Cleveland Clinic MyConsult

Thank you for your request for a second opinion consultation. An addendum report is ready and can be viewed by scrolling down to the report below. A profile of the physician who rendered your opinion is available at our website at: www.eclevelandclinic.org

The on-line copy of this addendum report is for preview purposes only. An original printed copy of the opinion will be mailed to you within 7-10 business days. Feel free to contact a Cleveland Clinic nurse at: 1-800-223-2273, ext. 43223, 8 a.m. - 5 p.m., Eastern Standard Time (EST), Monday through Friday, should you have additional questions or concerns.

Cleveland Clinic
MyConsult

ADDENDUM REPORT

CONFIDENTIAL

Cleveland Clinic MyConsult

9500 Euclid Avenue, Desk H2-260

Cleveland, Ohio 44195 USA

Tel: 216.444.3223

Fax: 216.445.6911

e-mail: eclevelandclinic@ccf.org

Date:	July 5, 2012
Patient Name:	Mohammed Banat
Physician's name:	Glen Stevens D.O., Ph.D., FAAN
Department:	Brain Tumor and Neuro-Oncology
Institute:	Neurological Institute

CCF#: (MRN)	7-045-6133
Date of Birth:	01/27/1978
Patient Address:	Wasfi Al Tal Street, Ever Home Building 3rd Floor, eSense Software Amman 11194 Jordan

Dear Mr. Banat:

You submitted additional questions after receiving your online medical second opinion consultation report. I will address your post consultation questions below:

1. I provided a CD that shows that the last MRI is actually stable. That fact wasn't part of the report, and hence I assume it's an important artifact that possibly was overlooked. I was wondering in fact what does it mean to have a progressing disease for 6 months then a stable one?

When following low grade tumors, we do not always see linear growth. The nature of these tumors is that they are infiltrating and often in a configuration that makes precise quantification difficult. We know that there has been some slow progression of the flair signal (representing tumor) over time. I do not think that we can read much into the current MRI findings although we are always pleased to see less change.

2. Dr. Rolando did confirm the co-deletions of 1p19q over e-mail few weeks after the operation. I cannot find that e-mail reference to share with you. This is critical to the second opinion obviously. So given that fact, what would you change in the report?

I am glad to hear that the tumor had a 1p19q deletion and as I stated to you previously, this is related to improved survival which is obviously a good thing. In these cases, when the decision is made to treat, we are more likely to give Temozolomide as the initial therapy. Secondary to the slow growth of your tumor, continued observation would still be a

reasonable option.

3. Is Temdar a one time chance? i.e. If I take chances today, does that mean I cannot use it again few years later? What about radiation? The same?

In terms of Temodar and radiation therapy use over time, I would say the following:

Temodar is a methylating / alkylating type drug and it can deplete the bone marrow. Long term or repetitive use increases the risk of secondary cancers such as leukemia. In 20 years, however, I have only seen 1 case so the risk is clearly low.

How much and how many chemotherapy regimens you can tolerate will depend on your bone marrow function and you will only know that through the trial and error of treatment. It is not uncommon for patients with your type of tumor to be treated with Temodar several different times over years. In terms of radiation therapy, most patients are treated once but we have been treated a second time in rare cases.

4. When survival rate is counted, when do we start? Supposedly I had the tumor for many years (at age 12). I assume it started as grade I. Insights? Is there a way to guess when grade II started?

Survival statistics for patients are usually based on the actual initial diagnosis of the tumor (so in your case, not at age 12 but when the abnormality was found. For oligodendrogliomas and oligoastrocytomas, the World Health Organization (WHO) recognizes only grade II and grade III tumors. There is no grade I type tumor. Only pure astrocytomas have a grade I designation. Grade I tumor are genetically different tumors and usually do not progress to higher grade tumors so I would say you never had a grade I tumor.

5. In survival rate. When you say "that five years after treatment about 35% of the patients had expired". It is not clear to me what this means for rest who lived after. Does it assume that study stopped there, and people afterwards were not monitored and therefore could have lived a year or ten?

