Title

ACTR-42. PI3K/mTOR PATHWAY ACTIVATION SELECTED PHASE II STUDY OF EVEROLIMUS (RAD001) WITH AND WITHOUT TEMOZOLOMIDE IN THE TREATMENT OF ADULT PATIENTS WITH SUPRATENTORIAL LOW-GRADE GLIOMA [NCT NCT02023905]

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Authors

Taylor, Jennie
Molinaro, Annette
Rodriguez Almaraz, Eduardo
et al.

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Nicholas Butowski[7], James Battiste[8], Jon Glass[9], Timothy Cloughesy[10], David Schiff[11], Martin van den Bent[12], Tobias Walbert[13], Manmeet Ahluwalia[14], Michael Badruddoja[15], Amandeep Kalra[16], Dawit Aregawi[17], Michael Weller[18], Vanitha Ramakrishnan[19], Kathy Zhang[19], Katie Wood[19], Ingo Mellinghoff[1], and Kent Shih[20]; [1]Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]The Ohio State University, Columbus, OH, USA, [3]Dana-Farber Cancer Institute, Boston, MA, USA, [4]Washington University School of Medicine, St. Louis, MO, USA, [5]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA, [6]Sarah Cannon Research Institute at Health One, Denver, CO, USA, [7]University of California San Francisco, San Francisco, CA, USA, [8]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, [9]Department of Neurological Surgery, Thomas Jefferson University, Philadelphia, PA, USA, [10]University of California Los Angeles, Los Angeles, CA, USA, [11]University of Virginia Health Systems Emily Couric Clinical Cancer Center, Charlottesville, VA, USA, [12]Erasmus University Medical Center, Rotterdam, Netherlands, [13]Henry Ford Health System, Detroit, MI, USA, [14]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA, [15]Center for Neurosciences, Tucson, AZ, USA, [16]Sarah Cannon Cancer Institute at Menorah Medical Center, Overland Park, KS, USA, [17]Penn State Milton S. Hershey Medical Center, Hershey, PA, USA, [18]Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland, [19]BeiGene USA, Inc., Emeryville, CA, USA, [20]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA

Pamiparib, an investigational, selective PARP1/2 inhibitor that has demonstrated potent PARP trapping and ability to cross the blood-brain barrier, showed synergistic cytotoxicity with TMZ preclinically. We report updated safety and antitumor effects from a phase 1b/2 study of pamiparib + RT and/or TMZ in patients with newly diagnosed or R/R GBM (SNO 2018, ACTR-30). The dose-escalation/expansion study has 3 arms: *Arm A*, pamiparib (2, 4, or 6 weeks) + RT in newly diagnosed GBM patients with unmethylated *MGMT* promoter (unmethylated-GBM); *Arm B,* pamiparib (6 weeks) + RT and increasing TMZ dosed in weeks 1 and 5 of RT in newly diagnosed, unmethylated-GBM patients; and *Arm C*, pamiparib + increasing TMZ doses in methylated/unmethylated R/R-GBM patients. *Arm A* and *B* patients receive maintenance treatment post-RT rest period at the *Arm* C expansion dose/schedule. As of 10 April 2019, accrual was completed for *Arms A* and *C* dose-escalation (*A*: n=20; *C*: n=17) and continues in the dose expansion (*A*: n=28/40; *C*: n=28/30); accrual was completed in dose escalation for *B* (n=9). Recommended phase 2 doses were established for *Arms A* (pamiparib 60 mg BID×6 weeks + 6–7 weeks RT) and *C* (pamiparib 60 mg BID d1–28 + TMZ 60 mg d1–7/28-d cycle). One dose-limiting toxicity (grade 3 febrile neutropenia) was reported in *Arm B*. Treatment-related adverse events (≥10%) were (overall/grade 3 [no grade 4/5]): *Arm A*, nausea (23%/2%); *B*, decreased WBC count (11%/11%); *C* (none). Of patients with tumor assessment post-RT: *Arm A* (n=17), 1 had cPR, 1 uPR, and 9 SD (disease control rate, 64.7% [95% CI, 38.3–85.8]); *C* (n=26), 1 had cPR (sustained 12 cycles), 1 uPR, and 5 SD (objective response rate, 7.7% [95% CI, 0.9–25.1]). Pamiparib 60 mg BID + RT/TMZ was generally well tolerated in patients with newly diagnosed or R/R GBM. **Clinical trial ID:** NCT03150862

