**Summary of treatments for Glioma patients**

***Group 1: No chemotherapy beyond CCRT (NCBC), N=7.***

Patient #62 and 63 did not complete daily TMZ during the 6-week CCRT because of early-onset myelosuppression. Patients #64 and her family declined further maintenance chemotherapy after a quick progressive disease following CCRT. Patient #66 was found dead at home 11 days after CCRT.

Three patients (#65, 67 and 68) did not take any chemotherapy and they were included in the NCBC group. Patient #65 gave up treatment after learning the poor prognosis for diffuse glioma at brainstem, which was later confirmed of H3F3A K27M mutant. Patient #67 could not take prescribed TMZ due to decreased renal function and other co-morbid medical conditions. Patient #68 did not recover from surgery due to cerebral herniation.

***Group 2 and 3: TIB regimen (N=24).***

Twenty-four glioma patients received TIB treatment. They were divided into two subgroups of receiving 1-5 (group 2, N=12) and 6-25 (group 3, N=12) TIB cycles.

***Group 4: Standard of care (N=37)***

Most recurrent glioma patients (29/37) received infusion of BEV with or without IRI after tumor progression, and 6 of these patients extended their TMZ beyond 12 cycles. Patient #29 received 49 BEV infusions without any maintenance TMZ cycles. Eight patients were treated with TMZ monotherapy alone. Some patients received TMZ as adjuvant chemotherapy and BEV/IRI treatments at tumor recurrence, but they were not used concurrently.

**Chemotherapy for brain metastatic patients**

Among 8 BM decedents, primary cancers were melanoma (patient #69 and #75), head and neck cancers (patient #70 and #72), breast cancer (#71), chronic myeloid leukemia (#76, CML) and non-small cell lung cancer (#73 and 74). Patient #69 was treated with one 42-day TMZ cycle followed by intrathecal treatment with cytarabine liposome. Patient #70 was treated with SRS, then on 7 doses of cetuximab. Patient #71 was treated with 19X capecitabine and 18X denosumab before BM was diagnosed. Patient was further treated with stereotactic radiosurgery (SRS) followed by intrathecal chemotherapy of cytarabine liposome (6X). Patient #72 was treated with paclitaxel (4X), docetaxel/ifec (2X) and an experimental drug of DM-CHOC-PEN (3X). Patient #73 did not receive chemotherapy. Patient #74 was treated with Paclitaxel and Carboplatin (1X) and received two doses of topotecan. Detailed chemotherapy records for patients #75 was not available. Patient #76 was diagnosed with CML containing BCR-ABL translocation, she was treated with dasatinib and hydroxyurea following induction therapy with Fludara-Idarubicin-Ara-C-Ponatinib and one maintenance course with ecitabine. Her treatment is complicated with severe myelosuppression and bone marrow blast crisis required multi blood and platelet transfusion.

**Myelosuppression adverse event in BM decedents**

Among 8 BM patients, four (#71, 73, 74 and 76) were confirmed to have severe hypocellularity and/or fibrosis at autopsy with one case have a matching CM history. In addition to possible toxicities from chemotherapy and radiation therapy, tumor infiltration/invasion such as metastatic breast ductal carcinoma, parotid gland carcinosarcoma and large clusters of blasts cells were found in the bone marrows of subjects #71, 72 and 76 respectively. Patient #76 was diagnosed with blast transformation of CML with brain involvement, experienced both grade IV thrombocytopenia and leukopenia, which required platelet and blood transfusions.

**Causes of death for BM decedents**

In addition to brain metastasis and leptomeningeal disease, breast ductal carcinoma tumor cells invaded many organs including bone marrow in subject #71. His bone marrow suppression lead to bacterial growth in the lungs and kidneys. Multi-organ failure from broad disease invasion is the main COD. Five out of 8 autopsy reports of BM cases mentioned multi-organ failure due to metastatic tumor, even tumor emboli were found in cardiac ventricles of patient #72. Severe myelosuppression was associated with bone marrow blast crisis induced by dasatinib while treating CML in patient #76. Patient #73 died from ARDS due to metastatic pulmonary adenocarcinoma. Respiratory failure contributed to the death of patients #69, 70, 72 and 73, there was evidence of aspiration pneumonia in patients #69 and 70. One decedent still had a Foley catheter at death. A kidney examination in two decedents reported autolysis and/or acute tubular necrosis of their kidneys. Both melanoma cases (#69 and 75) had intracranial hemorrhage.