The best data that is currently available on survival was presented at the large Oncology Meeting (ASCO) last month in Chicago. They looked at survival of patients treated on a study that started back in 1994. Those patients had anaplastic (WHO Grade III Oligodendroglioma) and were treated with radiation therapy alone or chemotherapy and radiation therapy. For the high grade patients with 1p19q deletions, the median life expectancy was just under 15 years. That means that at 15 years half of the patients expired. Since your tumor is low grade we would expect that you would do as well or better than a patient with a high grade tumor. In all studies of course, there are those patients that do worse than the average patient so how you as an individual will do is uncertain. Our pathologist also felt your tumor was an oligoastrocytoma and not a pure oligodendroglioma so the survival statistics may not be as good and we do not have the exact long term data.

6. For the next steps options. The bottom line I got was that I have options but no single recommendation as to where to go (assuming my symptoms remain stable, which is the case at the moment

I think that the next step will depend on what happens with your symptoms and your follow up MRIs. If your symptoms remain stable and the MRIs show no evidence for upgrade to a more aggressive tumor (usually see enhancement on the MRI), and the flair changes progress slowly, then continued observation is reasonable. If, however, you decide that you can not tolerate continued observation and you have to do something, then Temozolomide would be the next step. You can clearly see that there are black and white issues but mostly grey issues and that is the difficulty of living with this type of tumor.

We again appreciate you allowing us to provide to you a second opinion consultation and trust that you find this information helpful

Physician Signature:

Sincerely,

Glen HJ Stevens, M.D.

Electronically Signed

(See next page for your original consultation report of May 31, 2012)

Cleveland Clinic
MyConsult

CONFIDENTIAL

Cleveland Clinic MyConsult

9500 Euclid Avenue, Desk H2-260

Cleveland, Ohio 44195 USA

Tel: 216.444.3223

Fax: 216.445.6911

e-mail: eclevelandclinic@ccf.org

Date:	May 31, 2012
Patient Name:	Mohammed Banat
Physician's name:	Glen Stevens D.O., Ph.D.
Department:	Brain Tumor and Neuro-Oncology
Institute:	Neurological Institute

CCF#: (MRN)	7-045-6133
Date of Birth:	01/27/1978
Patient Address:	Wasfi Al Tal Street, Ever Home Building 3rd Floor, eSense Software Amman 11194 Jordan

Dear Mr. Banat:

It is our sincere pleasure to provide you a Cleveland Clinic MyConsult online second opinion consultation. We appreciate the medical records which were forwarded to the Cleveland Clinic for our review.

Diagnosis / Reason for Consultation:

In your preliminary material provided, you asked two specific questions. These include:

1. *Given that the tumor is non-operable (anymore beyond the resection), I would like to know my treatment options and sequence. i.e. role of Temodal*

2. *Life expectancy as per current stats, and tumor recurrence (re-growth) rate as per current stats.*

Diagnostic Summary / Treatment Summary:

Upon review of your medical records, you are a 34-year-old right handed male with a history of a right temporal low grade astrocytoma. The outside medical records from Dr. Del Maestro at the Montreal Neurological Institute (MNI) dated November 10, 2008 indicate that you might have had seizures dating back to age 12 years. At that time, it is reported that in bed at night you would have episodes of suddenly tensing up and difficulty moving which would last approximately 40 seconds. This would happen intermittently since age 12 years and the events were more likely if you took an afternoon nap. In 2005 you presented with numbness affecting your left leg. MRI of the spine was unremarkable, but MRI of the brain showed a non-enhancing mass involving the posterior aspect of the left temporal lobe. The decision was made to follow and a repeat MRI June 2008 showed progression of the left temporal lobe lesion. At this time you also started to develop a new symptom. It is reported that you had an event of difficulty being able to read. You knew what the letters were but could not identify what the word of the letters meant. It is reported that you were somewhat confused during the events, without tongue biting or incontinence, and that the event lasted for a number of minutes and passed. Over the next five months you had four similar episodes. Your wife also witnessed at least one of these events and it appears you were disconnected from the environment. These most likely represented simple partial seizures and complex partial seizures (CPS). You were treated with antiepileptic drugs (AED's). In December 2008 you were placed on Trileptal then Epanutin pre-operately and back to Trileptal post-operately. In March 2010 you had what sounds like complex partial seizures (CPS) and Keppra was started but you had increased sleepiness and hallucinations so Keppra was converted to Lamictal. You are currently managed with Trileptal and Lamictal.

