to be worse in Arm 2, with significant findings in treatment symptoms at wk 22 and wk 34; both affective and generalized disease symptoms were also significantly worse. For EORTC QLQ30/BN20, differential effects varied at each time point, with no persistent differences. For the MDASI-BT, B neurologic symptom grouping and EC in cognitive symptoms were prognostic for both OS and PFS. For the EORTC QLQ30/BN20, global QOL and motor dysfunction at B as well as EC in communication and leg weakness were prognostic for OS; whereas physical function at B and EC in headaches, seizures, and weak legs were prognostic for PFS. Conclusions: The longitudinal collection of PROs in this phase III trial revealed important treatment-related differences as there was overall more deterioration in symptoms and QOL in Arm 2 as compared to Arm 1, with persistent significant differences in treatment associated symptoms. B and EC tumor associated symptoms on both PRO tools were prognostic for OS and PFS. Longitudinal modeling is ongoing to further assess for differential impact of treatment on symptoms and QOL. Support: U10 CA21661, U10 CA37422 and Genentech, Inc. Clinical trial information: NCT00884741.
Neurocognitive function (NCF) outcomes in patients with glioblastoma (GBM) enrolled in RTOG 0825.

Jeffrey Scott Wefel, Stephanie L. Pugh, Terri S. Armstrong, Mark R. Gilbert, Minhee Won, Merideth M Wendland, David Brachman, Ritsuko Komaki, Ian R. Crocker, H. Ian Robins, R. Jeffrey Lee, Minesh P. Mehta; The University of Texas M.D. Anderson Cancer Center, Houston, TX; Radiation Therapy Oncology Group, Philadelphia, PA; University of Texas Health Science Center School of Nursing, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX; Willamette Valley Cancer Institute, Eugene, OR; Arizona Oncology Services Foundation, Phoenix, AZ; Department of Radiation Oncology, Emory University, Atlanta, GA; University of Wisconsin Hospitals and Clinics, Madison, WI; Intermtvn Medcl Ctr, Salt Lake City, UT; Northwestern Memorial Hospital, Chicago, IL

Background: RTOG 0825 evaluated overall survival (OS) and progression-free survival (PFS) differences in patients with newly diagnosed GBM treated with standard chemoradiation, maintenance temozolomide and placebo (Arm 1) or bevacizumab (Arm 2). While OS was equivalent, PFS was longer in Arm 2. Longitudinal NCF testing was performed to evaluate clinical benefit. Methods: NCF was evaluated at baseline and while on study and progression free with the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT) and Controlled Oral Word Association (COWA). Change in NCF from baseline was categorized using the reliable change index. Differences between treatment arms were compared at follow-up evaluations. Additionally, baseline (B) and early changes (EC) (B to week 10) in NCF were examined as prognostic factors. Results: 542 patients consented and 507 randomized patients participated, with test completion rates at weeks 0 (B), 10, 22, and 34 of 94-97, 69-73, 59-64, and 53-58%, respectively. Mean test performance at B was equivalent between arms and ranged from -0.8 to -4.8 SDs below healthy population norms with global NCF on a composite variable at -2.0 SDs. There were no statistically significant between arm differences in frequency of improvement through week 34. Decline on COWA (verbal measure of executive function) at week 34 relative to baseline was more common (16.1 vs 5.7%) in patients in Arm 1 (p<0.05); whereas, there were trends for more decline in Arm 2 on a visuomotor measure of executive function (TMT B, p< 0.06; 22.2 vs 35.4%). B performance and EC in global NCF, memory, executive function and processing speed were prognostic for OS. At B, global NCF was prognostic for PFS. EC in global NCF, memory and executive function were prognostic for PFS. Conclusions: There was a statistically significant difference in the frequency of decline on a verbal test of executive function at week 34 favoring Arm 2. However, this was not found at earlier time points and was not found on a visuomotor test of executive function. B and EC in NCF were prognostic for OS and PFS. Longitudinal modeling is ongoing to further evaluate the impact of treatment on patients’ NCF. Support: U10 CA21661, U10 CA37422 and Genentech, Inc. Clinical trial information: NCI-2009-01670.
Progression-free survival (PFS) and health-related quality of life (HRQoL) in AVAglio, a phase III study of bevacizumab (Bv), temozolomide (T), and radiotherapy (RT) in newly diagnosed glioblastoma (GBM).

Roger Henriksson, Andrew Bottomley, Warren Mason, Frank Saran, Wolfgang Wick, Ryo Nishikawa, Timothy Francis Cloughesy, Antoine F Carpentier, Khe Hoang-Xuan, Petr Kavan, Dana Cernea, Alba Ariela Brandes, Magalie Hilton, Ana Maria Abajo Guijarro, Arliene Ravelo, Oliver L. Chinot; Regional Cancer Center Stockholm; Umeå University Hospital, Stockholm/Umeå, Sweden; Quality of Life Department, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium; Princess Margaret Hospital, Toronto, ON, Canada; The Royal Marsden NHS Foundation Trust, London, United Kingdom; University of Heidelberg Medical Center, Heidelberg, Germany; Saitama Medical University International Medical Center, Saitama, Japan; University of California, Los Angeles, Los Angeles, CA; Department of Neurology, Hôpital Avicenne, AP-HP and Paris 13 University, Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne, Bobigny and Paris, France; Assistance Publique–Hôpitaux de Paris, UPMC, CRIMC, Paris, France; Department of Oncology, McGill University, Montreal, QC, Canada; Oncology Institute, Cluj-Napoca, Romania; Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna, Bologna, Italy; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Genentech Inc., South San Francisco, CA; Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France

Background: GBM has a high disease burden and poor prognosis, and impacts negatively on HRQoL. Symptomatic therapies for GBM, such as corticosteroids (CS), may impact patient status negatively.

Methods: AVAglio, a randomized, double-blind, placebo (P)-controlled trial in patients (pts) ≥18 yrs with newly diagnosed GBM, evaluated the addition of Bv or P (10mg/kg, q2w) to 6 wks of T (75mg/m²/d) + RT (2Gy, 5d/wk) followed by 28 treatment-free days, then 6 cycles of T (150–200 mg/m²/d, 5d q4w) with Bv or P (10 mg/kg, q2w), and then single-agent Bv or P (15 mg/kg, q3w) until disease progression (PD)/unacceptable toxicity. Co-primary endpoints were investigator-assessed PFS and overall survival. Secondary endpoints included HRQoL (EORTC QLQ-C30 and BN20, with 5 prespecified domains based on relevance in GBM). HRQoL time to definitive deterioration (TDD) was defined as time from randomization to ≥10 point deterioration from baseline with no subsequent improvement, PD, or death. Exploratory endpoints included KPS and CS use.

Results: Baseline characteristics were well balanced. Bv significantly prolonged PFS (HR 0.64, 95% CI 0.55–0.74, p<0.0001; median 10.6 vs 6.2 mo) and delayed TDD in HRQoL compared with P (p<0.0001; Table). Functional independence (KPS ≥ 70%) was maintained during PFS in both arms (median Bv vs P: 9 vs 6 mo). Among pts on CS (≥ 2mg) at baseline, discontinuation (≥ 5 consecutive days) was more frequent with Bv than P (66% vs 47%). In pts off CS at baseline (< 2mg), time to CS initiation was significantly longer with Bv than P (HR 0.71, 95% CI 0.57–0.88; median 12.3 vs 3.7 mo). Conclusions: Addition of Bv to RT/T provided a clinically meaningful and statistically significant PFS improvement associated with stable/improved HRQoL and KPS, and reduced CS requirement. Clinical trial information: NCT00943826.

<table>
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<tr>
<th></th>
<th>P + RT (n=463)</th>
<th>Bv + RT (n=458)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>KM-estimated median TDD, mo</td>
<td></td>
<td></td>
<td>3.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Global health status</td>
<td>6.4</td>
<td>6.4</td>
<td>0.64 (0.56–0.74)</td>
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</tr>
<tr>
<td>Physical functioning</td>
<td>6.1</td>
<td>6.1</td>
<td>0.70 (0.61–0.81)</td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>7.4</td>
<td>7.4</td>
<td>0.63 (0.55–0.73)</td>
<td></td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>8.6</td>
<td>8.6</td>
<td>0.67 (0.58–0.78)</td>
<td></td>
</tr>
<tr>
<td>Communication deficit</td>
<td>6.9</td>
<td>6.9</td>
<td>0.67 (0.58–0.77)</td>
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</tbody>
</table>
Phase III randomized, double-blind, placebo-controlled trial of donepezil in irradiated brain tumor survivors.

Stephen R. Rapp, Doug Case, Ann Peiffer, Michelle Joy Naughton, Volker W. Stieber, Gerald K. Bayer, Paul A. Bilodeau, Dennis Frederic Moore, Steven Charles Falchuk, Burton M. Needles, James Pletchoff, William J. Edenfield, Jeffrey K. Giguere, Nicholette Erickson, Monica Elena Loghin, Edward G. Shaw; Wake Forest University, School of Medicine, Winston Salem, NC; Wake Forest University, School of Medicine, Winston-Salem, NC; Forsyth Regional Cancer Center, Winston-Salem, NC; Green Bay Oncology, Green Bay, WI; Medical College of Georgia, Augusta, GA; Cancer Center of Kansas, Wichita, KS; Medical Arts Pavil, Newark, DE; St John’s Mercy Medical Center, St. Louis, MO; St. John’s Mercy Hospital, St Louis, MO; Cancer Centers of the Carolinas, Greenville, SC; Cancer Centers of the Carolinas, Seneca, SC; Central Maine Medical Center, Lewiston, ME; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: This RCT assessed the effect of 24 weeks of 5-10 mg per day of donepezil, an acetyl cholinesterase inhibitor, on cognitive functioning (primary endpoint) and fatigue, mood and QOL in long-term brain tumor survivors following partial or whole-brain irradiation. Cognitive results are reported herein. Methods: From 2/08-12/11, 198 adult primary and metastatic brain tumor survivors > 6 months post radiation treatment (>30 Gray) recruited at 24 sites affiliated with the Wake Forest Community Clinical Oncology Program Research Base, 3 CTSU sites and M.D. Anderson Cancer Center were randomly assigned to receive donepezil (n=99) or placebo (n=99). Cognitive function was assessed at baseline, 12 and 24 weeks with Hopkins Verbal Learning Test-Revised, Rey-Osterreith Complex Figure, Trail Making Test, Digit Span, Controlled Oral Word Association, and Grooved Pegboard. A Cognitive Composite (CC) score was the primary outcome. Results: The sample was 91% White, 54% female, and median age was 55 yrs. 66% had primary tumors, 27% brain metastases and 8% PCI. Median time since diagnosis: 38 mos. 95% had 0-1 ECOG performance status scores. 74% completed the study. CC score improved significantly by 24 weeks in both arms (p < .01); however, there was not a statistically significant difference between groups (p = .57). Donepezil group performed better than placebo on HVLT Recognition (p = .03) and Discrimination (p = .01) and GP-Dominant Hand (p = 0.02). Significant interactions were found between treatment arm and baseline cognitive scores for: CC (p = .01), HVLT Immed. Recall (p = .03), HVLT %Savings (p < .01), Digit Span Forward (p = .01), ROCF Copy (p = .03), TMT-B (p = .05) and GP-Dominant (p < .01). In all cases, the benefit of donepezil, relative to placebo, was greater for those with worse baseline scores. Conclusions: Long-term brain tumor survivors treated with brain irradiation who have cognitive impairment can benefit from 5-10mg of donepezil for 24 weeks. Improvements in verbal memory, working memory, visuo- and psychomotor performance and executive functioning were observed in this group. (Study supported by NIH/NINR grant 5R01NR009675-04, NIH/NCI grant 2 U10 CA 81851-09-13 and Eisai, Inc.) Clinical trial information: NCT00369785.

Temozolomide chemotherapy versus radiotherapy in molecularly characterized (1p loss) low-grade glioma: A randomized phase III intergroup study by the EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033).

Brigitta G Baumert, Warren P. Mason, Gail Ryan, Jacoline E Bromberg, Martin J. Van Den Bent, Khê Hoang-Xuan, Alba Ariela Brandes, Guy Kantor, Martin JB Taphoorn, Mohamed Ben Hassel, Jeremy Rees, Wolfgang Wick, Andreas Von Deimling, Christian Hartmann, Johan M Kros, Monika E. Hegi, Nicolas Dif, Denis A. Lacombe, Thierry Gorlia, Roger Stupp; Department of Radiation Oncology (MAASTRO), GROW (School for Oncology), Maastricht University Medical Center, Maastricht, Netherlands; Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada; Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; Erasmus MC, Rotterdam, Netherlands; Erasmus University Medical Center, Rotterdam, Netherlands; APHP-CHU Pitié-Salpêtrière, Paris, France; Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna, Bologna, Italy; Department of Radiotherapy, Institut Bergonié, Comprehensive Cancer Center, Bordeaux/University Bordeaux Segalen, Bordeaux, France; Department of Neurology, Medical Center Haaglanden, The Hague, Netherlands; Departments of Medical Oncology and Radiotherapy, Centre Eugène Marquis, Rennes, France; National Hospital for Neurology and Neurosurgery, London, United Kingdom; University of Heidelberg Medical Center, Heidelberg, Germany; Institute of Pathology, Dept Neuropathology, University of Heidelberg, INF 224, and CCU Neuropathology German Cancer Research Center (DKFZ, Heidelberg, Germany; Department of Neuropathology, Institute of Pathology, Medizinische Hochschule, Hannover, Germany; Department of Neuropathology, Erasmus MC–Daniel den Hoed Cancer Center, Rotterdam, Netherlands; University of Lausanne Hospitals, Lausanne, Switzerland; European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; European Organisation for Research and Treatment of Cancer, Brussels, Belgium; University Hospital Zurich, Zurich, Switzerland

Background: Outcome of low-grade glioma (LGG) is highly variable. We investigated whether primary chemotherapy in comparison to standard radiotherapy (RT) prolongs progression-free (PFS) and overall survival (OS), and whether prognostic molecular factors could be defined. Methods: Progressive, symptomatic or high-risk patients with a LGG requiring treatment other than surgery were randomized (after stratification for 1p-status) to either conformal RT (50.4 Gy/28 fractions) or dose-dense temozolomide [TMZ] (75 mg/m² daily x 21 days, q28 days, max. 12 cycles). Primary endpoint was PFS, secondary analyses included OS and impact of 1p status. Results: 477 patients were randomized (2005-2012, median FU 45.5 months). Analysis was performed after 246 progression events. Hematological toxicity was observed in 9.4% of TMZ patients. PFS was not significantly different, median OS not reached. 1p deletion was a positive prognostic factor irrespective of treatment (p-value stratified by treatment (PFS: 0.0003;HR=0.59 95% CI(0.45-0.78)/OS: 0.002;HR=0.49 95% CI (0.32-0.77)). Conclusions: First-line treatment with TMZ compared to RT did not improve PFS in high-risk LGG patients. Although interaction test was not significant, there was a trend for inferior PFS in patients treated by TMZ with 1p intact, while OS may be better when 1p-deleted patients receive TMZ upfront. Survival analysis requires further maturation of the data. Clinical trial information: EudraCT number 2004-002714-11.

Barbara Jean Fisher, Jeff Lui, David R. Macdonald, Glenn Jay Lesser, Stephen Coons, David Brachman, Samuel Ryu, Maria Werner-Wasik, Jean-Paul Bahary, Chen Hu, Miness P. Mehta, Radiation Therapy Oncology Group; Department of Radiation Oncology, London Regional Cancer Program, London, ON, Canada; Radiation Therapy Oncology Group, Philadelphia, PA; London Regional Cancer Program, London, ON, Canada; Wake Forest University, School of Medicine, Winston-Salem, NC; Barrow Neurological Institute, Phoenix, AZ; Arizona Oncology Services Foundation, Phoenix, AZ; Henry Ford Hospital, Detroit, MI; Thomas Jefferson University Hospital, Philadelphia, PA; Centre Hospitalier de l’Universite de Montreal, Montreal, QC, Canada; Northwestern Memorial Hospital, Chicago, IL

Background: The primary endpoint of RTOG 0424 was to compare the 3-year survival (OS) of a regimen of concurrent and adjuvant temozolomide (TMZ) and radiotherapy (RT) in a high-risk low-grade glioma (LGG) population to the 3 year (yr) OS rate of the high risk EORTC LGG patients (pts) reported by Pignatti et al (J Clin Oncol 2002;20(8):2076-84). Secondary endpoints were: progression-free survival (PFS), toxicity, neurocognitive and quality of life data and molecular analysis. Methods: Pts with LGG’s and >=3 high risk factors (age > = 40, astrocytoma dominant histology, tumor crossing midline, tumor > = 6 cm or preoperative neurological function status > 1) were eligible and treated with conformal RT (54 Gy/30 fractions) plus concurrent TMZ 75 mg/m2/day for 6 weeks and post-RT TMZ 150-200 mg/m2/day days 1-5 q28 days for up to 12 cycles. The study was designed to detect a 43% increase in median survival time (MST) from 40.5 to 57.9 months, and a 20% improvement in 3 yr OS rate from 54% to 65%, at a 10% significance level (1 sided) and 96% power. Results: Between January 2005-August 2009 136 pts were accrued, 129 (75 males, 54 females) were evaluable. Median age was 49 years, 91% had a Zubrod score 0-1 and 69%, 25% and 6% of pts had 3, 4 and 5 high risk factors respectively. With a median follow-up time of 4.1 yrs, minimum follow-up of 3 yrs, MST has not yet been reached. Three year OS rate was 73.1% (95%CI:65.3-80.8%), significantly improved from historical control with a p-value <0.0001. No difference in OS rates for pts with 3, 4 or 5 high risk factors was seen. 3 year PFS was 59.2% (95% CI:50.7-67.8%). Grade 3 adverse events (AE) occurred in 43% of pts and grade 4 AE in 10%, primarily hematologic, constitutional or gastrointestinal (nausea, anorexia) toxicity. One patient died of herpes encephalitis. Secondary analyses are ongoing. Radiation Quality Assurance was per protocol/ acceptable in 95% and 74% of pts completed chemotherapy per protocol. Conclusions: The 3 year OS rate of 73.1% for these high risk LGG pts is significantly higher than those reported for historical controls (54%, p < 0.0001, one-sided) and the study-hypothesized 65%. Supported by RTOG U10 CA21661 and CCOP U10 CA37422 grants from NCI and Merck Clinical trial information: NCT00114140.
Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with O\textsubscript{6}-methylguanine-DNA methyltransferase (MGMT) promoter methylation: Final results of the multicenter, randomized, open-label, controlled, phase III CENTRIC study.

Roger Stupp, Monika E. Hegi, Thierry Gorlia, Sara Erridge, Danica Grujicic, Joachim Peter Steinbach, Wolfgang Wick, Rafał Tarnawski, Do-Hyun Nam, Astrid Weyerbrock, Peter Hau, Martin JB Taphoorn, Louis B. Nabors, David A. Reardon, Martin J. Van Den Bent, James R. Perry, Yong Kil Hong, Christine Hicking, Martin Picard, Michael Weller, on behalf of the European Organisation for Research and Treatment of Cancer (EORTC), the Canadian Brain Tumor Consortium, and the CENTRIC Study Team; Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; EORTC Data Centre, Brussels, Belgium; Edinburgh Cancer Research UK Centre, Edinburgh, United Kingdom; Institute for Neurosurgery, Clinical Center Serbia, Belgrade, Serbia; Klinikum der J.W. Goethe Universität Frankfurt, Dr. Senkenbergisches Institut für Neuroonkologie, Frankfurt, Germany; Universitätsklinikum Heidelberg, Heidelberg, Germany; Maria Skłodowska-Curie Memorial Cancer-Center and Institute of Oncology Gliwice Branch, Radiotherapy and Chemotherapy Clinic, Gliwice, Poland; Samsung Medical Center, Seoul, South Korea; Universitätsklinikum Freiburg, Allgemeine Neurochirurgie, Freiburg, Germany; Universitätsklinikum Regensburg, Neurologie und Wilhelm Sander-Therapieeinheit NeuroOnkologie, Regensburg, Germany; Medical Center Haaglanden, The Hague, Netherlands; University of Alabama at Birmingham, Birmingham, AL; Dana-Farber Cancer Institute, Boston, MA; Erasmus MC, Rotterdam, Netherlands; Sunnybrook Health Sciences Centre, Toronto, ON, Canada; Catholic University of Korea, Seoul St Marys Hospital, Seoul, South Korea; Merck KGaA, Darmstadt, Germany; University Hospital Zurich, Zurich, Switzerland

The full, final text of this abstract will be available at abstract.asco.org at 7:30 AM (EDT) on Sunday, June 2, 2013, and in the Annual Meeting Proceedings online supplement to the June 20, 2013, issue of Journal of Clinical Oncology. Onsite at the Meeting, this abstract will be printed in the Sunday edition of ASCO Daily News.
Molecular predictors of outcome and response to bevacizumab (BEV) based on analysis of RTOG 0825, a phase III trial comparing chemoradiation (CRT) with and without BEV in patients with newly diagnosed glioblastoma (GBM).

Erik P. Sulman, Minhee Won, Deborah T. Blumenthal, Michael A. Vogelbaum, Howard Colman, Robert B. Jenkins, Arnab Chakravarti, Robert Jeraj, Paul D. Brown, Kurt A. Jaekle, David Schiff, James Dignam, James Norman Atkins, David Brachman, Maria Werner-Wasik, Ritsuko Komaki, Mark R. Gilbert, Minesh P. Mehta, Kenneth D. Aldape; The University of Texas MD Anderson Cancer Center, Houston, TX; Radiation Therapy Oncology Group, Philadelphia, PA; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; Cleveland Clinic Foundation, Cleveland, OH; University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; Mayo Clinic, Rochester, MN; Arthur G. James Cancer Center, The Ohio State University, Columbus, OH; Department of Medical Physics, University of Wisconsin, Madison, WI; Mayo Clinic, Jacksonville, FL; University of Virginia Medical Center, Charlottesville, VA; National Surgical Adjuvant Breast and Bowel Project and SCCC-CCOP, Goldboro, NC; Arizona Oncology Services Foundation, Phoenix, AZ; Thomas Jefferson University Hospital, Philadelphia, PA; University of Maryland, Baltimore, MD; The University of Texas M.D. Anderson Cancer Center, Houston, TX

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Optimizing the identification of anaplastic oligodendrogloma patients that benefit from adjuvant PCV chemotherapy using the Illumina platform: A further report from EORTC study 26951.

Martin J. Van Den Bent, Lale Erdem, Thierry Gorlia, Martin JB Taphoorn, Johan M Kros, Pieter Wesseling, Anouk Allgeier, Hendrikus J Dubbink, Ahmed Idbaih, Marc Sanson, Pim French, EORTC Brain Tumor Group; Erasmus University Medical Center, Rotterdam, Netherlands; Erasmus MC, Rotterdam, Netherlands; European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; Medical Center Haaglanden, The Hague, Netherlands; UMCN St Radboud, Nijmegen, Netherlands; Université Pierre et Marie Curie Paris VI, Paris, France; Université Pierre et Marie Curie-Paris 6, Centre de Recherche de l’Institut du Cerveau et de la Moelle épinière (CRIHM), Neurologie 2, Paris, France

Background: Adjuvant PCV chemotherapy improves overall survival (OS) in 1p/19q co-deleted grade 3 gliomas. Analyses of EORTC 26951 and RTOG 9402 suggest that other molecularly defined subsets of grade III tumors benefit as well. We previously identified a CpG-Island Hypermethylated Phenotype (CIMP+) as a candidate biomarker. This was further explored in a larger series using snap frozen (SF) or formalin fixed paraffin embedded (FFPE) tumor material, and compared to the value of 1p/19q, IDH1, and MGMT status.

Methods: Methylation profiles were assessed using the Infinium HumanMethylation 27 or 450 BeadChip (Illumina). MGMT promoter methylation was re-assessed with a logistic regression model (MGMT-STP27) using probes cg1243587 and cg12981137 of the platform as described (Bady et al, Acta Neuropathol 2012;124:547-60). These probes correspond to area’s of the promoter correlated to MGMT protein expression. Previously, MGMT promoter methylation had been assessed using methylation specific multiplex ligation-dependent probe amplification (MS-MLPA). Results: Methylation profiling was conducted in 115 patients. CIMP status correlation between FFPE and SF was excellent ($R^2$ 0.96). In multivariate analysis, 1p/19q co-deletion and CIMP status were independent prognostic factors. Although 1p/19q status and IDH mutational status identify subgroups with more benefit of PCV chemotherapy, tests for interaction remain negative (p 0.25 and 0.33 respectively); MGMT status (MS-MLPA) had no impact (p = 0.70). However, CIMP status was of borderline predictive significance (p = 0.07), and MGMT-STP27 was of statistical significance (p = 0.003; HR unmethylated 1.61, 95% CI [0.71, 3.66], HR methylated 0.37, 95% CI 0.23, 0.61). Conclusions: CIMP status and MGMT promoter methylation assessed with Illumina HumanMethylation BeadChips appear the most informative tests for identifying grade III glioma patients benefitting from the addition of PCV to RT. Validation in an independent dataset is required. Clinical trial information: NCT00002840.
Tumor pharmacokinetics (PK) and pharmacodynamics (PD) of SAR245409 (XL765) and SAR245408 (XL147) administered as single agents to patients with recurrent glioblastoma (GBM): An Ivy Foundation early-phase clinical trials consortium study.

Timothy Francis Cloughesy, Paul S. Mischel, Antonio Marcilio Padula Omuro, Michael Prados, Patrick Y. Wen, Bin Wu, Kevin Rockich, Yi Xu, Joanne J. Lager, Ingo K. Mellinghoff; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; Ludwig Institute for Cancer Research, La Jolla, CA; Memorial Sloan-Kettering Cancer Center, New York, NY; University of California, San Francisco, San Francisco, CA; Dana-Farber Cancer Institute, Boston, MA; Sanofi-Aventis, Cambridge, MA; Sanofi-Aventis, Bridgewater, NJ

Background: XL765 is a potent pan PI3K inhibitor with activity against mTOR and XL147 is a potent pan-PI3K inhibitor. Inhibition of the PI3K/mTOR pathway may be beneficial in the treatment of GBM.

Methods: Patients with GBM who were candidates for a surgical resection were eligible for this exploratory study. Cohorts of 6-10 patients were treated with one of three regimens: Cohort 1: XL765 50mg twice daily (BID), Cohort 2: XL147 200mg once daily (QD), Cohort 3: XL765 90mg QD for >10 days prior to undergoing tumor resection. Tumor tissue was obtained at ~12, 24 and 3 hours after the last dose, respectively. Frozen tumor tissue and blood were analyzed for drug concentration (PK) and pathway modulation was analyzed in post-dose frozen tumor tissue and compared to reference tumor samples from GBM patients not treated with XL765 or XL147. Pharmacodynamic impact (PD) on the pathway, apoptosis and proliferation was examined by immunohistochemistry (IHC) in an FFPE tumor sample from each patient and compared to an archived tumor sample from an earlier surgery. Results: Enrollment is complete with 21 patients enrolled; 6, 6 and 7 were evaluable for the PK/PD analysis in cohorts 1, 2 and 3, respectively. The toxicity profiles for both drugs were consistent with previous studies. PK analyses revealed a mean tumor to plasma ratio of 0.38 and 0.40 in cohorts 1 and 3 and 0.27 in cohort 2. PD analysis by IHC revealed reduction compared to archived tumor in pS6K1 in 4/6 and 7/7 patients in cohorts 1 and 3 and 6/6 patients in cohort 2. Reductions in Ki67 were observed in 6/6 and 5/7 patients in cohorts 1 and 3 and 4/6 patients in cohort 2. Conclusions: XL765 when given on a QD or BID schedule to patients with glioma yields moderately higher distribution of XL765 into CNS tumor compared to XL147 based on tumor to plasma ratios. Decreases in pS6K1, consistent with pathway inhibition, and decreases in Ki67, consistent with inhibition of proliferation, were observed following treatment with both XL147 and XL765. Clinical trial information: NCT01240460.
Interim analysis of a phase I/II study of panobinostat in combination with bevacizumab for recurrent glioblastoma.

Eudocia Quant Lee, David A. Reardon, David Schiff, Jan Drappatz, Alona Muzikansky, Samantha Hammond, Sean Aaron Grimm, Andrew David Norden, Rameen Beroukhim, Christine Sceppa McCluskey, Andrew S. Chi, Tracy Batchelor, Katrina H. Smith, Sarah C. Gaffey, Mary Gerard, Susan M. Snodgrass, Jeffrey J. Raizer, Patrick Y. Wen; Dana-Farber Cancer Institute, Boston, MA; University of Virginia Medical Center, Charlottesville, VA; University of Pittsburgh, Pittsburgh, PA; Massachusetts General Hospital Cancer Center, Boston, MA; University of Minnesota, Minneapolis, MN; Massachusetts General Hospital, Boston, MA; Novartis Pharmaceuticals, East Hanover, NJ; Northwestern University, Feinberg School of Medicine, Chicago, IL

Background: Bevacizumab is frequently used to treat recurrent GBM, but responses are generally not durable. Panobinostat is a histone deacetylase inhibitor with anti-neoplastic and anti-angiogenic effects in GBM and may work synergistically with bevacizumab. We conducted a multicenter phase I/II trial of panobinostat in combination with bevacizumab in patients with recurrent GBM. Methods: In the phase II trial, patients with recurrent GBM were treated with oral panobinostat 30 mg three times per week, every other week, in combination with bevacizumab 10 mg/kg every other week. The primary endpoint was 6-month progression-free survival (PFS6) and the study was powered to discriminate between a 35% and 55% PFS6 rate (85% power at an alpha level of 0.07). A planned interim analysis specified suspension of accrual and careful data review if 12 or more of the first 21 patients accrued to the study progress within 6 months of initiating treatment. Patients with recurrent GBM enrolled in the phase I study at the maximum tolerated dose (which is the phase II dose) were eligible for inclusion in the interim analysis. Results: Thirteen of the first 21 patients accrued to the GBM arm of the study had progressed within 6 months of initiating treatment. The study was closed to further accrual and a planned interim analysis was performed. Median age was 53 (range 22-66) and median KPS was 80% (60%-100%). PFS6 rate was 33.9% [95% CI 12.8, 56.5], median was PFS 5 months [95% CI 3 months, NR], and median OS was 342 days [95% CI 203 days, NR]. Five patients (23.8%) achieved partial responses. Conclusions: Although reasonably well-tolerated, this phase I/II study of panobinostat and bevacizumab in recurrent GBM did not meet criteria for continued accrual and the study was closed. Updated outcome and safety data will be presented at the meeting. Study Supported by: Novartis and Genentech Clinical trial information: NCT00859222.
NCCTG (Alliance) N0572: A phase II trial of sorafenib and temsirolimus in recurrent glioblastoma (GBM) patients who progress following prior RT/temozolomide (TMZ) and VEGF inhibitors (VEGFi).

Kurt A. Jaeckle, David Schiff, S. Keith Anderson, Evanthia Galanis, Philip J. Stella, Patrick J. Flynn, Jann Nagina Sarkaria, Caterina Giannini, Bradley J. Erickson, Jan C Buckner; Mayo Clinic, Jacksonville, FL; University of Virginia Medical Center, Charlottesville, VA; Mayo Clinic, Rochester, MN; Saint Joseph Mercy Health System, Ann Arbor, MI; Metro Minnesota Community Clinical Oncology Program, St. Louis Park, MN

Background: PFS6 is low (2.3%) and med OS brief (4 mos) for recurrent GBM pts who progress after prior RT/TMZ and bevacizumab (Bev), and then receive non-Bev containing regimens (Reardon et al, Br J Canc 2012). Following VEGFi exposure, tumor cell resistance potentially may result from activation of Ras/Raf/MEK/ERK (MAPK) and PI3K/Akt/mTOR signaling pathways. Temsirolimus (mTOR inhibitor) and sorafenib (Raf, PDGFR, VEGFR inhibitor) have previously shown limited single agent activity in GBM. Methods: Recurrent GBM pts who showed radiographic progression despite prior surgery, RT/TMZ Temozolomide, and VEGFi (initially or at recurrence) received sorafenib 200 mg PO bid and temsirolimus 20 mg IV weekly (the NCCTG N0572 phase I MTD) until progression. All pts had received 2 prior chemo regimens. A two-stage design was used, with 90% power to detect an increase in PFS6 from 8% to 23%, requiring 41 evaluable pts. The primary endpoint was PFS6; secondary endpoints included OS, TTP, and ORR. Toxicity (TOX) was assessed using CTC ver 3.0. Results: 44 evaluable pts were accrued. Four of the first 40 (10%) reached PFS6, but this did not meet the pre-study threshold for success. Median TTP was 1.8 mos. (40 events, 95% CI: 1.5 – 2.3); median OS was 5 mos. (36 events, 95% CI: 6.6 – 3.1), and no objective responses were reported. Eight pts are alive; 4 have not progressed (median F/U 3.1 mos.; max, 12.2 mos.). Grade 3+ non-heme AE were observed in 51% (23/45; fatigue-5, hypophosphatemia-7, hypercholesterolemia-5, hypertriglyceridemia-5). One grade 4 hematologic AE (thrombocytopenia) occurred. 13.3% (6/45 pts) went off due to TOX, and 71.1% (32/45) due to disease progression. Conclusions: Sorafenib plus temsirolimus was tolerable, but the primary endpoint threshold for success (PFS6) was not met in post-VEGF recurrent GBM patients. Nevertheless, PFS6 (10%) and OS (5 mos.) compared favorably to contemporary series of Bev-refractory, recurrent GBM pts who are subsequently treated with a non-Bev containing regimen. Supported by NCI CA-25224. Clinical trial information: NCT00329719.
Phase II trial of the phosphatidyinositol-3 kinase (PI3K) inhibitor BKM120 in recurrent glioblastoma (GBM).