[**Clinically undiagnosed tumors found at autopsy**](http://onlinelibrary.wiley.com/doi/10.1111/j.1699-0463.1990.tb01062.x/pdf)

Follicular adenoma, or follicular variant of papillary carcinoma was found in decedents #36 and #60. Breast fibroadenoma was found in decedent #49. Prostate cancer was found in decedent #53. Bile duct adenoma was found in decedent #58. Lipoma on arms and myxoid liposarcoma (on abdominal wall) were found in decedents #20 and #63 respectively.

Supplement Table 1. Patient characteristics and treatment history for individual decedent.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Case No. | OS\*\* (Months) | Age at Dx | Sex | Race | Histology | | Chemo and/or monoclonal antibody | | | | CMS |
| Initial | Autopsy | TMZ | BEV | IRI | Other |
| Group 3: 6-25 TIB cycles | 1 | 83.5 | 62 | M | C | GBM | GBM | 35 | 12 | 12 | Cediranib | 0 |
| 2 | 52.6 | 71 | M | AS | GBM | GBM | 40 | 37 | 21 |  | 0 |
| 3 | 39.9 | 56 | F | HS | II | II | 12 | 27 | 27 |  | 0 |
| 4 | 38.9 | 26 | M | C | GBM | GBM | 27 | 22 | 22 | Topotecan (31); CCNU (3) | 3 |
| 5 | 38.3 | 41 | M | C | ODG/ III | GBM | 26 | 54 | 52 | Dox (1); Nivo (1);  EVE (2 yrs) | 0 |
| 6 | 33.3 | 63 | M | C | GBM | GBM | 20 | 36 | 37 | CCNU (1) | 0 |
| 7 | 28.5 | 27 | F | C | LFS; III | GBM | 20 | 32 | 30 |  | 0 |
| 8 | 26.8 | 27 | M | C | III, GC | III, GC | 21 | 59 | 42 |  | 3 |
| 9 | 26.5 | 33 | F | AS | II, spine | DMG | 7 | 35 | 24 |  | 0 |
| 10 | 16.6 | 61 | M | C | GBM | GBM | 12 | 20 | 20 |  | 0 |
| 11 | 15.7 | 69 | M | C | GBM | GBM | 11 | 15 | 15 |  | 0 |
| 12 | 15.4 | 45 | F | C | III | GBM | 15 | 13 | 13 |  | 0 |
| Group 2: 1-5 TIB cycles | 13 | 83.2 | 52 | M | C | GBM | GBM | 47 | 11 | 7 | Pembrolizu-mab (2) | 0 |
| 14 | 50.4 | 62 | M | C | GBM | GBM | 47 | 11 | 11 |  | 0 |
| 15 | 35.7 | 58 | M | C | GBM | GBM | 28 | 9 | 5 |  | 0 |
| 16 | 24.3 | 53 | M | C | GBM | GBM | 16 | 12 | 1 | DM-CHOC-PEN (2) | 0 |
| 17 | 18.9 | 58 | F | C | GBM | GBM | 10 | 12 | 1 |  | 3 |