Dr. Del Maestro felt your left temporal lesion had increased in size from 2005 to 2008 and ordered a PET and functional MRI which were completed. The tests showed your speech to be predominately on the LEFT with very little speech on the right. Your motor and sensory areas appeared to be a substantial distance away from the lesion. There did not appear to be definite language function within the lesion itself. Various options were discussed. You elected to undergo a resection at the MNI Feb 19, 2009 with what sounds like an awake craniotomy with speech and neuron-cognitive function assessment. During the resection you did develop some difficulty with word recognition that halted further resection. These symptoms were worse post-operatively but are reported to have improved quickly. Post op MRI showed a "substantial" resection of the tumor per Dr. Del Maestro although some T2 abnormality could be seen on the scan. The pathology was reported as a World Health Organization (WHO) II Astrocytoma and MGMT promoter was methylated. Post-op, continued observation was the recommendation. It sounds like you still have occasional expressive aphasia (speech problems) and possibly even mild seizures but have been clinically stable over the past six months. Your most recent MRI scan from May14, 2012

shows some flair progression without enhancement and you are wondering what your next step should be.

The outside pathology has also been reviewed by the Cleveland Clinic and I have included the report findings below:

Specimen #: S12-43478*

FINAL DIAGNOSIS

Left temporal lobe, resection (NP-09-000195; 02/19/2009) **- Low-grade oligoastrocytoma (low-grade mixed glioma), WHO grade II.**
- See comment.

RAP/mal/05/22/2012

COMMENT
The tumor is marked by geographically distinct areas resembling low-grade astrocytoma and low-grade oligodendroglioma. Vascular proliferative changes and necrosis are not identified. A **Ki-67 labeling index of approximately 4%** is focally noted. GFAP positivity is noted within the neoplasm. The tumor does not stain for antibody to p53.

Brain and Spinal Cord Tumor Case Summary:

Specimen type: Excision
Specimen handling: Permanent and immunostained sections for review.
Site: Temporal lobe
Laterality: Left
Diagnosis: Low-grade oligoastrocytoma (low-grade mixed glioma)
WHO Grade: II
Ancillary test(s) ordered: Ki-67, GFAP, and p53 immunostains available for review.

Past medical history: As above

Past surgical history: As above; hernia repair age six years

Social History: Works in Information technology (CEO), divorced and has one child approximately six years old. Non-smoker or drinker

Family medical history: No cancer syndrome in the family; parents are listed as alive and well, father approximately 64 years old and mother approximately 54 years old.

Allergies: no known drug allergies

Current Medications:

Trileptal 300 mg. 1 orally in the morning and at 2 p.m.

Lamictal 100 mg. 1 orally twice a day

Second Opinion Recommendations:

1*. Given that the tumor is non-operable (anymore beyond the resection), I would like to know my treatment options and sequence. i.e. role of Temodal*

We would like to thank you again for placing confidence in the Cleveland Clinic and look to provide you with helpful and tangible information regarding the questions that you have asked.

We did have your pathology slides reviewed by our Cleveland Clinic Neuropatholgist who felt that the slides submitted were most consistent with a **mixed low grade glioma** called an **oligoastrocytoma** rather than an astrocytoma. The WHO grading is still a II. In order to have a mixed glioma, the pathologist must feel that at least 20% of each cell type is present. As you know asytocytomas and oligoastrocytomas are both glial based primary brain tumors. The Ki-67 of 4% and the lack of vascular proliferation or necrosis seen in the surgical tissue are consistent with low grade pathology. It has previously been documented that your tumor has MGMT promoter gene methylation. What I do not see is that your tissue underwent **1p19q analysis** or **IDH1 analysis**. Dr. Del Maestro does comment about 1p19q analysis possibly being done prior to surgery but I do not see any documentation post-op in his notes or the pathology report of it being completed. **Why would it be important to know the 1p19q or IDH1 status of your tumor?**

Comment: Allelic loss on chromosome 1p has been shown to correlate with chemotherapy responsiveness and long progression-free survival in some gliomas. This correlation is stronger when there is concomitant allelic loss on 19q. An association of chemotherapy responsiveness and/or long progression-free survival with allelic loss on 19q in the absence of loss on 1p has not been established. In patients with 1p/19q loss, aneusomy for chromosome 1 and 19 may be associated with earlier recurrence. References: Cairncross et al J Natl Cancer Inst 90:1473-1479, 1998; Smith et al, J Clin Oncol 18:636-645, 2000; Ino et al, J Neurosurg 92:983-990, 2000; Schmidt et al, J Neuropathol Exp Neurol 61:321-328, 2002; Snuderl et al, CliniCancer Res 15:6430-7, 2009.