Patrick Y. Wen, W. K. Alfred Yung, Ingo K. Mellinghoff, Kathleen Lamborn, Shakti Ramkissoon, Timothy Francis Cloughesy, Mikael Rinne, Antonio Marcielo Padula Omuro, Lisa Marie DeAngelis, Mark R. Gilbert, Andrew S. Chi, Tracy Batchelor, Howard Colman, Susan Marina Chang, Cristian Massacesi, Emmanuelle DiTomaso, Michael Prados, David A. Reardon, Keith L. Ligon; Dana-Farber Cancer Institute, Boston, MA; The University of Texas MD Anderson Cancer Center, Houston, TX; Memorial Sloan-Kettering Cancer Center, New York, NY; University of California, San Francisco, San Francisco, CA; David Geffen School of Medicine at University of California, Los Angeles, CA; Dana-Farber Cancer Institute, Boston, MA; Massachusetts General Hospital, Boston, MA; University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; Novartis Pharma SAS, Rueil-Malmaison, France; Novartis Institutes for BioMedical Research, Inc., Cambridge, MA; Dana-Farber Cancer Institute/Brigham and Women’s Hospital/ Boston Children’s Hospital, Boston, MA

Background: The PI3K pathway is activated in most GBMs and represents a potential therapeutic target. BKM120 is an oral, pan-Class I PI3K inhibitor that enters the brain at therapeutic concentrations demonstrated to inhibit PI3K pathway, and potently inhibits the growth of U87 GBM tumors and human glioma tumor spheres in vitro and in vivo. Methods: The Ivy Foundation Early Phase Clinical Trials Consortium is conducting a phase II study of BKM120 in recurrent GBM patients with activation of the PI3K pathway (mutation, homozygous deletion or loss of IHC of PTEN, PIK3CA or PIK3RI mutations, or detectable pAKT). Additional eligibility criteria included radiologic progression, 1st or 2nd relapse, > 18 yrs, KPS > 60, adequate bone marrow and organ function, controlled blood glucose, and no enzyme-inducing antiepileptic drugs. Patients received BKM120 100mg daily. The study consisted of 2 parts conducted concurrently. Part 1 involved up to 15 patients who received BKM120 daily for 8-12 days prior to surgery for recurrent disease. Patients underwent FDG PET, pharmacokinetic (PK) studies, and tumor was obtained for drug concentrations and pharmacodynamic effects. Part 2 consisted of up to 50 patients with unresectable GBM treated with BKM120. The primary endpoint for Part 2 was 6-month progression-free survival (p0 = 15%; p1 = 32%). Results: To date 7 patients have been enrolled into Part 1, 33 into part 2. There were 5 women and 35 men. Median age was 54 yrs (29-68). Treatment was fairly well-tolerated. Major grades 3/4 toxicities were asymptomatic lipase elevation (5), fatigue (3), hyperglycemia (3), rash (3) elevated AST (1), and depression (1). Analysis of tumor from Part 1 showed reduction of pAkt by IHC. Genotyping of tumor specimens is ongoing. To date 33 patients had positive pAkt, 21 had PTEN loss by IHC. Of the first 19 patients who underwent whole exome sequencing, 3 had PIK3Ca mutations and 6 had PTEN mutations. Conclusions: BKM120 is generally well tolerated in patients with recurrent GBM and achieves adequate tumor concentration to inhibit pAkt. Updated PK and efficacy data and correlation of the latter with tumor genotype will be presented. Clinical trial information: NCT01339052.
Integrated data review of the first-in-human dose (FHD) study evaluating safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the oral transforming growth factor-beta (TGF-ß) receptor I kinase inhibitor, LY2157299 monohydrate (LY).

Jordi Rodon, Michael Anthony Carducci, Juan Manuel Sepúlveda, Analia Azaro, Emiliano Calvo, Joan Seoane, Irene Brana, Elisabet Sicart, Ivelina Gueorguieva, Ann Cleverly, Sada Pillay, Durisala Desai, Michael M. F. Lahn, Luis Paz-Ares, Matthias Holdhoff, Jaishri O’Neill Blakeley, José Baselga; Experimental Therapeutics Group, Vall d’Hebron Institute of Oncology, Barcelona, Spain; Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; Uro-Oncology Unit, 12 de Octubre University Hospital, Madrid, Spain; Medical Oncology, Vall d’Hebron, Barcelona, Spain; START Madrid, Centro Integral Oncológico Clara Campal - Hospital Universitario San Chinarro, Madrid, Spain; Vall d’Hebron Institute of Oncology, Vall d’Hebron University Hospital, Barcelona, Spain; Molecular Therapeutics Research Unit, Vall d’Hebron University Hospital, Barcelona, Spain; Vall d’Hebron University Hospital, Barcelona, Spain; Eli Lilly and Company, Erl Wood, United Kingdom; Eli Lilly and Company, Indianapolis, IN; Division of Early Phase Oncology Clinical Investigation, Eli Lilly and Company, Indianapolis, IN; University Hospital Virgen del Rocio, Seville, Spain; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; The Johns Hopkins University, School of Medicine, Baltimore, MD

Background: Activated TGF-ß signaling has been associated with poor survival in several tumors, including glioma (GM). Hence, we investigated the safety, PK and antitumor responses of the novel TGF-ß inhibitor LY in cancer patients, mainly in GM. Methods: There were 3 study parts: Part A: dose escalation of LY monotherapy in patients with solid tumor (cohorts 1 and 2, continuous dosing) and with GM (cohorts 3 to 5, intermittent dosing 14 days on/14 days off); Part B: intermittent LY dosing in combination with lomustine; Part C: monotherapy of 300 mg/day in solid tumors after completing a relative bioavailability study. Safety, antitumor activity, PK and PD were assessed as previously described (Calvo-Aller, et al. JCO 2008;26:abstract #14554; Rodon, et al. JCO 2011;29:abstract #3011; Azaro, et al. JCO 2012;30:abstract #2042). Results: 79 patients participated in this study (Part A, n = 39, 7 solid tumor, 32 GM; Part B, n = 26, all GM; Part C, n = 14 solid tumor, 9 GM, 2 hepatic cell carcinoma [HCC], 2 gastrointestinal [GI] and 1 melanoma). The integrated safety and efficacy evaluation confirms that LY has a manageable toxicity profile with antitumor activity. For GM patients the median progression-free survival (PFS) in months (range) was: 2.5 (0.0 to 36.9) in Part A; 2.5 (0.0 to 20.5) in Part B; 1.9 (0.0 to 6.4) in Part C. PFS duration in months were (range): 2.1-3.8 for HCC; 1.2-3.9 for GI and 2.2 for melanoma patient. Responders were observed in primary GM (Part A: 3/16; Part B: 2/20) and secondary GM (Part A: 5/14; Part B: 4/6). As of January 2013, 3 GM patients are still on treatment for 34, 36, and 31 months. P450-inducing medications including proton pump inhibitors or enzyme-inducing anti-epileptic drugs did not influence the PK parameters. Approximately, 90 biomarkers have been assayed and the results will be presented during the meeting. Conclusions: Because of the manageable toxicity profile of LY, the 300 mg/day dose administered as an intermittent dosing has been advanced into phase II investigation, either as a monotherapy or in combination with approved chemotherapies. Clinical trial information: NCT01682187.
A randomized phase II study of carboplatin and bevacizumab in recurrent glioblastoma multiforme (CABARET).

Kathryn Maree Field, John Simes, Helen Wheeler, Elizabeth J. Hovey, Anna K. Nowak, Lawrence Cher, Chris Brown, Ann Livingstone, Kate Sawkins, Mark Rosenthal, CABARET/COGNO Investigators; Royal Melbourne Hospital, Parkville, Australia; NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia; Royal North Shore Hospital, Sydney, Australia; Prince of Wales Hospital, Randwick, Australia; Sir Charles Gairdner Hospital, Perth, Australia; Austin Health, Melbourne, Australia; NHMRC Clinical Trials Centre, Sydney, Australia; Cooperative Trials Group for Neuro-Oncology, Sydney, Australia

Background: The optimal use of bevacizumab (bev) in recurrent glioblastoma (GBM) remains uncertain including the choice between monotherapy or combination therapy as well as the role of continuing bev beyond disease progression. Methods: This was a sequential stratified two part randomized phase II study. Eligibility criteria included: recurrent GBM after radiotherapy and temozolomide, no other chemotherapy for GBM, ECOG PS 0-2. The primary objective (Part 1) was to determine the effect of bev plus carboplatin versus bev alone on 6 month progression-free survival (6PFS) using modified RANO criteria. Bev was given 2-weekly 10mg/kg, carboplatin 4-weekly AUC5. On progression, patients (pts) able to continue treatment were randomized to continue or cease bev (Part 2). Secondary endpoints included response rate (RR); cognitive function; quality of life; toxicity and overall survival (OS). Results: 122 pts (median age 55) were enrolled from 18 Australian sites. 87 (71.3%) were PS 0-1. The current median follow up is 14.7 months with median on-treatment time 3.7 months. 6PFS was 26% (combination) versus 24% (monotherapy) (HR 0.96, 95%CI (0.66, 1.39), p = 0.82). RR (CR+PR) was 15% versus 13%. Median OS was 6.9 versus 6.4 months (HR 1.08, 95%CI (0.74, 1.59), p = 0.68). There were 2 treatment (bev) related deaths in the combination arm (one GI perforation, one CNS hemorrhage). To date, overall incidence of bev-related AEs is similar to prior literature with 10 (8.3%) venous thromboembolic events and 5 (4.2%) hemorrhages (all grades) reported. There were 3 episodes of G3-4 neutropenia, all in the combination arm (5%) and 9 episodes of G3-4 thrombocytopenia. As of January 14, 2013, 47 pts have continued on to Part 2. Data for bev beyond progression is not yet available. Conclusions: In this study of patients with recurrent GBM, the addition of carboplatin to bev did not result in additional clinical benefit compared to bev monotherapy. This large multicentre population-based study demonstrated that clinical outcomes in patients with recurrent GBM treated with bev were inferior to previously reported studies. Ongoing follow-up of patients on bev beyond progression, and novel secondary and exploratory endpoints continues. Clinical trial information: ACTRN12610000915055.

A first-in-human study of neural stem cells (NSCs) expressing cytosine deaminase (CD) in combination with 5-fluorocytosine (5-FC) in patients with recurrent high-grade glioma.

Jana Portnow, Behnam Badie, Timothy W. Synold, Alexander Annala, Bihong Chen, Joseph Frank, Rex A. Moats, John Wood, Massimo D’Apuzzo, Victoria Bedell, Paul Henry Frankel, Karen S. Aboody; City of Hope, Duarte, CA; National Institutes of Health, Bethesda, MD; Children’s Hospital of Los Angeles, Los Angeles, CA; Children’s Hospital Los Angeles, Los Angeles, CA; City of Hope Beckman Research Institute, Duarte, CA

Background: Human NSCs are inherently tumor-tropic, making them attractive drug delivery vehicles. This pilot-feasibility study assessed the safety of using genetically-modified NSCs for tumor selective enzyme/prodrug therapy. An immortalized, clonal NSC line was retrovirally-transduced to stably express CD, which converts the prodrug 5-FC to 5-fluorouracil (5-FU), producing chemotherapy locally at sites of tumor in the brain. Methods: Patients 18 years or older with recurrent high-grade glioma underwent intracranial administration of NSCs during tumor resection or biopsy. Four days later, 5-FC was administered orally every 6 hours for 7 days. Study treatment was given only once. A standard 3+3 dose escalation schema was used to increase doses of NSCs from 1 x 10^7 to 5 x 10^7 and 5-FC from 75 to 150 mg/kg/day. Intracerebral microdialysis was performed to measure brain levels of 5-FC and 5-FU; serial blood samples were obtained to assess systemic drug concentrations. Three patients received iron-labeled NSCs for MRI tracking. Brain autopsies were done on 2 patients. Results: Fifteen patients received study treatment. Three were inevaluable for toxicity and replaced. All patients tolerated the NSCs well. There was 1 dose-limiting toxicity (grade 3 transaminitis) possibly related to 5-FC. At the highest dose level of NSCs, the average steady-state concentration of 5-FU in the brain was 63.9±7.9 nM. The average maximum 5-FU level in brain was 104±88 nM compared to 24±36 nM in plasma, indicating local production of 5-FU in the brain by the NSCs. MR imaging of iron-labeled NSCs showed preliminary evidence of NSC migration. Autopsy data documented (by IHC, FISH, and PCR) NSCs at distant sites of tumor in the brain and no development of secondary tumors. Conclusions: This first-in-human study has demonstrated safety and proof-of-concept regarding NSC-mediated conversion of 5-FC to 5-FU and NSC tumor-tropism. NSCs have the potential to overcome obstacles of drug delivery that limit current gene therapy strategies. Results of this pilot study will serve as the foundation for future NSC studies. (Supported by NCI 1R21 CA137639-01A1, CIRM DR-01421). Clinical trial information: NCT01172964.
BTTC08-01: A phase II study of bevacizumab and erlotinib after radiation therapy and temozolomide in patients with newly diagnosed glioblastoma (GBM) without MGMT promoter methylation.

Jeffrey J. Raizer, Pierre Giglio, Jethro Lisien Hu, Morris D. Groves, Ryan Merrell, Charles A. Conrad, Surasak Phuphanich, Vinay K. Puduvalli, Monica Elena Loghin, Nina Paleologos, W. K. Alfred Yung, Brian D. Vaillant, Jeremy David Rudnick, Marc C. Chamberlain, Nicholas Vick, Sean Aaron Grimm, Ivo Tremont-Lukats, John Frederick De Groot, Kenneth D. Aldape, Mark R. Gilbert; Northwestern University, Feinberg School of Medicine, Chicago, IL; MUSC Hollings Cancer Center, Charleston, SC; Cedars-Sinai Medical Center, Los Angeles, CA; Texas Oncology, Austin, TX; Northshore University, Evanston, IL; The University of Texas MD Anderson Cancer Center, Houston, TX; Neuro-Oncology Program, Cedars-Sinai Medical Center, Los Angeles, CA; Rush University, Chicago, IL; The Methodist Hospital, Houston, TX; University of Washington, Seattle, WA; University of Minnesota, Minneapolis, MN; The University of Texas M.D. Anderson Cancer Center, Houston, TX

Background: Patients (pts) with GBM with unmethylated MGMT have a worse prognosis than those with methylated MGMT. Novel approaches for this poor risk group are warranted. The Brain Tumor Trials Collaborative (BTTC) performed a phase II trial evaluating standard chemoradiation followed by bevacizumab and erlotinib in patients with MGMT unmethylated GBM. EGFR and VEGFR are upregulated during radiation suggesting that this combination could be more effective than post-radiation adjuvant temozolomide (TMZ).

Methods: After informed consent, adult patients with supratentorial GBM, KPS ≥ 70 and > 1 cm² tumor block for MGMT promoter analysis were screened. Only tumors with confirmed unmethylated MGMT promoter were enrolled. All patients received RT/TMZ and then approximately 4 weeks after RT they received bevacizumab 10 mg/kg every 2 weeks and erlotinib 150 mg/day, continuously. One cycle was 4 weeks; evaluation by MRI was every 2 cycles. Treatment continued until disease progression or intolerable adverse events. Results: 115 patients were screened; 48 were enrolled (2 unevaluable: 1 for an infratentorial GBM and 1 withdrew after 7 days of treatment) with 29 men, 17 women. Median age was 56 yrs (29-75); median KPS was 90 (70-90). The median number of cycles was 8 (2-38) with 4 patients remaining on trial at the time of analysis. Objective responses: 4 CR, 12 PR and 30 SD. There were no unexpected toxicities; grade 3/4 rate < 5%. Conclusions: Adjuvant bevacizumab and erlotinib in GBM with unmethylated MGMT is well tolerated. Preliminary efficacy data is comparable with outcomes in similar unmethylated MGMT patient populations from the EORTC/NCIC and RTOG 0525 studies. Tissue correlation is being performed. Clinical trial information: NCT00720356.
Temozolomide plus bevacizumab in elderly patients with newly diagnosed glioblastoma and poor performance status: An Anocef phase II trial.

German Reyes-Botero, Jerôme Honorat, Oliver L. Chinot, Luc Taillandier, Isabelle Catry-Thomas, Jerome Barriere, Jean Sebastien Guillamo, Michel Fabbro, Didier Frappaz, Alexandra Benouaich Amiel, Emilie Le Rhun, Chantal Campello, Isabelle Tennevet, François Ghiringhelli, Marie-Laure Tanguy, Karima Mokhtari, Jean-Yves Delattre, ANOCEF: Association des Neuro-Oncologues d’Expression Française; Service de Neurologie 2-Mazarin, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; Hopital Pierre Wertheimer, Lyon, France; Centre Hospitalier Universitaire La Timone, Marseille, France; Centre Hospitalier Universitaire Nancy, Nancy, France; Hopital Saint-Andre CHU, Bordeaux, France; Centre Antoine Lacassagne, Nice, France; Centre Hospitalier Universitaire Caen, Caen, France; Centre Val d’Aurelle, Montpellier, France; Centre Léon Bérard, Lyon, France; Centre Hospitalier Universitaire Rangueil, Toulouse, France; Centre Oscar Lambret, Lille, France; Centre Hospitalier Universitaire Nimes, Nimes, France; Centre Henri Becquerel CLCC, Rouen, France; Georges-François Leclerc Cancer Center, Dijon, France; APHP-CHU Pitié-Salpêtrière, Paris, France; Hôpital Pitié-Salpêtrière, Paris, France; Pitié-Salpetrière Hospital-Pierre et Marie Curie Paris VI University, Paris, France

Background: The optimal treatment of glioblastoma multiforme (GBM) in elderly patients (age ≥70 years) with impaired functional status (Karnofsky performance status, KPS ≤70) remains to be established. A previous study using temozolomide (TMZ) alone suggested an increase in median overall survival (OS) compared to supportive care (25 weeks vs. 12-16 weeks, respectively). Median progression-free survival (PFS) was 16 weeks and 26% of patients became transiently capable of self-care (IK ≥70) (J Clin Oncol. 2011; 29: 3050-5). The present clinical trial evaluated the efficacy and safety of the combination of TMZ with bevacizumab (BV) as an initial treatment for elderly patients with GBM and KPS ≤70. Methods: Patients aged ≥70 years with KPS < 70 and a newly supratentorial GBM diagnosed by biopsy were eligible for this multicentric, prospective and non-randomised phase II trial. The primary endpoint was the OS and secondary endpoints included median PFS, quality of life, safety and cognition. Treatment consisted of TMZ 130-150 mgs/m²/d for 5 days every 4 weeks plus BV 10mgs/kg every 2 weeks, until 12 cycles or tumoral progression. Neither surgical resection nor radiotherapy was performed. Follow-up included clinical assessment every 2 weeks and brain MRI every 8 weeks. Results: Between October 2010 and March 2012, 66 patients (median age, 77 years; median KPS, 60) were enrolled. Median OS was 24 weeks (95% CI, 19-27.6) and median PFS was 16 weeks (95% CI, 13.1–19.3). Twenty-five patients (38%) became transiently capable of self-care (IK >70). Grade 3 and 4 haematological toxicity occurred in 13(19.6%) cases, whereas non-haematological toxicities were reported in 21(32%), including high blood pressure in 7(10%), thromboembolic events in 3(4.5%), intracerebral haemorrhage in 2(3%) and intestinal perforation in 2(3%) cases. Conclusions: This study confirms that TMZ-based treatment is of help in elderly GBM patients with poor KPS. However, the addition of bevacizumab does not appear to be of benefit in term of PFS and OS.
A large prospective Italian population study (Project of Emilia-Romagna Region in Neuro-Oncology; PERNO) in newly diagnosed GBM patients (pts): Outcome analysis and correlations with MGMT methylation status in the elderly population.

Enrico Franceschi, Alicia Tosoni, Luca Morandi, Serenella Cerasoli, Giovanni Lanza, Roberta Depenni, Alessandro Gamboni, Claudio Dazzi, Gianluca Marucci, Giorgio Gardini, Eugenio Pozzati, Benedetta Urbini, Isabella Dascola, Stefania Bartolini, Claudia Biasini, Paolo Carpeggiani, Elena Zunarelli, Enrico Maria Silini, Mario Ermani, Alba Ariela Brandes; Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna, Bologna, Italy; Department of Haematology and Oncological Sciences Section of Pathology, Bellaria Hospital, University of Bologna, Bologna, Italy; Department of Human Pathology, AUSL Cesena Bufalini Hospital, Cesena, Italy; Department of Experimental and Diagnostic Medicine, Section of Anatomic Pathology, Ferrara, Italy; Oncology, Haematology and Respiratory Diseases Department, University Hospital of Modena, Modena, Italy; Oncology Unit, Infermi Hospital, Faenza, Italy; Department of Oncology and Hematology, General Hospital, Ravenna, Italy; Section of Pathology, Department of Haematology and Oncology, University of Bologna, Bellaria Hospital, Bologna, Italy; Department of Pathology, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Department of Neurosurgery, IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy; Clinical Oncology Unit, St Anna University Hospital, Ferrara, Italy; Neurosurgery Department, Azienda Ospedaliero-Universitaria, Parma, Italy; Department of Oncology and Hematology, Oncology Unit, Azienda Ospedaliero Guglielmo da Saliceto, Piacenza, Italy; Neuroradiology Department, Nuovo Ospedale Civile S. Agostino Estense, Azienda USL, Modena, Italy; Pathology Department, Azienda Ospedaliero-Universitaria, Policlinico, Modena, Italy; Pathology Unit, Azienda Ospedaliero-Universitaria, Parma, Italy; Neurosciences Department, Statistic and Informative Unit, Azienda Ospedaliero-Università, Padova, Italy

Background: The role of temozolomide concurrent with and adjuvant to radiotherapy (RT/TMZ) in elderly pts with GBM remains unclear. We therefore evaluated the efficacy of this approach in pts ≥70 years in the context of the Project of Emilia-Romagna Region in Neuro-Oncology (PERNO), the first Italian prospective observational population-based study in neuro-oncology. Methods: The criteria for selecting pts enrolled in the PERNO study were: age ≥70 years; PS 0-3; histologically confirmed GBM; postoperative radiotherapy after surgery; residence in the Emilia Romagna region. Data were collected prospectively. Results: Pts accrual, started on January 1 2009, was closed, as planned, on December 31 2010. In the pts enrolled (n=53), median overall survival (mOS) was 11.1 months (95% CI: 8.8 - 13.5); survival rates at 1-, 2- and 3-years were 41.5% (95% CI: 28.2 – 54.8%), 15.2% (95% CI: 4.8 – 25.6%) and 6.1% (95%CI: 0 – 15.9%), respectively. Twenty-eight pts received RT/TMZ, and 25 pts RT alone. mOS was 11.6 months (95% CI: 8.6 – 14.6) following RT/TMZ and 9.3 months (95% CI: 8.1 – 10.6) following RT alone. mOS for pts with MGMT methylated status (n=17) was 13.5 months (95% CI: 7.7 – 19.2), being 17.2 months (95% CI: 11.5 - 22.9) in those treated with RT/TMZ (n=6) and 8.8 months (95% CI: 2 – 15.6) in those treated with RT alone (n=11, p=0.09). Elderly pts with MGMT unmethylated status (n=25) had a mOS of 8.5 months (95% CI: 6 – 11, p=0.014), being 8.5 months (95% CI: 2.3 – 14.7) in pts treated with RT/TMZ (n=10), and 8 months (95% CI: 3 – 12.9) in those treated with RT (n=15, p = 0.55). Conclusions: RT/TMZ appears to be more effective in prolonging the mOS of elderly pts in those with MGMT methylation status (17.2 vs 8.5 months), and seem to perform better than TMZ alone, for which mOS was 9.7 months in the Nordic phase III trial. These findings underline the value of the ongoing randomized EORTC 26062-22061/NCIC CE.6 phase III comparing RT/TMZ with short course RT alone.
The Stupp regimen preceded by early post-surgery temozolomide versus the Stupp regimen alone in the treatment of patients with newly diagnosed glioblastoma multiforme (GBM).

LF Zhou, Yu Yao, Shuyuan Yang, Xuejun Yang, Xiang Wang, Xiang Zhang, Liwei Zhang, Yicheng Lu, Zhong-ping Chen, Jianmin Zhang, Songtao Qi, Renzhi Wang, Chao You, Ying Mao, Jisheng Wang, Juxiang Chen, Qun-ying Hong, Hong Shen, Zhiyong Li, Ma WB; Department of Neurosurgery, Huashan Hospital SMC FDU, Shanghai, China; Department of Neurosurgery, Huashan Hospital SMC FDU, Shanghai, China; Department of Neurosurgery, General Hospital, Tianjin Medical University, Tianjin, China; Department of Neurosurgery, General Hospital, Tianjin Medical University, Tianjin, China; Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China; Department of Neurosurgery, Xijing Hospital, Fourth Military Medical University, Xi’an, China; Department of Neurosurgery, Tiantan Hospital affiliated to Capital University of Medical Sciences, Beijing, China; Department of Neurosurgery, Changzheng Hospital Second Military Medical University, Shanghai, China; Department of Neurosurgery/Neuro-oncology, Cancer Center, Sun Yat-sen University, Guangzhou, China; Department of Neurosurgery, Second Affiliated Hospital; Zhejiang University College of Medicine, Hangzhou, China; Department of Neurosurgery, Nanfang Hospital, Southern Medical University, Guangzhou, China; Department of Neurosurgery, Peking Union Medical College Hospital, Beijing, China; Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China; Department of Neurosurgery, Huashan Hospital SMC FDU Affiliated to Fudan University, Shanghai, China; Department of Neurosurgery, Peking Union Medical College Hospital, Beijing, China

Background: In treatment of newly diagnosed GBM with the Stupp chemo-radiotherapy regimen, following by adjuvant chemotherapy, patients were treated with temozolomide (TMZ) & combined radiotherapy 4-5 weeks after surgery. In the interval between surgery and chemo-radiotherapy, it is not known whether additional TMZ treatment will improve efficacy or safety. This trial evaluated the safety and efficacy of the Stupp regimen + early post-surgery TMZ chemotherapy in the treatment of patients with newly diagnosed GBM. Methods: The trial was a multi-center, randomized open-label study. 99 newly diagnosed GBM patients were enrolled and randomly assigned to the Stupp regimen + early post-surgery TMZ chemotherapy arm (experimental group, n = 52) or to Stupp regimen alone (control group, n = 47). Fourteen days after surgery, the patients in experiment group received TMZ orally at 75mg/m²/day for 14 days. The primary endpoint of the study was the overall survival (OS). The secondary endpoints included the progression-free survival (PFS), objective tumor assessment and adverse events (AEs). Results: The median OS time was 17.58 months (95% CI: 15.18 – 23.03 months) in the experiment group and 13.17 months (95% CI: 11.14 – 18.76 months) in the control group (log-rank test, p = 0.021). There is no significantly difference in the median PFS between experiment group and control group (8.74 months, 95% CI: 6.41-14.85 months vs 10.38 months, 95% CI: 8.18-15.44 months, p = 0.695). No statistically significant difference was detected as regards to the objective tumor assessments. There is no significance in OS or PFS between MGMT positive and MGMT negative groups. TMZ treatment was well tolerated in the study. AE types and rates were generally similar between the two groups. There were 22 SAEs in this study, with only 1 SAE (lung infection) in Stupp regimen group was possibly drug-related. Conclusions: The addition of early post-surgery TMZ chemotherapy to the Stupp regimen for newly diagnosed GBM resulted in a statistically significant survival benefit with minimal additional toxicity. Clinical trial information: NCT00686725.
**Biomarker (BM) evaluations in the phase III AVAglio study of bevacizumab (Bv) plus standard radiotherapy (RT) and temozolomide (T) for newly diagnosed glioblastoma (GBM).**

Ryo Nishikawa, Frank Saran, Warren Mason, Wolfgang Wick, Timothy Francis Cloughesy, Roger Henriksson, Magalie Hilton, Josep Garcia, Tobias Vogt, Celine Pallaud, Oliver L. Chinot; Saitama Medical University International Medical Center, Saitama, Japan; The Royal Marsden NHS Foundation Trust, London, United Kingdom; Princess Margaret Hospital, Toronto, ON, Canada; University of Heidelberg Medical Center, Heidelberg, Germany; University of California, Los Angeles, Los Angeles, CA; Regional Cancer Center Stockholm; Umed University Hospital, Stockholm/Umeå, Sweden; F. Hoffmann-La Roche Ltd, Basel, Switzerland; Genentech Inc., South San Francisco, CA; Aix-Marseille University, AP-HM, Service de Neuro-Oncologie, CHU Timone, Marseille, France

**Background:** Bv plus 1st-line standard of care (SoC; T + RT) achieved a PFS benefit in the AVAglio phase III, randomized, double-blind, placebo [P]-controlled trial in patients (pts) with newly diagnosed GBM. AVAglio includes BM evaluation to identify pts benefiting most from Bv. Analysis of plasma VEGF-A and VEGFR-2 was prioritized based on encouraging findings in Bv trials in several tumor types. **Methods:** AVAglio includes an optional, exploratory correlative BM analysis; participating pts provided informed consent for BMs. Baseline (BL) plasma samples were analyzed using the Roche IMPACT platform, based on multiplex ELISA technology. Pts were dichotomized according to BM levels using either Q1, median or Q3 cut-offs. Potential interactions between BL BM levels and PFS were tested using Cox regression analyses. **Results:** Of 921 patients enrolled, 571 (62%) were evaluable in the BM study. Baseline characteristics and PFS outcome were comparable in the ITT and BM-evaluable populations. Median BL VEGF-A and VEGFR-2 levels were 77.0 pg/mL and 12.6 ng/mL, respectively. No significant interaction for PFS was seen at α=0.025. **Conclusions:** The potential predictive (VEGF-A, VEGFR-2) and prognostic (VEGF-A) value seen in breast, pancreatic and gastric cancers was not apparent in BL BM samples from AVAglio using a median, Q1 or Q3 cut-off. Additional plasma and tumor BM analyses are ongoing. Clinical trial information: NCT00943826.

<table>
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<tr>
<th>VEGF-A</th>
<th>Median (IQR)</th>
<th>N/Events</th>
<th>Median PFS (mo)</th>
<th>HR (95% CI)</th>
<th>P</th>
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<tr>
<td>Bv</td>
<td>69.7 (59.4-81)</td>
<td>275/270</td>
<td>11.2 (10.9-11.6)</td>
<td>0.62 (0.48-0.79)</td>
<td>0.001</td>
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<tr>
<td>Q1</td>
<td>48.2 (37.9-59)</td>
<td>145/139</td>
<td>10.5 (10.3-10.9)</td>
<td>0.54 (0.36-0.84)</td>
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<td>Q2</td>
<td>75.3 (65.0-85)</td>
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<td>11.6 (11.3-11.8)</td>
<td>0.61 (0.49-0.78)</td>
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<tr>
<td>Q3</td>
<td>100.0 (90.5-110)</td>
<td>73/62</td>
<td>11.5 (11.2-11.7)</td>
<td>0.61 (0.41-0.92)</td>
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<tr>
<th>VEGFR-2</th>
<th>Median (IQR)</th>
<th>N/Events</th>
<th>Median PFS (mo)</th>
<th>HR (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Bv</td>
<td>12.6 (11.4-13.8)</td>
<td>275/270</td>
<td>11.8 (11.5-12.1)</td>
<td>0.61 (0.48-0.78)</td>
<td>0.001</td>
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<tr>
<td>Q1</td>
<td>6.7 (5.6-7.8)</td>
<td>145/139</td>
<td>11.2 (11.0-11.5)</td>
<td>0.54 (0.36-0.81)</td>
<td>0.005</td>
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<tr>
<td>Q2</td>
<td>9.3 (8.2-10.4)</td>
<td>216/209</td>
<td>11.7 (11.4-11.9)</td>
<td>0.61 (0.49-0.92)</td>
<td>0.001</td>
</tr>
<tr>
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<td>0.61 (0.41-0.92)</td>
<td>0.059</td>
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Q = quartile.
Association of matrix metalloproteinase 2 (MMP2) baseline plasma level to objective response (OR), progression free survival (PFS), and overall survival (OS) and changes under treatment in patients treated with bevacizumab (Bev) for recurrent high-grade glioma (HGG).

Emeline Tabouret, Francoise Boudouresque, Jaime Callego Perez-Larraya, Maryline Barrie, Giuseppe Lombardi, Mona Matta, Anna Luisa Di Stefano, Marianne Labussiere, Celine Boucard, Anderson Loundou, Sylvie Romain, Antoine F Carpentier, Marc Sanson, L'houcine Ouafik, Oliver L. Chinot; University Hospital Timone, Marseille, France; Aix Marseille University, Marseille, France; Assistance Publique–Hôpitaux de Paris, Paris, France; Medical Oncology 1, Venetian Institute of Oncology-IRCCS, Padua, Padua, Italy; Université Pierre et Marie Curie-Paris 6, Centre de Recherche de l’Institut du Cerveau et de la Moelle épineure (CRICM), Neurologie 2, Paris, France; Centre de Recherche de l’Institut du Cerveau et de la Moelle Epinière, UMR U975, Paris, France; Laboratoire de Transfert Biologique Oncologique, Marseille, France; Department of Neurology, Hôpital Avicenne, AP-HP, Bobigny, France; Timone University Hospital, Marseille, France; Centre Hospitalier Universitaire La Timone, Marseille, France

Background: Predictive marker of Bev activity is an unmet medical need. We evaluated predictive value of selected circulating prebiomarkers involved in neoangiogenesis and invasion on patient outcome in recurrent HGG treated with Bev. Methods: A set of eleven prebiomarkers of interest (VEGF, VEGF-R2, bFGF, SDF1, PI GF, uPA, PAI1, MMP2, MMP7, MMP9, and adrenomedulline) were analyzed in plasma, using ELISA, at baseline from Bev initiation in a prospective cohort of 26 patients (Cohort1). Correlations were validated in a separate retrospective Bev treated cohort (Cohort2; n = 50) and then tested in a cohort of patients treated with cytotoxic agents without Bev (Cohort3; n = 34). Dosages were correlated to OR, PFS, and OS. MMP2 and MMP9 were then analyzed at multiple time points up to progression. Results: In cohort1, high MMP2 baseline level was associated with an OR rate of 83.3% for high levels versus 15.4% for low MMP2 levels (p = 0.001). In multivariate analysis, MMP2 baseline level was correlated with PFS (hazard-ratio (HR), 3.92; 95% confidence-interval (CI): 1.46-10.52; p = 0.007) and OS (HR, 4.62; 95%CI 1.58-13.53; p = 0.005), as MMP9 (p = 0.016 for PFS and p = 0.025 for OS). Similar results were found in cohort2 for MMP2, (MMP2: p<0.001 for OR; p = 0.009 for PFS; p = 0.009 for OS) but not for MMP9. In cohort3, no association was found between MMP2, MMP9 and outcome. Significant changes in MMP2 and MMP9 plasma levels were observed during treatment. MMP2 increased after Bev initiation (p = 0.002), and decreased at progression (p = 0.002) while MMP9 initially decreased (p = 0.007) then increased at progression (p = 0.031). Conclusions: In patients with recurrent HGG treated with bevacizumab, but not with cytotoxic agents, high MMP2 plasma levels are associated with prolonged tumor control and survival while changes over time may reflect tumor control. MMP2 should be tested in randomized clinical trials that evaluate bevacizumab efficacy, and its biological role should be reassessed.
Impact of adjuvant temozolomide and IDH mutation status among patients with anaplastic astrocytoma.