ACTR-40. PHASE 2 SAFETY AND EFFICACY OF AR-67 (7-T-BUTYLDIMETHYLSILTYL-10-HYDROXYCAMPTOTHECIN) IN PATIENTS WITH RECURRENT GLIOBLASTOMA MULTIFORME (GBM) OR GLIOSARCOMA

Priya Kumthekar[1], Jeffrey Raizer[2], Robert Cavaliere[3], Craig Devoe[4], Randy Jensen[5], Volker Stieber[6], Tina Runk[7], Jai Grewal[8], Elise Brownell[9], Alex Zukiwski[7], Stefan Proniuk[10], Susanne Arnold[11], and James Vredenburgh[12]; [1]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA, [2]Northwestern University, Evanston, USA, [3]Baptist MD Anderson Cancer Center, Jacksonville, FL, USA, [4]Northwell Health, Long Island, NY, USA, [5]University of Utah, Salt Lake City, UT, USA, [6]Novant Health, Winston Salem, NC, USA, [7]Vivacitas Oncology, Walnut Creek, CA, USA, [8]Neurologic Surgery PC of RVC, Rockville Centre, NY, USA, [9]Vivicitas Oncology, Walnut Creek, CA, USA, [10]Vivacitas, Walnut Creek, CA, USA, [11]University of Kentucky, Lexington, KY, USA, [12]Trinity Health of New England, Hartford, CT, USA

BACKGROUND: AR-67 (formerly DB-67) is a novel 3rd generation camptothecin with improved safety and lipophilicity than current drugs in this class. Safety and efficacy of AR-67 were evaluated in a Phase 2 study in recurrent GBM/gliosarcoma in adult patients. METHODS: AR-67 (7.5 mg/m2) was administered once daily by IV infusion for 5 consecutive days on a 21-day cycle. Cohort 1 patients (N=31/46 enrolled) had not received (or had not recently failed) bevacizumab. Cohort 2 patients (N=13/46 enrolled) had failed bevacizumab within 90 days before screening. Cohort assignments for 2/46 patients were undetermined. Tumor response was assessed ≥14d after every second cycle and before every third cycle using MRI. Primary endpoints were 6-month PFS (Cohort 1), and 2-month PFS (Cohort 2). RESULTS: 45/46 patients received ≥ one dose of AR-67; one patient (Cohort 1) died prior to dosing. Efficacy: 6/30 (Cohort 1) and 2/13 (Cohort 2) treated patients achieved the primary endpoints of 6- and 2-month PFS, respectively. Across the study, PR was the best overall response in 3/45 treated patients, all in Cohort 1. SD was the best overall disease response in 7/45 treated patients (5 in Cohort 1 and 2 in Cohort2). Safety: AR-67 was well tolerated; 17 patients (38%) exhibited serious adverse events (SAEs) including headache and Grade 4/5 muscular weakness (2.2%). Most TEAEs were mild/moderate in intensity and Grade 1–3 intoxicity. Notably absent was Grade 4 diarrhea, a hallmark of other approved camptothecin chemotherapies. CONCLUSIONS: AR-67 was well tolerated and exhibited a safety profile consistent with or better than currently approved camptothecins. 6/30 treated patients in Cohort 1 and 2/13 patients in Cohort 2 achieved the primary endpoints of 6- and 2-month PFS, respectively. PR was the best overall response in 3/45 treated patients and SD was the best overall response in 7/45 patients.