Comment: Mutations in isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) have been implicated in tumorigenesis of gliomas. Patients with high-grade astrocytomas with IDH1 or IDH2 mutations were reported to have a better survival. IDH1 mutations were present in the majority of progressive astrocytomas. No mutations in IDH2 were found. For low grade gliomas, presence of IDH1 mutations were early events and significantly improved overall survival (median survival 48 vs. 98 months). These results indicate that IDH1 mutations identify a subgroup of gliomas with an improved survival. Dubbink et al, Neurology Nov 24;73 1792-5, 2009

A more recent review from Germany by Ahmadi et al J Neurooncology 2012 April (Epub ahead of print) looked at 100 low grade astrocytoma patients and found no difference in overall survival or progression free survival relative to IDH1 mutation state in patients who did not receive adjuvant treatment.

While the IDH1 mutational data is still a relatively new finding and will require further investigation, the 1p19q implications have been well characterized and co-deletions of 1p19q, while not definitive for treatment modality, are prognostic which in turn might then affect the order of treatment. In general terms, if we have a low grade glioma patient that has a 1p19q deletion and we feel they need treatment, and surgery is not an option, we are more likely to treat with chemotherapy first and that treatment is usually Temozolomide. Having a low grade mixed glioma vs. a low grade astrocytoma increases the likelihood of 1p19q deletions.

The **European Association of Neuro-Oncology** (EANO) published guidelines for the management of low grade gliomas in 2011:

Prognostic factors: The following is a breakdown of current prognostic factors determined by various studies by the EANO Task force for low grade gliomas. Studies were classified based on the class of data they represented with Class I evidence providing the strongest support and Class IV the weakest support.

Class I: evidence derived from prospective, randomized, well controlled clinical trials

Class II: evidence was derived from prospective studies including observational studies, cohort studies and case control studies

Class III: evidence was derived from retrospective studies

Class IV: evidence was derived from uncontrolled case series

Recommendations were based on the class of evidence available:

Level A: at least 1 Cass I study or 2 consistent Class II studies

Level B: at least one Class II study or overwhelming Class III evidence and

Level C: at least 2 consistent Class III studies

PROGNOSTIC FACTORS:

Age > 40 years and presence of pre-operative neurological deficits are adverse prognostic factors (Class I) - **you do not have either of these**

Larger tumors and tumors crossing the midline correlate with shorter overall survival (Class III)- **your tumor does not cross the midline**

Oligodendrogliomas have a better prognosis than astrocytomas, whereas oligoastrocytomas have an intermediate outcome (Class I) - **your tumor prognosis is therefore better having a mixed tumor vs. a pure astrocytoma**

1p loss is a favorable prognostic marker (Class II) – **we do not know your molecular status**

MGMT promoter methylation could predict a shorter time to progression in untreated patients, while predicting longer progression free survival and overall survival in patient receiving chemotherapy with Temozolomide (Class III) - **this could be an argument used to recommend treatment with chemotherapy as you have been recommended previously**

IDH1 mutations are prognostic for overall survival in diffuse gliomas of WHO grade II (Class III)- **would be reasonable to have this run on your pathology if a block of tissue is still available**

Treatment: It is important to understand that you have options and that there is no "best treatment". You have to weigh the likelihood of any treatment benefit with the risk or side effects associated with that intervention.

Radiotherapy:

Four phase III randomized trials have been performed for low grade gliomas. Higher dose radiation of 64 Gy has not been shown to be beneficial to lower dose XRT. Radiation therapy has been shown to **improve progression free survival but not overall survival** for those who had delayed radiation therapy. For this reason radiation therapy is usually delayed unless the MRI scan shows clear evidence of progression to a higher grade tumor, more rapid progression of low grade tumor, or progressive neurological symptoms and **you do not fulfill any of these categories at this time**.

Chemotherapy:

Chemotherapy as an initial therapy has been looked at in several trials and can have some

benefit (Class IV). The response rate is higher and the duration of response is longer in patients with 1p19q loss than those who are intact (Class III). Overall quality of life appears to be maintained (Class II).