Sani Haider Kizilbash, Caterina Giannini, Jesse S Voss, Paul A. Decker, Robert B. Jenkins, Nadia N. Laack, Ian F Parney, Joon H. Uhm, Jan C. Buckner; Mayo Clinic, Rochester, MN

Background: Although adjuvant radiation has demonstrated a clear survival benefit in anaplastic astrocytomas (AA), the role of concurrent temozolomide (TMZ) remains controversial. Methods: All adult patients diagnosed with AA from 2001 to 2011 and treated with standard doses of adjuvant radiation were identified retrospectively using the neuro-oncology database at the Mayo Clinic (Rochester, MN). Clinical data was extracted from the electronic medical record. IDH mutation status was also determined by obtaining either IDH1R132H immunostain on existing unstained slides or paraffin block sections, or by sequencing. Cumulative survival probabilities were estimated using the Kaplan-Meier method. Univariable and multivariable Cox proportional hazards regression models were fit to compare patients who did/did not receive TMZ. Results: 218 patients were identified that met inclusion criteria. 34 patients were excluded due to missing data on adjuvant chemotherapy. 146 patients had received adjuvant TMZ while 38 had not. Of these, IDH mutation status was determined on 124 patients who received TMZ and 33 of those who had not. The median duration of follow up was 36.4 months. On univariable analysis, adjuvant TMZ demonstrated a trend towards improved median survival from 35.2 to 53.1 months (p=0.06). As an independent variable, patients with IDH mutations had longer median survivals (111.7 months) when compared to IDH wild-type patients (23.3 months) (p<0.001). On multivariable analysis, five-year-survival was significantly impacted by receipt of adjuvant TMZ (HR = 0.56, p=0.03) and IDH mutation status remained a significant prognostic factor (HR = 0.19, p < 0.001) (see Table). Conclusions: IDH mutation strongly predicts a favorable outcome in patients with AA. Secondarily, concurrent TMZ is also associated with improved survival in patients with AA who are receiving adjuvant radiotherapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Concurrent TMZ</td>
<td>0.56 (0.33-0.94)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>1.06 (1.04-1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.91 (0.55-1.50)</td>
<td>0.71</td>
</tr>
<tr>
<td>Subtotal or gross total resection</td>
<td>0.91 (0.55-1.53)</td>
<td>0.73</td>
</tr>
<tr>
<td>IDH mutation</td>
<td>0.19 (0.09-0.42)</td>
<td>&lt;0.001</td>
</tr>
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</table>
Use of DNA copy number analysis of grade 2-4 gliomas to reveal differences in molecular ontogeny associated with IDH mutation status.

Mariko Sato, Kenneth D. Aldape, Clinton C Mason, Kristin Diefes, Lindsey Heathcock, Lisa Abegglen, Joshua David Schiffman, Howard Colman; University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; The University of Texas M.D. Anderson Cancer Center, Houston, TX; Huntsman Cancer Institute, Salt Lake City, UT

Background: The genetic alterations of glioma have been studied extensively. IDH1 mutation is associated with younger age and better survival. However, differences in molecular ontogeny within glioma related to IDH1 mutation remain unknown. Here we describe a detailed analysis of copy number alterations (CNA) between IDH1mut vs IDH1wt gliomas of grade 2-3 and 4. Methods: CNA were detected by molecular inversion probes (Affymetrix) and analyzed with Nexus Copy Number Software (BioDiscovery). DNA was extracted from 94 patient FFPE samples including grade 2-3: IDH1wt (n = 17) and IDH1mut (n = 28), and grade IV: IDH1wt (n = 25) and IDH1mut (n = 24). Chromothripsis was detected using a stringent criteria of at least ten switches of CNA in individual chromosomes. Results: We validated prior findings that IDH1wt GBM have higher frequency of Chr7 amplification (including EGFR) and loss of Chr10 (including PTEN). Other CNA across all grades were: gain of 19q12 and loss of 14q11 in IDH1wt, and gain of 11q21, 10p11, 8q21 and loss of 11p15, 19q13 in IDH1mut. Within grade 2-3 samples, few CNA were associated with mutation status: 2-3wt demonstrated higher frequencies of gain of 7q and loss of 10q, 14q11, and 22q13, while 2-3mut demonstrated higher frequencies of 11q21 gain and 19q13 loss. Grade 4 tumors demonstrated more CNA that differed by mutation status, with 4wt tumors demonstrating gain of 7 and loss of 10 and 14q11, while 4mut demonstrated gains of 8q, 10p, 12p13, 1q23, and loss of 11p15, 3p, 19q13, among others. Comparison of grade 2-3mut vs grade 4mut tumors demonstrated larger number of CNA in the grade 4mut tumors including gain of 1p, 14q, 13q33, 9p, 8q and loss of 22q, 11p15, 10q, and 3p, among others. A significantly higher incidence of chromothripsis events was observed in grade 4mut compared to grade 4wt (p = 0.0374). Conclusions: CNA analysis showed significant differences in molecular ontogeny between IDH1wt and IDH1mut, some of which may further elucidate pathogenesis. Significant CNA increases and increased chromothripsis in grade 4mut support malignant transformation of low grade gliomas through accumulation of genomic instability and genomic catastrophe.
Long-term survival in primary glioblastoma revisited: The contribution of isocitrate dehydrogenase mutations.

Michael Weller, Bettina Hentschel, Matthias Simon, Manfred Westphal, Gabriele Schackert, Joerg Christian Tonn, Markus Loefl, Guido Reifenberger, Torsten Pietsch, Andreas von Deimling, Christian Hartmann, German Glioma Network; University Hospital, Zurich, Switzerland; University of Leipzig, Leipzig, Germany; Department of Neurosurgery, University of Bonn, Bonn, Germany; Department of Neurosurgery, UKE Hamburg, Hamburg, Germany; Department of Neurosurgery, University of Bonn, Dresden, Germany; Department of Neurosurgery, LMU Munich, Munich, Germany; Institute for Medical Informatics, Statistics and Epidemiology, Leipzig University, Leipzig, Germany; Institute of Neuropathology, University of Duesseldorf, Duesseldorf, Germany; Institute of Neuropathology, University of Bonn, Bonn, Germany; Neuropathology, University Hospital of Heidelberg, Heidelberg, Germany; Neuropathology, German Cancer Research Center, Heidelberg, Germany

Background: The determinants of long-term survival in glioblastoma have remained largely obscure. Isocitrate dehydrogenase (IDH) 1 or 2 mutations are common in WHO grade 2/3 gliomas, but rare in primary glioblastomas, and associated with longer survival. Methods: We compared clinical and molecular characteristics of 69 patients with centrally confirmed glioblastoma and survival > 36 months (LTS-36), including 33 patients surviving > 60 months (LTS-60), with 259 patients surviving < 36 months. MGMT promoter methylation, 1p/19q codeletions, EGFR amplification, TP53 mutations and IDH1/2 mutations were determined by standard techniques. Results: The rate of IDH1/2 mutations in LTS-36 patients was 34% (23/67 patients) as opposed to 4.3% in controls (11/257 patients). Long-term survivors with IDH1/2 -mutant glioblastomas were younger, had almost no EGFR amplifications, but exhibited more often 1p/19q codeletions and TP53 mutations than LTS patients with IDH1/2 wild-type glioblastomas. Among LTS-36 patients, wild-type TP53 status, MGMT promoter methylation, and absence of EGFR amplification, but not IDH1/2 mutation, were associated with prolonged survival. Among 11 patients with IDH1/2-mutant glioblastomas without long-term survival, the only difference to IDH1/2-mutant long-term survivors was less frequent MGMT promoter methylation. Compared with LTS-36 patients, LTS-60 patients had been treated initially with radiotherapy alone and had TP53 mutations less frequently. Conclusions: IDH1/2 mutations define a subgroup of tumors of LTS patients that exhibit molecular characteristics of WHO grade 2/3 gliomas and secondary glioblastomas. Determinants of LTS with IDH1/2 wild-type glioblastomas, which exhibit typical molecular features of primary glioblastomas, beyond MGMT promoter methylation, remain to be identified.
Association of VEGFA SNP rs2010963 with prognosis and prediction of vascular toxicity of bevacizumab in recurrent glioblastomas.

Anna Luisa Di Stefano, Giuseppe Lombardi, Jaime Gallego Perez-Larraya, Blandine Boisselier, Marianne Labussiere, Francois Ducray, Vittorina Zagonel, Caroline Cheneau, Jean-Yves Delattre, Marc Sanson; Université Pierre et Marie Curie-Paris 6, Centre de Recherche de l’Institut du Cerveau et de la Moelle épinière (CRICM), Neurologie 2, Paris, France; Medical Oncology 1, Venetian Institute of Oncology-IRCCS, Padua, Padua, Italy; Centre de Recherche de l’Institut du Cerveau et de la Moelle Epinière, UMR U975, Paris, France; Medical Oncology 1, Veneto Institute of Oncology-IRCCS, Padova, Italy; Pitie-Salpetriere Hospital-Pierre et Marie Curie Paris VI University, Paris, France

Background: VEGFA has become an attractive target in high grade gliomas but there is no predictor of response or toxicity to anti-VEGF therapy. We investigated here the association between functional single nucleotide polymorphism (SNP) +405 G>C (rs2010963), located in 5’ untranslated terminal region of VEGFA gene, survival, response to bevacizumab (BVZ), and vascular toxicity. Methods: The rs2010963 was analyzed in blood DNA using a Taqman SNP Genotyping Assay and confronted to Progression Free Survival (PFS), Overall Survival (OS) in the general population of gliomas, and -for the glioblastomas (GBM) treated with BVZ at recurrence- with Response, PFS, and thrombo-hemorragic events. Results: In the general population of 954 gliomas stratified per grade (362 grade 2, 269 grade 3, 323 grade 4) there was no association between rs2010963 and OS or PFS. In the population of 123 recurrent GBM treated with BVZ, we observed a favourable trend in PFS associated with the C allele of rs2010963 (5.4 vs 4.2 months, \( p = 0.07 \)). Most importantly the CC genotype was associated with the occurrence of thrombo-hemorragic events (6/16 vs 2/107 in CG+GG, \( p <0.0001 \)). Conclusions: Our data suggest that rs2010963 status has not prognostic significance in gliomas, but is associated with vascular events in recurrent GBM treated with BVZ. The impact of rs2010963 on response to BVZ needs to be further investigated.
Association of PIK3CA-activating mutations with more disseminated disease at presentation and earlier recurrence in glioblastoma.

Shota Tanaka, Tracy Batchelor, Anthony John Iafrate, Dora Dias-Santagata, Darrell R. Borger, Leif William Ellisen, Daniel Yang, David N. Louis, Daniel P. Cahill, Andrew S. Chi; Massachusetts General Hospital, Boston, MA; Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: The PI3K signaling pathway is a potent pro-survival pathway and associated with increased grade of malignancy in glioma. Activating mutations in PIK3CA are observed in 6% to 15% of glioblastomas, although their clinical significance is unknown. Our objective was to examine whether PIK3CA activating mutation is associated with a specific phenotype in newly diagnosed glioblastoma patients. Methods: We molecularly profiled 183 consecutive adult glioblastomas from December 2009 to June 2012. We included in our analysis all newly diagnosed primary glioblastoma patients with a KPS score of 60 or greater who were treated with standard chemoradiation. Molecular profiling consisted of SNaPshot genotyping, FISH for gene amplification (EGFR, MET, PDGFRA), and methylation-specific PCR for MGMT promoter methylation. Results: 158 patients were included in the study (median age: 58 years (range, 23-85), 90 males, median KPS: 90). With a median follow-up of 13.8 months, median progression-free survival (PFS) and overall survival (OS) were 11.6 and 26.2 months, respectively. Established molecular prognostic factors such as IDH1 mutation and MGMT promoter methylation were associated with longer PFS and OS (IDH1: PFS p=0.001, OS p=0.02; MGMT: PFS p=0.0005, OS p=0.0002). 12 patients (7.6%) harbored PIK3CA activating mutation by SNaPshot assay (4 at R88, 4 at hotspots 542-546, 4 at H1047). PIK3CA mutation was associated with younger age (p=0.02) and shorter PFS (6.8 vs. 11.8 months, p=0.0004). Shorter PFS for PIK3CA mutation remained significant after adjusting for age, KPS, gross total resection, IDH1 mutation, and MGMT promoter methylation (p=0.01). There was a significant association between PIK3CA mutation and more disseminated disease at diagnosis, as defined by gliomatosis, multicentric lesions, or distant leptomeningeal lesions. Eight of 12 (66.7%) PIK3CA mutant GBMs were disseminated versus 15.1% of PIK3CA wild-type tumors (p=0.0002). Conclusions: PIK3CA activating mutations are associated with younger age and early recurrence in primary glioblastoma. The aggressive behavior of these tumors may be related to their propensity to present with widespread disease.
Combined whole genome copy number genotyping and multiplex somatic mutation profiling of FFPE brain tumor specimens for clinical diagnosis and trial selection.

Brian Michael Alexander, Shakti Ramkissoon, Patrick Y. Wen, David A. Reardon, Eudocia Quant Lee, Mikael Rinne, Andrew David Norden, Lakshmi Nayak, Sandra Ruland, Lisa M. Doherty, Debra C. LaFrankie, Loretal E Brown, Nils D. Arvold, Ian F. Dunn, Sandro Santagata, Barrett J Rollins, Neal Ian Lindeman, Rameen Beroukhim, Azra Ligon, Keith L. Ligon; Dana-Farber Cancer Institute/Brigham and Women’s Hospital, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Dana-Farber Cancer Institute, Boston, MA; Harvard Radiation Oncology Program, Boston, MA; Brigham and Women’s Hospital, Boston, MA; Dana-Farber Cancer Institute/Brigham and Women’s Hospital/ Boston Children’s Hospital, Boston, MA

Background: Multi-dimensional cancer genotyping is increasingly needed for clinical diagnostics and trial selection. Whole genome copy number is relevant for glioblastoma and other brain tumors but routine prospective FFPE-based multiplex copy number and somatic mutation genotyping for clinical trials has not been achieved. Methods: Using novel DNA extraction protocols we implemented whole genome copy number (Agilent aCGH stock 1M feature arrays) and somatic mutation profiling (Oncomap v4.4 Sequenom) assays into a CLIA-certified laboratory setting. Twenty-three copy number aberrations (CNAs) relevant to brain tumors were reported from whole genome data and Oncomap results were reported for 471 cancer-related mutations in 41 genes. Results: During the initial eight months of our combined copy number and mutation-testing program, aCGH and Oncomap were performed prospectively on 239 and 157 brain tumor patients respectively. Copy number was reported in 90% of patients (214/239) and failures were due to insufficient DNA from small biopsies. GBMs (n = 94) harbored gains and losses at expected rates and included amplifications of common drug targets (EGFR, EGFRv3, MET, MDM2, MDM4, PDGFRA, CDK4, CDK6). Emerging candidate drug targets were identified including variant EGFR deletions (e.g. EGFRv2) and FGFR3-TACC3 gains for which other clinical tests are not available. Oncomap results for 78 GBMs revealed mutations in TP53, PTEN and IDH1. Less frequent mutations occurred in BRAF, RB1, PIK3CA, PIK3R1 and KRAS. We integrated copy number and mutation data for 27 GBMs, allowing for improved evaluation of tumor suppressor inactivation status (e.g. PTEN mutation with monosomy 10). In combination, our assays reported data on 10 clinically actionable drug targets relevant for 15 clinical trials open at the time of patient testing. Conclusions: We implemented complementary assays for efficiently detecting genome-wide CNAs and mutations on FFPE brain tumor samples in a CLIA-certified environment. Systematic integration of these results broadens the range of diagnostic and actionable data available to identify patients for trials of targeted therapeutics.
Whole brain radiation therapy (WBRT) with or without oral topotecan (TPT) in patients (pts) with non-small cell lung cancer (NSCLC) with brain metastases: Final analysis of an open-label phase III study.

Rodryg Ramlau, Jacek Jassem, Zsolt Papai-Szekely, Pierre Chabot, Philippe Legenne, Jeremy Levin, Jadwiga Sherlock, Stephen R. Lane, John J Brennan, Tracey Sessa, Paul Stephen Wissel, Philip Bonomi; Poznan University of Medical Sciences, Wielkopolskie Centrum Pulmonologii i Torakochirurgii, Poznan, Poland; Medical University of Gdansk, Department of Oncology and Radiotherapy, Gdansk, Poland; Department of Pulmonology, St George Hospital, Székesfehervar, Hungary; Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; GlaxoSmithKline, Uxbridge, United Kingdom; GlaxoSmithKline, Collegeville, PA; GlaxoSmithKline, Oncology, Collegeville, PA; Rush University Medical Center, Chicago, IL

Background: Brain metastases from NSCLC occur in ~ 20% of pts and if untreated are associated with a 1 to 2 month overall survival (OS). Pre-clinical studies show that TPT added to radiation results in a radiotherapy enhancement ratio of 1.4 to 1.6. This trial was designed to test the effect of TPT co-administered with WBRT on OS. Methods: Pts with NSCLC and at least one measurable brain lesion were eligible. 472 pts were randomized to WBRT (3 Gy/day x 10 days) or WBRT and TPT 1.1 mg/m$^2$/day for 10 days. Stratification factors: number of brain metastases and recursive partitioning analysis (RPA) class. Two weeks following WBRT, systemic anti-cancer therapy could be restarted at the treating physician’s discretion. Results: 468 pts were in the modified ITT population; 235 pts (WBRT + TPT) and 233 pts (WBRT + best supportive care [BSC]). Of the 235 pts administered WBRT + TPT, 91 also received TPT after WBRT. The treatment arms were balanced for gender, age and smoking history. Median daily TPT dose was 2.25 mg. The median OS in the TPT arm was not better than in the BSC alone arm; 4.0 months (95%CI 3.4, 4.8) vs. 3.6 months (95%CI 3.0, 4.0), respectively; HR 0.88 (0.73, 1.07), P=0.1862. In the ITT population analysis by stratification variables, RPA class (I vs. II/III) was significantly different (HR 0.59) whereas baseline brain lesions (1 vs >1) were not (HR 0.97). Complete response and overall response rates in the WBRT+ TPT were 10% and 27%, and with BSC 5% and 26%, respectively. There were no differences in time to response or neurologic signs and symptoms. All adverse events (AEs) were more frequent in the TPT arm (87% vs. 64%) as were AEs related to study treatment (57% vs. 21%), serious AEs (41% vs. 18%) and fatal AEs (5% vs. 0%). The AEs more frequently seen in the TPT arm were typical for TPT (hematologic toxicity, febrile neutropenia and diarrhea). Conclusions: The study did not achieve its primary objective. There was no difference in OS achieved by the addition of TPT to WBRT. AEs were more common in the TPT arm. Clinical trial information: NCT00390806.
Multicenter randomized phase II trial of methotrexate (MTX) and temozolomide (TMZ) versus MTX, procarbazine, vincristine, and cytarabine for primary CNS lymphoma (PCNSL) in the elderly: An Anocef and Goelams Intergroup study.

Antonio Marcilio Padula Omuro, Oliver L. Chinot, Luc Taillardier, Herve Ghesquieres, Carole Soussain, Vincent Delwail, Thierry Lamy, Remy Gressin, Sylvain Choquet, Pierre-Louis Soubeyran, Jean Philippe Maire, Alexandra Benouaich Amiel, Sophie Lebouvier-Sadot, Emmanuel Gyan, Maryline Barrie, Monica Sierra del Rio, Alberto Gonzalez, Caroline Houillier, Marie-Laure Tanguy, Khê Hoang-Xuan; APHP-CHU Pitié-Salpêtrière, Paris, France; Centre Hospitalier Universitaire La Timone, Marseille, France; Centre Hospitalier Universitaire Nancy, Nancy, France; Centre Léon Bérard, Lyon, France; Centre René Huguenin-Institut Curie, St Cloud, France; Centre Hospitalier Universitaire La Milette, Poitiers, France; Centre Hospitalier Universitaire Pontchaillou, Rennes, France; Centre Hospitalier Universitaire Michallon, Grenoble, Grenoble, France; Institut Bergonie, Bordeaux, France; Centre Hospitalier Universitaire St André, Bordeaux, France; Centre Hospitalier Universitaire Rangueil, Toulouse, France; Centre René Gauducheau, St Herblain, France; Centre Hospitalier Universitaire Bretonneau, Tours, France

Background: There is no standard chemotherapy defined in PCNSL. Elderly patients (pts) are not candidates for whole brain radiotherapy and therefore establishing an optimal MTX-based regimen is crucial. This prospective multicenter study conducted in 13 French institutions tested two promising MTX-based chemotherapy regimens in elderly pts with newly diagnosed PCNSL.

Methods: Pts with histologically confirmed newly diagnosed PCNSL with age ≥60 and KPS ≥40 were stratified by institution and KPS, then randomized to receive three 28-day cycles of MTX (3.5 g/m² D1 and D15) and TMZ (100-150mg/m² D1-5 and 15-19) [MT arm] or 3 cycles of MTX (3.5 g/m² D1 and D15), procarbazine 100mg/m² (D1-7), vincristine (1.4mg/m2 D1 and 15), followed by cytarabine consolidation (3g/m²/d X2d) [MPV-A arm]. Neither arm included radiotherapy; prophylactic G-CSF and standardized corticosteroids (methylprednisolone 60mg/d D1-5) were given to both arms. The primary endpoint was PFS (one-stage Fleming design; α = 5%; β = 10%). Evaluations included neuropsychological testing and quality of life.

Results: Accrual has been completed (7/2007-3/2010), with 98 pts randomized and 95 analyzed (MT: 48 pts; MPV-A: 47). Pre-treatment characteristics were well balanced between the two arms (all pts: median age=72; range 60-85; median KPS = 70; range 40-100). In the MPV-A arm, the CR rate = 62% (vs 45% in MT arm [p=0.11]), objective response rate = 82% (vs 71%; p=0.23), median PFS = 9.5m (vs 6.1m; HR = 1.14-95% CI [0.72; 1.81]; p=0.6) and median OS = 31m (vs 13.8m; HR = 1.4 - 95% CI [0.84 ; 2.34]; p=0.2). The incidence of grades 3-4 toxicities was 72% in the MPV-A vs 71% in the MT arm. Abnormal liver function test was the most common toxicity (MPV-A: 18 pts; MT: 21). Baseline cognitive impairment (MMSE >24 vs ≤24) predicted OS (p=0.04). Conclusions: This is the first randomized PCNSL study testing two different MTX-based combination regimens. In this elderly population, toxicities were frequent but similar in both arms, and all efficacy endpoints tended to favor the MPV-A arm. The MPV-A regimen is recommended for further development in PCNSL. Clinical trial information: NCT00503594.
Preirradiation chemotherapy with methotrexate, rituximab, and temozolomide and post-irradiation temozolomide for primary central nervous system lymphoma: RTOG 0227 phase II study results.

Jon Glass, Minhee Won, Christopher J. Schultz, Daniel Brat, Nancy Bartlett, John H. Suh, Barbara Jean Fisher, Marcia K. Liepman, Minesh P. Mehta; Thomas Jefferson University, Philadelphia, PA; Radiation Therapy Oncology Group, Philadelphia, PA; Medical College of Wisconsin, Milwaukee, WI; Emory University, Atlanta, GA; Washington University School of Medicine in St. Louis; Siteman Cancer Center, St. Louis, MO; Cleveland Clinic, Cleveland, OH; Department of Radiation Oncology, London Regional Cancer Program, London, ON, Canada; West Michigan Cancer Center, Kalamazoo, MI; University of Maryland, Baltimore, MD

Background: This prospective phase II study tested a methotrexate (MTX), temozolomide (TMZ) and rituximab (RTX) pre-irradiation regimen with hyperfractionated whole brain radiation therapy (hWBRT) followed by post-irradiation TMZ for patients with primary CNS lymphoma (PCNSL). The primary phase II endpoint was the 2-year overall survival (OS) rate compared with the 2-year OS from RTOG 93-10 (MTX, procarbazine, vincristine, whole brain radiation therapy, cytarabine). Secondary endpoints were pre-irradiation chemotherapy tumor response rates (compared to RTOG 93-10), progression free survival (PFS), acute and late neurologic toxicities, and quality of life. Methods: 53 patients (28 women, 25 men), median age 57.5 years, median Zubrod 1 were treated with RTX 375 mg/m² 3 days prior to first cycle of MTX; 5 cycles of intravenous MTX 3.5 g/m² with leucovorin rescue on weeks 1, 3, 5, 7, 9; TMZ 100 mg/m² daily for 5 days weeks 4 and 8; hWBRT 1.2 Gy twice daily fractions 5 days/week on weeks 11, 12, 13 for a total of 36 Gy and TMZ 200 mg/m² daily for 5 days on weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50. Results: Dosing of pre-irradiation temozolomide at 100 mg/m² was determined in the phase I portion of the study. With a median follow-up of 3.6 years, 2-year OS and PFS rates were 80.8% and 63.6%, respectively. Compared with historical controls from RTOG 93-10, 2-year OS and PFS were significantly improved (p = 0.006 and 0.03). The overall response rate to the pre-irradiation chemotherapy was 37.7% (complete response 11.3%, partial response 26.4%). 38% experienced grade 3 and 25% experienced grade 4 toxicities before the start of hWBRT, 33% experienced grade 3 and 21% experienced grade 4 toxicities attributable to post-hWBRT chemotherapy. Conclusions: The combination of MTX, TMZ, RTX followed by hWBRT and TMZ for PCNSL is safe with demonstrated improved 2 year OS and PFS compared with RTOG 93-10. Further investigations regarding the role of hWBRT and post-hWBRT TMZ are indicated. This project was supported by RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the National Cancer Institute (NCI) and Schering-Plough. Clinical trial information: NCT00068250.
High-dose methotrexate with and without rituximab for the treatment of newly diagnosed primary CNS lymphoma: Johns Hopkins Hospital experience.

Matthias Holdhoff, Guneet Sarai, Ahmed Abdelaziz, David Bonekamp, Stuart A. Grossman, Xiaobu Ye; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Johns Hopkins Hospital, Baltimore, MD

Background: The current institutional standard for treatment of patients with newly-diagnosed primary CNS lymphomas (PCNSL) at Johns Hopkins Hospital (JHH) consists of treatment with high-dose methotrexate plus rituximab (hd-MTX/R) every 2 weeks until complete response (CR), progression or unacceptable toxicities. Once CR is achieved, this is followed by monthly treatments for a total of up to one year for consolidation. Prior to 2008, the institutional standard had been treatment with hd-MTX alone. The benefit of adding rituximab to hd-MTX has not been formally evaluated. Methods: This is a retrospective study of HIV-negative adult patients with newly-diagnosed PCNSL treated at JHH with either hd-MTX or hd-MTX/R as initial therapy. Patients were identified using the cancer center registry (1995-2012) and were included if they had received at least one cycle of therapy (intention-to-treat). Primary objectives were CR rate (patients with sufficient imaging data; centrally reviewed) and overall survival (OS, all patients included).

Results: A total of 81 patients were analyzed (median age of 65 yrs; 52% male). 54 patients received hd-MTX alone (median age, 65 yrs) and 27 patients received hd-MTX/R (median age, 66 yrs). 37 and 24 patients in the two groups were evaluable for response, respectively. Among these, the CR rate was 51% in patients treated with hd-MTX alone (overall response rate, ORR, 76%) and 79% in patients treated with hd-MTX/R (ORR 96%). The median number of cycles to CR was 5 and 4.5, respectively. Median OS among all patients (both groups combined) was 26 months (95% CI: 11-44).

Conclusions: These data show potential clinical benefit from the addition of rituximab to hd-MTX for newly diagnosed patients with PCNSL based on a higher CR rate. Analysis of OS benefit between patients treated with hd-MTX and hd-MTX/R is pending maturation of further survival data.
A prospective phase II study to determine the efficacy of GDC 0449 (vismodegib) in adults with recurrent medulloblastoma (MB): A Pediatric Brain Tumor Consortium study (PBTC 25B).

Amar J. Gajjar, Sridharan Gururangan, Ibrahim A Qaddoumi, Roger Packer, Stewart Goldman, Michael Prados, Amnick Desjardins, Maryam Fouadi, Naoko Takebe, Shaoyi Li, David W. Ellison, Tom Curran, Richard J. Gilbertson, James M. Boyett; St. Jude Children’s Research Hospital, Memphis, TN; Duke University Medical Center, Durham, NC; Children’s National Medical Center, Washington, DC; Children’s Memorial Hospital, Chicago, IL; University of California, San Francisco, San Francisco, CA; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; Investigational Drug Branch, Cancer Therapy Evaluation Program, Rockville, MD; St Jude Children’s Research Hospital, Memphis, TN; Children’s Hospital of Philadelphia, Philadelphia, PA

Background: Almost 80% of adult medulloblastoma are of the SHH subtype. Second line therapy for adult MB is limited; therefore we tested the efficacy of vismodegib, a small molecule inhibitor of Smoothened (SMO) among patients with this disease. Methods: Adult patients with refractory or recurrent MB and who had measurable disease were enrolled on the study. Immunohistochemistry (IHC) was used to stratify patients to Stratum A (non-SHH group); Stratum B (SHH tumors) and Stratum C (indeterminate). All patients were treated with vismodegib at 150 mg/day PO daily. Tumor response, which had to be maintained for 8 weeks to meet protocol definition of sustained response, was assessed using RECIST criteria and central imaging review. Separate but identical Simon 2-stage MinMax designs (α = 0.10) were used in strata A and B to test for evidence that sustained response rates exceeded 5% with 90% power to detect 25% sustained response rates. Thus, 3/20 sustained responses were needed to declare potential activity of vismodegib. Results: 32 patients with a median age of 30 years (range 22.4-51.9) were enrolled on the study [Stratum A (n = 8); Stratum B (n = 20); Stratum C (n = 4)], including 18 males and 14 females. No responses were observed in Strata A or C and the median duration of treatment was 1.5 months (range 0.66-2.33). Three of 20 patients enrolled on Stratum B had sustained responses. The median duration of therapy for Stratum B patients was 2.76 months (range 0.33- 13.61). Six patients were on treatment for ≥6.44 months and 3 remain on treatment after 5.42, 9.34 and 13.61 months. During course 1, 2 patients experienced grade 3 decrease in lymphocytes; 1 experienced a grade 4 thromboembolic event; and 2 experienced grade 3 toxicities (back pain & syncope). During course 2, 3 patients experienced grade 3 toxicities (decrease in lymphocytes; myalgia & seizure). One other patient experienced grade 3 hypophosphatemia in courses 1 and 2. Conclusions: Vismodegib has activity against recurrent or refractory adult ‘SHH-subtype’ medulloblastoma and should be considered as a therapeutic option for newly diagnosed patients with this disease. Clinical trial information: NCT00939484.
A phase I clinical trial of veliparib and temozolomide in children with recurrent central nervous system tumors: A Pediatric Brain Tumor Consortium report.

Jack M. Su, Patrick Andrew Thompson, Adekunle Adesina, Xiao-Nan Li, Lindsay Baker Kilburn, Arzu Onar-Thomas, Mehmet Kocak, Brenda Chyla, Evelyn Mary McKeegan, Katherine E. Warren, Stewart Goldman, Ian Pollack, Maryam Fouladi, Alice Chen, Malcolm A. Smith, Vincent L. Giranda, James M. Boyett, Susan Blaney, Larry E. Kun, Pediatric Brain Tumor Consortium; Texas Children’s Cancer Center, Baylor College of Medicine, Houston, TX; Texas Children’s Cancer Center, Houston, TX; Baylor College of Medicine, Houston, TX; Children’s National Medical Center, Washington, DC; St. Jude Children’s Research Hospital, Memphis, TN; Abbott Laboratories, Abbott Park, IL; Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD; Children’s Memorial Hospital, Chicago, IL; Pittsburgh Children’s Hospital, Pittsburgh, PA; Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; National Cancer Institute, Rockville, MD; Cancer Therpy Evaluation Program, Washington, DC

Background: A phase I trial of veliparib (ABT-888), an oral poly(ADP-ribose) polymerase (PARP) inhibitor, and temozolomide (TMZ) was conducted in children with recurrent brain tumors to: 1) estimate the maximum tolerated doses (MTD) or recommended phase II doses (RP2D) of veliparib and TMZ using the Continual Reassessment Method; 2) describe the toxicities of this regimen; and 3) evaluate plasma pharmacokinetics (PK) and peripheral blood mononuclear cell (PBMC) PARP inhibition after veliparib treatment. Methods: TMZ was given once daily and veliparib twice daily for 5 days, every 28 days. Five veliparib/TMZ dose levels were studied: 20/180; 15/180; 15/150; 20/135; and 25/135 mg/m²/dose, respectively. Baseline and serial veliparib PK samples were obtained on days 1 and 4. PBMC poly(ADP-ribose) (PAR) levels were also measured using an ELISA assay. A total of 12 subjects were enrolled at the RP2D. Results: Thirty-one patients (29 evaluable) with a median age of 7.0 years (range 1.3-19.8) were enrolled. Dose-limiting toxicities (DLT) included grade 4 neutropenia and thrombocytopenia at the 20/180 and 15/180 mg/m²/dose levels. Based on the toxicity profile, PKs and PBMC PAR results, the RP2D were veliparib, 25 mg/m² BID, and TMZ, 135 mg/m²/day, for 5 days every 28 days. No objective responses were observed, although 4 subjects had SD > 6 months duration, including one patient each with glioblastoma multiforme, anaplastic ependymoma, pilocytic astrocytoma, and optic pathway glioma. At the veliparib RP2D, the PK parameters included: Cmax, 1.2 ± 0.7 μM; AUC0-12 hr, 1.53 ± 0.61 μg•hr/mL; and Cl/F, 173 ± ml/min/m². PARP inhibition was observed in PBMC but did not correlate with veliparib dose levels. Conclusions: The combination of veliparib and TMZ was well tolerated in children with recurrent CNS tumors. Veliparib PK parameters at RP2D are similar to those in adults. PBMC PARP inhibition did not correlate with veliparib dose levels, perhaps due to the smaller number of patients at each dose level and the technical limitations of specimen collection/processing and the ELISA assay. A phase II trial of veliparib/TMZ in children with recurrent primary brain tumors is planned. Clinical trial information: NCT00946335.
Prognostic utility of neuraxis imaging in leptomeningeal metastasis (LM): A retrospective case series.