ACTR-41. AN ARGUMENT THAT MORE ADJUVANT TEMOZOLOMIDE THERAPY IS BETTER FOR GLIOMA PATIENTS

Victor Levin[1], Alyssa Patel[2], Amy Le[3], Piia Thomas[4], and Peak Scott[4]; [1]Kaiser Permanente Redwood City Hospital, Greenbrae, CA, USA, [2]Kaiser Permanente Redwood City Hospital, Redwood City, CA, USA, [3]Regional Neuro-Oncology Pharmacy, Kaiser Permanente, Livermore, CA, USA, [4]Kaiser Permanente, Redwood City, CA, USA

Current guidelines for adjuvant temozolomide (TMZ) treatment of glioma patients advocates 6 to 12 monthly cycles. Is that best? Will patients who receive > 12 cycles live longer? To find out, we conducted a 10-year (2006–2016) chart review of 1300 glioma patients treated at NorCal Kaiser Permanente facilities to determine the impact of dose-week (AUC) quartiles and duration of TMZ therapy quartiles on median overall survival (mOS) in new low- and mid-grade gliomas (Group A) and glioblastoma (Group B) patients. Group A had 357 patients with WHO grade II and III astrocytic and oligodendroglial tumors; Group B had 943 patients with glioblastoma. The median AUC in Group A was 337 mg/m2 (IQR 129, 1095) and the median weeks of TMZ 15 (IQR 1, 42). In Group B, median AUC was 210 mg/m2 (IQR 79,581) and median weeks of TMZ 24 (IQR 9. 45). Based on quartile ranking of AUC, a higher AUC was found to be associated with longer mOS in Group A and B. In Group A, for increasing AUC quartiles, mOS was 134, 146, 369, and 397 weeks (p=0.0014); for Group B, mOs were 30, 48, 74, and 117 weeks (p< 0.0001). Based on increasing quartiles for TMZ treatment duration for quartiles 2–4, Group A patient mOS increased from 122 weeks to 431 weeks (p = ns) and Group B patients, increased mOS from 51 to 143 weeks (p< 0.0001). This retrospective analysis of 10-years of neuro-oncology practice brings into question limiting TMZ dose in WHO grade 2–3 glioma and WHO grade 4 glioblastoma patients as higher dose toleration and longer duration of treatment appears to be associated with longer mOS in both groups. Or does it show that patients who do well elect to take TMZ longer and maybe these findings reflect reverse causality?

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Jennie Taylor[1], Annette Molinaro[2], Eduardo Rodriguez Almaraz[2], Ciara Downey[2], Joanna Phillips[3], Nancy Ann Oberheim-Bush[2], Nicholas Butowski[2], Susan Chang[2], Mitchel Berger[2], Michael Prados[2], Daphne Haas-Kogan[4], and Jennifer Clarke[2]; [1]Division of Neuro-Oncology UCSF, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA, [3]Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA, [4]Dana-Farber Cancer Center, Boston, MA, USA

Functional activation of the PI3K/AKT/mTOR pathway is seen in ~50% of low-grade gliomas and correlates with worse survival. Everolimus is a selective inhibitor of mTOR that targets mTOR-raptor signaling, halting proliferation and indirectly inhibiting angiogenesis. This phase 2 study evaluated the efficacy of everolimus in untreated grade II diffuse glioma. Patients were stratified by 1p19q status and PI3K pathway activation (via phosphorylation of PRAS-40) into three arms: 1) 1p19q intact, PRAS-40 phosphorylated received everolimus monotherapy; 2) 1p19q intact, PRAS-40 not phosphorylated received everolimus with temozolomide; and 3) 1p19q co-deleted received everolimus monotherapy. Primary outcome was landmark PFS-33 months for Arms 1 and 2; and PFS-38 months for Arm 3 (null hypothesis 50% for all arms individually). Key eligibility criteria included central pathology confirmation, no prior treatment, and initiation of everolimus within 120 days of most recent tissue sampling. From 05/2014 to 07/2018, 27 patients were enrolled – 16 into Arm 1; 2 into Arm 2; and 9 into Arm 3. Median age at enrollment was 38 years (range 21 – 65); median KPS 90 (range 70 – 100) and a majority were male (74%). Although follow-up is not complete, as of 05/2019 11 of 16 patients had progressed