In general I think we can make several statements about low grade (WHO II) gliomas. In general, it is not a question of if, but when, a low grade tumor will undergo additional mutation to a higher grade tumor. At this point there has been some slow progression of the flair signal most likely representing growth of your low grade tumor and at some point it will mutate and start growing much more aggressively. At that point there is little question that treatment needs to be initiated and if you have not had previous treatment then you would most likely be treated with a combination of radiation therapy and chemotherapy. If you have had previous radiation therapy at that point then you will most likely be treated with various chemotherapy agents, or possibly be put on a clinical trial.

If testing showed that your tumor had 1p19q co-deletions then treatment with Temozolomide at this point would be an option.

2). Life expectancy as per current stats, and tumor recurrence (re-growth) rate as per current stats.

Life expectancy is a very tough one to answer and of course as an individual it is difficult to know how you fit in the equation. We also do not know your 1p or IDH1 status which will influence your prognosis. As mentioned earlier, there have been four Phase III trials looking at radiation and chemotherapy for low grade gliomas in various combinations. The five year overall survival for those four trials was ~ 64% which means that five years after treatment about 35% of the patients had expired.

In summary, I agree with the treatment you have had to date, surgery followed by observation. You should have additional molecular testing completed for 1p and IDH1 status if tissue is available. If your symptoms remain stable and flair progression remains mild then continued observation is a reasonable option. If your symptoms progress or you can no longer tolerate the “wait and watch” approach, treatment with Temozolomide on the 5/28 day schedule would be an option. In our practice if we decide to treat with radiation therapy, we usually combine it with concomitant low dose Temozolomide during the six weeks of treatment on the Stupp Regimen. The studies would suggest that delayed radiation therapy

for low grade gliomas is an option.

We appreciate the opportunity to provide you with a second opinion consultation through the Cleveland Clinic MyConsult program. We hope that you find the report informative and helpful. We encourage you to share it with your local treating physician(s) prior to making any changes to your treatment or medication regime.

Physician Signature:

Sincerely,

Glen Stevens D.O., PhD, FAAN

Electronically Signed

Disclaimer:

By using this Second Opinion service, you agree to abide by the Terms and Conditions posted at our Second Opinion Web Site, including particularly the Terms and Conditions described below:

Diagnostic Service:

The service provided through our Web site is different from the diagnostic services typically provided by a physician. The Cleveland Clinic Foundation (CCF) physicians providing this service will not have the benefit of information that would be obtained by examining you in person and observing your physical condition. Therefore, the physician may not be aware of facts or information that would affect his or her opinion of your diagnosis. TO REDUCE THE RISK TO YOU OF THIS LIMITATION, CCF STRONGLY ENCOURAGES YOU TO SHARE THE SECOND OPINION WITH YOUR PHYSICIAN. BY DECIDING TO ENGAGE THIS SERVICE, YOU ACKNOWLEDGE AND AGREE THAT YOU ARE AWARE OF THIS LIMITATION AND AGREE TO ASSUME THE RISK OF THIS LIMITATION.

By REQUESTING A SECOND OPINION PURSUANT TO THIS WEB SITE, YOU ACKNOWLEDGE AND AGREE THAT:

THE DIAGNOSIS THAT YOU WILL RECEIVE IS LIMITED AND PROVISIONAL; THE SECOND OPINION IS NOT INTENDED TO REPLACE A FULL MEDICAL EVALUATION OR A FACE-TO-FACE VISIT WITH A PHYSICIAN; * THE PHYSICIAN DOES NOT HAVE IMPORTANT INFORMATION THAT IS USUALLY OBTAINED THROUGH A PHYSICAL EXAMINATION; * THE ABSENCE OF A PHYSICAL EXAMINATION MAY AFFECT THE PHYSICIAN'S ABILITY TO DIAGNOSIS YOUR CONDITION, DISEASE OR INJURY; BY ENGAGING OUR SERVICES, YOU ACKNOWLEDGE AND AGREE TO ASSUME THE RISK OF THESE LIMITATIONS. YOU FURTHER UNDERSTAND THAT NO WARRANTY OR GUARANTEE HAS BEEN MADE TO ME CONCERNING ANY PARTICULAR RESULT OR CURE OF MY CONDITION.