Marc C. Chamberlain; Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA

Background: Correlate imaging of the central nervous system that includes both brain and spine MRI and radio-isotope cerebrospinal fluid [CSF] flow studies with survival in a retrospective case series of patients with LM. Methods: 240 adult patients with LM (125 non-brain solid tumor patients with positive CSF cytology; 40 non-brain solid tumor patients with negative CSF cytology and MRI consistent with LM; 50 lymphoma and 25 leukemia patients with positive CSF flow cytometry), all considered appropriate for LM-directed treatment, underwent prior to treatment brain and entire spine MRI and radio-isotope CSF flow studies. Results: Median overall survival was significantly shortened in patients with large volume MRI defined disease (defined as measurable tumor > 5 x 10 mm in orthogonal diameters) and in patients with non-corrected CSF flow obstruction irrespective of primary tumor histology. Additionally, cause of death differed wherein patients with large volume of disease or uncorrected obstructed CSF flow more often died of progressive LM disease whereas patients with normal or small volume disease and patients with normal or re-established CSF flow more often died of progressive systemic disease. Conclusions: Neuraxis imaging utilizing brain and spine MRI as well as radio-isotope CSF flow studies appears to have prognostic significance and may be predictive of median overall survival in this large cohort of patients with LM all of whom were considered for treatment with LM.
Background: Glioblastoma patients suffer from thromboembolism, aggravating the disease. Recently, increased activity was shown for coagulation factors II, VIII, IX, X, XI, and XII in patient peripheral blood. In vitro, the high potential of FXa-PAR1-loop as growth factor system and significant effects of its blockade were proven. Methods: Patient samples (n=108) were analyzed for FXa and PAR-1. In immunodeficient mice, glioblastoma xenografts were established and treated with low-molecular weight heparins (LMWH) (30mg/kg SC daily for 3 wks). Phosphate buffered saline served as control. Tumor growth rates, final tumor size, tumor proliferation (Ki67), and tumor vascularization (CD31) were determined. Results: Human glioblastomas overexpressed FXa and PAR-1 in the compact tumor center (FXa: p=.001; PAR-1: p=.001) and in the invasion zone (FXa: p=.006; PAR-1: p=.005). Neoangiogenic endothelial cells disproportionately high expressed FXa and PAR-1 with rising intensity in the invasion zone (FXa: p=.001; PAR-1: p=.001), and the compact tumor mass. (FXa: p=.001; PAR-1: p=.001). Growth curves of LMWH-treated tumors slowed (p=.001). Final tumor size was reduced (s.c.: p=.001; i.c.: p=.05). Tumor cell proliferation was massively inhibited in situ (tinzaparin: p=.001; enoxaparin: p=.001) as was the number of CD31 positive endothelial cells ((tinzaparin: p=.001; enoxaparin: p=.001) and the tumor vascularization (p=.001 each). Conclusions: Glioblastoma patients display abnormal activation of coagulation factors in peripheral blood and show high levels of FXa and PAR-1 in the tumor center, invasion zone and angiogenic endothelia. LMWH caused tumor growth retardation and size reduction with blockade of proliferation and vascularization. FXa inhibition should be considered as continuous thrombosis prophylaxis and adjuvant glioblastoma treatment.
Phase Ib study evaluating safety and pharmacokinetics (PK) of the oral transforming growth factor-beta (TGF-β) receptor I kinase inhibitor LY2157299 monohydrate (LY) when combined with chemoradiotherapy in newly diagnosed malignant gliomas.

Cristina Suarez, Jordi Rodon, Annick Desjardins, Peter A. J. Forsyth, Ivelina Gueorguieva, Ann Cleverly, Tiana Burkholder, Durisala Desaiah, Michael M. F. Lahn, Wolfgang Wick; Vall d’Hebron University Hospital, Barcelona, Spain; Experimental Therapeutics Group, Vall d’Hebron Institute of Oncology, Barcelona, Spain; Duke University Medical Center, Durham, NC; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Eli Lilly and Company, Erl Wood, United Kingdom; Eli Lilly and Company, Indianapolis, IN; Division of Early Phase Oncology Clinical Investigation, Eli Lilly and Company, Indianapolis, IN; University of Heidelberg Medical Center, Heidelberg, Germany

Background: Based on preclinical data suggesting an additive antitumor effect of combining TGF-β inhibitors with temozolomide based chemoradiation (TMZ/RT), a Phase 1b study was initiated to evaluate the safety and PK of LY combined with TMZ/RT in patients with newly diagnosed glioma. Methods: LY was evaluated sequentially in 2 doses (160 mg/day and 300 mg/day) combined with TMZ/RT. TMZ/RT was administered as approved and LY given as intermittent dosing (14 days on/14 days off = 1 cycle). Toxicity was assessed using the CTCAE, version 4. The PK profile of LY in combination with TMZ/RT was determined. Results: 19 patients with glioma (16 World Health Organization Grade 4; 3 Grade 3 were treated with LY (160 mg/day, n=10; 300 mg/day, n=9) and TMZ. The median number of cycles was 5 (range 1-13). Regardless of relatedness to study treatment, the following treatment-emergent adverse events (TEAEs) were observed in ≥25% of patients: nausea (n=11), fatigue (n=11), thrombocytopenia (n=11), headache (n=9), vomiting (n=8), lymphopenia (n=6), anorexia (n=6), constipation (n=5), radiation skin injury (n=5), and alopecia (n=5). The following TEAEs were related specifically to at least LY: thrombocytopenia (n=3, 2 Gr 3 and 1 Gr 4), fatigue (n=2), maculopapular rash (n=2, Gr 3), dermatitis acne form (n=3, 1 Gr 3) and in 1 patient each: nausea, vomiting, hypertension, hypersensitivity and leukopenia (Gr 4). No change in the PK profile of LY was shown when LY was combined with TMZ/RT. In the combination therapy, area under the curve (0-∞) at steady state was observed geomean (%CV) to be 5.5 (48%) mg*h/L following 300 mg/day (n=9). Following monotherapy with LY, these exposures were similar with a median (20th-80th percentiles) of 4.7 (2.5-8.8) mg*h/L (n=37). Conclusions: No dose-limiting toxicities and no clinically meaningful cardiotoxicities were observed; hence, the treatment of LY at 300 mg/day in combination with standard chemoradiation has a manageable toxicity profile. A Phase 2a trial has been initiated to relate the pharmacodynamic effects with overall survival. Clinical trial information: NCT01220271.
Characterization of candidate tissue and blood biomarkers in a rare cohort of myxopapillary ependymoma patients.

Aysegul Ilhan-Mutlu, Anna Sophie Berghoff, Friedrich Wrba, Christine Marosi, Ludwig Wagner, Christoph Zielinski, Matthias Preusser; Department of Medicine I, Comprehensive Cancer Center CNS Tumours Unit, Medical University of Vienna, Vienna, Austria; Department of Medicine I and Comprehensive Cancer Center CNS Tumours Unit, Medical University of Vienna, Vienna, Austria; Department of Pathology, Medical University of Vienna, Vienna, Austria; Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Center, Medical University Vienna, Vienna, Austria; Department of Medicine III, Medical University of Vienna, Vienna, Austria; Department of Medicine I and Comprehensive Cancer Center, Medical University Vienna, Vienna, Austria; Department of Medicine I and Comprehensive Cancer Center CNS Tumours Unit, Medical University of Vienna, Austria, Vienna, Austria

Background: Myxopapillary ependymoma (MPE) is a very rare tumor of the distal spinal cord. Despite benign histopathology, local recurrences occur in approximately 30% of patients and distant metastases have been described in few cases. We investigated candidate tissue and blood biomarkers in a rare MPE series.

Methods: Formalin fixed paraffin embedded (FFPE) tumour tissues from 21 MPE patients were immunohistochemically investigated for expression of isocitrate dehydrogenase 1 R132H (IDH-R132H), Secretagogin, glial fibrillary acidic protein (GFAP), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), estrogen receptor (ER), Ki-67, arg, plateled derived growth factor a (PDGFRa) and b (PDGFRb), pc-kit and pc-abl. EGFR gene was evaluated using exon-sequencing. In addition, we analyzed circulating plasma-GFAP using ELISA in 3 patients with completely resected MPE, 1 patient with locally advanced MPE, 2 patients with pleuropulmonary metastases of MPE and 12 control subjects.

Results: Secretagogin and GFAP were expressed in all tissue samples. arg, PDGFRa, PDGFRb, pc-kit and pc-abl were positive in 15, 1, 2, 3 and 2 patients, respectively. The Ki-67 index ranged from 1% to 12.8% (median=7.1%). We detected no expression of EGFR, IDH-R132H, HER2, PR or ER. One patient showed a silent mutation in exon 21 of the EGFR gene (c.2508C>T). We found very high concentrations of plasma-GFAP in two MPE patients with pleuropulmonary metastases, while all other MPE patients were negative.

Conclusions: Our data indicate that (i) targeted tyrosine kinase inhibitors may be rational for the therapy of selected MPE patients and that (ii) circulating GFAP could be useful as circulating marker for the early detection or follow-up of distant metastases in MPE patients.
Background: Glioblastoma multiform (GBM), the most aggressive CNS cancer, has limited effective therapeutic options, with underlying molecular heterogeneity contributing to the differences in treatment response. Our study was designed to interrogate biomarkers from a large cohort of GBM patients to seek therapeutic implications. Methods: Data was analyzed from 570 high grade astrocytoma patients (vast majority GBM) who received tumor profiling at Caris Life Sciences from 2009 to 13. Test methodologies included IHC, FISH, CISH, Sanger SEQ, MGMT promoter methylation and NextGen SEQ (Illumina TruSeq). Results: In our patient cohort, 59% had MGMT methylation and 70% had negative MGMT IHC, predicting potential response to temozolomide. Protein expression for ERCC1, TOPO1, and TS was 53% negative, 49% positive, and 37% negative, indicating potential benefit from cisplatin, irinotecan and fluorouracil, respectively. Drug pumps PGP and MRP1, were positive by IHC in 10% and 67% of patients, suggesting possible resistance to etoposide, vinca alkaloids and methotrexate. For targeted therapies, c-Kit IHC was positive in 7% patients, mutated in 6% and PDGFRA IHC was positive in 27%, indicating potential benefit from imatinib and other TKI’s. RAS/RAF and PIK3CA/mTOR pathway activation was also noted with BRAF, KRAS, PIK3CA mutations and PTEN loss, observed in 8%, 3%, 7% and 10% of cases, respectively. TS negativity was seen in 91% of MGMT methylated patients and in 37% of MGMT unmethylated patients \( (p = 0.025, \text{ student’s t-test}) \), revealing a possible novel combination therapy of fluoropyrimidines with temozolomide for a select cohort. Similarly, biomarker profiles of molecular subgroups defined by EGFR amplification (44% in our cohort) and IDH1, p53 mutations will be analyzed for therapeutic implications. Conclusions: By profiling tumor biomarkers from a large cohort of GBM patients using validated assays in a single facility, we demonstrate the vast molecular heterogeneity of GBM and highlight the importance of individualized therapy based on a patient’s unique tumor profile. Incorporating a comprehensive biomarker analysis into clinical management of this aggressive cancer allows for an informed selection of more effective therapies.
Survival outcome of early versus delayed bevacizumab treatment in patients with recurrent glioblastoma.

Mohamed Ali Hamza, Jacob Mandel, Charles A. Conrad, Mark R. Gilbert, W. K. Alfred Yung, Vinay K. Puduvalli, John Frederick De Groot; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Bevacizumab (BEV) is widely used for treatment of patients with recurrent glioblastoma (GB). Differences in outcome between early versus delayed BEV treatment of recurrent GB are not well defined. We examined the relationship between the time of start of BEV treatment and outcomes in patients with recurrent GB. Methods: In this retrospective chart review derived from our longitudinal database, we identified patients with recurrent GB between 2001 and 2011, who were treated with BEV alone or BEV-containing regimens. Data was analyzed to determine overall survival (OS) from time of diagnosis and progression free survival (PFS) from time of BEV start. Early BEV was defined as start of BEV treatment at first recurrence, while delayed BEV was defined as start of treatment at second recurrence or later. Results: A total of 298 patients with recurrent GB who received BEV were identified, of whom 149 patients received early BEV, 134 patients received delayed BEV, and 15 patients who were excluded because they received BEV upfront. There were no significant differences in the age, sex, performance status and extent of resection between patients treated with early BEV and those treated with delayed BEV. The median time from diagnosis to first recurrence was more than 6 months (mos.) for both groups (6.5 mos. for early BEV and 7.6 mos. for delayed BEV, p = 0.01). The median time from diagnosis to start of BEV was 7.9 mos. for patients with early BEV and 15.6 mos. for patients with delayed BEV (p<0.001). There was no significant difference in PFS between patients that received early BEV and those that received delayed BEV (5.73 mos. vs. 4.33 mos., p = 0.07). Patients who were treated with delayed BEV had longer OS when compared to those treated with early BEV (25.9 mos. vs. 19.7 mos., p = 0.0002). Conclusions: In patients with recurrent GB, there was no significant difference in PFS between early and delayed BEV; however, patients treated with delayed BEV have longer OS when compared to those treated with early BEV. These results indicate that delaying treatment with BEV is not detrimental and may be associated with a favorable survival outcome.
Efficacy and safety of radiotherapy (RT) plus temozolomide (TMZ) in elderly patients (EP) with glioblastoma (GBM).

Giuseppe Lombardi, Luisa Bellu, Franco Berti, Patrizia Farina, Sara Galuppo, Fable Zastovich, Alessandro Della Puppa, Carla Carollo, Roberta Bertorelle, Domenico D’Avella, Vittorina Zagonel; Medical Oncology 1, Veneto Institute of Oncology-IRCCS, Padova, Italy; Medical Oncology 1, Veneto Institute of Oncology-IRCCS, Padua, Italy; Radiotherapy and Nuclear Medicine Unit, Veneto Institute of Oncology-IRCCS, Padua, Italy; Medical Oncology 1, Istituto Oncologico Veneto IOV - IRCCS, Padua, Italy; Neurosurgery Department, Azienda Ospedaliera di Padova, Padua, Italy; Oncological Radiology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy; Molecular Immunology and Oncology, Veneto Institute of Oncology-IRCCS, Padua, Italy; Department of Neurosurgery, University of Padova, Padua, Italy

Background: the optimal management of EP with GBM remains controversial. The role of RT with TMZ for EP is unclear, and EP are often treated with RT alone, TMZ alone or palliative approaches. We describe our experience of combining RT with concurrent TMZ for treatment of EP with GBM.

Methods: medical records of patients ≥65 years old with newly GBM, histologically confirmed at Veneto Institute of Oncology – Padua, and treated with RT plus TMZ, were reviewed. Concomitant TMZ was 75mg/m²/die. The adjuvant treatment consisted of TMZ 150-200mg/m²/die for six cycles. Median progression-free survival (PFS) and overall survival (OS) were estimated with Kaplan-Meier method. Toxicity was scored according to CTCAE 4.0.

Results: we analyzed 60 patients (PTS), 34 males and 26 females; the average age was 70 (range 65-82); ECOG PS was 0-1 in 35 PTS and 2 in 25 PTS; complete surgery was performed in 35 PTS, partial surgery in 25 PTS. 40 and 20 PTS received RT within 6 or more weeks (range 7-9) from surgery. MGMT and IDH1 were analyzed in 43 PTS: MGMT methylated in 20 PTS (46%), all PTS had wild-type IDH1. 34 PTS were treated with RT 40Gy in 15 fractions, 26 PTS with RT 60Gy in 30 fractions with no significant difference in ECOG PS, MGMT and type of surgery between the two subgroups. For all PTS, PFS and OS were 9.5 and 12.7 ms, respectively. OS was 13.7 and 12.4 ms (p=0.9) in PTS receiving RT within 6 or more weeks from surgery, respectively. 13% of PTS showed grade 3-4 haematological toxicity, 12% grade 3-4 asthenia, 3% nausea/vomiting. MGMT methylated and complete surgery was associated with a longer survival. PFS was 9 vs 10 months (p=0.4) and OS was 11.7 vs 13.7 ms (p=0.1), for PTS treated with 40Gy and 60Gy, respectively. Regarding toxicity: grade 3-4 haematological toxicity was 9% vs 23%, severe asthenia was 9% vs 15%, nausea/vomiting was 3% vs 4% of PTS receiving RT 40Gy and 60Gy, respectively. Conclusions: RT plus TMZ is effective and safe in EP with GBM and good ECOG PS. PFS and OS was not statistically different between PTS receiving RT 40Gy or 60Gy, although we showed a trend for longer OS with RT 60Gy; in contrast, severe toxicity was higher in PTS with RT 60Gy. OS was similar between PTS receiving RT within 6 or more weeks (7-9ws) from surgery.
Imaging biomarkers of ramucirumab and olaratumab in patients with recurrent glioblastoma.

Jaishri O’Neill Blakeley, Joy D. Fisher, Frank S. Lieberman, Janine Lupo, Louis B. Nabors, Jason Crane, Patrick Y. Wen, Andre Cote, David M. Peereboom, Qiuting Wen, Timothy Francis Cloughesy, H. Ian Robins, Serena Desideri, Stuart A. Grossman, Xiaobu Ye, Sarah Nelson, The Adult Brain Tumor Consortium; The Johns Hopkins University, School of Medicine, Baltimore, MD; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; University of Pittsburgh Cancer Institute, Pittsburgh, PA; University of California, San Francisco, San Francisco, CA; University of Alabama at Birmingham, Birmingham, AL; Dana-Farber Cancer Institute, Boston, MA; Cleveland Clinic, Cleveland, OH; David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA; University of Wisconsin Hospitals and Clinics, Madison, WI

Background: VEGF and PDGF receptors are overexpressed in glioblastoma (GBM). Both receptor families may be important therapeutic targets. We explored early biologic markers of VEGFR-2 or PDGFRα inhibition with functional MRI. Methods: A subset of patients (pts) from a multicenter phase II study of monoclonal antibodies to VEGFR-2 (ramucirumab 8mg/kg IV q2wks) or PDGFRα (olaratumab 20mg/kg IV q2wks) in adult patients with recurrent GBM underwent a standardized MRI brain protocol with dynamic contrast enhanced (CE); diffusion tensor; perfusion weighted and routine sequences at -1d, 1d, 28d and every +56d from treatment initiation. ACRIN performed site qualification and imaging QA. Regions of CE and T2w hyperintensity were manually defined; percent change in volumes and change in normalized image intensities was calculated. Results: 28 patients were evaluable. Pts receiving ramucirumab (n=11; 7 male) had a median age of 54 (43-67), KPS 90 (70-100) and Dex dose 2mg (0-8). Pts receiving olaratumab (n=17; 14male) had a median age of 58 (24-72), KPS 80 (70-100) and Dex dose 2mg (0-4mg). KPS and Dex were stable over time. Conclusions: Preliminary results show that within 1 day of ramucirumab, CE volume, relative CE intensity and blood volume decreased and by 28 days, T2 volume and ADC decreased suggesting a potent antiangiogenic effect. PDGFRα inhibition had no effect on lesion volume, but reduced relative CE intensity and blood volume at 28 days. Clinical efficacy results are anticipated in mid-2013. Clinical trial information: NCT00895180.
Background: Aim of this prospective longitudinal study was to evaluate whether $^{18}$FET-PET allow to monitor and quantify the therapeutic effects of surgery, radiotherapy and chemotherapy in newly diagnosed glioblastoma and whether $^{18}$FET-PET can provide additional prognostic information on response to therapy and outcome. Methods: 92 patients with newly diagnosed glioblastoma considered eligible for radiochemotherapy (RcX) were included; diagnosis was obtained by biopsy ($n=46$) or resection ($n=46$). Patients were to undergo $^{18}$FET-PET and cocomitant MRI scans prior to surgery, following RcX and as well as after three cycles of adjuvant temozolomide (TMZ). At each time point, biological tumor volume (BTV), maximal $^{18}$FET uptake as ratio to background (SUV$_{\text{max}}$/BG), and tumor uptake kinetics (TAC) were obtained. Overall survival (OS) was primary endpoint, progression-free survival (PFS) as defined by MRI using Macdonald criteria was a secondary endpoint. ROC analyses were done to determine optimal cut-off values of $^{18}$FET-PET parameters for survival outcome. To identify predictors for OS/PFS, Cox regression analysis was performed. Results: 79 patients were eligible for further evaluation. ROC analysis revealed cut-off values for pre-RcX BTV (9.5 ccm) and SUV$_{\text{max}}$/BG (2.95) with a sensitivity and specificity of both 70% for BTV and 68/73% for SUV$_{\text{max}}$/BG. Both pre-therapeutic BTV and SUV$_{\text{max}}$/BG were associated with PFS and OS ($p<0.05$). In contrast to MRI-based volume, the prognostic value of BTV remained highly significant in the multivariate Cox analysis independently of MGMT status. Furthermore, $^{18}$FET TAC pattern and its changes were related to OS and PFS. Conclusions: Serial $^{18}$FET-PET imaging in glioblastoma before and after concomitant radio-/chemotherapy is a highly powerful tool to provide prognostic information for the outcome in newly diagnosed glioblastoma patients. These findings might help to personalize therapy and response evaluation in forthcoming clinical investigations. Clinical trial information: NCT01089868.
Phase I/II trial of vorinostat combined with temozolomide (TMZ) and radiation therapy (RT) for newly diagnosed glioblastoma (GBM) (N0874-ABTC0902, Alliance): Final results of the phase I trial.

Evanthia Galanis, Jann Nagina Sarkaria, S. Keith Anderson, Wenting Wu, Kurt A. Jaeckle, Caterina Giannini, Jan C. Buckner, Patrick Y. Wen, Alliance for Clinical Trials in Oncology; Mayo Clinic, Rochester, MN; Mayo Clinic, Jacksonville, FL; Dana-Farber Cancer Institute, Boston, MA

Background: Vorinostat (VOR) is a histone deacetylase inhibitor that represents a rational targeted agent in GBM treatment. Given its single-agent activity in recurrent disease (Galanis, et al, 2009) and radiosensitizing properties, this phase I/II trial was designed to test the addition of VOR to standard chemoradiation in newly diagnosed GBM patients (pts): the phase I portion of the trial is the focus of this report. Methods: A standard cohorts of three design was used to assess the safety of VOR in combination with RT and concomitant TMZ and establish the phase II dose of the combination. VOR was given orally days 1 - 5 every wk beginning with the first dose of RT (total dose 60 Gy) and (75mg/m²/day). Following a 4 - 6 week rest, pts received up to 12 cycles of standard adjuvant TMZ in combination with VOR on days 1-7 and 15 – 21 of each cycle; dose was based on NABTT trial 04-03 (Lee, et al, 2012). Results: The phase I component is complete with 15 pts, 12 pts at dose level 0 (VOR 300 mg/day days 1 - 5, weekly x 6 wks), and 3 pts at dose level 1 (VOR 400 mg/day, days 1 – 5 weekly x 6 wks) in combination with RT/TMZ. Dose limiting toxicity (DLT) in dose level 1 included grade 3 fatigue in 2 pts, grade 3 wound dehiscence in 1 pt, and grade 4 neutropenia and thrombocytopenia in 1 pt. In dose level 0, 1/6 pts had DLT (gr 3 dyspnea). An MTD expansion cohort of 6 additional patients was added to dose level 0; one patient experienced grade 4 thrombocytopenia and grade 3 fatigue, and 1 patient experienced grade 3 febrile neutropenia. In the 12 pts treated in the phase II dose, most common toxicities were hematologic, including lymphopenia (gr 3/4 in 66.7%), thrombocytopenia (gr 3 in 16.7%, gr 4 in 16.7%) and neutropenia (gr 3 in 16.7%, gr 4 in 8.3%). Grade 3 fatigue was observed in 8.3% of the pts. Conclusions: MTD for VOR in combination with TMZ/RT in newly diagnosed GBM patients is 300 mg/d, days 1 - 5 weekly during RT. Toxicity was primarily hematologic. This dose was used in the recently completed phase II trial of the combination (110 pts). RNA expression profiling in patient samples is in process to assess vorinostat responsive signatures observed in preclinical models. Clinical trial information: NCT00731731.

Praeksh Chinnaiyan, Minhee Won, Patrick Y. Wen, Amyn Rojiani, Merideth M. Wendland, Thomas A. DiPetrillo, Benjamin W. Corn, Minesh P. Mehta; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Radiation Therapy Oncology Group, Philadelphia, PA; Dana-Farber Cancer Institute, Boston, MA; Georgia Health Sciences University, Augusta, GA; Willamette Valley Cancer Institute, Eugene, OR; Department of Radiation Oncology, Rhode Island Hospital, Providence, RI; Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; University of Maryland, Baltimore, MD

Background: To determine the safety of the mTOR inhibitor everolimus (RAD001) administered daily with concurrent radiation and temozolomide in newly diagnosed glioblastoma patients. Methods: Everolimus was administered daily with concurrent radiation (60 Gy in 30 fractions) and temozolomide (TMZ) (75 mg/m$^2$/day). Everolimus was escalated from 2.5 (Dose Level 1), to 5 (Dose Level 2), to 10 mg/day (Dose Level 3). Maintenance TMZ was delivered at 150-200 mg/m$^2$ on days 1 to 5 every 28 days for up to 12 cycles with concurrent everolimus at the previously established daily dose of 10 mg/day. Dose escalation continued if a dose level produced DLTs in ≤ 2 of the first 6 evaluable patients. Results: Between October 28, 2010 and July 2, 2012, the Radiation Therapy Oncology Group (RTOG) 0913 protocol initially registered a total of 35 patients, with 25 patients successfully meeting enrollment criteria, receiving drug and evaluable for toxicity. Everolimus was successfully escalated to the predetermined MTD of 10 mg/day. Two of the first 6 eligible patients experienced a DLT at each dose level, receiving drug and evaluable for toxicity. Everolimus was successfully escalated to the predetermined MTD of 10 mg/day. Two of the first 6 eligible patients experienced a DLT at each dose level. DLTs included: gait disturbance, febrile neutropenia, rash, fatigue, thrombocytopenia, hypoxia, ear pain, headache, and mucositis. Other common toxicities were Grade 1/2 hypercholesterolemia and hypertriglyceridemia. At the time of analysis, there was one death reported, which was attributed to tumor progression. Conclusions: Daily oral everolimus (10 mg) combined with both concurrent radiation therapy and TMZ followed by maintenance TMZ, is well tolerated, with an acceptable toxicity profile. A phase II randomized clinical trial with mandatory correlative biomarker analysis is currently underway, designed to both determine the efficacy of this regimen and identify molecular determinants of response. Supported by RTOG U10 CA21661 and CCOP U10 CA37422 grants from NCI and Novartis. Clinical trial information: NCT01062399.
Final results from a large prospective Italian population study on glioblastoma and correlations with $MGMT$ status: The Project of Emilia-Romagna Region in Neuro-oncology (PERNO).

Alba Ariela Brandes, Mario Ermani, Roberto D’Alessandro, Fiorenzo Albani, Enrico Franceschi, Michele Cavallo, Antonella Valentini, Anna Maria Cremonini, Claudia Mucchiari, Marina Faedi, Girolamo Crisi, Enrico Fainardi, Norina Marcello, Anna Pisanello, Raffaele Agati, Maria Michiara, Giuseppe Pasini, Ermanno Giombelli, Franco Servadei, Agostino Baruzzi; Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna, Bologna, Italy; Neurosciences Department, Statistic and Informatic Unit, Azienda Ospedale-Università, Padova, Italy; IRCCS Institute of Neurological Sciences of Bologna, University of Bologna, Bologna, Italy; IRCCS Istituto delle Scienze Neurologiche, Department of Neurological Sciences, University of Bologna, Bologna, Italy; Neurosurgical Department, S. Anna Hospital, Ferrara, Italy; Neurosurgery, Nuovo Ospedale Civile S. Agostino-Estense, Modena, Italy; Neurosurgery Department, Bufalini Hospital, Cesena, Italy; Department of Oncology and Haematology, Ramazzini Hospital, Carpi, Italy; Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cara dei Tumori (IRST-IRCCS), Cesena, Italy; Department of Neuroradiology, Azienda Ospedaliero-Università, Parma, Italy; Neuroradiology Unit, Department of Neuroscience and Rehabilitation, Azienda Ospedaliera Universitaria, Arcispedale S. Anna, Ferrara, Italy; Neurology Department, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Neuroradiology Department, IRCCS of Neurological Sciences, Bellaria Hospital, Bologna, Italy; Medical Oncology Unit, University Hospital of Parma, Parma, Italy; Department of Medical Oncology, Infermi Hospital, Rimini, Italy; Neurosurgical Department, General Hospital, Parma, Italy; Neurosurgery-Neurotraumatology Unit, University Hospital of Parma, Emergency Neurosurgery, Neuromotory Department, Hospital of Reggio Emilia, Parma, Italy; IRCCS Istituto delle Scienze Neurologiche, Department of Neurological Sciences, University of Bologna, Bologna, Italy

Background: The impact on the general population of temozolomide concurrent with and adjuvant to radiotherapy (RT/TMZ) was assessed in the context of the Registry of the Project of the Emilia-Romagna Region in Neuro-Oncology (PERNO), the first Italian prospective observational population-based study in the field of neuro-oncology. Methods: Patients (pts) meeting the following inclusion criteria were evaluated: age $\geq$18 years; PS 0-3; histologically confirmed GBM, no previous or concomitant non-glial tumoral disease, residence in the Emilia Romagna region. The data were collected prospectively. Results: Study accrual, started on January 1 2009, was closed, as planned, on December 31 2010. Two hundred sixty-eight pts (F=111, M=157; median age, 63.5 [range 29-34] years) were studied. mOS was 10.7 months (95%CI: 9.2 – 12.3). $MGMT$ status, assessed in 186 (89%) of 210 pts who had at least radiotherapy was evaluable in 174 pts (83%), being methylated in 76 (43.7%), and unmethylated in 98 (56.3%) pts. mOS for pts with $MGMT$ methylated status was 18.5 months (95%CI: 14.4-22.6), and 12.4 months for those with $MGMT$ unmethylated status (95%CI: 10.5 - 14.3, $p<0.0001$). 140 pts $<70$ years were treated with RT/TMZ; mOS in this group was 16.4 months (95% CI: 14.5 – 18.4). mOS was 20 months in the 59 pts (42%) harboring $MGMT$ methylation (95% CI: 12.8 - 27.2), and 13.5 months in the 73 pts (52%) without $MGMT$ methylation (95% CI: 10.8 – 16.2, $p<0.0001$). At multivariate analysis, a significant prognostic role was found for performance status ($p=0.001$), extent of surgery ($p=0.009$), age ($p=0.004$), postsurgical treatment ($p=0.03$), and $MGMT$ status (methylated vs unmethylated, $p=0.01$). Conclusions: The data from the present large prospective population study are in line with those reported in the EORTC/NCIC randomized trial, confirming that this successful approach has been widely incorporated in daily practice.
Marrow-ablative chemotherapy followed by tandem autologous hematopoietic cell transplantation (AuHCT) in pediatric patients with malignant brain tumors.

**Background:** In an effort to both improve cure rates and quality of survival in young children with malignant brain tumors, irradiation-avoiding or at least minimizing marrow-ablative chemotherapy with AuHCT has been incorporated in both up-front as well as recurrent therapies. To decrease the toxicity of single cycle marrow-ablative chemotherapy regimens, and possibly enhance cure through overall dose intensification, use of fractionated multiple (tandem) cycles of marrow-ablative chemotherapy with AuHCT has been explored. **Methods:** In this retrospective analysis, we investigated the outcome of children with malignant brain tumors treated with marrow-ablative chemotherapy and tandem AuHCT at Children’s Hospital Los Angeles between June 1999 and July 2012. **Results:** Forty-four children (24 males) with a median age of 7.1 years (range 0.6-19.0 years) with malignant brain tumors were studied. Twenty-one had medulloblastomas/primitive neuro-ectodermal tumors, 8 atypical teratoid/rhabdoid tumors, 5 high-grade gliomas, 4 malignant germ cell tumors, 3 ependymomas and 3 choroid plexus carcinomas. Twenty-nine patients receive 3 and 15 received 2 tandem transplants, respectively. Twenty-seven patients were newly-diagnosed and 17 recurrent disease. Thirty-one patients received irradiation at some time. The 5-year post-transplant progression-free (PFS) and overall survivals (OS) for all patients were 46.3±8.2% and 51.7±8.5% respectively. The PFS and OS for newly-diagnosed patients were 68.9±9.9% and 73.5±9.3% respectively, compared with those transplanted at relapse 11.8±9.8 (p <0.001) and 15.1±12.3% (p = 0.0231) respectively. The 5-year post-transplant PFS and OS in unirradiated patients was 74.0±13.0% and 74.0±13.0% versus33.2±9.8% and 40.2±10.6% in irradiated patients (p = 0.11 and p = 0.239 respectively). One patient (2.3%) died of transplant-related toxicity. **Conclusions:** Marrow-ablative chemotherapy with tandem AuHCT is feasible and safe in children with malignant brain tumors with encouraging irradiation-free survival in newly-diagnosed children.
Background: Transforming growth factor-β (TGF-β) signaling is involved in glioma development. GC1008 is a monoclonal antibody that has demonstrated significant neutralization of all mammalian isoforms of TGF-β in preclinical models (Lonning, Curr Pharm Biotechnol 2011). The aim of this study was to investigate whether GC1008 uptake in brain tumors can be visualized using the 89Zirconium (Zr)-GC1008 PET scan and to assess treatment outcome in patients with recurrent glioma treated with GC1008 (NCT01472731). Methods: Patients with WHO II-IV glioma who presented with recurrent disease were eligible. After iv administration of 37 MBq (5 mg) 89Zr-GC1008, 89Zr-GC1008 PET scans were performed on day 2 and day 4 post injection. Thereafter, patients were treated with 5 mg/kg GC1008 iv every 3 weeks. MRI scans were made for response evaluation after 3 courses or as clinically indicated. Results: Twelve patients with 1st-8th recurrent disease were included (10 glioblastoma, 1 anaplastic oligodendroglioma, 1 anaplastic astrocytoma), all underwent an 89Zr-GC1008 PET scan on day 4. 4 patients also underwent a PET scan on day 2 after tracer injection. Median SUVmax on day 4 was in tumor lesions 4.6 (range 1.5-13.9) and median SUVmean in normal brain tissue 0.3 (range 0.2-0.5). In 3 out of 4 patients who underwent a day 2 and day 4 whole body scan uptake decreased in most normal organs but not in tumor lesions, supporting tumor specific 89Zr-GC1008 uptake. No major toxicity of GC1008 treatment was observed, but all patients showed clinical and/or radiological progressive disease after 1-3 cycles. Median progression free survival was 61 days (range 25-80) and median overall survival 106 days (range 37-287+). Conclusions: 89Zr-GC1008 showed excellent uptake by recurrent gliomas. Clinical trial information: 01472731.
Quality of life (QOL) and cognitive status among irradiated brain tumor survivors treated with donepezil or placebo.

Doug Case, Michelle Joy Naughton, Volker W. Steiber, Gerald K. Bayer, Paul A. Bilodeau, Dennis Frederic Moore, Steven Charles Falchuk, Burton M. Needles, James Ptephoff, William Jeffery Edenfield, Jeffrey K. Giguere, Nicolette Erickson, Monica Elena Loghin, Edward G. Shaw, Stephen R. Rapp; Wake Forest University, School of Medicine, Winston Salem, NC; Wake Forest University, School of Medicine, Winston-Salem, NC; Forsyth Regional Cancer Center, Winston-Salem, NC; Green Bay Oncology, Green Bay, WI; Medical College of Georgia, Augusta, GA; Cancer Center of Kansas, Wichita, KS; Medical Arts Pavil, Newark, DE; St John’s Mercy Medical Center, St, Louis, MO; St. John’s Mercy Hospital, St Louis, MO; Cancer Centers of the Carolinas, Greenville, SC; Cancer Centers of the Carolinas, Seneca, SC; Central Maine Medical Center, Lewiston, ME; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cognitive problems after cancer therapy can decrease QOL. This phase III randomized trial tested the effect of donepezil (5-10 mg daily for 24 weeks) on cognition and QOL in brain cancer patients.