prior to 33 months in Arm 1, and 5 of 9 patients had progressed prior to 38 months in Arm 3. Toxicity was as expected with frequent grade 1/2 AEs of diarrhea, rash, and mucositis. Headache was the most common grade 3 AE and was seen in three cases. The study was closed prematurely secondary to slow accrual and loss of drug support. Updated survival data as well as results of secondary and exploratory analyses will be reported. In summary, everolimus was well tolerated in previously untreated low-grade gliomas. However, it failed to meet primary outcome of extending PFS in this population.

ACTR-43. GENOMIC ANALYSIS OF RESPONDERS OF PHASE II TRIAL OF TEMOZOLOMIDE AND TRC-102 (BASE EXCISION REPAIR INHIBITOR) IN BEVACIZUMAB-NAÏVE GLIOBLASTOMA AT FIRST RECURRENCE

Manmeet Ahluwalia[1], Harshil Dhruv[2], Jaleh Fallah[3], Michael Berens[4], Jan Drappatz[5], Xiaobu Ye[6], Glenn Lesser[7], Timothy Cloughesy[8], Tobias Walbert[9], Matthias Holdhoff[10], David Peereboom[11], Louis Nabors[12], Patrick Wen[13], Stuart Grossman[10], and Lisa Rogers[14]; [1]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH, USA, [2]TGen, Phoenix, AZ, USA, [3]Taussig Cancer Institute, Cleveland, OH, USA, [4]TGen, Phoenix, AZ, USA, [5]University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA, [6]Johns Hopkins University, Baltimore, MD, USA, [7]Wake Forest Baptist Health, Winston-Salem, NC, USA, [8]UCLA, Los Angeles, CA, USA, [9]Henry Ford Health System, Detroit, MI, USA, [10]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [11]Cleveland Clinic, Cleveland, OH, USA, [12]University of Alabama at Birmingham, Birmingham, AL, USA, [13]Dana-Farber Cancer Institute, Boston, MA, USA, [14]University Hospitals, Cleveland, OH, USA

BACKGROUND: Temozolomide forms O^6-methylguanine (O^6mG), 7-methylguanine (N^7mG), and 3- methyladenine (N^3mA) DNA adducts. The O^6mG DNA adduct is repaired by MGMT. N^7mG and N^3mA DNA adducts are removed by the base excision repair (BER) pathway, initiated by N- methylpurine DNA glycosolase (MPG). TRC-102 is a BER inhibitor that binds to the apurinic site created through the action of MPG. METHODS: A phase II study of adult glioblastoma in first recurrence was performed in the Adult Brain Tumor Consortium with temozolomide, 150 mg/ m^2 and TRC-102, 150 mg (1–5/ 28 days). Primary objective included radiographic response rate. Secondary objectives included safety and PFS-6. Exploratory objectives included tumor expression of N-methylpurine DNA glycosylase (MPG). The study tested hypothesis that combination therapy will achieve 30% RR. To understand the context of vulnerability to TRC102 we performed RNA sequencing on treatment naïve tissue from 7 patients. RESULTS: Nineteen patients were enrolled in first stage. Median age was 60 years (range: 48–76), 53% females, median KPS was 80 (range: 70–90). Median cycles of treatment was 2 (range: 1–12). No responses were observed. Median OS was 11.0 months (95% CI: 8–18 months), median PFS was 2.0 months (95% CI: 1.8–3.6 months). PFS-6 rate was 10.5 % (2/19). The combination was safe. MPG staining was negative in six, 1+ in five and 2+ in three patients. PFS of 11 + months in two patients (exceptional responders) was associated with MPG expression. Preliminary analysis on RNA sequencing revealed significant enrichment for DNA Damage Response pathways (MsigDB), chromosomal instability gene signature (CIN70 and CIN25), and proliferative gene signature (PCNA25) in these 2 patients. CONCLUSIONS: TRC 102 with temozolomide has acceptable safety but did not meet the primary endpoint of response. Gene signature of MsigDB, CIN70, CIN25 and PCNA25 was seen in exceptional responders and biomarker driven study is planned.