| 18 | 17.2 | 67 | F | AS | GBM | GBM | 14 | 13 | 11 |  | 0 |
| 19 | 16.4 | 58 | M | AA | GBM | GBM | 11 | 2 | 1 | Gliadel wafer | 3 |
| 20 | 15.4 | 36 | M | C | III | GBM | 14 | 9 | 5 |  | 0 |
| 21 | 14.9 | 25 | F | C | GBM | GBM | 5 | 5 | 3 | MTX (2); ARA-C (2) | 3 |
| 22 | 12.4 | 75 | F | C | GBM | GBM | 5 | 9 | 2 | Nivo (2); FPA (1) | 3 |
| 23 | 9.1 | 65 | M | C | GBM | GBM | 3 | 11 | 5 | ARA-C (1); Octreotide (5) | 3 |
| 24 | 3.5 | 56 | M | C | GBM | GBM | 2 | 3 | 2 |  | 0 |
| Group 1:NCBC | 62 | 33.1 | 40 | F | AA | GBM | GBM | 0 | 0 | 0 |  | 4 |
| 63 | 5.2 | 54 | F | C | GBM | GBM | 0 | 0 | 0 |  | 3 |
| 64 | 4.8 | 71 | F | C | GBM | GBM | 0 | 0 | 0 |  | 0 |
| 65 | 3.6 | 30 | F | C | III | DMG | 0 | 0 | 0 |  | 0 |
| 66 | 2.7 | 42 | M | AA | GBM | GBM | 0 | 0 | 0 |  | 0 |
| 67 | 2.7 | 69 | F | AA | GBM | GBM | 0 | 0 | 0 |  | 3 |
| 68 | 0.3 | 61 | F | O | GBM | GBM | 0 | 0 | 0 |  | 0 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Case No. | OS\*\* (Months) | Age | Sex | Race | Histology | | Chemo and/or immunotherapy | | | | CMS |
| Initial | Autopsy | TMZ | BEV | IRI | Other |
| Group 4: Standard of care | 25 | 65.0 | 65 | F | C | GBM | GBM | 12 | 9 | 6 |  | 3 |
| 26 | 56.9 | 72 | M | C | GBM | GBM | 1 | 35 | 0 | Erlotinib (4 yrs) | 0 |
| 27 | 38.3 | 70 | M | C | GBM | GBM | 13 | 4 | 0 | EVE | 0 |
| 28 | 36.9 | 72 | M | C | GBM | GBM | 22 | 9 | 0 |  | 0 |
| 29 | 36.8 | 64 | F | C | GBM | GBM | 0 | 49 | 0 |  | 0 |
| 30 | 35.1 | 54 | M | C | GBM | GBM | 6 | 17 | 0 | Imatinib (3 wks) | 0 |
| 31 | 29.8 | 60 | M | Uk | GBM | GBM | 5 | 0 | 0 | DXP vaccine; Plerixafor | 0 |
| 32 | 26.6 | 63 | F | C | GBM | GBM | 0 | 28 | 0 |  | 10 |
| 33 | 25.0 | 64 | M | C | GBM | GBM | 2 | 26 | 0 |  | 0 |
| 34 | 24.6 | 50 | M | C | GBM | GBM | 6 | 19 | 8 | ABT (placebo X11); Topo X7 | 4 |
| 35 | 23.8 | 76 | M | C | III, GC | III, GC | 6 | 0 | 0 |  | 0 |
| 36 | 22.9 | 53 | F | C | GBM | GBM | 15 | 7 | 0 | Sunitinib (1) | 8 |
| 37 | 21.7 | 51 | M | C | GBM | GBM | 16 | 0 | 0 | ICT-107 Vaccine; EVE | 0 |