Methods: Between 2/2008-12/2011, 198 (99 placebo; 99 donepezil) adult primary and metastatic brain tumor survivors > 6 months post radiation (> 30 Gy) were recruited at 24 sites affiliated with the Wake Forest CCOP Research Base, 3 CTSU sites, and M.D. Anderson. Outcomes were assessed at baseline, 12 and 24 weeks. Regression analyses examined the association of demographics, fatigue (FACIT-Fatigue), and a cognitive performance composite score (CC) (comprised of the Controlled Oral Word Association Test, Hopkins Verbal Learning Test-Revised, Digit Span Test, Trail Making Test A&B, Rey-Osterreith Complex Figure-modified, Grooved Pegboard) on QOL, measured by the FACT-Brain (FACT-Br) total score.

Results: Participants had a median age of 55, were predominantly female (54%) and non-Hispanic White (91%), with a median time from diagnosis of 38 months. Study completion was 74%. At 12 and 24 weeks, treatment had no significant effect on QOL, unadjusted and adjusted for race/ethnicity, age, sex, fatigue, baseline FACT-Br, and baseline CC. However, for those below the median on the baseline FACT-Br subscale (i.e., greater cognitive symptoms), donepezil was associated with higher (better) post-tx FACT-Br total scores (p=0.004), unadjusted for covariates. After adjustment for covariates, donepezil was borderline significantly associated with higher post-tx QOL (p=0.052). Improvement in QOL was associated with being female (p=0.017) and less baseline fatigue (p=0.005). For participants with baseline FACT-Br subscale scores above the median, only lower baseline FACT-Br total scores (p=0.015) were significantly related to greater improvements in FACT-Br. Donepezil treatment was not significant (p=0.48). Conclusions: The impact of donepezil on QOL was greater in survivors with more cognitive symptoms at baseline, although the results were borderline significant. Fatigue continued to be a major factor in lower QOL. Other interventions to better manage survivors’ symptoms are needed. Clinical trial information: NCT00369785.
Patterns of relapse after concurrent temozolomide and dose-escalated intensity-modulated radiation therapy (IMRT) in newly diagnosed glioblastoma (GBM).

Corey Speers, Larry Junck, Jason Heth, Yue Cao, Theodore Steven Lawrence, Christina Tsien; University of Michigan Health System, Ann Arbor, MI; University of Michigan, Ann Arbor, MI; Department of Radiation Oncology, University of Michigan Health System, Ann Arbor, MI

Background: We hypothesized that IMRT would permit us to safely escalate the dose of radiation with concurrent temozolomide substantially above the current standard of 60 Gy and that this increased dose would more adequately control local disease leading to an alteration in the patterns of relapse in patients with GBM. Methods: Between 2003 and 2012 a total of 69 patients were treated with dose-escalated IMRT with concurrent temozolomide. 39 patients were initially treated in a combined phase I/II trial with IMRT doses of 66 to 81 Gy over 6 weeks with concurrent daily temozolomide (75 mg/m2) followed by adjuvant cyclic temozolomide (200 mg/m2 d1-5 q28d for 6 or more cycles). Subsequently, 30 additional patients were treated to 66-72 Gy based on the reported efficacy and safety of the initial phase I/II study. Results: All 69 patients were assessed to evaluate the effect of dose escalation on late toxicity and patterns of progression. Median RT dose was 72 Gy and median overall survival was 19.0 months. Late CNS grade III toxicity was observed at 78 (2 of 7 patients) and 81 Gy (1 of 9 patients). 0 of 53 patients receiving 75 or less Gy developed necrosis. 64% (44/69) of patients had progression of their disease after dose-escalated chemoradiotherapy. The patterns of progression differ, however, from previous studies which identify in-field relapse of 72-80% with standard dose radiation (Brandes AA, Tosoni A, Franceschi E, et al: J Clin Oncol. 27:1275-9, 2009). In this cohort, 41% (18/44) of patients developed marginal or distant relapse compared to 59% (26/44) who developed local, in-field relapse. Conclusions: Patients with GBM can safely receive standard temozolomide with up to 75 Gy in 30 fractions, delivered using IMRT. Dose-escalated chemoradiotherapy improves local control and leads to an increased percentage of patients progressing distally, highlighting the need for improved tumor targeting with newer imaging modalities to identify the initial extent of tumor involvement as well as the need for more effective systemic treatment.
Phase II study of PX-866 in recurrent glioblastoma.

Marshall W. Pitz, Elizabeth A. Eisenhauer, Mary Valeria MacNeil, Brian Thiessen, David R. Macdonald, Jacob C. Easaw, David Daniel Eisenstat, Ankineedu Saranya Kakumanu, Jeremy Squire, Ming Sound Tsao, Suzanne Kamel-Reid, Aurelie Tassignon, Diana Felice Hausman, Warren P. Mason; University of Manitoba, Winnipeg, MB, Canada; Queen’s University, Department of Oncology, Kingston, ON, Canada; Dalhousie University, QE II Health Sciences Centre, Halifax, NS, Canada; BC Cancer Agency, Vancouver, BC, Canada; London Regional Cancer Program, London, ON, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; University of Alberta, Edmonton, AB, Canada; Allan Blair Cancer Center, Regina, SK, Canada; Department of Pathology and Molecular Medicine, Queen’s University, Kingston, ON, Canada; Department of Pathology, University Health Network, University of Toronto, Toronto, ON, Canada; University Health Network, Department of Pathology and Laboratory Medicine, Toronto, ON, Canada; Queen’s University - NCIC CTG, Kingston, ON, Canada; Oncothyreon, Inc., Seattle, WA; Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada

Background: Glioblastoma (GBM) is the most aggressive malignancy of the central nervous system. The majority have genetic changes that increase the activity of the phosphatidylinositol-3-OH kinase (PI3K) signal transduction pathway, critical for cell motility, proliferation, and survival. We present the results of PX-866, an oral PI3K inhibitor, in patients (pts) with recurrent GBM. Methods: A multinomial design of response and early progression (< 8 weeks on study) was used. In stage 1 (15 pts), 0 responses and ≥ 10 early progressions would stop accrual; after full accrual, ≥ 4 responses OR ≤ 13 early progressions was prespecified as of interest. Pts with histologically confirmed GBM, at first recurrence after chemoradiation and adjuvant temozolomide were given PX-866 8 mg daily on this single-arm phase II study. MRI and clinical exam were done every cycle (8 weeks). Tumour tissue was collected for analysis of potential markers of PI3K inhibitory activity (PTEN, EGFRviii, PIK3CA mutations). Results: A total of 33 pts were enrolled, eligible and evaluable. Median age was 56 (range 35-78), 12 were female; 29 had performance status (PS) 0-1 and 4 had PS 2. Median time from initial diagnosis to enrolment was 308 days (range 141-1256). Median number of cycles was 1 (range 1-7). Thirty-two pts have discontinued therapy, 26 due to disease/symptomatic progression and 6 due to toxicity (5 LFT elevation and 1 allergic reaction). Other adverse effects (AE): fatigue (16 pts/2 grade 3), diarrhea (11 pts/5 grade 3), nausea (19 pts/1 grade 3), vomiting (11 pts/1 grade 3) and lymphopenia (29 pts/7 grade 3/4). Five pts had related serious AEs (1 LFTs, 1 GI and 3 venous thromboembolism) All pts were evaluable for response; 25 had a best response of progression, 1 had partial response (overall response rate 3%) and seven (21%) had stable disease (SD, median 7.3 months; range 3.1-13.6). Six month PFS was 17%. In preliminary analyses, no statistical association was found between SD and PTEN or EGFRviii status (results pending in 16 pts). Conclusions: PX-866 was relatively well tolerated. Overall response rate was low, and the study did not meet its primary endpoint; however, 21% of pts obtained durable stable disease. Further correlative work is required to identify the predictor of this effect. Clinical trial information: NCT01259869.
A phase I study of cediranib in combination with cilengitide in patients with recurrent glioblastoma.

Elizabeth Robin Gerstner, Mike Levine, Xiaobu Ye, Tom Mikkelsen, Louis B. Nabors, Jeffrey J. Olson, Thomas Joseph Kaley, Patrick Y. Wen, Tracy Batchelor, Stuart A. Grossman; Massachusetts General Hospital, Boston, MA; Martinos Center for Biomedical Imaging, Charlestown, MA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Henry Ford Health System, Detroit, MI; University of Alabama at Birmingham, Birmingham, AL; Emory University, Atlanta, GA; Memorial Sloan-Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA

Background: Despite high vascularity, duration of response of glioblastoma (GBM) to anti-angiogenic therapy is short. One proposed mechanism of resistance is via co-option of native brain blood vessels and tumor infiltration into normal appearing brain. We designed a Phase I study of cediranib, a VEGFR tyrosine kinase inhibitor, in combination with cilengitide, an integrin inhibitor, to block this infiltrative relapse.

Methods: A phase I study was conducted through the Adult Brain Tumor Consortium in patients with recurrent GBM. Once the MTD was determined, 40 patients enrolled in a dose expansion cohort. Standard eligibility criteria were included and all patients needed to have at least 1 cm of residual disease to assess tumor response. In the dose expansion cohort, 20 patients had received prior anti-VEGF therapy and 20 had never received anti-VEGF therapy. The primary endpoint was the safety of cediranib with cilengitide. Secondary endpoints were overall survival, the proportion of patients alive and progression free at 6 months (APF6), radiographic response (RR), and exploratory analyses of advanced MRI (perfusion, permeability, diffusion imaging) and blood biomarkers.

Results: Forty-five patients were enrolled with a median age of 54 (23-80) and a median KPS 80 (60-100). No DLTs were observed and the MTD was cediranib 30mg daily and cilengitide 2000 mg twice weekly. There were no unexpected Grade 3 or 4 toxicities. Thirty patients experienced disease progression, 8 patients went off study for toxicity, and 5 patients withdrew from the study. Thirty nine patients have died. Partial response was seen in 2 patients, stable disease in 13, progression in 21, and 7 patients were not evaluable for RR. Median OS was 6.4 months, median PFS was 2.4 months, and APF6 was 7.5%. Conclusions: Combination cediranib/cilengitide was well tolerated but the median PFS/OS, APF6, and RR were not very promising. Ongoing analysis of the correlative imaging and blood biomarkers may shed light on a subset of patients who might benefit from this regimen and if anti-VEGF therapy blocked the penetration of cilengitide into the tumor. Clinical trial information: NCT00979862.
Contrast-enhanced T1-weighted subtraction maps for response assessment in recurrent glioblastoma treated with bevacizumab.

Benjamin M. Ellingson, Hyun J. Kim, Davis C. Woodworth, Whitney B. Pope, Jonathan N. Cloughesy, Robert J. Harris, Albert Lai, Phioanh L. Nghiemphu, Timothy F. Cloughesy; Department of Radiological Sciences, Biomedical Physics, and Bioengineering; University of California, Los Angeles, Los Angeles, CA; Center for Computer Vision and Imaging Biomarkers, University of California, Los Angeles, Los Angeles, CA; Departments of Radiological Sciences and Biomedical Physics; University of California, Los Angeles, Los Angeles, CA; Dept. of Radiological Sciences; University of California, Los Angeles, Los Angeles, CA; Department of Neurology, University of California, Los Angeles, Los Angeles, CA; Department of Neurology: University of California, Los Angeles, Los Angeles, CA; University of California, Los Angeles, Los Angeles, CA

Background: Antiangiogenic therapy in glioblastoma (GBM) results in decreased enhancement on post-contrast T1w images, which complicates standard response assessment and is likely the reason no studies have found predictive value in enhancing tumor size or change in size. The current study examined whether contrast-enhanced T1-weighted subtraction maps (CE-ΔT1w) calculated from subtracting pre-contrast (T1) from post-contrast T1w images (T1+C) can improve quantification and predict response in GBM patients treated with bevacizumab. Methods: Recurrent GBM patients (n=160) from the BRAIN trial (AVF3708g), a multicenter Phase II trial evaluating bevacizumab, were used in the current study. CE-ΔT1w maps were calculated 2 weeks before and 6 weeks after the first dose of bevacizumab by: 1) performing registration between T1 and T1+C images, 2) image intensity normalization of T1 and T1+C images, and 3) subtraction of T1 from T1+C images. The volume of tumor regions with positive contrast enhancement after subtraction was retained for analysis. Results: CE-ΔT1w maps greatly improved detectability of subtly enhancing lesions, particularly post-treatment. Results for PFS and OS are summarized in the table below. In all scenarios, CE-ΔT1w maps outperformed conventional tumor segmentation. Results show that size and change in size are both predictive of PFS and OS. Conclusions: CE-ΔT1w maps improve visualization and quantification of contrast enhancing tumor regions in recurrent GBM, allowing for more accurate response assessment.

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<th>Univariate Cox</th>
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<td>(HR, p value)</td>
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Neuropilin-1 (Nrp-1) as a prognostic biomarker and potential drug target for pediatric medulloblastoma.

Lars Riedemann, Matija Snuderl, Ana Batista, Nathaniel David Kirkpatrick, Carmen Ruiz de Almodovar, Martin Hasselblatt, Claudia Rossig, Gabriel Dan Duda, Lei Xu, Dai Fukumura, Peter Carmeliet, Rakesh K. Jain; Massachusetts General Hospital, Boston, MA; Katholieke Universiteit Leuven, Leuven, Belgium; University Hospital Münster, Münster, Germany

Background: Medulloblastoma survival rates have significantly improved over the last decades due to surgery and chemoradiation regimens. However, pediatric patients with high-risk disease and those with recurrence often succumb to their disease. The majority of children suffer from severe adverse effects of intense therapy regimens. We recently demonstrated the role of the Placental Growth Factor (PlGF)/Nrp-1 signaling pathway in medulloblastoma progression in preclinical models (Snuderl et al., Cell 2013). The aim of this study was to evaluate the role of Nrp-1 as a biomarker and therapeutic target in medulloblastoma patients.

Methods: Thirty-two surgical samples of pediatric medulloblastoma were analyzed for expression of Nrp-1 and its ligand PlGF by immunohistochemistry, array-comparative genomic hybridization and deep gene sequencing. On an independent, clinically annotated cohort of 42 medulloblastoma samples, we evaluated the correlation between Nrp-1 expression and 5-year overall survival. The therapeutic relevance of Nrp-1 signaling was tested in a D283 orthotopic human xenograft mouse model using shRNA and a monoclonal antibody against Nrp-1.

Results: Nrp-1 expression was detectable in 100% and PlGF in 90% of all medulloblastoma samples. No significant differences in expression could be detected between known histological or molecular medulloblastoma subtypes. Patients with high Nrp-1 expression had a significantly worse 5-year overall survival compared to patients with a low or moderate expression (40% vs. 86%, p = 0.0058). Treatment with an antibody against Nrp-1 or genetic silencing of Nrp-1 with shRNA significantly prolonged survival in a D283 orthotopic human xenograft mouse model (for both experiments: p < 0.01).

Conclusions: Nrp-1 is widely expressed across all molecular subgroups of medulloblastoma and its expression levels are inversely associated with survival of patients. Targeting Nrp-1 leads to a significant survival benefit in an orthotopic human xenograft mouse model. This data support the hypothesis that targeting the PlGF/Nrp-1 signaling pathway may be a novel therapy approach for pediatric medulloblastoma.
Survival benefit from bevacizumab in newly diagnosed glioblastoma (GBM) according to transcriptional subclasses.

Jason T. Huse, Kathryn Beal, Jianan Zhang, Edward R. Kastenhuber, Thomas Joseph Kaley, Lauren E. Abrey, Philip H. Gutin, Cameron W Brennan, Antonio Marcilio Padula Omuro; Memorial Sloan-Kettering Cancer Center, New York, NY

Background: Genome-wide transcriptional studies (TCGA and others) have identified distinct GBM molecular subtypes, but to date this has not translated into prognostic or therapeutic implications. Bevacizumab has emerged as a new treatment option for GBMs, although a survival benefit has yet to be demonstrated in unselected patients (pts). We analyzed outcomes from a prospective phase II trial in newly diagnosed GBM treated with hypofractionated stereotactic radiotherapy (HFSRT) combined with temozolomide and bevacizumab, and correlated with GBM transcriptional subclasses. Methods: Pts with newly diagnosed GBM with tumor volume < 60cc were eligible. Treatment consisted of HFSRT (6x6 Gy to contrast-enhancing tumor and 6x4 Gy to FLAIR hypersignal with dose painting), concomitant with bevacizumab (10 mg/kg Q2 weeks) and temozolomide (75mg/m² daily), followed by standard adjuvant bevacizumab/ temozolomide. Primary endpoint was 1-y overall survival (OS). To establish TCGA transcriptional subclasses, mRNA from formalin-fixed paraffin-embedded tissue blocks was analyzed with a validated, 151-probe Nanostring gene expression assay. Results: A total of 40 evaluable pts were accrued, achieving a 1-y OS of 90% (95% CI 76-96), 2-y OS of 32% (95% CI 19-47) and median OS of 17.4m. The molecular subclass could be defined in 31 pts, as follows: Mesenchymal: 14 (45%) pts, pro-neural: 8 (26%), classical: 7 (23%), neural: 2 (6%). The pro-neural phenotype was associated with reduced overall survival: median OS of 13.5m vs 21.2m for non pro-neural tumors (univariate: p = 0.015; multivariate: p = 0.003). MGMT promoter methylation did not predict survival (p = 0.13). Conclusions: We provide proof-of-principle that GBM transcriptional classification is biologically and therapeutically relevant, identifying non pro-neural GBMs as the best candidates for bevacizumab treatment. Our findings imply that angiogenesis and tumor invasion mechanisms in proneural tumors may be distinct from other subtypes, and we suggest such pts should not be offered bevacizumab treatment upfront. Future randomized trials focusing on non-proneural tumors may finally demonstrate a survival advantage for bevacizumab in GBM. Clinical trial information: NCT01392209.
Methotrexate, rituximab, and temozolomide in CNS lymphoma: The Mayo Clinic experience.

Vinay Gupta, Robert C. Wolf, Patrick B. Johnston; Mayo Clinic, Rochester, MN

Background: We present a tertiary center experience with high-dose methotrexate, rituximab and temozolomide (MRT) chemotherapy in both primary and secondary CNS lymphoma. Methods: A retrospective analysis was performed for a total of 27 patients (20 male, 7 female) who underwent treatment at Mayo Clinic, Rochester between November 2010 and October 2012. The median age was 63 years (range 23-73). Of these, 12 patients were diagnosed with primary CNS lymphoma, while 15 patients had secondary CNS lymphoma. All patients received at least 1 cycle of MRT. The most common histological subtype was diffuse large cell lymphoma (23 of 27 patients). Other histological subtypes were high grade lymphoma (2 patients), Burkitt’s lymphoma (1 patient) and Mantle cell lymphoma (1 patient). Results: Of 26 patients, who underwent imaging studies for response assessment after MRT, 14 patients achieved complete response (CR), 4 patients achieved partial response (PR), 2 patients had stable disease, while 6 patients had evidence of disease progression. Overall, the median number of chemotherapy cycles with MRT was 3 (range 1-6). For patients, who achieved CR, the median number of MRT cycles was 4 (range 2-6). MRT was well tolerated. Of 27 patients, who underwent their entire treatment at Mayo Clinic, grade 3 or higher treatment related toxicity were noted to be as follows – neutropenia (9/27), thrombocytopenia (4/27), anemia (7/29), and transaminitis (10/27). 16 of 27 patients proceeded to high dose chemotherapy and autologous stem cell transplant. Out of 16 patients, 14 received BCNU/Thiotepa as conditioning regimen, while 2 patients underwent BEAM conditioning. All 16 patients who underwent transplantation remain in CR at this time. Of the remaining 11 patients, 4 are being planned for autologous transplantation, 2 received and responded to salvage chemotherapy, while 5 patients died of progressive disease. Conclusions: Overall, the MRT regimen was well tolerated. Overall response rate was noted to be 67% (18 of 27 patients) and achieved CR in 54% patients (14 of 26 patients). Patients who underwent autologous stem cell transplantation as consolidation therapy continue to do well at a median followup of 12.5 months (range 2-20 months).
Evaluation of invasion patterns and their correlation with integrin alphavbeta expression in brain metastases of solid cancers.

Anna Sophie Berghoff, Orsolya Rajky, Frank Winkler, Michael Weller, Christoph Zielinski, Jens Schittenhelm, Matthias Preussner; Department of Medicine I and Comprehensive Cancer Center CNS Tumours Unit, Medical University of Vienna, Vienna, Austria; Department of Medicine I and Comprehensive Cancer Center CNS Tumours Unit, Medical University of Vienna, Austria, Vienna, Austria; Neurology Clinic and National Center for Tumor Disease, University of Heidelberg, Heidelberg, Germany; University Hospital, Zurich, Switzerland; Department of Medicine I and Comprehensive Cancer Center, Medical University Vienna, Vienna, Austria; Institute of Pathology and Neuropathology, University of Tübingen, Tübingen, Germany

**Background:** Understanding the pathobiology of brain metastases (BM) could guide the establishment of new targeted therapies. **Methods:** We collected 57 autopsy specimens of BM (primary tumor: 27 lung cancer, 6 breast cancer, 8 melanoma, 1 kidney cancer, 2 colorectal cancer, 13 other) and histologically evaluated the patterns of invasion into the surrounding brain parenchyma. Expression of the following integrins was evaluated using immunohistochemistry: with novel antibodies for $\alpha v \beta 5$, $\alpha v \beta 6$, and $\alpha v \beta 8$ integrin. **Results:** We observed three main invasion patterns: well-demarcated (29/57, 51%), vascular co-option (10/57, 18%) and diffuse infiltration (18/57, 32%). There was no association of invasion pattern with primary tumor type, although vascular co-option was most common in melanomas (4/10, 40%). $\alpha v$ subunit expression was lowest in the vascular co-option group ($p = 0.05$, t-test). $\alpha v \beta 6$ levels were higher in the well-demarcated group than in the vascular co-option group ($p = 0.025$; t-test) and were higher in lung cancer BM than in melanoma BM ($0.01$, t-test). $\alpha v \beta 3$ and $\alpha v \beta 5$ were frequently expressed in tumoral ($\alpha v \beta 3$: 30/57, 53%; $\alpha v \beta 5$: 55/57, 97%) and peritumoral ($\alpha v \beta 3$: 29/57, 51%. $\alpha v \beta 5$: 54/57 (95%) vascular structures and 27/57 (47%) specimens showed $\alpha v \beta 5$ and 6/57 (11%) $\alpha v \beta 3$ expression on tumor cells. Prior radio- or chemotherapy did not correlate with invasion pattern or integrin expression. **Conclusions:** We delineate three distinct invasion patterns of BM into the brain parenchyma: well-demarcated growth, vascular co-option and diffuse infiltration. Integrin expression is frequent on tumor and vascular cells in BM and associated with distinct invasion patterns. Anti-integrin therapy could be a valid treatment option in patients with BM.
Prophylactic anticonvulsants in patients (pts) with primary brain tumor (PBT): Have we really agreed to a consensus?

Julia Andrade De Oliveira, Iuri Amorim De Santana, Inacelli Queiroz de Souza Caires, Rafael Caires-Lima, Vanessa Costa Miranda, Bruno Mendonça Protásio, Lucila Soares Da Silva Rocha, Henrique Faria Braga, Ana Cristina Malacarne Mencarini, Manoel Jacobsen Teixeira, Luiz Henrique Martins Castro, Olavo Feher; Instituto do Cancer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil; Hospital das Clínicas, Universidade de São Paulo, São Paulo, Brazil; Hospital das Clínicas - Universidade de São Paulo, São Paulo, Brazil; Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

Background: Routine prophylactic antiepileptic drugs (AED) use to prevent seizures in PBT seizure-naïve pts is not supported by current guidelines. However, the best management of prophylactic AED started in the perioperative setting is still unclear. Additionally, AED can have serious side effects, might have a negative impact on cognition and may present significant drug interactions. Little is known about actual current practice patterns regarding prophylactic AED in PBT. In this report we investigated prophylactic AED use in a tertiary care institution. Methods: We reviewed medical files of 260 consecutive patients, registered in our center between 2008 and 2012, focusing on prophylactic AED use. Collected data included: patient demographics, starting date, AED type, and indication. A descriptive analysis was performed with SPSS IBM version 20.0. Results: Median age was 44.5 years (11 - 83). Most pts had an ECOG PS ≤ 1 (76.4%). Overall, AED were used by 218 pts. Most common agents were: phenytoin (68.8%), carbamazepine (27.1%) and phenobarbital (16.1%). Among 141 seizure-naïve pts, 99 (70.2%) received AED as primary prophylaxis (PP). Only 14 pts (14.1%) had the drug eventually discontinued, in a median time of 5.9 months (1.1 – 76.8m). AED were used as PP in 60% of pts with low-grade gliomas, 73.3% with anaplastic gliomas and 93.9% with glioblastomas. Twenty-seven pts (27.3%) on PP presented seizures, generally associated with tumor progression. For most of them a new anticonvulsant was added for seizure control. Of the 42 seizure-naïve pts who did not receive prophylactic AED, only two presented seizures during or within the first week post-radiotherapy. Conclusions: In our study population, prophylactic AED use in PBT was extremely high (70.2% of seizure-naïve pts). Postoperatively, AED were discontinued in a small minority of pts, and even so, only after a prolonged period of time. Very few seizures occurred in pts not receiving prophylactic AED. Our results suggest that practice patterns regarding prophylactic AED in PBT still contradict established guidelines.
Safety interim data from a three-arm phase II study evaluating safety and pharmacokinetics of the oral transforming growth factor-beta (TGF-β) receptor I kinase inhibitor LY2157299 monohydrate in patients with glioblastoma at first progression.

Antoine F Carpentier, Alba Ariela Brandes, Santosh Kesari, Juan Manuel Sepúlveda, Helen Wheeler, Oliver L. Chinot, Lawrence Cher, Joachim Peter Steinbach, Pol M. Specenier, Ann Cleverly, Irene Tomlin, Durisala Desaiah, Michael M. F. Lahn, Wolfgang Wick; Department of Neurology, Hôpital Avicenne, AP-HP, Bobigny, France; Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL of Bologna, Bologna, Italy; University of California, San Diego, La Jolla, CA; Uro-Oncology Unit, 12 de Octubre University Hospital, Madrid, Spain; Royal North Shore Hospital, Sydney, Australia; Centre Hospitalier Universitaire La Timone, Marseille, France; Austin Health, Melbourne, Australia; Senckenberg Institute of Neurooncology, Frankfurt, Germany; Antwerp University Hospital (UZA), Edegem, Belgium; Eli Lilly and Company, Erl Wood, United Kingdom; Eli Lilly and Company, Indianapolis, IN; Division of Early Phase Oncology Clinical Investigation, Eli Lilly and Company, Indianapolis, IN; University of Heidelberg Medical Center, Heidelberg, Germany

Background: Based on preclinical data suggesting an additive antitumor effect of a TGF-β inhibitor and lomustine, a phase II study was initiated to evaluate the activity of this combination in patients with glioblastoma after first progression. We here report are the safety and PK interim data. Methods: Lomustine was given every 6 weeks as approved, starting on day 7 of cycle 1. LY2157299 (300 mg/day) was administered as intermittent dosing (each cycle = 14 days on followed by 14 days off). Patients received lomustine with either LY2157299 or placebo thereby blinding for LY2157299, while patients receiving LY2157299 alone were unblinded (randomization 2:1:1). Toxicity was assessed using CTCAE, version 4.0. Results: After 31 patients had completed at least 1 cycle (28 days, 3 weeks of lomustine), 50 patients had received at least 1 dose of study drug (LY2157299 or lomustine). Aggregate safety data of the 31 patients are provided: 1 patient died on treatment due to multi-organ failure, not considered related to study treatment. At least 3 patients had the following TEAEs with severity, of grade 3 or 4, and drug relatedness (DR, specific drug not indicated): vomiting (n = 5, 4 DR), fatigue (n = 5, 3 DR, 1 gr 3), dysphasia (n = 4, 1 gr 3), other nervous system disorder (n = 4, 3 gr 3), constipation (n = 3), nausea (n = 3, 3 DR), confusion (n = 3, 1 gr 3). Other grade 3/4 TEAEs observed were: abdominal pain, allergic reaction (DR), fall, syncope, pain, lymphocytes, ANC and thrombocytopenia (all DR) and alanine aminotransferase – in 1 patient each. No difference in the LY2157299 concentrations between LY2157299 monotherapy and combination arms was observed. Conclusions: The combination of lomustine with LY2157299 or placebo is consistent with the known profile of lomustine with no unexpected clusters of adverse events and similar to a previous phase I study (Azaro et al. abstract 2042, J Clin Oncol. 30, 2012). The phase II study continues after the first interim assessment on safety. Clinical trial information: NCT01582269.
Clinical outcome of 1,968 cases of meningiomas from Kaiser Permanente Northern California.

Nathalie T. Nguyen, Liisa L Lyon, Gregory S Moes, Kamran Sahrakar, John L. Villano; Kaiser Permanente, Rancho Cordova, CA; Kaiser Permanente, Oakland, CA; Kaiser Permanente, Sacramento, CA; University of Kentucky, Lexington, KY

Background: Meningioma is the most common primary brain tumor in the United States, but there is limited data on clinical outcomes. Methods: We performed descriptive and survival analysis of meningioma cases diagnosed 2001-2010 from the Kaiser Permanente Northern California Cancer Registry, which began inclusion of benign brain tumors in 2001. Datasets provided variables on gender, age at diagnosis, race, and vital status. Chart review extracted additional information on mortality, histology, imaging, tumor size, tumor site, and treatment. We used Kaplan Meier method to calculate overall survival (OS) and disease-free survival (DFS) and log-rank test to compare survival rates by variables. Cox proportional hazard models were used to analyze variables relative to endpoints. Results: 1968 cases in 1792 patients with meningioma were analyzed. 55% of cases had histological confirmation. 5- and 10-year OS and DFS for all groups were 76% & 61% and 89% & 82%. Disease progression and recurrence presented in 10% of cases at 10 years, resulting in 4% disease-specific mortality (DSM). Statistically significant prognostic factors of worse DFS were age >= 80, WHO grade 2-3, tumor size >= 18 mm, peritumoral edema on imaging, Simpson grades (SG) 4 or 5, and no surgery. Factors associated with significantly worse OS included age >= 60, male gender, tumor size >= 42 mm, peritumoral edema, SG 4 or 5, no histology and no treatment (NT). SG 1-3 groups provided statistically the highest OS and DFS. There was no significant difference in DFS or OS for definitive RT versus surgery and adjuvant RT groups. Definitive RT showed significantly better OS than NT (HR=0.46, 95% CI: 0.21-0.98). Cases with progression or recurrence had 51% DSM with 65% of deaths associated with lack of salvage therapy. Salvage RT provided better OS benefit compared to other salvage groups (HR=0.35, 95% CI: 0.14-0.91). Conclusions: We demonstrated favorable long-term outcome for meningiomas and confirmed the prognostic benefit of Simpson grading. We have identified additional adverse factors affecting outcome. While surgery remains standard, definitive RT demonstrates comparable outcome to cases not amenable to gross total resection. Salvage RT is effective, providing a survival benefit.
Clinical and prognostic features of adult patients with gangliogliomas.

Shlomit Yust-Katz, Mark Daniel Anderson, Diane Liu, Ying Yuan, Greg Fuller, John Frederick De Groot; The University of Texas M.D. Anderson Cancer Center, Houston, TX; The University of Texas MD Anderson Cancer Center, Houston, TX

**Background:** Gangliogliomas (GG) represent less than 1% of primary brain tumors in adults. Little is known regarding prognostic features, clinical characteristics or the impact of treatment on patient (pt) outcomes. **Methods:** In this IRB approved retrospective study, our neuro-oncology longitudinal database was screened for pts with GG from 1992-2012. 67 adult pts (age > 18) were identified. **Results:** 60 pts presented with low grade GG and 7 with anaplastic GG. The median age at diagnosis was 27 years (18-59). 22 pts developed recurrent disease (18 low grade and 4 high grade) with a median time to recurrence of 87 weeks from surgery. 7 of the pts with low grade GG had malignant transformation to a malignant tumor (anaplastic GG or GBM). 22 pts received radiation therapy, 16 at diagnosis. 14 pts received chemotherapy at recurrence. Pts with incomplete resections or higher grade tumors were more likely to receive chemotherapy or radiation. The median overall survival (OS) time for these pts was not reached with a median follow-up time of 4.6 years. The 2-, 5- and 10-year OS were 98%, 87%, and 76%. Factors on univariate analysis that were significantly associated with OS were KPS at presentation (HR 10.1; 95% CI 2.6, 39.1; p = 0.0008), extent of resection (EOR) (biopsy vs gross total; HR 12.1; 95% CI 2.3, 63.6; p = 0.003), histologic grade (Grade 1-2 vs Grade 3-4; HR 0.06; 95% CI 0.01, 0.3; p = 0.0002), and seizure control following surgery (Engel I vs Engel 2-3; HR 0.1; 95% CI 0.01, 0.9; p = 0.02). Factors on univariate analysis that were significantly associated with progression free survival (PFS) were EOR (biopsy vs gross total; HR 4.0; 95% CI 1.4, 11.9; p = 0.01) and histologic grade (Grade 1-2 vs .Grade 3-4; HR 0.3; 95% CI 0.08, 0.8; p = 0.02). On multivariate analysis, EOR is most significant for PFS (p = 0.01), while tumor grade is most significant for OS (p = 0.004). **Conclusions:** While GG have an excellent prognosis, malignant histological grade, diagnosis with a biopsy only, poor initial KPS, and presence of seizures following surgery could indicate a worse prognosis. The role of chemotherapy and radiation therapy for incompletely resected or inaccessible low grade GG is unclear.
Alteration of the p53 and Rb tumor suppressor pathways by p16/INK4a and p14/ARF promoter methylation and loss of protein expression in recurrent and nonrecurrent meningiomas.