ACTR-44. FEASIBILITY, PHARMACODYNAMICS, AND BIOLOGIC ACTIVITY OF THE GLIOMA ATKINS-BASED DIET (GLAD) FOR PREVENTING TUMOR RECURRENCE IN GLIOMA PATIENTS

Karisa Schreck[1], Fang-Chi Hsu[2], Adam Berrington[1], Bobbie J Henry-Barron[1], Lindsay Blair[1], Adam Hartman[3], Eric Kossoff[1], Linda Easter[2], Mary Self[2], Chris Whitlow[2], Peter Barker[1], Mackenzie Cervenka[1], Jaishri O Blakeley[1], and Roy Strowd[2]; [1]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [2]Wake Forest School of Medicine, Winston-Salem, NC, USA, [3]National Institutes of Health, Bethesda, MD, USA

INTRODUCTION: Exploiting metabolic vulnerabilities via ketosis is a promising approach for gliomas. The modified Atkins diet is a ketogenic diet therapy efficacious in adults with refractory epilepsy. We evaluated the feasibility, pharmacokinetics/pharmacodynamics(PK/PD), and cerebral activity of this dietary intervention intended to induce ketosis. METHODS: 25 patients with biopsy-confirmed WHO Grade 2–4 astrocytoma with stable disease after adjuvant chemotherapy were enrolled in an 8-week GLioma Atkins-based Diet (GLAD). GLAD consisted of 2 'intermittent fasting' days(IF; calories ≤ 20% of recommended daily allowance) interleaved between 5 modified-Atkins diet days(MAD; carbohydrates ≤ 20 gm/day) each week. The primary outcome was dietary compliance. Secondary outcomes were PK assessed by urine ketones post-FAST and post-MAD, PD assessed by serum insulin and IGF-1, and cerebral activity measured by MR spectroscopy at baseline and week 8. RESULTS: Grade 2(n=2;8%), Grade 3(n=11;44%) and GBMs(n=12;48%) were enrolled. While only 48% of participants satisfied pre-defined compliance criteria, overall compliance with MAD(80%) was higher than IF(72%). Weight loss was observed (-4.8 + 2.2kg,p< 0.0001) consisting primarily of decreased fat mass (-2.5 + 3.1%,p< 0.0001), with increased lean body mass (2.4 + 3.2%,p< 0.0001), stable nutritional status (phase angle, -0.26 + 0.94%,p=0.22), and normalization of BMI. Urine acetoacetate significantly increased with 55% achieving moderate ketosis at week 8 (p=0.0005). Serum insulin and IGF-1 significantly decreased indicating systemic dietary response and were associated with higher ketones post-IF, but not post-MAD. MRS demonstrated cerebral activity with increased ketones in lesional (0.06±0.03- >0.27±0.06i.u,p=0.005) and contralateral brain at week 8 (0.041±0.01- >0.16±0.04i.u.,p=0.004). Higher cerebral acetone correlated with higher urine ketones (r >0.75,p< 0.02) and lower fasting glucose (r >-0.74,p< 0.05). CONCLUSIONS: The GLAD diet was challenging to maintain but demonstrated quantifiable biologic effects systemically and intratumorally. MAD was more feasible than IF, but changes in PD markers correlated most strongly with IF. The role of ketogenic diet therapy for preventing glioma growth remains uncertain.