| 38 | 20.5 | 46 | M | Uk | II | GBM | 0 | 24 | 17 |  | 8 |
| 39 | 20.3 | 61 | M | C | GBM | GBM | 7 | 9 | 4 |  | 3 |
| 40 | 20.1 | 62 | M | C | GBM | GBM | 13 | 14 | 0 |  | 0 |
| 41 | 19.1 | 54 | M | C | GBM | GBM | 2 | 33 | 0 |  | 0 |
| 42 | 18.1 | 58 | M | C | GBM | GBM | 1 | 19 | 19 | Topotecan (7) | 0 |
| 43 | 18.0 | 58 | F | C | GBM | GBM | 3 | 9 | 8 |  | 0 |
| 44 | 16.6 | 61 | F | Uk | GBM | GBM | 3 | 11 | 6 | CCNU (1) | 3 |
| 45 | 15.2 | 61 | M | C | GBM | GBM | 3 | 14 | 0 |  | 3 |
| 46 | 14.1 | 25 | M | C | GBM | GBM | 4 | 4 | 0 |  | 0 |
| 47 | 13.6 | 31 | M | C | II | GBM | 7 | 5 | 3 |  | 0 |
| 48 | 12.8 | 67 | M | C | GBM | GBM | 5 | 0 | 0 |  | 0 |
| 49 | 11.7 | 74 | F | C | GBM | GBM | 1 | 0 | 0 | Nivo (8); CAB (8) | 0 |
| 50 | 11.2 | 61 | M | C | GBM | GBM | 1 | 3 | 0 | ABT/placebo (5) | 0 |
| 51 | 11.1 | 80 | F | C | GBM | GBM | 2 | 0 | 0 |  | 3 |
| 52 | 10.6 | 49 | M | C | GBM | GBM | 2 | 9 | 10 | ARA-C (2); Topotecan (11); Thiotepa (8); CCNU (2) | 11 |
| 53 | 10.6 | 75 | M | C | GBM | GBM | 2 | 6 | 0 |  | 0 |
| 54 | 10.3 | 67 | M | C | GBM | GBM | 1 | 8 | 0 |  | 0 |
| 55 | 9.1 | 23 | F | C | GBM, spine | DMG | 2 | 5 | 0 |  | 0 |
| 56 | 8.3 | 48 | M | C | II | GBM | 30 | 14 | 0 |  | 0 |
| 57 | 7.9 | 52 | M | C | GBM | GBM | 3 | 5 | 0 |  | 0 |
| 58 | 7.7 | 69 | M | C | GBM | GBM | 2 | 8 | 6 | ARA-C (6) | 0 |
| 59 | 5.8 | 51 | M | C | II | GBM | 6 | 8 | 0 |  | 0 |
| 60 | 7.0 | 64 | F | C | GBM | GBM | 1 | 0 | 0 |  | 0 |
| 61 | 3.0 | 63 | M | C | III | GBM | 9 | 0 | 0 | Toca FC (1) | 0 |
| Brain Metastasis | 69 | 18.3 | 61 | M | C | Melanoma | | 1\* |  |  | See chemotherapy records above | 0 |
| 70 | 10.5 | 75 | M | C | Squamous cell CA | |  |  |  | 0 |
| 71 | 7.9 | 59 | F | C | Breast CA | |  |  |  | 0 |
| 72 | 7.8 | 56 | M | C | Parotid CA | |  |  |  | 0 |
| 73 | 2.1 | 73 | M | C | NSCLC | |  |  |  | 0 |
| 74 | 1.6 | 39 | M | HS | Lung adenocarcinoma | |  |  |  | 0 |
| 75 | 0.1 | 74 | F | C | Melanoma | |  |  |  | 0 |
| 76 | 0.1 | 44 | F | C | CML | |  |  |  | 11 |