Juan Carlos Martinez, Santiago Ropero, Concepcion Mateos, Maria DEL VAL Toledo, Rafael Samaniego, Silvia Sacristan, Manel Esteller; Instituto Oftalmico/Hospital Universitario Gregorio Marañon, Madrid, Spain; Departamento de Bioquímica y Biología Molecular, Univ. de Alcalá, Alcalá de Henares, Spain; Facultad de Veterinaria, UNEX, Cáceres, Spain; Universidad de Alcalá Facultad Biología Celular y Genética, Alcalá de Henares, Spain; Unidad de Microscopia Confocal, Hospital Universitario Gregorio Marañon, Madrid, Spain; Departamento de Investigación, Servicio de Neurobiología, Hospital Universidad Ramón y Cajal, Madrid, Spain; Institut d’Investigación Biomedica de Bellvitge, Barcelona, Spain

Background: Promoter methylation inactivates tumor suppressor genes (TSG). The INK4a/ARF locus encodes p16INK4a and p14ARF cell cycle regulatory proteins, which control Rb and p53 TSG pathways. Most meningiomas are slow growing tumors, but in spite of complete surgical removal, the recurrence rate at 5 years is 5%, rising to 19% in long-term follow-up. However, there are no markers predictive of this evolution. Epigenetic changes in low-grade meningiomas have not been previously addressed. To get insights into the possible role of p16INK4a and p14ARF TSG alterations in grade 1 meningiomas, we study the methylation status and protein expression of these genes in 140 specimens of meningiomas: 29 nonrecurrent and 57 recurrent in one, two or three times. Methods: Methylation specific PCR and bisulfate modification followed by bisulfate genomic sequencing of CpG islands and staining with p16INKa and p14ARF antibodies (Ab’s). Results: Our data show p16INK4a and p14ARF methylation in 43.4% and 14.2% meningiomas respectively. Methylation of p16INK4a is found in a similar proportion in non-recurrent meningiomas (37.9%) and the first biopsy of recurrent cases (38.8%) and increases to a 52.3% in successive biopsies of recurrent cases. Methylation of p14ARF occurs in 13.8% of nonrecurrent vs. 9.6% recurrent meningiomas (first biopsy) and 19.6% of successive recurrent meningiomas. Loss of p16INK4a and p14ARF protein expression was shown in 13.8% of nonrecurrent meningiomas respectively. Methylation of p14ARF occurs in 13.8% of nonrecurrent vs. 9.6% recurrent meningiomas (first biopsy) and 19.6% of successive recurrent meningiomas. Loss of p16INK4a and p14ARF methylation was associated with loss of protein expression in 54.7% and 18.8% of meningiomas. Loss of p16INK4a and p14ARF expression was shown in 52.7% and 18.6% of meningiomas respectively. p16INK4a and p14ARF methylation was associated with loss of protein expression in 52.9% and 17.6% of cases respectively. Conclusions: Epigenetic changes of p16INK4a and p14ARF genes and loss of protein expression leading to Rb and p53 TSG pathways alterations, may have a pathogenic role in human meningiomas. Loss of p16INK4a and p14ARF protein expression associated with unmethylated promoters, could be due to loss of heterozigosity or gen mutation. Increase of p16INK4a and p14ARF methylation along the following biopsies of recurrent cases suggests a possible role of methylation in tumor progression.
Phase I adult brain tumor consortium (ABTC) trial of ABT-888 (veliparib), temozolomide (TMZ), and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM) including pharmacokinetic (PK) data.

Lawrence Kleinberg, Jeffrey G. Supko, Tom Mikkelsen, Jaishri O’Neill Blakeley, Glen Stevens, Xiaobu Ye, Serena Desideri, Samuel Ryu, Bhardwaj Desai, Vincent L. Giranda, Stuart A. Grossman; The Johns Hopkins University, Baltimore, MD; Massachusetts General Hospital, Boston, MA; Henry Ford Health System, Detroit, MI; The Johns Hopkins University, School of Medicine, Baltimore, MD; Cleveland Clinic Foundation, Cleveland, OH; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Henry Ford Hospital, Detroit, MI; Abbott Laboratories, Abbott Park, IL

Background: ABTC conducted a dose finding trial of ABT-888, an orally administered Poly(ADP-ribose) polymerase [PARP] inhibitor, during daily TMZ with post-operative RT for GBM. PARP is important in repair pathways for RT induced DNA injury and TMZ induced alkylation at N7-methylguanine and N3-methyldenine. Methods: An initial safety group (no concurrent RT), received ABT-888 10 mg BID po during 42 days of daily TMZ 75 mg/m². After this, the planned dosing steps included ABT-888 BID concurrent with standard RT and TMZ, with planned ABT-888 dose escalation or de-escalation based on observed toxicity. Dose limiting toxicity (DLT) is ≥ grade 3 non-hematologic or neurologic not responding to steroids, and hematologic ANC<500/mm³ and platelets (PLT) < 25K/mm³. The pharmacokinetics (PK) of ABT-888 were characterized for dose 1 and at steady-state. Results: Without concurrent RT, DLT (thrombocytopenia) occurred in 1/6 patients. With concurrent RT/TMZ and ABT-888 10 mg BID, 4/12 patients had DLT (thrombocytopenia). As per the planned dose de-escalation, ABT-888 10 mg BID was then given every other week during TMZ/RT. This resulted in 3/6 patients with DLT (2 thrombocytopenia, 1 neutropenia). The hematologic toxicity with this regimen was judged high enough that accrual was discontinued. In the setting of continuous dosing for 6 weeks, the total body clearance of ABT-888 for the first dose (27.5±9.5 L/h, n = 15) and at steady-state after BID dosing (23.5±10.4 L/h, n = 18) were similar. Accumulation of bid was 56±33%. Steady-state peak and trough concentrations of the drug in plasma were 66±29 ng/mL and 18±10 ng/mL, respectively. Additional PK data will be presented. Conclusions: Administering ABT-888 BID po in combination with standard RT/TMZ was not tolerable in GBM patients as a result of hematologic toxicity. ABT-888 PK in GBM patients were very similar to findings reported for solid tumor patients. There is strong scientific rationale for continued development of an appropriate dosing regimen for this agent in the initial therapy of GBM. Clinical trial information: NCT00770471.
Validation of a gene expression-based diagnostic system for malignancy of glioma by multi-institute prospective-retrospective analysis.

Kikuya Kato, Mitsuaki Shirahata, Yoshitaka Narita, Yoshihiro Muragaki, Motohiko Maruno, Ryo Matoba; Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; Kitano Hospital, Osaka, Japan; National Cancer Center Hospital, Tokyo, Japan; Faculty of Advanced Technology, Tokyo Women's Medical University, Tokyo, Japan; Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; DNA Chip Research Inc., Yokohama, Japan

Background: Histopathological classification of gliomas is often clinically inadequate due to the diversity of tumors that fall within the same class. Based on the strong correlation between malignancy and gene expression profile in gliomas, we constructed a diagnostic system based on gene expression profiling of 152 glioma samples (Shirahata et al., Cancer Sci, 2009, 100, 165). The diagnostic system was converted to that based on expression value of 27 genes measured with real-time PCR (Kawarazaki et al., BMC Med Genomics, 2010, 3, 52). Methods: First, the diagnostic system was validated with 75 retrospective samples from the National Cancer Center Hospital, and threshold values of the diagnostic score (PC1-score) were determined. Second, the system was evaluated by prospective-retrospective analysis of 127 samples from the four institutions using the threshold. The analysis corresponded to the category C proposed by Simon et al. (JNCI, 2010, 101, 1446). Results: In general, the PC1-score gradually increased with the grade of the glioma from grade II to IV. The prognostic classification by the diagnostic system was compared with that by WHO grade classification using 66 grade IV and 39 grade 3 samples. Harrell's C-index was 0.673 and 0.573 for the diagnostic system and grade classification, respectively. Hazard Ratio was 5.31 and 4.97, respectively. By the system the 66 grade 4 patients were confirmed to be classified into two prognostic groups (PFS, p = 0.013; OS, p = 0.098). The 39 grade III patients were classified into two prognostic groups (PFS, p = 0.112; OS, p = 0.022). Median observation time is 12 months for PFS and 15.5 months for OS, respectively. As for grade 3 patients, IDH1 mutation had better prognostic ability (PFS, p = 0.007; OS, p = 0.002). Conclusions: Based on two retrospective and one prospective-retrospective analysis, our diagnostic system was demonstrated to be an objective prognostic indicator complementing the grade classification. The prognostic ability within grade 3 or grade 4 may be useful in therapeutic decision making.
Heterogeneity in the geographic distribution of diffuse grade II and III gliomas in France.

Luc Bauchet, Amelie Darlix, Sonia Zouaoui, Jean Marc Virion, Valerie Rigau, Helene Mathieu Daude, Marie Blonski, German Reyes-Botero, Faiza Bessaoud, Brigitte Tretarre, Fabienne Bauchet, Laurent Capelle, Michel Fabbro, Christine Kerr, Dominique Figarella-Branger, Hugues Duffau, Luc Taillandier, Societe Francaise de Neurochirurgie, Societe Francaise de Neuropathologie, and ANOCF; INSERM U1051 - Institut de Neurosciences de Montpellier, Montpellier, France; Department of Medical Oncology and Department of Radiation Oncology, CRLC Val d’Aurelle, Montpellier, France; Department of Neurosurgery, Centre Hospitalier Universitaire Montpellier, Montpellier, France; Epidemiologie et Evaluation Cliniques CHU Nancy, Nancy, France; Pathological Department CHU Montpellier, Montpellier, France; Department of Epidemiology, Centre Régional de Lutte contre le Cancer Val d’Aurelle, Montpellier, France; Department of Neurology - CHU - Hôpital Central, Nancy, France; Service de Neurologie 2-Mazarin, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; Registres des Tumeurs de l’Hérault, CRLC Val d’Aurelle, Montpellier, France; Registres des Tumeurs de l’Hérault, Montpellier, France; Department of Neurosurgery, AP-HP Hôpital Pitié-Salpêtrière, Paris, France; Val d’Aurelle-Paul Lamarque Regional Cancer Centre, Montpellier, France; Department of Neuropathology CHU La Timone, Marseille, France; Neurosurgery CHU Montpellier, Montpellier, France; Centre Hospitalier Universitaire Nancy, Nancy, France

Background: Diffuse WHO grade II and III gliomas (DGII/IIIG) are rare tumors (incidence \( \leq 2/10^6\) person-years). Specific epidemiological studies are very rare. The main objective of this work is to study the geographical distribution of all newly diagnosed and histologically confirmed DGII/IIIG in metropolitan France. Methods: The methodology is based on a multidisciplinary national network already established by the French Brain Tumor DataBase. Personal addresses at the moment of the surgical procedure for all DGII/IIIG cases were collected for the years 2006-2009. For each area, the incidence of DGII/IIIG was analyzed and standardized on age and sex distribution of the French population (pop).

Results: The total number of patients with newly diagnosed and histologically confirmed DGII/IIIG was 4790 (1220, 1190, 1228, and 1152 for years 2006-2009). The Table shows the number of tumors by histology, sex and median age at diagnosis. The overall crude rate was 19.4/10^6. To enable international comparisons, standardized rates were calculated as follows: 19.8/10^6 (reference pop, Europe), 18.8/10^6 (reference pop, US 2000), and 16.0/10^6 (reference pop, world). The geographic distribution by regions in France showed significant differences. For example, the standardized rates (for 10^6 person-years, 95% confidence intervals, reference pop: France) for Auvergne, Champagne-Ardenne, and Basse-Normandie, were 30.9 (26.4-35.5), 28.5 (24.0-33.0), and 13.9 (10.9-17.0), respectively. Conclusions: To our knowledge, this work is the first to study the geographical distribution of DGII/IIIG across one entire country, and it shows significant heterogeneity. These results will enable to look for different environmental and genetic factors in these different regions.

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Retrospective multicentric study on adult intramedullary spinal cord gliomas from a cohort of 319 patients.

Chantal Campello, Fabrice Parker, Sonia Slimani, Anne Le Floch, Nozar Aghakhani; Department of Neurology CHU, Nimes, France; Department of Neurosurgery Centre Hospitalier Universitaire, Bicêtre, France; Department of Neurology CHU, Nîmes, France

Background: Intramedullary spinal cord tumors (IMST) are among the rarest types of tumors, account for 2 to 4% of all central nervous system tumors. This study was conducted to describe clinical features, radiological imaging, anatomopathological characteristics, management and outcome of neuroepithelial IMST.

Methods: In this retrospective review, a total of 319 patients were included from 7 French neurosurgical University Hospital Centers, between 1984 and 2011. The patient's pre and postoperative neurological state were classified according to the Mac Cormick scale. Only patients with a preoperative MRI and confirmed histological were included. Results: Mean age at diagnostic was 42.4 for ependymomas, 39.6 for astrocytomas, (included 20 patients older than 65 years old). The male/female ratio was 1.6 for ependymomas, and 1.1 for astrocytomas. Ependymomas were associated with neurofibromatosis in four patients. Pain was the most common presenting symptom (74%), followed by motor (72%), and sensory (66%) complaints. Pre and post operative neurological states were more severe in astrocytomas than ependymomas. The most frequently involved localization was the cervical region for ependymomas, and the thoracic region for astrocytomas. Partial and total resection was achieved in 80% of ependymomas, and 20% of astrocytomas, (diagnostic of other tumors was performed by biopsy). Histological types, according to WHO classification were ependymomas in 72% patients, (94% were low grades), astrocytomas in 24% patients, (29% were high grades), oligoastrocytomas in 2.4%, and oligodendroglia in 1.7%. Postoperative radiotherapy was used especially in high-grade tumors, (67% of ependymomas, 71% of astrocytomas), in absence of severe toxicity. 18% of low-grade astrocytomas received radiotherapy. Chemotherapy was used only in 33% of ependymomas and 24% of astrocytomas. Conclusions: Histology, preoperative functional score, and grades tumors are confirmed as prognostic factors in this study. Questions about adjuvant therapy for astrocytomas, like intracranial tumors, are answered.
Racial disparities in survival of glioblastoma patients not treated with radiation.

Jigisha P. Thakkar, Therese A. Dolecek, Andra M Popa, John L. Villano; University of Kentucky, Lexington, KY; University of Illinois at Chicago, Chicago, IL

**Background:** Race-based outcomes have been documented for inpatient hospital care for glioblastoma (GBM), however, SEER-based population studies do not replicate the differences in race for outcomes in GBM. Moreover, most advanced cancers demonstrate differences in race based outcomes. We hypothesized that there is a difference in race based outcomes for GBM with advanced clinical involvement preventing an established standard of care such as radiation therapy (RT).

**Methods:** We analyzed survival estimates and procedure frequencies by race for GBM patients (n=4931) 20 years and older, not treated with radiation in the initial round of therapy; from 2000-2008, using the Surveillance, Epidemiology, and End Results (SEER) 17 registries database and listed them by surgery type. Kaplan–Meier relative survival rates were calculated by surgery type and race group (blacks and whites) followed by evaluation of association between race and survival rate. Race comparisons were limited to 1 year because of small numbers in the subgroups.

**Results:** We found no statistically significant support for a racial disparity in survival among GBM patients with different surgical interventions (tumor destruction/biopsy, partial or total resection). However, for those receiving no surgery (and no RT), blacks actually had better one-year survival than whites. By surgery, those receiving gross total resection had higher survival in both blacks and whites. In whites only, any type of surgery (tumor destruction/biopsy, partial or total resection) had better survival than none. **Conclusions:** Overall, there are no statistically significant differences between blacks and whites in terms of survival in GBM patients not receiving RT in the initial round of therapy. Differences in race based care for GBM have not been found outside of inpatient hospital based care, which is unusual for an aggressive cancer needing specialized multi-modality care.

<table>
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<tr>
<th>Surgery type</th>
<th>1-year relative survival in blacks</th>
<th>1-year relative survival in whites</th>
<th>P value</th>
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<tr>
<td>No surgery</td>
<td>11.5%</td>
<td>4.87%</td>
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</tr>
<tr>
<td>Tumor destruction/biopsy</td>
<td>11.3%</td>
<td>14.38%</td>
<td>0.47</td>
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<tr>
<td>Partial resection</td>
<td>12.3%</td>
<td>11.8%</td>
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<tr>
<td>Total resection</td>
<td>29.6%</td>
<td>20.7%</td>
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Background: The Graded Prognostic Assessment (GPA) is a commonly used index based on 5 prior randomized trials performed by the RTOG (Protocols 7916, 8528, 8905, 9104, and 9508). The purpose of this study was to validate GPA index in a recent cohort of lung cancer patients with brain metastases (LBM) at a larger tertiary care center. Methods: Cleveland Clinic Brain Tumor and Neuro-Oncology Center’s database was used to identify LBM treated in the recent era (2000-12). A proportional hazards model was used to assess overall survival (OS), measured from the date of diagnosis of brain metastases to death or last follow-up. Results: 490 LBM (250 males) median age 61 years (range 35-86) were included. Histology included small cell (64, 13%) adenocarcinoma (289, 59%), squamous (53, 11%), large cell (26, 5%) and unknown (55, 11%). The median number of brain metastases was 1 (range, 1-47). Karnofsky Performance Scale (KPS) was 90-100 in 187 (41%), 70-80 in 238 (52%) and <70 in 33 (7%). Extracranial Metastases was present in 327 patients (67%). OS was 14.1 months (95% C.I. 12.3-15.7). GPA for lung cancer is derived from KPS, the number of brain mets, the presence/absence of extracranial metastases, and age. GPA was 0-1.0 in 83 patients, 1.5-2 in 211, 2.5-3 in 135 and 3.5-4 in 18 patients. Although overall GPA was prognostic for survival (p<.0001), not all of the factors used to derive it were significant (Table). Factors noted to be prognostic for survival included primary controlled (p=.0001), squamous cell histology (p=.0001), age (p=.0002), KPS (p=.0002). The new index divided the patients into unfavorable, intermediate, favorable that was prognostic for survival in this cohort (p<.0001). Conclusions: New index developed based on a revised set of independent prognostic factors (primary controlled, squamous cell histology, age and performance status) is proposed.

<table>
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<tr>
<th>Factor</th>
<th>Median survival (months)</th>
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<td>KPS</td>
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<td>90-100</td>
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An EGFRvIII-specific IHC IUO test for patient selection in AMG 595 phase I trial.


Background: EGFRvIII is a mutant version of EGF receptor resulting from the genomic deletion of exons 2 through 7 and is expressed only in certain tumors. AMG 595 is an experimental therapeutic specifically targeting EGFRvIII and consists of an EGFRvIII-specific antibody conjugated to the maytansinoid antimicrotubule agent DM-1. Due to its specificity, mechanism of action, and pre-clinical activity, AMG 595 is expected to have clinical effect only in tumors expressing EGFRvIII. Since the reported prevalence of EGFRvIII in glioblastoma multiforme (GBM) is ~30%, prospective selection of patients with EGFRvIII positive tumors was desired for clinical development. An immunohistochemical (IHC) assay developed with Dako using a novel EGFRvIII antibody is currently being employed for patient selection for the AMG 595 phase I study in recurrent GBM (NCT01475006). Methods: An appropriate IHC reagent for human tissue was created using the variable region of a novel EGFRvIII-specific antibody developed using Xenomouse technology. Staining conditions were optimized using Dako pharmDx reagents, the Dako Link 48 Autostainer, and FFPE tissue sections. Confirmatory transcript analyses of adjacent sections were conducted using the NanoString platform. Results: Robust and reproducible staining for EGFRvIII was observed using archived GBM resections. Percentage of stained cells correlated with levels of EGFRvIII transcripts, and tumors without staining did not express EGFRvIII transcripts. Although some tumors exhibited homogenous staining, most were heterogeneous with varying distribution and percentages of stained tumor cells similar to literature reports of IHC analysis utilizing other EGFRvIII-specific antibodies. Tumor samples from patients entering into the AMG 595 Phase I study analyzed with this IHC test have displayed the predicted staining prevalence. Conclusions: The developed EGFRvIII IHC assay, approved under an Investigational Device Exemption, is currently being successfully employed to prospectively select patients in an ongoing phase I trial. Use of this well characterized IHC test will enable correlation of clinical outcome and staining characteristics to inform subsequent studies.
Genotypes of human glioma xenografts compared with glioma stem cell-derived tumors.

Selby Chen, Timothy Peterson, S. Keith Anderson, Jeanette Eckel-Passow, Paul A. Decker, Jann Nagina Sarkaria, Ian F Parney; Mayo Clinic, Rochester, MN

Background: Human glioma stem cells and xenograft lines are common translational models in neuro-oncology but it has not been established if they are genetically and phenotypically comparable. This study aimed to determine if human glioma xenografts and stem cell-derived tumors had similar genotypes.

Methods: Matched glioma stem cell cultures and subcutaneous xenograft lines were generated from four human glioblastoma specimens (BT114, BT116, BT120, BT132). Comparison was made between subcutaneous stem cell-derived tumors (flank) and xenografts established in nude mice. Copy number variation (CNV) and gene expression microarray studies were performed.

Results: Various differences in copy number and gene expression were seen. Observed CNVs included regions within EGFR, myc, and p16 (INK). For example, EGFR copy number was two fold higher in xenografts vs. stem cell-derived tumor in one line (BT114). This difference was corroborated by western blot. Other differences included a heat shock protein homolog (DNAJA4), tetraspanin 13, and a p53 family target gene (ISG20L1). Two lines (BT114, BT116) had a greater than two fold increase in DNAJA4 expression in xenografts vs. stem cell-derived tumors (p = 0.04, 0.01). Two cell lines (BT116, BT120) had a two to eight fold increase in tetraspanin 13 expression in xenografts (p = 0.02, 0.05). However, neither copy number nor gene expression variations were consistent across all cell lines.

Conclusions: Xenografts and glioma stem cell-derived tumors established from the same patient specimens have distinct genotypes. Further work is needed to establish if these differences are random or represent characteristic changes selected by different in vitro or in vivo pressures. However, these variations raise questions regarding which model is ideal for studying glioma biology, and which ones best replicate glioma characteristics in human patients.
Effect of RTVP-1 on the mesenchymal transformation of glioma stem cells (GSCs) and their self-renewal and migration.

Chaya Brodie, Nissim Giladi, Amotz Ziv-Av, Hae Kyung Lee, Susan Finniss, Simona Cazacu, Cunli Xiang, Laila Poisson, Shimon Slavin, Tom Mikkelsen; Bar Ilan University, Ramat-Gan, Israel; Bar-Ilan University, Ramat-Gan, Israel; Henry Ford Health System, Detroit, MI; International Center for Cell Therapy and Cancer Immunotherapy, Tel Aviv, Israel

Background: Glioblastoma (GBM), the most aggressive primary brain tumors, exhibit increased invasiveness and resistance to anti-tumor treatments. GBM are categorized into proneural, neural, classical and mesenchymal subgroups, the latter being characterized by increased invasion and poor prognosis. We recently reported that RTVP-1 is highly expressed in GBM and its expression is correlated with astrocytic tumor grade. Methods: We employed promoter and Chip analyses, analysis of tumor specimens submitted to TCGA, GSC self-renewal and migration assays, mesenchymal and neural differentiation, gene array analysis and pull-down assay followed by FRET. Results: The RTVP-1 promoter binds STAT3 and C/EBPβ, the transcription factors that regulate mesenchymal transformation of GBM. The expression of RTVP-1 is higher in mesenchymal GBM and is inversely correlated with patient survival in the proneural group. We examined the expression and functions of RTVP-1 in GSCs, a small population of cancer stem cells that are implicated in the increased migration, radio- and chemo-resistance of GSCs and tumor recurrence. RTVP-1 was expressed in the different GSCs but not in the normal human neural stem cells (NSCs). Overexpression of RTVP-1 in NSCs induced their mesenchymal transformation, whereas silencing of RTVP-1 in GSCs decreased their mesenchymal and increased their neural phenotypes. Moreover, RTVP-1 promoted the self-renewal and migration of GSCs. Using gene array analysis of RTVP-1 silenced cells we identified IL-6 and CXCR4 as major mediators of RTVP-1 effects on the mesenchymal transformation and self-renewal of GSCs. In addition, using a pull down assay with His-tagged RTVP-1 we identified N-WASP and hnRNPK as novel interacting proteins of RTVP-1 that mediate its effects on glioma cell migration. Conclusions: RTVP-1 expression is associated with mesenchymal transformation of GSCs. RTVP-1 promotes self-renewal and migration of GSCs and these effects are mediated by the increased expression of IL-6 and CXCR4 and via interaction with N-WASP and hnRNPK. Collectively, these results suggest that RTVP-1 may represent a novel diagnostic marker and a therapeutic target in GBM.
Tumor perfusion during bevacizumab and irinotecan in recurrent glioblastoma: A multimodal approach.

Marica Eoli, Anna Luisa Di Stefano, Domenico Aquino, Alessandro Scotti, Elena Anghileri, Lucia Cuppini, Elena Prodi, Gaetano Finocchiaro, Maria Grazia Bruzzone; Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Université Pierre et Marie Curie-Paris 6, Centre de Recherche de l’Institut du Cerveau et de la Moelle épinière (CRICM), Neurologie 2, Paris, France

Background: Angiogenesis is a requirement for progression of glioblastoma (GBM) and vascular endothelial growth factor (VEGF) is a mediator of neo-angiogenesis in this tumor. Bevacizumab (Bev), an antibody directed to VEGF, was recently used to treat GBM. However in vivo modifications induced by treatment are still not clearly understood. Aim of this study is to analyze tumor changes induced by Irinotecan (Ir) and Bev, using two different methodologies: relative CBV variation (rCBV) and Difference Perfusion Maps (DPMs). Methods: 42 recurrent GBM patients underwent Bev (10 mg/kg) and Ir (125 or 340 mg/m²) treatment every 2 weeks and were followed up with a radiological protocol, including Dynamic Susceptibility Contrast MRI every 8 weeks. Radiological responses were assessed based on RANO criteria (Wen et al, 2012). Two methods were used to assess perfusion changes. In method A, relative CBV variation after 8 weeks of treatment was calculated through semi-automatic ROI placement in the same anatomic region as in baseline. In method B, relative CBV variations with respect to baseline values were calculated into the evolving tumour region by means of a voxel-by-voxel difference. DPMs were created showing where rCBV significantly increased, decreased or remained unchanged. Results: After a median follow-up of 33.5 months median overall survival (OS) was 35.0 weeks and median progression free survival (PFS) was 20.0 weeks. Method A showed a significant decrease of rCBV for patients with stable disease or partial response after 8 weeks of treatment (p < 0.01) while progressing patients maintained elevated levels of rCBV (p = 0.38). Method B, based on DPMs, showed that patients presenting rCBV increase higher than 25 percentile (corresponding to rCBV increase higher than 18% of tumor volume) had a significantly longer PFS (p = 0.045) and OS (p = 0.016). Conclusions: Using DPM we observed that early increase in global perfusion is related to better survival. This may suggest that Bev, when effective, reduces blood-brain barrier permeability with a higher contrast retention in vessels. If confirmed by further studies this measure could be useful in identifying responders to Bev.

Raymond Huang, Rifaquat Rahman, Alhafidz Hamdan, Caroline Kane, Christina Chen, Andrew David Norden, David A. Reardon, Srinivasan Mukundan, Patrick Y. Wen; Brigham and Women’s Hospital, Boston, MA; Harvard Medical School, Boston, MA; Dana-Farber Cancer Institute, Boston, MA

Background: Although antiangiogenic therapies can induce a dramatic clinical and imaging response in patients with recurrent glioblastoma, their benefit on overall survival is less pronounced. We assessed whether tumor volume based on magnetic resonance imaging (MRI) before and after treatment with bevacizumab can stratify patients in terms of progression-free survival (PFS) and overall survival (OS).

Methods: Baseline and post-treatment MRI scans of 93 patients with recurrent glioblastoma treated with bevacizumab were evaluated for volume of the enhancing tumor, as well as volume of the T2/FLAIR hyperintensity. The Cox proportional hazards model was used in univariate and multivariate settings to identify volume parameters prognostic and predictive for PFS and OS. Results: Our results show that baseline enhancing tumor volume were predictive of PFS (p = 0.047) and OS (p = 0.011). Specifically, patients with pretreatment enhancing tumor volume less than 18 cm$^3$ have a median OS of 45 weeks, while patients with tumor volume greater than 18 cm$^3$ have a median OS of 26 weeks. In addition, enhancing tumor volume 3 to 6 weeks after treatment, as well as percentage change in volume, are independent predictors of PFS and OS. Neither T2/FLAIR volume nor percentage change in T2/FLAIR volume was associated with survival. Conclusions: These results indicate that measurement of enhancing tumor volume can help identify patients more likely to benefit from bevacizumab therapy.
Final results of a single-arm phase II study of bevacizumab and temozolomide following radiochemotherapy in newly diagnosed adult glioblastoma patients.

Martin Kelly Nicholas, Rimas Vincas Lukas, Christine Amidei, Nicholas Vick, Nina Paleologos, Mark Gordon Malkin, Hendrikus Krouwer, Larry Junck, Jean Arzbaecher, Albert Lai, Ryan Merrell; The University of Chicago, Chicago, IL; University of Chicago, Chicago, IL; Northshore University, Evanston, IL; Rush University, Chicago, IL; Medical College of Wisconsin, Milwaukee, WI; Waukesha Memorial Hospital, Waukesha, WI; University of Michigan, Ann Arbor, MI; Department of Neurology, University of California, Los Angeles, Los Angeles, CA

Background: This study evaluated efficacy and safety of bevacizumab (BEV) added to the post-radiation treatment phase for patients with newly diagnosed glioblastoma (GBM). Methods: Sixty-two participants with newly diagnosed GBM were enrolled between May 2007 and June 2010. Participants received standard radiation therapy (RT) within 6 weeks of surgery, and concomitant administration of temozolomide (TMZ). Four weeks after radiation, treatment with TMZ (Days 1-5 of a 28 day cycle) with BEV, (days 1 and 15 of a 28 day cycle) was started, and continued until disease progressed or adverse effects indicated need to stop treatment. Analyses were completed for all participants by intention to treat (ITT), with progression-free survival (PFS) and overall survival (OS) serving as primary and secondary endpoints respectively. Results: Subjects completed a mean of 7.7 (range 0-29) cycles of post-RT with BEV and TMZ. Twenty participants (32%) were unable to proceed to the post-RT phase. The forty-two participants who did proceed to the post-RT phase completed a mean of 11.5 cycles of treatment. Thirty-eight participants (61%) stopped the study due to disease progression; 6 participants (14%) voluntarily discontinued treatment after 24 cycles with at least stable disease. At a median follow-up time of 24 months, median progression-free survival (PFS) for all participants was 8.8 months while median overall survival (OS) was 16.5 months for all participants. With These results also compare favorably with recently reported results from the AVAglio study (PFS = 10.6 mo.). The toxicity profile was consistent with that reported in similar studies. MGMT promoter methylation status is under investigation. Conclusions: Participants in this study demonstrated a median 1.9 month PFS benefit as compared to the 6.9 median OS reported by Stupp, et al. (2005) and a median 1.9 month OS benefit as compared to the 14.6 month median OS reported by Stupp, et al. (2005). Results suggest that the addition of bevacizumab to the post-RT phase of treatment improves both PFS and OS for persons with GBM despite the high percentage of participants being unable to progress to post-radiation treatment. Clinical trial information: NCT005906.
Use of axitinib, a new-generation tyrosine kinase inhibitor, to decrease glioblastoma growth despite primary resistance to the VEGF-antibody bevacizumab.

Tobias Kratzsch, Viktor Gruenwald, Peter Vajkoczy, Susanne Antje Kuhn; Max-Delbrueck-Center for Molecular Medicine, Berlin, Germany; Department of Hematology and Oncology, MHH, Hannover, Germany; Department of Neurosurgery, Charite Universitaetsmedizin Berlin, Berlin, Germany; Department of Neurosurgery, Hospital Ernst von Bergmann, Potsdam, Germany

**Background:** Targeted therapies are increasingly important in oncology. Axitinib is a novel orally available tyrosine kinase inhibitor which is mainly directed against the VEGFR family. VEGF-antibody bevacizumab is the acting drug of running clinical trials in glioblastoma. **Methods:** In immunodeficient mice, cell line- and patient-derived glioblastoma xenografts were established and treated with axitinib. Temozolomide, bevacizumab, and phosphate buffered saline served as controls. Tumor size, vascularization (CD31), vascular pericyte coverage (NG-2), apoptosis in tumor and endothelial cells as well as expression of EGFR, VEGFR1, VEGFR2, PDGFRβ, VEGF, and PlGF were determined. Experiments were approved by local ethics committee. **Results:** Positive control temozolomide always caused growth inhibition whereas primary resistances to bevacizumab as primary drug were observed. As most delighting result, axitinib caused a delay of tumor growth in a glioblastoma xenograft with primary resistance to bevacizumab. Tumor cell proliferation (Ki67) was significantly lower than in controls (p<.05). The number of CD31 positive endothelial cells decreased (p<.001). Numbers of NG2 positive pericytes were reduced (p<.001) and triple immunofluorescence showed a significant reduction of NG2 positive pericyte coverage of CD31 positive endothelial cells (p<.001). Expression of EGFR, PDGFRβ, and VEGFR1 proteins showed no alterations under axitinib treatment, but RT-PCR revealed a significantly decreased mRNA expression of VEGF-A and PlGF. **Conclusions:** Axitinib had significant effects on glioblastoma xenografts even with primary resistance to bevacizumab in a so far untreated tumor. There are currently two recruiting phase II trials with axitinib in glioblastoma multiforme. Further comparative studies with bevacizumab should urgently define the potential of this substance in glioblastoma therapy.
The prognostic value of cognition in patients with glioblastoma multiforme.

Birgit Flechl, Cornelia Sax, Michael Ackerl, Richard Crevenna, Alexander Gaiger, Karin Dieckmann, Georg Widhalm, Christine Marosi; Medical University of Vienna, Vienna, Austria; Medical University Hospital, Vienna, Austria; Department for Radiation Therapy and Radiation Biology, Medical University of Vienna, Vienna, Austria; Department for Neurosurgery, Medical University of Vienna, Vienna, Austria; Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Center, Medical University Vienna, Vienna, Austria

Background: In patients with glioblastoma multiforme (GBM) progressive disease leads sooner or later to cognitive decline. In this study we evaluated if two cognitive assessments performed early in the treatment course have a prognostic significance for predicting progression free survival (PFS). Methods: We assessed the cognition of 35 patients with GBM using the program NeuroCogFX with four subscales: working memory, attention, verbal and figural memory and verbal fluency. Baseline evaluation was done at initiation of radiotherapy (11-57 days after diagnosis) and second evaluation three months later (82-117 days after baseline). Results in subscales were categorized in “declined”, “stable” and “improved”. Tumor progression was based on MRI scans. Results: The patients (12 women, 23 men) were in median 54 years old (21-75 years). The majority (61%) showed stable cognitive results, 22% improved and 14% decreased in the summary scale of cognition. The median PFS was 11 months (2.6-27.4 months). An improvement of attention correlated significantly with longer PFS ($p = 0.015$) whereas the other three cognitive subscales were not associated with PFS. Conclusions: The present study shows evidence, that an increase or decrease of attention scales measured within the first 5 months of disease has prognostic value for PFS.
Induction of atypical anoikis in glioma cells through inhibition of integrin functions.