ACTR-45. FATTY ACID SYNTHASE INHIBITOR TVB-2640 INCREASES PROGRESSION FREE SURVIVAL IN RECURRENT GBM

Brandon Konkel[1], Joel Michalek[1], Enrique Diaz Duque[1], Qiangia Liu[1], Laura Caflisch[1], Vinu Madhu[1], and Andrew Brenner[2]; [1]Mays Cancer Center, UT Health San Antonio, San Antonio, TX, USA, [2]University of Texas Health Science Center San Antonio, San Antonio, TX, USA

BACKGROUND: Standard of care for glioblastoma (GBM) is surgical resection followed by temozolamide, with bevacizumab (bev) given at relapse. Responses to bev remain brief; resistance may involve overexpression of Fatty Acid Synthase (FASN). METHODS: This is a prospective phase 2 study of bev with TVB-2640 in patients with rGBM at first relapse. Primary end point is progression free survival (PFS). Inclusion criteria are: age ≥ 18, ECOG 0 to 2, GBM progression following standard combined modality treatment. An exploratory phase randomization into 2 separate arms of single agent bev or in combination with TVB-2640 with MR-Spectroscopy (MRS) and serum sampling for exosome analysis obtained on all patients at day 1 and 28 of first cycle. Starting on cycle 2 day 1, all patients converged to a single arm and continue to receive bev in combination with TVB-2640. A total sample size of 24 patients will provide 90% power to detect a 4 month difference in PFS (3–4 months for Bev alone (historic controls) (i.e., a hazard ratio of 0.43) using a one-sided log-rank test with alpha=0.1. RESULTS: Enrollment is complete with 28 patients to date. 3 failed screening. 21 came off study and 4 are active. No grade 4 or higher treatment-related AEs have occurred, with Grade 3 events included 3 cases of palmar-plantar erythrodysesthesia; 1 each of hypertension, stomatitis, optic neuritis, DVT, and wound infection. 95.2% of patients have achieved at least stable disease by RANO Criteria, with a 66.7% overall response rate (ORR). Median time to progression was 5.9, which is statistically superior to historical controls. Overall survival as well as biomarker analysis (exosome, MRS), is pending. CONCLUSIONS: The combination of TVB2640 with bev appears well tolerated and with PFS6 significantly improved over historical controls. Final data analysis as well as exploratory biomarker analysis will be presented.

ACTR-46. TUMOR TREATING FIELDS COMBINED WITH RADIOTHERAPY AND TEMOZOLOMIDE FOR THE TREATMENT OF NEWLY DIAGNOSED GLIOBLASTOMA: FINAL RESULTS FROM A PILOT STUDY

Rachel Grossman, Dror Limon, Felix Bokstein, Deborah Blumenthal, Camit Ben Harush, and Zvi Ram; Tel Aviv Medical Center, Tel Aviv, Israel

BACKGROUND: Tumor Treating Fields (TTFields) are a non-invasive, loco-regional, anti-mitotic treatment comprising low intensity alternating electric fields approved for GBM. Preclinical data show that TTFields have a radio-sensitizing effect. This pilot study evaluated the safety and feasibility of TTFields/RT/TMZ in ndGBM patients. METHODS: Patients with histologically confirmed ndGBM were treated with TTFields/RT/TMZ followed by maintenance TTFields and TMZ for up to 24 months. TTFields (200kHz) were delivered for ≥18 hours/day with removal of the transducer arrays during RT delivery. TMZ was administered at 75 mg/m^2/ daily for 6 weeks and RT at a total dose of 60 Gy. The primary endpoint was safety of the combined TTFields/RT/TMZ; secondary endpoints included progression-free survival (PFS), overall survival (OS) and toxicity. Adverse events (AEs) were graded per CTCAE V4.0. RESULTS: Ten patients were enrolled at a single center in Israel between April and December 2017. All patients had recovered from maximal debulking surgery or biopsy. Five patients (50%) had undergone gross total resection; rest had biopsy only. Median age was 59 and median KPS was 80. Median dose of RT was 60 Gy. Six patients (60%) reported at least one AE. The most common AE