Patrick Roth, Manuela Silginer, Michael Weller; University Hospital, Zurich, Switzerland; University Hospital Zurich, Zurich, Switzerland

**Background:** Integrins regulate cellular adhesion and transmit signals important for cell survival, proliferation, differentiation and motility. Both αvβ3 and αvβ5 integrins are upregulated in glioma cells, and therefore, integrin inhibition may represent a promising therapeutic strategy in glioblastoma. **Methods:** SMA-560 and GL-261 mouse glioma cells were cultured as adherent monolayers in serum-containing medium or as sphere cultures in neurobasal medium. Integrin function was inhibited using RNA interference, blocking antibodies or pharmacological inhibitors. Cell death after integrin inhibition was examined by flow cytometry. Immunoblot was used to assess apoptosis and autophagy. **Results:** GL-261 and SMA-560 glioma cells grown under standard conditions uniformly detached and formed large cell clusters after integrin gene silencing or pharmacological inhibition using EMD-121974 (cilengitide), a synthetic Arg-Gly-Asp-motif peptide, or GLPG0187, a non-peptidic integrin inhibitor. After 120 h, the clusters induced by integrin inhibition disintegrated and cells died. In contrast, no morphological effects were observed when cell lines were grown as stem-like sphere cultures. Since Poly-HEMA-mediated detachment had similar effects on cell viability as integrin inhibition, we postulated that cell death may result from detachment alone which was confirmed using various permissive and non-permissive substrates. No signs of apoptosis or autophagy were found using Annexin V/PI staining, DEVD-amc cleaving assay or caspase-3 and LC3A/B immunoblot. Recently, we demonstrated that integrin inhibition results in an inhibition of the TGF-β pathway in human glioma cells. Addition of recombinant TGF-β2 indeed partially rescued integrin inhibition-induced cell death, whereas exposure to the TGF-β receptor inhibitor SD-208 increased the number of dead cells. **Conclusions:** Cell death following integrin inhibition is essentially necrotic and may involve the TGF-β pathway.
Response assessment of novoTTF-100A versus best physician’s choice chemotherapy in recurrent glioblastoma.

Eric Wong, Edwin Lok, Kenneth D. Swanson, Shiva Gautam, Herbert H. Engelhard, Frank S. Lieberman, Sophie Taillibert, Zvi Ram, John L. Villano, on behalf of the EF-11 Trial Investigators; Beth Israel Deaconess Medical Center, Boston, MA; University of Illinois at Chicago, Chicago, IL; University of Pittsburgh Cancer Institute, Pittsburgh, PA; Pitie-Salpetriere Hospital-Pierre et Marie Curie Paris VI University, Paris, France; Tel Aviv University, Tel Aviv, Israel; University of Kentucky, Lexington, KY

Background: The NovoTTF-100A device emits tumor treating electric fields and was tested against Best Physician’s Choice (BPC) chemotherapy in a randomized phase III trial. We analyzed post hoc the characteristics of responders and non-responders in both cohorts. Methods: Macdonald criteria were used to determine tumor response and progression. Kaplan-Meier and Chi-squared statistics were computed for time to response, response duration, progression-free survival (PFS) with and without Simon-Makuch correction, and overall survival (OS). Prognostic factors were compared using the Wilcoxon rank sum test. Relative hazard rates for responders and non-responders were plotted. Results: The median response duration was 7.3 versus 5.6 months for NovoTTF-100A and BPC chemotherapy respectively (p=0.0009). Five of 14 NovoTTF-100A responders but none of 7 BPC responders had prior low-grade histology. The mean cumulative dexamethasone dose was 35.9 mg for responders versus 485.6 mg for non-responders in the NovoTTF-100A cohort (p<0.0001) as compared to 525.6 mg for responders and 431.0 mg for non-responders in the BPC cohort (p=0.9520). Hazard rate analysis showed delayed tumor progression in responders compared to non-responders. The Simon-Makuch conditional plot, which adjusted for unequal progression-free states, still showed longer PFS in responders than non-responders treated with NovoTTF-100A ($\chi^2=11.5$, P=0.0007) or BPC chemotherapy ($\chi^2=5.2$, P=0.0222). The median OS was 24.8 months for responders that is longer than 6.2 months for non-responders treated with NovoTTF-100A ($\chi^2=25.7$, P<0.0001). In the BPC chemotherapy cohort, the median OS was 20.0 months for responders and 6.8 months for non-responders ($\chi^2=5.1$, P=0.0235). There was strong Pearson correlation between response and OS in NovoTTF-100A (P<0.0002) but not in BPC cohort (P=0.2952). Conclusions: Response duration, adjusted Simon-Makuch PFS and OS favor NovoTTF-100A over BPC chemotherapy. Data on prior low-grade histology and dexamethasone dose suggest potential genetic and epigenetic determinants of NovoTTF-100A response. Clinical trial information: NCT00379470.
Effect of silencing thymosin beta 4 gene expression on stemness and invasiveness in glioblastoma.

Ghazaleh Tabatabai, Shanmugarajan Krishnan, Ana-Maria Florea, Karl Frei, Kathy Hasenbach, Guido Reifenberger, Niklaus Krayenbuehl, Michael Weller, Hans-Georg Wirsching; Department of Neurology, University Hospital Zurich, Zurich, Switzerland; Institute of Neuropathology, University Hospital Düsseldorf, Düsseldorf, Germany; Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland; Institute of Neuropathology, University of Duesseldorf, Duesseldorf, Germany; University Hospital, Zurich, Switzerland

Background: Thymosin ß4 (TB4) is a pleiotropic actin-sequestering polypeptide that is involved in wound healing and developmental processes. TB4 gene silencing promotes differentiation of neural progenitor cells whereas TB4 overexpression initiates cortical folding of developing brain hemispheres. However, a role of TB4 in malignant gliomas has not yet been investigated. Methods: We first analyzed TB4 expression on tissue microarrays and performed REMBRANDT and TCGA database interrogations. We analyzed TB4 expression in a panel of 8 long-term glioma cell lines and 7 glioma-initiating cell lines. Using lentiviral transduction, we modulated TB4 expression in LNT-229, U87MG and the glioma-initiating cell line GS-2. We studied clonogenic survival, migration, invasion, self-renewal, differentiation capacity of TB4-depleted or TB4-overexpressing glioma cells in vitro and tumorigenicity upon orthotopic implantation in vivo. Finally, we performed an Affymetrix gene chip analysis to unravel the molecular network of TB4 signaling effects. Results: TB4 expression increased with the grade of malignancy in gliomas and correlated with patient survival. In vitro, TB4 gene silencing by lentiviral transduction decreased migration, invasion, growth and self-renewal, and promoted differentiation and the susceptibility to undergo apoptotic cell death upon nutrient depletion in LNT-229, U87MG and the glioma stem-cell line GS2, respectively. In vivo, survival of nude mice bearing tumors derived from TB4-depleted glioma cells was improved and the tumorigenicity of the GS2 glioma stem-cell line was decreased. The gene expression pattern was shifted from the mesenchymal towards the pro-neural gene signature upon TB4 gene silencing. The clustering of differentially regulated genes involved TGF-ß and p53 signaling networks. Conclusions: TB4 may be a key regulator of malignancy in glioblastoma and therefore a novel candidate molecular target for anti-glioma therapies.
Safety analysis of bevacizumab plus NovoTTF-100A in patients with recurrent malignant gliomas.

Grace Elzinga, Amy T Chung, Eric Wong; Beth Israel Deaconess Medical Center, Boston, MA

Background: Both bevacizumab and the NovoTTF-100A device are treatments approved by the FDA for recurrent glioblastoma. We examined our single-institution experience in using this combination for patients with recurrent malignant gliomas. Methods: We identified retrospectively the side effects experienced by patients while on both bevacizumab and NovoTTF-100A. Overall survival was also tabulated from initiation of this combined modality treatment. Results: There were 14 men and 6 women. Their median age was 54 (range 29-76). All had Karnofsky Performance Status of 60 or above. Fourteen patients received NovoTTF-100A after failure of bevacizumab treatment while the other 6 received both treatments concurrently. The median duration of bevacizumab plus NovoTTF-100A treatments was 2.3 (95% CI 1.8-4.7) months. There were 2 patients who experienced electric shock sensation on the scalp from a poorly-applied transducer array that resulted in minor scalp burns, 3 patients developed scalp rashes (2 moderate and 1 severe), 4 patients experienced liquefied hydrogel from the arrays as a result of high ambient temperature during summer months, 2 experienced vivid dreams of applying the arrays and 3 removed the arrays while periods of sleep or confusion. Only one patient required NovoTTF-100A treatment interruption because of severe scalp rash. No hemorrhage into the malignant glioma or thromboembolism was seen in this cohort. From the time of initiation of bevacizumab plus NovoTTF-100A treatments, the Kaplan-Meier median overall survival was 5.6 (95% CI 4.2-N/A) months. Conclusions: No additive or synergistic side effects were observed when patients were treated with both bevacizumab and NovoTTF-100A. Further evaluation in a prospective manner would be needed to evaluate both side effects and efficacy of this treatment combination.
Prognostic factors and outcome of atypical and anaplastic meningioma with and without radiation.

Hannah Yoon, Irene B. Helenowski, Karthikeyan Perumal, MaryAnne H. Marymont, James Chandler, Bernard R. Bendok, Joshua M. Rosenow, Minesh P. Mehta; Northwestern Memor Hosp - McGaw Medical Center, Chicago, IL; Northwestern University Department of Preventive Medicine, Chicago, IL; University of Wisconsin, Department of Neurological Surgery, Madison, WI; Northwestern Memorial Hospital, Chicago, IL; Northwestern University, Chicago, IL; University of Maryland, Baltimore, MD

Background: We evaluated outcome and prognostic factors for high grade meningioma (G2-3) and the role of early post-operative radiotherapy (RT). Methods: From 2000 to 2010, 136 patients were diagnosed with G2-3 meningioma at Northwestern: 124 with atypical (G2) and 12 with anaplastic (G3) meningioma. All were treated with or without RT after initial or subsequent resection. The primary endpoint was progression-free survival (PFS). Results: 21 patients received adjuvant RT, and 115 did not. Median PFS for G2 with and without RT was 68 vs. 89 mos. Median PFS for G3 with and without RT was not reached=nr (mean 5) vs. 60 mos (mean 35). Median PFS for Simpson G1-3 with and without RT was 18 vs. 96 mos. Median PFS for Simpson G4 with and without RT was nr (mean 55) vs. 59 mos (mean 44). For median follow-up of 33 mos for Simpson G1-3 and 29 mos for G4, recurrence rate for Simpson G1-3 with and without RT was 40 vs. 6%, and for Simpson G4 with and without RT, 9 vs. 31%. 3-yr OS for G2 with and without RT was 93 vs. 94%. 3-yr OS for G3 with and without RT was 80 vs. 80%. In multivariate analysis, G3 histology and Simpson grade were predictive for relapse, while brain invasion, mitoses, adjuvant RT, and location of tumor were not. For those who received adjuvant RT, mean dose of external beam radiation (EBRT) in 2 patients was 58 Gy, while mean dose of stereotactic radiosurgery (SRS) in 15 patients was 15 Gy. 51% EBRT patients recurred, while 22% SRS patients recurred (p = 0.45). Median PFS with EBRT was 43 vs. 51 mos for SRS (p = 0.34). Patients were maldistributed between the with and without RT arms in terms of brain invasion, extent of resection, and G3 histology. Conclusions: Patients who received RT had lower PFS compared to those who did not; survival was comparable. This may be due to inherent selection bias for patients with more aggressive disease getting adjuvant RT. Our study may be underpowered to determine the true role of RT in G2-3 meningioma. Patients with subtotal resection, Simpson G4, who received RT had fewer recurrences and higher PFS compared to those who did not. 3-yr OS was equivalent in both G2 and G3 tumors with and without RT. G3 histology and Simpson grade were predictive for relapse while brain invasion, mitoses, adjuvant RT, and location of tumor were not.
Resectable central nervous system (CNS) metastases from colorectal cancer (CRC): Patient characteristics, outcome, and molecular correlations between primary tumor and metastases.

Elisa Bellini, Mario Airoldi, Paola Francia di Celle, Sara Mariani, Roberta Ruda, Riccardo Soffietti; 2nd Medical Oncology Division, A. O. Città della Salute e della Scienza di Torino, Turin, Italy; Department of Pathology, Città della Salute e della Scienza Hospital, Turin, Italy; Division of Neuro-Oncology, University Hospital San Giovanni Battista, Turin, Italy; Division of Neuro-Oncology University Hospital S Giovanni Battista, Turin, Italy

Background: Aim of this study is to describe clinical characteristics and outcome of CRC patients with CNS metastases undergone to surgical resection, and report preliminary data on the comparison between molecular aspects of primary tumor and metastasis. Methods: Thirty-two pts (17 males, 15 females) with a median age of 65 yrs (range 38-80 yrs) with brain metastases from colon (23 pts, 72%) or rectum (9 pts; 28%) adenocarcinoma (G1 in 3 pts, 9%; G2 in 12 pts, 37%; G3 in 17 pts, 53%) underwent total surgical resection. Primary tumor TNM was: T2 in 1 pt (3%), T3 in 22 pts (69%) and T4 in 9 pts (28%); no patient had N0 status, 10 pts had N1 lesions (31%) and 22 pts had N2 (69%) lesions; 25 pts were M0 (78%) while 7 (22%) were M1. Results: One patient had neurological symptoms as first manifestation of CRC; the other cases had metachronous metastases in the SNC after a median of 35.5 months (range 4-96). The CNS location was cerebellum in 15 pts (47%), frontal lobe in 9 pts (28%), spinal cord in 5 pts (16%), parietal lobe in 2 pts (6%) and occipital lobe in 1 pt (3%). Perioperative mortality was 3%. Ten pts (31%) received post-operative whole-brain radiotherapy. Six patient (19%) had local recurrence. Primary cancers harbored a K-RAS mutation in 13 cases (41%) and a BRAF mutation in 1 case (3%). Preliminary data in 20 pts indicate a 100% mutation concordance between primary tumor and CNS metastases. Conclusions: Resectable CNS metastases from CRC adenocarcinoma were seen after a median of 3 yrs originating from T3-4 N1-2 M0-1 lesions. The preferential locations in the CNS were cerebellum and frontal lobe, being spinal metastases relatively frequent. The total resection was feasible with a good long-term local control; the whole-brain irradiation given to one third of cases could have contributed to local control. Almost all pts died of extraneurvous metastases. There was a concordance of KRAS and BRAF mutation in primary and CNS lesions.
Association of human neurotropic JC virus with pediatric gangliogliomas.

Jennifer Rose Mullinax, Amanda Parker Struckhoff, Jimena Trillo-Tinoco, Michael Ripple, Randall Craver, Luis Del Valle; Louisiana State University Health Sciences Center, New Orleans, LA

Background: JC virus (JCV), a member of the Polyomaviridae family, is a widespread ubiquitous human pathogen found in greater than 80% of the adult population, where it persists in a latent state, most likely in the kidneys and bone marrow. JCV is tumorigenic in animals and is associated with a variety of human malignancies, including brain tumors where it infects glial cells. JCV exerts its oncogenic effects through the oncoprotein T-Antigen, which binds and inactivates tumor suppressor proteins p53 and Rb. In addition, T-Antigen can translocate IRS-1 to the nucleus, where it impedes faithful DNA repair. In this study, we will investigate the presence of JC virus and the oncoprotein T-Antigen and explore their role in pediatric gangliogliomas.

Methods: Formalin-fixed paraffin-embedded tissue samples of pediatric gangliogliomas were obtained from the archives of the Pathology Department at Children’s Hospital in New Orleans. PCR amplification was performed with specific primers for the T-Antigen coding region of JCV. Immunohistochemistry for T-Antigen, p53, Rb, and IRS-1, the docking molecule of the IGF-1 pathway, was also performed.

Results: Our study included 15 samples of pediatric gangliogliomas. JCV genomic sequences were amplified in 12 of the 15 samples (80%). T-Antigen expression was found in the nuclei of tumor cells in 7 of the 15 samples (47%) by immunohistochemistry. T-Antigen was present in both the glial and neuronal components of the tumors. Of the seven samples positive for T-Antigen, five were positive for both p53 and Rb, one was positive for p53, and one was negative for both p53 and Rb, but positive for nuclear IRS-1.

Conclusions: The presence of JCV genomic sequences in pediatric tumors suggests that primary infection occurs early in life. The expression of T-Antigen in both the glial and neuronal components of gangliogliomas suggests that these mixed tumors most likely originate in a common primitive cell, which then differentiates into two different phenotypes. The co-localization of T-Antigen with p53 and Rb suggests that cell cycle deregulation is one oncogenic pathway in gangliogliomas. Nuclear IRS-1 suggests alterations on faithful DNA repair mechanisms. These findings warrant further investigation.
Background: Medulloblastoma (MB) accounts for less than 1% of adult intracranial tumours. While pediatric MB has been investigated in several randomized studies, the evidence in adults is limited to case reports and retrospective series, with no accepted standard of care. The Australian Cooperative Trials Group for Neuro-Oncology (COGNO) sought to determine the range and consistency of clinicians’ approaches to management as a basis for future trials. Methods: We aimed to identify current treatment strategies for adult MB through an international electronic survey launched at the 2012 meeting of the Society of Neuro-Oncology and by email invitation. Clinicians who had treated at least 1 adult patient with MB, central primitive neuroectodermal tumor (cPNET), or pinealoblastoma in the preceding year were asked about their most recent patient and asked to discuss their approach to management of a typical clinical scenario. Results: Between Nov 2012 and Jan 2013, 45 clinicians (11 medical oncologists, 7 radiation oncologists, 5 pediatric oncologists, and 22 others) from Australia (n = 24), USA (n = 3), Europe (n = 4) and other countries (n = 14) completed the survey. Responding clinicians had treated 54 cases in the past 12 months. The commonest histological type was MB (64%), followed by cPNET (20%). Most patients were male (68%), and most had high-risk disease (65%). 56% had complete surgical resection and 32% had molecular testing. Radiotherapy was predominantly craniospinal (92%) and mostly post-resection (80%). Combination chemotherapy was more common than single agent. Vincristine, cisplatin, cyclophosphamide was the most common protocol (43%). Others included carboplatin, etoposide, ifosfamide (29%), vincristine, lomustine, cisplatin (19%), vincristine, lomustine, prednisone (5%). Further details will be presented at the 2013 ASCO Annual Meeting. Conclusions: Our study has shown substantial international variation in the treatment of adult MB, most pronounced in the choice of chemotherapeutic agents, highlighting the need for further collaborative research to guide evidence-based treatment strategies.
Bevacizumab in combination with TMZ in patients with recurrent GBM: Final OS and PFS analysis.

Juan Manuel Sepulveda, Cristobal Belda-Iniesta, Miquel Gil, Pedro Pérez Segura, Alfonso Berrocal, Gaspar Reynes, Oscar Gallego, Jose Manuel Ordonez, Beatriz La Orden, Carmen Balana; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital U. La Paz (actually at Hospital Madrid Norte Sanchinarro), Madrid, Spain; Instituto Catalán de Oncología, Bellvitge, Spain; Hospital Clínico Universitario San Carlos de Madrid, Madrid, Spain; Consorcio Hospital General Universitario de Valencia, Valencia, Spain; Hospital Universitario La Fe, Valencia, Spain; Hospital De Sant Pau, Barcelona, Spain; Roche Farma, S.A., Madrid, Spain; Institut Catala d’Oncologia Badalona, Barcelona, Spain

Background: BEV provides a consistent clinical benefit in the treatment of relapsing GBM in terms of a delayed progression and increased median overall survival compared to historical controls. The aim of this study is to evaluate the efficacy and toxicity profile of the combination of BEV with dose dense TMZ, reporting the final results of PFS, OS and the toxicity experienced. Methods: A phase II multicenter, national, open-label study in pts diagnosed of recurrent GBM treated with BEV 10 mg/kg day q2w and TMZ 150 mg/m² days 1-7 and 15-21 q28d d until disease progression or unacceptable toxicity or medical decision, as first line of treatment all pts received radiotherapy and at least 3 cycles of adjuvant TMZ. This study evaluates efficacy by PFS as primary endpoint and as secondary endpoints: OS, RR based on the adapted MacDonald criteria and toxicity profile (NCI CTC v3.0). Results: From June 10 to July 11, 32 evaluable pts were recruited in 8 sites. The baseline characteristics were as follows: 17 males and 15 females, median age 57.5 y (29-74), ECOG PS 0: 25%, PS 1: 50% and PS 2: 25%, 44% patients had gross total resection, 50% had subtotal resection and 6% biopsy only, MGMT promotor was methylated in 12 pts, unmeth in 6 pts and missing in 14 pts. The median number of TMZ or BEV cycles administered across all patients was 4 (TMZ range 1-9 and BEV range 1-25) The median PFS was 4.4 m [IC 95% (3.7 – 5.6)]. The 6m-PFS probability was 29.25%. The median OS (75% events) was 7.5 m [IC 95% (5.98 – 9.11)]. No significant association with MGMT status was found in terms of OS or PFS. BEV related AEs have been reported in 56.2% of the population being most of them mild or moderate. Grade 3-4 most frequent toxicity: lymphopenia 31% and fatigue 12.5%. Six of 32 pts were long term survivors, in this population the median PFS was 9.8 m [IC 95% (8.2 – 24.4)] and median OS (50% events) was 15.9 m [IC 95% (9.2 – NA)]. No differences in baseline characteristics were identified in comparison with total population. The median number of TMZ cycles administered was 4 and median BEV cycles were 9. Conclusions: Although the combination don’t met the previous reported activity of BEV, 19% of patients had longer survivals which suggest the need to identify patients that benefit for this treatment. Clinical trial information: NCT01115491.
Background: C-met is a tyrosine kinase receptor involved in growth, invasiveness and malignant progression in glioblastoma multiforme (GBM). Activation of the C-met pathway increases resistance towards DNA damage in glioma cell lines and it has been shown that an orally administrated C-met kinase inhibitor inhibits intracranial glioma growth in immunodeficient mice, suggesting that C-met is a potential target in glioma treatment. The purpose of the present study was to investigate the prognostic value of C-met in GBMs and subsequently correlate the prognostic value to known clinical variables, identified in a population-based cohort.

Methods: Tissue samples from 186 GBM patients were analyzed using immunohistochemical staining and advanced quantitative image analysis. This provided continuous measurements based on staining intensity.

Results: Median intensity was 70.8 (range 15.5-200.1). When divided at the median C-met was not prognostic. Further exploration showed that dichotomizing at an intensity of 75 (60% vs. 40%), high levels of C-met were associated with poor survival. However; C-met is a time-dependent factor and no prognostic effect was observed within the first 8.5 months after diagnosis (HR 0.97, 95% CI 0.62-1.51, p = 0.892). After 8.5 months, patients with high levels of C-met had a significantly poorer survival as compared to patients with low levels (HR 2.06, 95% CI 1.33-3.18, p = 0.001). This was significant in multivariate analysis adjusted for clinical variables; C-met (HR 1.89, 95% CI 1.22-2.93, p = 0.004), age (HR 1.02, 95% CI 1.00-1.03, p = 0.037), performance status (HR 1.55, 95% CI 1.38-1.74, p = 0.004), and tumor crossing midline (HR 1.72, 95% CI 0.75-3.92, p = 0.201). Interestingly; C-met was only prognostic in patients who received post-surgical treatment, whereas no effect was observed in the 31 patients who underwent surgery only (HR 0.54, 95% CI 0.26-1.15, p = 0.113).

Conclusions: Using advanced quantitative image analysis, we found that C-met was an independent prognostic factor of poor survival in GBMs. The effect did not appear within the first 8.5 months after the diagnosis and it was only seen in patients who received post-surgical treatment.
Chemopredictive assay for patients with primary brain tumors.

Pier Paolo Claudio, Jagan Valluri, Sarah E Mathis, Anthony Alberico, James Denvir, Gerrit A. Kimney, Mark Jeffrey Mogul, Rajesh Sehgal, Aneel A. Chowdhary, Mohammad Mozayen, Maria R. B. Tria Tirona, Laurie Beth Matt, Gerald Oakley, Krista L Denning, Thomas Dougherty; Department of Biochemistry and Microbiology, Joan C. Edwards School of Medicine, Translational Genomic Research Institute, Marshall University, Huntington, WV; Marshall University, Department of Biology, Huntington, WV; Department of Biochemistry and Microbiology, Joan C. Edwards School of Medicine, Translational Genomic Research Institute, Marshall University, Huntington, WV; Department of Neurosurgery, Marshall University, Huntington, WV; Department of Neurosurgery, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV; Huntington Internal Medcn Grp, Huntington, WV; Department of Pediatrics, Marshall University, Huntington, WV; Department of Medical Oncology, Edwards Cancer Center, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV; Department of Pathology, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Background: Cancer stem-like cells (CSLCs) in primary brain tumors can resist certain chemotherapies, thereby causing relapse of the disease. Thus, development of a test that identifies the most effective chemotherapeutic management offers great promise for personalized anticancer treatments.

Methods: We have developed an ex vivo ChemoID assay designed to predict the sensitivity and resistance of CSLCs and bulk of tumor cells of a given patient’s solid tumor to a variety of chemotherapy agents by measuring the percentage of cell death. In a retrospective study of five patients with malignancies of the central nervous system, we assessed the correlation between the results of the ChemoID assay and clinical response. Two anaplastic WHO grade-III ependymomas, two IDH-1 negative WHO grade 4 glioblastomas, and one medulloblastoma were tested. Tumors were classified as responsive (50-100% cell kill), intermediately responsive (30-50% cell kill), and nonresponsive (0-30% cell kill) to chemotherapy. Treatment selection was blinded to assay results. MRI and CT scan determined response to therapy.

Results: The ChemoID assay performed on the tumor bulk produced a correct prediction in 4 out of 5 cases ($p = 0.4$, Fisher’s Exact Test; PPV = 75%, NPV = 100%) when compared to the drugs received. The same assay performed on the CSLCs produced a correct prediction in all 5 cases ($p = 0.1$, Fisher’s Exact Test; PPV = NPV = 100%).

Conclusions: An assay such as ChemoID that measures cell death of CSLCs and bulk of tumor cells appears to be beneficial in selecting specific standard chemotherapy agents ex vivo for patients with malignancies of the central nervous system.
Analysis of high-dose methotrexate with rituximab versus other treatment regimens for primary central nervous system (CNS) lymphoma.

Scott Michael Lindhorst, Frances McSherry, Annick Desjardins, Henry S. Friedman, Katherine B. Peters; Duke University Medical Center, Durham, NC

Background: The most effective and least toxic treatment regimen for primary CNS lymphoma is a matter of debate. Most current regimens utilize various doses of high-dose methotrexate combined with other agents. The utility of deferred radiation is also under study. Methods: We evaluated 28 patients with primary CNS lymphoma treated with methotrexate 3.5 g/m² and rituximab, as well as alternative regimens. Median, 12-month, and 24-month survival were compared for the various treatment regimens, as well as for patients who received radiation and those who did not. Results: Survival rates were significantly better in the methotrexate-rituximab treatment cohort than the other regimens examined (Log-Rank p-value 0.0437). 12-month survival for the methotrexate-rituximab cohort was 72.7% (95% CI, 37.1% to 90.3%) versus the alternative treatment cohort 12-month survival of 49.4% (95% CI, 23.7% to 70.8%). 24-month survival for the methotrexate-rituximab cohort was 72.7% (95% CI, 37.1% to 90.3%) versus the alternative treatment cohort 24-month survival of 39.5% (95% CI, 14.9% to 63.6%). Median survival for the alternative treatment cohort was 11 months (95% CI, 2.2 to 28.6), while the median survival for the methotrexate-rituximab regimen was not reached. Stratified by radiation, survival rates were significantly better in the radiation cohort than the cohort without radiation (Log-Rank p-value 0.0040). 12-month survival for the radiation cohort was 90% (95% CI, 47.3% to 98.5%) versus the cohort without radiation 12-month survival of 40.5% (95% CI, 17.7% to 62.3%). 24-month survival for the radiation cohort was 90% (95% CI, 47.3% to 98.5%) versus the cohort without radiation 24-month survival of 33.7% (95% CI, 12.9% to 56.1%). Median follow-up for all patients was 21.5 months (95% CI, 16 to 42.1). Conclusions: The combination of methotrexate at 3.5 g/m² with rituximab is a valid treatment regimen for primary CNS lymphoma. Patients may be spared toxicity by using a methotrexate dose of 3.5 g/m² rather than 8 g/m². The addition of radiation provided a significant survival advantage in this observational study, however, radiation deferred until progression may be a viable alternative.
Effect of metformin and statins in high-grade brain tumors.

Guek Eng Lee, Iain B. Tan, Chee Kian Tham; National Cancer Centre, Singapore, Singapore; Department of Medical Oncology, National Cancer Centre Singapore, Singapore, Singapore

Background: Metformin and statins are thought to have anti-cancer properties. Metformin induces AMPK activation and may be implicated in potentiating the therapeutic outcome of temazolamide. Statins at low dose are thought to have anti-cancer properties by inhibiting pro-angiogenic factors with resultant inhibition of tumor growth, but statins at high dose are thought to have counter-productive effects. Hyperglycaemia was shown to be associated with a poorer outcome in patients with newly diagnosed glioblastoma. Hence we investigate the effect of metformin and statins in high grade brain tumours. Methods: Among 249 patients with brain tumour, we identified 142 patients with high grade gliomas. 116 patients did not receive metformin or statins and 26 patients received metformin or statins. Patients’ demographics, clinical and histopathological characteristics were recorded. Overall survival was evaluated. Results: Among 142 patients with high grade gliomas, there were 86 patients with glioblastoma multiforme, and 56 patients with anaplastic astrocytoma or anaplastic oligodendroma. Median age was 60 years old. The average value of HbA1c value for patients on metformin was 7.2%. The average dose of simvastatin used was 20 mg and average total cholesterol was 5.1mmol/l. For patients who did not receive metformin or statins, the median survival was 72.9 months (95% confidence interval, 47.8 – 98.1); patients who received metformin or statins, the median survival was 39.1 months (95% confidence interval, 21.7 – 56.4) p = 0.24. Conclusions: There is a trend towards shorter overall survival of patients who received metformin and statins. Despite the anti-cancer properties of metformin and statins, patients with diabetes mellitus and hyperlipidaemia still fare worse. The effect of diabetes mellitus, hyperlipidaemia, as well as sugar and cholesterol control deserves a larger cohort study in patients with high grade brain tumours.
Phase I study of anti-PlGF monoclonal antibody (mAb) RO5323441 (RO) and anti-VEGF mab bevacizumab (BV) in patients with recurrent glioblastoma (GBM).

Ulrik Niels Lassen, Oliver L. Chinot, Catherine McBain, Morten Sorensen, Vibeke Andree Larsen, Maryline Barrie, Patrick Roth, Oliver Krieter, Karen Wang, Kai Habben, Jean Tessier, Angelika Lahr, Matt Whiley, Michael Weller; Rigshospitalet, Copenhagen, Denmark; Centre Hospitalier Universitaire La Timone, Marseille, France; The Christie Hospital NHS Foundation Trust, Manchester, United Kingdom; University Hospital, Zurich, Switzerland; Roche Diagnostics GmbH, Penzberg, Germany; Hoffmann La Roche Pharmaceuticals, Nutley, NJ; F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background: BV inhibits VEGF and is approved for progressive GBM following prior therapy. The placental growth factor (PlGF) is a member of the VEGF family and PlGF expression has been shown to correlate with tumor stage and survival in several human malignancies. In cancer patients (pts) PlGF is up-regulated upon treatment with VEGF inhibitors. RO is a humanized IgG1 mAb directed against PlGF that has demonstrated antitumor activity in an orthotopic GBM model. Single agent RO was previously tested in advanced solid tumors. Methods: Eligibility criteria included histologically confirmed GBM with documented radiographic progression upon front line therapy, ≥18 years of age, KPS ≥70, adequate bone marrow reserve and organ function. Prior treatment with VEGF/PLGF targeted therapies was not permitted. Three to six pts were enrolled per dose level (DL), the MTD defined as the dose with DLTs ≤ 1/6 pts during 28-days of cycle 1, using CTCAE v4. Results: A total of 22 pts (16m/6f) have been enrolled in 3 DLs: RO 625mg (4 pts), 1250mg (6), and 2500mg (12) IV every 2 weeks (q2w), each in combination with BV 10mg/kg IV q2w. Median age: 58 years (range 37-72). RO serum concentrations increased proportionally, while serum exposures of BV were similar between all DLs. Two pts experienced a DLT: Meningitis G3 (1250 mg) and cerebral infarction G3 (2500 mg). Most commonly reported adverse events included hypertension (14 pts), headache (11), dysphonia (10), fatigue (6), nasopharyngitis (5), epistaxis (4), constipation (4), nausea (3), and arthralgia (3). Across all DLs tested, the overall response rate by RANO criteria was 22.7%. Conclusions: The tolerability of RO in combination with BV is acceptable; a MTD was not determined. Anti-PlGF treatment does not appear to add on clinical activity observed for single agent BV in recurrent GBM. Clinical trial information: NCT01308684.
Phase I/II study of dianhydrogalactitol in patients with recurrent malignant glioma or progressive secondary brain tumor.

James D. Peyton, Howard A. Burris, Jeffrey A. Bacha, Dennis Brown, William J. Garner, Richard Stephen Schwartz, Kent C. Shih; Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN; Del Mar Pharmaceuticals, Vancouver, BC, Canada

Background: Recurrent glial tumors of the brain continue to be one of the most challenging malignancies to treat, and median survival for patients with recurrent disease is approximately 6 months for glioblastoma multiforme (GBM). The front-line therapy for GBM - temozolomide (TMZ) - is subject to resistance by DNA repair protein O\textsuperscript{6}-methylguanine-DNA methyltransferase (MGMT), leading to poor prognoses for patients with recurrent GBM. Dianhydrogalactitol (VAL-083) is a first-in-class bi-functional N\textsuperscript{7} DNA alkylating agent shown to cross the blood-brain barrier, accumulate in brain tissue, and have activity against GBM. Studies suggest that VAL-083 overcomes MGMT-driven drug resistance \textit{in vitro} and targets cancer stem cells. The purpose of this study is to determine the maximal tolerated dose (MTD) of VAL-083 in patients with recurrent GBM or progressive secondary brain tumor, and explore the safety, pharmacokinetics and tumor responses to treatment.

Methods: Open-label phase I/II dose-escalation study of VAL-083 in patients with histologically confirmed primary WHO grade 4 malignant GBM, now recurrent, previously treated for GBM with surgery and/or radiation, if appropriate, and have failed both bevacizumab and temozolomide; or progressive secondary brain tumor, has failed standard brain radiotherapy, and has brain tumor progression after at least one line of systemic therapy. The study uses a 3+3 dose escalation design, until reaching the MTD or maximum specified dose. Patients receive IV VAL-083 on days 1, 2, and 3 of each 21-day treatment cycle. In phase II, additional patients are treated at the MTD (or selected optimum dose) to measure tumor responses.

Results: Cohort 1 (3 patients) and cohort 2 (4 patients) were completed without any DLT’s. Adverse events (AEs) have all been grade 1/2, with only 1 grade 3 AE, unrelated to treatment. Cohort 3 currently has 4 patients enrolled, without reaching the MTD. 1/7 (14.3%) patients in cohorts 1 and 2 has prolonged stable disease (15+ cycles) on VAL-083 treatment.

Conclusions: VAL-083 up to the 2nd dose level was well tolerated without any safety signals. Dose escalation is continuing. Clinical trial information: NCT01478178.
**Dose-finding and safety study of an oncolytic polio/rhinovirus recombinant against recurrent glioblastoma.**

Annick Desjardins, John Howard Sampson, Katherine B. Peters, Tulika Ranjan, Gordana Vlahovic, Stevie Threatt, James Emmett Herndon, Allan H. Friedman, Henry S. Friedman, Darell D. Bigner, Matthias Gromeier; Duke University Medical Center, Durham, NC

**Background:** Current therapies for glioblastoma are limited by ineffective delivery beyond the blood-brain barrier, limited diffusion of macromolecules, and lack of tumor specificity. Sustained direct intracerebral infusion at slow flow rates (convection-enhanced delivery [CED]) can overcome delivery barriers. PVSRIPO is the live attenuated, oral (SABIN) serotype 1 poliovirus vaccine containing a heterologous internal ribosomal entry site stemming from human rhinovirus type 2. PVSRIPO recognizes nectin-like molecule-5, an oncofetal cell adhesion molecule and tumor antigen widely expressed ectopically in malignancy. We report the results of an ongoing phase I study evaluating PVSRIPO when delivered by CED.

**Methods:** Eligible on study are adult patients with: 1-5 cm of measurable supratentorial recurrent glioblastoma ≥1 cm away from the ventricles; ≥4 weeks after chemotherapy, bevacizumab or study drug; adequate organ function; KPS ≥70%; and positive anti-poliovirus titer. PVSRIPO is delivered intratumorally by CED over 6.5 hours. PVSRIPO dose escalation is accomplished by increasing agent concentration, allowing flow-rate and infusion volume to remain constant. Two-step continual reassessment method is used for dose escalation, with one patient each treated on dose levels 1-4, and a possibility of up to 13 patients on dose level 5. **Results:** Thus far, a total of five patients have been treated on study. No related or unrelated grade 3 or higher adverse events have been observed. Grade 1 adverse events possibly related to the study drug or procedure include one each of fever, cough, nasal congestion, vomiting, headache, hemiparesis, and lethargy. Grade 2 adverse events include one each of diarrhea and seizure. Patient #1 had failed bevacizumab prior to enrollment and remains disease free more than 9 months post PVSRIPO. Two more patients are disease free 8+ and 2+ months post treatment, respectively. One patient had pathology confirmed disease recurrence two months post treatment and one patient came off study due to clinical decline four months post treatment. **Conclusions:** Infusion of PVSRIPO via CED is safe thus far and encouraging efficacy results are observed. Updated results will be presented. Clinical trial information: NCT 01491893.
Phase I trial of temsirolimus (TEM) and perifosine (PER) for recurrent or progressive malignant glioma (MG).

**Background:** PI3K/AKT/mTOR signaling is important in MG biology, and therefore a potential therapeutic target. The mTOR inhibitor TEM and the AKT inhibitor PER are well tolerated as single agents but have limited activity. Preclinical data demonstrate synergistic anti-tumor effects during combined therapy including extensive tumor apoptosis, cell-cycle arrest among surviving cells, and inhibition of both AKT and mTOR. Therefore, we initiated a phase I trial of combined therapy in recurrent MGs. **Methods:** Adults with recurrent MG, KPS ≥ 60, and not taking enzyme inducing AEDs were enrolled. There was no limitation on prior therapies except prior RT and temozolomide were mandatory. The dose of TEM was escalated in each cohort using standard 3+3 design from 15 mg to 170 mg administered once weekly. The dose of PER was fixed as a 600 mg load on day 1 followed by 100 mg nightly (the single dose MTD) until dose level 7 when the load increased to 900mg. **Results:** Thirty-four patients (24 men) with median age 52 (range, 21-71) and median KPS 80 (range, 60-100) participated. Diagnoses included GBM (18), AA (7), AO (7) or transformed LGG (2). Twenty-one received bevacizumab previously. There were a total of 5 DLTs: 1 at dose level 3 (50mg TEM), then 2 at dose level 7 expansion (170mg TEM), and then 2 at dose level 6 expansion (170mg TEM). DLTs included thrombocytopenia (n=3), intracerebral hemorrhage (n=1) and lung infection (n=1). Two uPR were seen at 170mg TEM. **Conclusions:** Combination therapy with TEM 115 mg weekly and PER 100 mg daily (following 600 mg load) is tolerable in heavily pre-treated adults with recurrent MGs. Clinical trial information: NCT01051557.
Graded prognostic assessment index for breast cancer patients with brain metastases (BCBM).

Vyshak Alva Venur, Saurabh Dahiya, Lingling Du, Rohan Garje, Kwabena Osei-Boateng, Paul Elson, John H. Suh, Samuel T. Chao, Manmeet Singh Ahluwalia; Fairview Hospital, Cleveland Clinic, Cleveland, OH; Cleveland Clinic, Cleveland, OH; Cleveland Clinic Foundation, Cleveland Clinic, OH; Cleveland Clinic/Fairview, Cleveland, OH; Cleveland Clinic Foundation, Cleveland, OH

Background: The Graded Prognostic Assessment (GPA) is a commonly used prognostic index based on RTOG protocols in patients with brain metastases (BM). The purpose of this study was to evaluate prognostic factors to predict for overall survival (OS) in breast cancer BM (BCBM) treated at a single tertiary care center. Methods: After obtaining IRB approval, the Cleveland Clinic Brain Tumor and Neuro-Oncology Center’s database was used to identify BCBM who were treated in the recent years (2000-12). A proportional hazards model was used to assess OS, which was measured from the date of diagnosis of brain metastases to death or last follow-up. Results: 161 BCBM (160 females) median age 52 years (range 27-84) were included for analysis. 48% of patients were ER positive, 31% were PR positive, 50% were HER2 positive while 31% of patients were triple negative. The median number of BM was 2 (range, 1-15). Karnofsky Performance Scale (KPS) of the patient was 90-100 in 50%, 70-80 in 47%) and <70 in 43%. Extracranial Metastases was present in 85% of patients. Overall 85% of patients had died at the time of analysis; median OS was 19.0 months (95% C.I. 15.7-23.2). Breasta GPA that includes age, KPS and subtype was 0-1.0 in 5%, 1.5-2 in 31%, 2.5-3 in 35% and 3.5-4 in 29% of patients. Although GPA was statistically significant (p=0.002), some but not all of the factors used to derive it were significant (KPS [p=0.05], subtype [p=0.003] age [p=0.50]). Factors noted to be independently prognostic for OS (multivariable Cox proportional hazards model) included location of BM, number of extracranial metastases and uncontrolled primary tumor (Table). Conclusions: New GPA based on a set of independent prognostic factors is proposed.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Hazard ratio</th>
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<tr>
<td>BM location</td>
<td></td>
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<tr>
<td>Supra- or infratentorial</td>
<td>1.87 (1.21-2.89)</td>
<td>0.005</td>
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<tr>
<td>Both</td>
<td></td>
<td></td>
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<tr>
<td>No. of extracranial metastasis</td>
<td></td>
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<tr>
<td>0-2</td>
<td>1.55 (1.01-2.37)</td>
<td>0.05</td>
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<tr>
<td>&gt;2</td>
<td></td>
<td></td>
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<tr>
<td>Control of primary tumor</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>0.60 (0.37-0.93)</td>
<td>0.02</td>
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<tr>
<td>No</td>
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Characterization of glioblastoma (GBM) vasculature and protein expression of surrounding tumor cells on single FFPE sections with a multicycle multiplexed in situ immunofluorescent staining technology.

Jingyu Zhang, Colin McCulloch, Yunxia Sui, Sean Dinn, Qing Li, Alberto Santamaria-Pang, Christopher J Sevinsky, Jeremy Richard Graff, Lawrence Weiss, Teng Jin Ong, Fiona Ginty; GE Global Research, Niskayuna, NY; Google, Mountain View, CA; Molecular Imaging and Diagnostics Advanced Technology Program, General Electric Global Research Center, Niskayuna, NY; Lilly Research Labs Cancer Biology and Patient Tailoring Lilly, Indianapolis, IN; GE Healthcare, Aliso Viejo, CA; GE Healthcare, Princeton, NJ

Background: GBM is the most common brain tumor in humans and has a dismal prognosis. Although antiangiogenic therapy (bevacizumab) is an option for GBM, there is still unmet need to understand tumor pathophysiology and predictive biomarkers. We built a tissue based multiplexed immunofluorescent assays and developed algorithms to identify and quantify tumor vasculature, that enabled quantification, visualization, and colocalization of multiple protein in surrounding tumor cells at single cell and subcellular levels. This assay provides unique opportunity to explore tumor heterogeneity of tissue morphology and their relationships to vasculature, and is a novel tool for biomarker and treatment discovery.

Methods: Tissue micro arrays (TMAs) were constructed from 141 GBM patients. Fluorescent dye labeled antibodies against 18 biomarkers were sequentially applied on single sections of these TMAs. Metrics were built to identify vessels, quantify distance of tumor cells to vessels, and analyze expression profiles of biomarkers, including signaling molecules in EGFR, PI3K/AKT, TGF-beta pathways, and hypoxia marker Glut1, in proximity to blood vessels. Results: CD31 was successfully used to identify blood vessels in GMB. Vessel segmentation and quantification were performed on all of the images. Biomarker profiling in the context of blood vessels demonstrated different patterns in close proximity to vessels, with some biomarkers showing increased levels (e.g. SMA, EGFR, pS6), some showing decreased levels (e.g. p4EBP), and others remain the same (FOXO3a, S6). Quantification of biomarkers showed heterogeneous expression within the same sample and across the cohort. In addition, co-localization of the above markers was visualized and demonstrated on single cell and subcellular levels. Conclusions: We were able to use a novel fluorescent multiplexing technology (MultiOmyx) to study GBM biology. This technology allowed the simultaneous analyses of multiple biomarkers of GBM, and provides new insights on the relationship of markers to each other, tumor heterogeneity and angiogenesis.
Post-bevacizumab treatment and clinical outcomes in recurrent malignant glioma.

Yongjun Cha, Yu Jung Kim, Tae Min Kim, Seung Hong Choi, Se-Hoon Lee, Dong-Wan Kim, Chul-Kee Park, Il Han Kim, Jee Hyun Kim, Eunhee Kim, Byung Se Choi, Chae-yong Kim, In Ah Kim, Dae Seog Heo; Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; Department of Radiology, Seoul National University Hospital, Seoul, South Korea; Department of Neurosurgery, Seoul National University Hospital, Seoul, South Korea; Department of Radiation Oncology, Seoul National University Hospital, Seoul, South Korea; Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; Department of Radiology, Seoul National University Bundang Hospital, Seongnam, South Korea; Department of Neurosurgery, Seoul National University Bundang Hospital, Seongnam, South Korea; Department of Radiation Oncology, Seoul National University Bundang Hospital, Seongnam, South Korea

Background: Bevacizumab (Bev) and irinotecan combination therapy is effective against recurrent malignant glioma. However, post-Bev treatment and its clinical outcomes are not well investigated.

Methods: We identified 103 consecutive recurrent malignant glioma patients who received Bev plus irinotecan at our institutions. Clinical records and magnetic resonance images were reviewed. Response and progression were assessed by RANO criteria. Results: Bev and irinotecan treatment produced response rate of 37.9% (95% CI, 29.1-47.5%). At a median follow-up time of 41 weeks, the median progression-free survival (PFS) was 17.1 weeks (95% CI, 14.3-20.0), and 6-month PFS (6M-PFS) was 27.8% (95% CI, 18.4-37.2). The median overall survival (OS) was 33.4 weeks (95% CI, 27.8-39.1). Response predicted for superior PFS (25.0 weeks vs. 11.0 weeks, p < .001) and OS (45.9 weeks vs. 26.7 weeks, p < .001). A total of 93 patients discontinued Bev treatment and the reasons for discontinuation were: disease progression in 59 (63.4%), toxicities in 4 (4.3%), physician’s decision in 5 (5.4%), patient’s refusal to further treatment in 25 (26.9%). The median OS was 26.7 weeks in 59 patients who discontinued Bev due to disease progression, and 45.7 weeks in 34 patients who discontinued Bev for reasons other than disease progression (p < .001). Among 85 patients who progressed after Bev, 42 (49.4%) received further therapy: chemotherapy in 32 (37.6%), radiotherapy in 9 (10.6%), and surgery in 1 (1.2%). Further chemotherapy regimens included temozolomide (31.2%), ACNU/CDDP (25.0%), Bev reintroduction (18.8%), erlotinib (12.5%), PCV (9.4%), and intrathecal methotrexate (3.1%). The median survival time after Bev failure was 15.6 weeks (95% CI, 13.3-17.8). Patients who received further therapy showed longer median OS (18.6 weeks vs. 12.9 weeks, p < .001). In patients who received chemotherapy, the median PFS and OS was 6.6 weeks and 20.6 weeks, respectively. Conclusions: Prognosis after Bev failure was poor. Proper selection of patients who may benefit from further treatment is warranted.

Descriptive epidemiology of meningiomas in the United States.

John L. Villano, Stephen Todd Anderson, Therese A. Dolecek; University of Kentucky, Lexington, KY; University of Illinois at Chicago, Chicago, IL

Background: Although meningioma is the most common tumor in the central nervous system (CNS), the incidence, epidemiology, and clinical outcomes have historically been poorly defined. Our analysis follows the implementation of Public Law 107–260, the Benign Brain Tumor Cancer Registries Act mandating collection of non-malignant meningiomas. Methods: Surveillance Epidemiology End Results Program (SEER) 18 registries research data on cases diagnosed during 2004-2009 with meningioma (ICD-O-3 histology codes 9530-9534 & 9537-9539) in brain or CNS primary site (C70.0-72.9, 75.1-75.3) were analyzed. Population-based statistics were generated using SEER*Stat 8.0.1 software. Results: A total of 35,302 cases (34,718 non-malignant; 584 malignant) were available providing a rate of 7.18/100,000, with meningioma, NOS (9530/0) the most common histology. Rates increased with age (0.13/100,000, 0-19 years; 37.78/100,000, 75+ years). The annual percentage change in incidence rates showed a statistically significant increase of 2.57% over 2004-2009. Significant increases were also observed for males, females, whites, blacks, non-Hispanics, and older age groups. The gender ratio M:F was 0.35 in the 0-49 age group and 0.48 in the 50+ age. Primary site location included cerebral meninges (83%) with almost 5% in the spinal meninges. 51% of cases were diagnosed pathologically versus imaging. However, diagnosis among 85% of spinal cases was surgically based. Older age and females were less likely to have a surgical diagnosis. 3.4% received radiation therapy (RT) with 97% receiving RT following surgery. For grade III or malignant cases, 22% received RT, and in grade 1 and 2 nearly 97% of cases did not receive RT, with older age groups less likely to receive RT. For grade III or malignant cases, 22% received RT, and in grade 1 and 2 nearly 97% of cases did not receive RT, with older age groups less likely to receive RT. Overall survival was high, except for grade 3 or malignant cases where 5 year relative survival was 61.7%. Conclusions: Our analysis following Public Law 107–260 demonstrates an increasing incidence of meningiomas and provides new information, including a decrease in the gender difference with age. Clinical diagnosis is common and higher in women and older adults. Use of RT is low, even in malignant meningiomas, and employed following surgery. These observations were similar for white and black cases.
Vorinostat as a radiosensitizer for CNS malignancies: Preclinical results and phase I trial in brain metastasis.

Wenyin Shi, Yaacov Richard Lawrence, Hak Choy, Phyllis R. Wachsberger, David W. Andrews, Maria Werner-Wasik, Adam Dicker; Department of Radiation Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA; Sheba Medical Center, Tel HaShomer, Israel; The University of Texas Southwestern Medical Center, Dallas, TX; Thomas Jefferson University, Philadelphia, PA; Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA; Thomas Jefferson University Hospital, Philadelphia, PA

**Background:** To evaluate the effect of vorinostat as radiosensitizer in human Glioblastoma cell lines in preclinical study, as well as a phase I study to evaluate the safety, and tolerability of vorinostat, an HDAC inhibitor, when combined with whole brain radiation treatment (WBRT) for patients with brain metastasis. **Methods:** Preclinical studies evaluated the effect of vorinostat on DNA repair enzyme expression, repair of radiation induced DNA damage, and cell survival to radiation treatment as a proof of concept. Further phase I clinical trial included patients with histological diagnosis of malignancy and radiographic evidence of brain metastasis. WBRT was 37.5 Gy in 2.5 Gy fractions delivered over 3 weeks. Vorinostat was administrated by mouth, once daily, Monday through Friday, concurrently with radiation treatment. The vorinostat dose was escalated from 200 mg to 400 mg daily using a 3+3 trial design. **Results:** Preclinical studies showed with increasing doses of vorinostat more profoundly decrease expression of key genes involved in DNA repair, inhibiting the repair of DNA damage induced by ionizing radiation and leading to decreased clonogenic survival. It enhanced the radiation effect in vitro. In the phase I trial, 17 patients were enrolled, 4 patients were excluded from the analysis due to either incorrect radiation dose (n=1), or early treatment termination due to disease progression (n=3). There were no treatment related grade 3 or higher toxicities in the 200 mg and 300 mg dose levels. In the 400mg cohort there was a grade 3 pulmonary embolus and one death within 30 days of treatment. Although both events were most likely related to disease progression rather than treatment. However, to be more conservative, we defined the death as a dose limiting toxicity. **Conclusions:** Preclinical studies demonstrated that vorinostat profoundly decrease expression of key genes involved in DNA repair, inhibiting the repair of DNA damage induced by ionizing radiation and leading to decreased clonogenic survival. Vorinostat administered orally once daily with concurrent whole brain radiation treatment is well tolerated to the dose of 300 mg. This is the recommended dose for phase II study. Clinical trial information: NCT00838929.
Diffuse intrinsic pontine gliomas (DIPG) in adolescents can have differing presentations but similar outcomes compared to those of middle childhood.

Background: DIPG are invasive, treatment-resistant, brainstem tumors that generally affect children in middle childhood. The triad of cranial neuropathies, long tract signs, and ataxia are characteristic presenting signs; most patients have a short history of symptoms. Median survival is less than one year, but young children (<3 years) and adults with DIPG may have a better prognosis. Other positive clinical prognostic factors include longer duration of symptoms and absence of cranial neuropathies. We assessed the presentation and outcome of adolescents with DIPG. Methods: Patients were enrolled on an IRB-approved protocol. Clinical data for patients age >10 years and <20 years with a diagnosis of DIPG who were evaluated and treated at the authors’ institutions were reviewed. Results: A total of 46 patients were identified. M:F was 0.77:1. Median age at diagnosis was 13 (range 10-20) yrs. Frequent presenting symptoms included headache (39%), dizziness (25%), diplopia (27%) and cranial neuropathies (27%). Two were diagnosed as incidental findings. The interval between onset of symptoms and diagnosis ranged from 2 days-5 years, and only 9 of 41 patients (22%) reported symptom duration of less than 2 weeks. The majority (39/42) received radiation therapy, with or without adjuvant chemotherapy. Of patients for whom data is available, 8/22 (36%) did not improve or worsened during radiation therapy and 17 of 27 (63%) remained on steroids at the end of radiation. Two patients are alive with stable disease and 1 is actively receiving initial treatment. Of the patients with progressive disease for whom data is available (n=32), median time to progression was 8 mo (range 2 mo-2.5 yrs). Conclusions: Presenting symptoms of DIPG in adolescents commonly include headache, dizziness and diplopia for several weeks-months. Although the vast majority are treated with radiation therapy, clinical benefit was not observed in a significant number of patients. Overall outcome is similar to those patients diagnosed in middle childhood rather than the adult population.
Phase I/II dose-escalation study of VB-111, an antiangiogenic gene therapy, in patients with recurrent glioblastoma multiforme.

Andrew Jacob Brenner, Yael Cohen, James J Vredenburgh, Katherine B. Peters, Eyal Breibart, Livnat Bangio, Naamit Sher, Dror Harats, Patrick Y. Wen; Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio, TX; VBL Therapeutics, Or Yehuda, Israel; Saint Francis Hospital and Medical Center, Hartford, CT; Duke University Medical Center, Durham, NC; Dana-Farber Cancer Institute, Boston, MA

**Background:** VB-111 is an anti-angiogenic agent consisting of a non-replicating adenovirus vector (Ad-5) with a modified murine pre-proendothelin promoter leading to apoptosis of tumor vasculature by expressing a fas-chimera transgene in angiogenic endothelial cells. In a phase I/II dose-escalation study, safety and efficacy of VB-111 in patients with recurrent Glioblastoma Multiforme (GBM) were evaluated. **Methods:** VB-111 was administered as a single intravenous infusion at escalating doses from $1 \times 10^{12}$ to $3 \times 10^{12}$ viral particles (VPs), followed by repeat doses of $3 \times 10^{12}$ or $1 \times 10^{13}$ every 2 months. Assessments included safety, pharmacokinetics, tumor response (RANO criteria) and overall survival (OS). Results: Twenty eight patients aged 26 – 74 years at 3 medical centers in the US received up to 8 repeat doses of VB-111. The median OS was 360 [range: 70-574] and 266 days [range: 28-664] for patients receiving at least one dose of $1 \times 10^{13}$ VPs (high dose) vs. subjects who received lower doses, respectively (p NS). Progression free survival was 87 vs 55 days for patients who received high dose and for lower doses, respectively (p = 0.01). Median follow-up was 232 days. Three patients had a partial response (PR) at 82, 86 and 408 days post initial VB-111 dosing. Twenty one of the patients who progressed on VB-111 treatment received bevacizumab off study; 7 of the 15 evaluable patients (47%) had a PR compared to 30% expected according to literature. VB-111 was safe and well tolerated, 53 adverse events were reported, 14 were classified as possibly related to VB-111. All events were of CTCAE grade 1-2 except one grade 3 pulmonary embolism. There were no study related deaths. One patient developed peri-tumoral edema, which resolved with corticosteroid therapy. Events occurring in > 10% of the patients included headache and fatigue. Conclusions: VB-111 was safe and well tolerated in patients with recurrent GBM with repeat doses of up to $1 \times 10^{13}$ VPs. Tumor responses were seen. Overall survival was about 3 months longer than historical data in recurrent GBM, including standard of care anti-angiogenic agents. Data suggests that VB-111 potentiates the response to bevacizumab given at further progression. Clinical trial information: NCT01260506.
Dose-intensified rechallenge with temozolomide: One week on/one week off versus 3 weeks on/one week off in patients with progressive or recurrent glioblastoma (DIRECTOR).

Ghazaleh Tabatabai, Wolfgang Wick, Guido Reifenberger, Joachim Peter Steinbach, Oliver Schnell, Peter Hau, Ulrich Herrlinger, Michael Sabel, Ralf Ketter, Uwe S. Schlegel, Christine Marosi, Roland Goldbrunner, Krzysztof Homicsko, Guido Nikkhah, Josef Pichler, Peter Vajkoczy, Juergen Meixensberger, Michael Weller; Department of Neurology, University Hospital Zurich, Zurich, Switzerland; University of Heidelberg Medical Center, Heidelberg, Germany; Institute of Neuropathology, University of Duesseldorf, Duesseldorf, Germany; Senckenberg Institute of Neurooncology, Frankfurt, Germany; Department of Neurosurgery, University Hospital Munich LMU, Munich, Germany; Department of Neurology and Wilhelm Sander NeuroOncology Unit, University Hospital Regensburg, Regensburg, Germany; Division of Clinical Neurooncology, Department of Neurology and Center of Integrated Oncology Cologne/Bonn, University of Bonn, Bonn, Germany; Department of Neurosurgery, University Hospital Dusseldorf, Dusseldorf, Germany; Department of Neurosurgery, University Hospital Homburg, Homburg, Germany; Knappschaftskrankenhaus University Hospital, Bochum, Germany; Department of Medicine I, Clinical Division of Oncology and Comprehensive Cancer Center, Medical University Vienna, Vienna, Austria; Department of Neurosurgery, University of Cologne and Center of Integrated Oncology Cologne/Bonn, Cologne, Germany; Clinical Trial Unit, CHUV, Lausanne, Switzerland; University of Erlangen, Erlangen, Germany; Landesnervenklinik Linz, Linz, Austria; Department of Neurosurgery, Charité Universitätsmedizin Berlin, Berlin, Germany; Department of Neurosurgery, University Hospital Leipzig, Leipzig, Germany; University Hospital Zurich, Zurich, Switzerland

Background: No standard of care has been defined for patients with glioblastoma who relapse or progress on or after standard temozolomide (TMZ)-based radiochemotherapy. Rechallenge with TMZ using various dose-intensified regimens is a common approach for recurrent glioblastoma. O6-methylguanin-methyltransferase (MGMT) promoter methylation is a strong prognostic marker in newly diagnosed glioblastoma. However, in recurrent glioblastoma, the prognostic value of the MGMT status has remained unclear. Methods: The DIRECTOR trial is an open-label prospectively randomized phase II trial investigating 2 different TMZ rechallenge regimens, i.e. 1 week on/1 week off (Arm A, 120-150 mg/m² per day for 7 days) versus 3 weeks on/1 week off (Arm B, 80-100 mg/m² per day for 21 days) in recurrent glioblastoma. Patients were enrolled at first progression after having completed the first-line TMZ radiochemotherapy and at least 2 adjuvant TMZ cycles. At randomization, MGMT gene promoter methylation status from the primary or recurrent tumor was mandatory. The study treatment was monitored every 2 months by MRI using MacDonald criteria. Translational studies included blood biomarker (e.g. regulatory T cell counts, MGMT activity in peripheral blood). In addition, quality-of-life was evaluated by QLQ-C30 and QLQ-BN20 EORTC scores. Neurocognitive testing using the NeuroCogFx was optional. The primary endpoint is median time-to-treatment failure that was defined as progression, toxicity or death from any cause. Secondary endpoints are progression-free survival, overall survival, response and MGMT correlations. The trial was performed in 16 sites in Austria, Germany, and Switzerland. 105 of 166 patients have been enrolled (53 patients in Arm A and 52 patients in Arm B) before the enrollment was prematurely stopped on 30 June 2012. The database will be closed on 30 June 2013. Clinical trial information: NCT00941460.
Phase II trial of triple-receptor tyrosine kinase receptor inhibitor nintedanib (BIBF 1120) in recurrent high-grade gliomas.

Andrew David Norden, David Schiff, Manmeet Singh Ahluwalia, Glenn Jay Lesser, Lakshmi Nayak, Eudocia Quant Lee, Alona Muzikansky, Jorg Dietrich, Katrina H. Smith, Sarah C. Gaffey, Christine Sceppa McCluskey, Keith L. Ligon, David A. Reardon, Patrick Y. Wen; Dana-Farber Cancer Institute, Boston, MA; University of Virginia Medical Center, Charlottesville, VA; Cleveland Clinic, Cleveland, OH; Wake Forest University, School of Medicine, Winston-Salem, NC; Massachusetts General Hospital Cancer Center, Boston, MA; Massachusetts General Hospital, Boston, MA; Dana-Farber Cancer Institute/Brigham and Women’s Hospital/ Boston Children’s Hospital, Boston, MA

Background: Bevacizumab is the standard of care for patients with recurrent high-grade glioma (HGG). However, with current treatment options the median duration of response is only approximately 4 months. Potential mechanisms of resistance include upregulation of fibroblast growth factor (FGF) and increased pericyte coverage mediated by platelet-derived growth factor (PDGF). Nintedanib is an oral, small-molecule tyrosine kinase inhibitor of PDGFR \(\alpha/\beta\), FGFR 1/3, and vascular endothelial growth factor receptor (VEGFR) 1-3 that may overcome the problem of resistance to prior anti-VEGF therapy. Methods: This is an open-label, phase II trial in adults with first or second recurrence of HGG, stratified by prior therapy with bevacizumab. The primary endpoint is 6-month progression-free survival (PFS6) in the bevacizumab-naive arm and PFS3 in the post-bevacizumab arm. A Simon two-stage design is employed. Although the glioblastoma (GBM) comparison is the one of primary concern, 10 anaplastic glioma (AG) participants will be accrued to each arm in exploratory cohorts. Results: Nine of 40 GBM patients and 10 of 10 AG patients have been accrued in the bevacizumab-naive arm. Data in this arm are maturing. In the post-bevacizumab arm, 14 patients have been accrued, 10 of whom had GBM (71%). There were 11 men (79%), median age was 52 years (range 32-70), and median KPS was 90 (range, 60-100). One patient with anaplastic astrocytoma was not evaluable for response analysis because of early withdrawal of consent. There have been no responses. Two patients (1 with GBM and 1 with anaplastic oligodendroglioma) achieved stable disease. Median PFS was 28 days (95% CI: 27-28), and maximum PFS was 56 days. Median OS was 57 days (95% CI: 29-155). The post-bevacizumab arm was stopped after stage 1. Treatment was well tolerated, with limited Grade 3 liver function test abnormalities (n = 3), abdominal pain (n = 1), and hypertension (n = 1). Grade 1-2 adverse events also included diarrhea, nausea/vomiting, fatigue, and bleeding. Conclusions: Despite limited toxicity, nintedanib is ineffective in the cohort of recurrent HGG patients who failed bevacizumab. Updated results in the bevacizumab-naive arm will be presented. Clinical trial information: NCT01380782.
Sequential therapy with the selective T-type calcium channel blocker mibefradil and temozolomide in patients with recurrent high-grade gliomas: An Adult Brain Tumor Consortium phase I study (ABTC1101).

Matthias Holdhoff, Stuart A. Grossman, Jeffrey G. Supko, Xiaobu Ye, Joy D. Fisher, Serena Desideri, Richard L. Wahl, David Schiff; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; Massachusetts General Hospital, Boston, MA; The Johns Hopkins University, School of Medicine, Baltimore, MD; University of Virginia Medical Center, Charlottesville, VA

Background: Despite recent advances in their treatment, high-grade gliomas (HGG) carry a dismal prognosis. Treatment options at recurrence are particularly limited and a re-challenge with temozolomide (TMZ) frequently appears as the most appropriate systemic treatment option in patients whose progression occurred off TMZ. This study investigates the sequential treatment of mibefradil (MIB), a selective Cav3 calcium channel blocker, and standard dose TMZ. Preclinical data showed that Cav3 inhibitors such as MIB can slow tumor growth without significant effect on normal tissues and can induce cell cycle arrest in cancer cells at the G1/S-phase checkpoint. We hypothesize that withdrawal of MIB could synchronize and release cells into S-phase, thereby potentiating the cytotoxic effect of TMZ. Methods: This trial is an open-label, multicenter phase I study, structured into a dose escalation phase to determine the maximum tolerated dose of MIB (MTD; Primary Objective) and an expansion cohort of 10 patients at the MTD level. Adults with recurrent HGG (WHO grade 3 or 4) who have previously received standard adjuvant therapy with radiation (RT) and TMZ (last dose ≥ 3 months prior to enrollment) and who have not received other cytotoxic therapy (except for carmustine wafers) are eligible. Patients receive oral MIB for 7 days on a 4 x/day (QID) schedule, followed by standard dose TMZ at 150-200 mg/m² for 5 days each 28-day cycle. Dose finding uses a modified 3+3 design, starting at MIB 25 mg po QID (100 mg/day) with dose increases of 25 mg/dose per dose level. The target dose-limiting toxicity (DLT) rate is ≤ 33%. Secondary Objectives: (1) safety and adverse event analysis (incl. cardiac monitoring during cycle 1), (2) pharmacokinetic profile of MIB, (3) response assessment (RANO criteria), and (4) assessment of the potential effect of MIB on tumor DNA synthesis as determined by fluorothymidine positron emission tomography (FLT PET; extension cohort). Enrollment status as of January 2013: cohort 1 completed without DLT; cohort 2 enrolling at MIB 200 mg/day. Clinical trial information: NCT01480050.
Phase I lead-in to a 2x2x2 factorial trial of dose-dense temozolomide, memantine, mefloquine, and metformin as postradiation adjuvant therapy of glioblastoma (GBM).

Marta Penas-Prado, Morris D. Groves, Aaron G. Mammoser, Isaac Melguizo, John Frederick De Groot, Charles A. Conrad, Ivo Tremont-Lukats, Monica Elena Loghin, Vinay K. Puduvalli, Erik P. Sulman, Kenneth R. Hess, Kenneth D. Aldape, Mark R. Gilbert, W. K. Alfred Yung; The University of Texas MD Anderson Cancer Center, Houston, TX; Texas Oncology, Austin, TX; University of Michigan Health System, Ann Arbor, MI; Neuro-Oncology Associates at Baylor Charles A. Sammons Cancer Center, Dallas, TX; James Cancer Center University of Ohio, Columbus, OH; The University of Texas M.D. Anderson Cancer Center, Houston, TX

Background: Treatment for GBM is an area of unmet need. Despite optimal therapy, survival is poor and 2nd line therapies are scarce. There is an urgent need to find better treatments for recurrence, but also more effective 1st line therapies. Dose-dense temozolomide (ddTMZ) using the 7/14-day regimen has shown promising preliminary results in combination with cytostatic agents. Memantine (MEM) is a glutamate receptor (NMDA) blocker with antiproliferation properties and possibly neuroprotective effect. Mefloquine (MFQ) induces autophagy and apoptosis. Metformin (MFM) has mTOR inhibitor properties. Methods: Trial Design: Phase I/II trial to evaluate adjuvant ddTMZ with MEM MFQ and MFM. Primary objective Phase I: MTDs of ddTMZ with MEM/MFQ/MFM, 3×3 design. MTDs will be the recommended Phase II doses for a subsequent randomized factorial Phase II trial (ddTMZ alone and single, double and triple combinations). Accrual of about 55 eligible patients was calculated for Phase I (48-144). Clinical trial registry number is NCT01430351. Treatment planned: Patients accrued sequentially to ddTMZ with 1, 2, or 3 drugs. Arm 1 (ddTMZ alone) will be enrolled in Phase II only. Patients were first accrued to 1-drug Arms 2-4. Once MTDs were determined, accrual started to 2-drug Arms 5-7. Once completed, accrual to Arm 8 will start. Arms 2-4 were started at a predetermined target dose, and deescalated if excessive toxicity. Treatment in Arms 5-8 will be escalated for each drug to reach MTDs of Arms 2-4. Major eligibility criteria: Adults (≥ 18) with supratentorial GBM, KPS ≥60, adequate bone marrow and organ function. Post chemoradiation MRI ≤14 days before enrollment on stable/decreasing steroids and no progression; registration ≤5 weeks of chemoradiation. Patients on MFQ: no EIAED, EKG without prolonged QTc or arrhythmia. Pregnancy not allowed; adequate contraception required. Informed consent in keeping with IRB policies. Current enrollment: To date, 49 patients started treatment and 18 are still active. Enrollment to Arms 2-4 and 6 is completed and MTDs determined. Accrual is ongoing in Arms 5 and 7, and pending in Arm 8. Clinical trial information: NCT01430351.