AA: African American; ABT/placebo: depatuxizumab mafodotin, placebo is listed because study drug was administered in a double-blinded way; AS: Asian; ABT: Depatuxizumab mafodotin (ABT-414); Ara-C: Cytarabine; C: Caucasian; CA: cancer; CAB: cabiralizumab (FPA-008); CMS: Clinical myelosuppression scores; DMG: diffuse midline glioma; Dox: Doxorubicin; Dx: diagnosis; EVE: everolimus; F: Female; GC: gliomatosis cerebri; HS: Hispanic; LFS: [Li-Fraumeni syndrome](http://www.cancer.net/cancer-types/li-fraumeni-syndrome); M: Male; MTX: methotrexate; Nivo (nivolumab): NSCLC: Non-small-cell lung carcinoma; O: other; ODG: oligo-dendroglioma; Toca FC: an extended-release formulation of flucytosine: Topo: Topotecan; Uk: unknown. \* Patient #69 was treated with one 42 consecutive days of low-dose TMZ. \*\*OS is calculated from the time of diagnosis of GBM, secondary GBM or brain mets. Exception for individual cases, for example, is allowed.

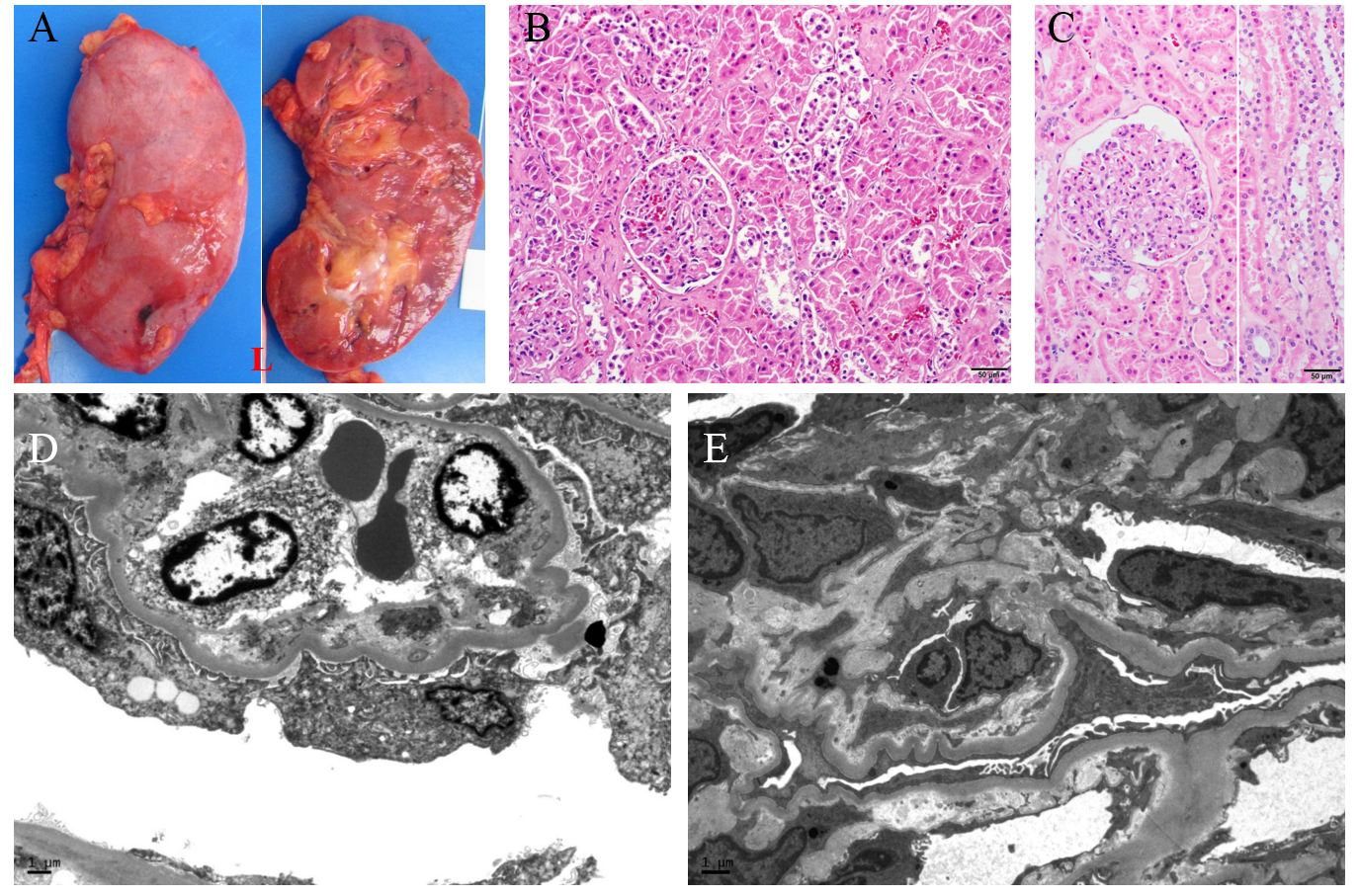
Genomic test (Foundation Medicine, Cambridge, MA) reported H3F3A K27M mutant in tumor tissue of patient #65 and two spine glioma cases (patients #9 and #55). Therefore, the diagnosis for these three subjects were classified as DMG. DMG is classified as WHO grade IV glioma, regardless of histological features and is predominantly found in children. All three DMG decedents were young female patients (23, 30 and 33 years old respectively) at the time of their initial diagnosis.

Patient #8 had a history of multiple sclerosis and [Li-Fraumeni syndrome](http://www.cancer.net/cancer-types/li-fraumeni-syndrome); patient #62 was diagnosed with Huntington’s disease prior to brain tumor diagnosis, she survived almost 3 years without maintenance cancer therapy. Nine glioma patients were participants of clinical trials and then were off trials due to tumor progression.

Supplement Table 2. Immediate cause of death and pathological findings from autopsy

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Metastatic tumor  (N=8) | Recurrent gliomas, treatment based (N=68) | | | |
| NCBC (N=7) | 1-5 TIB (N=12) | 6-25 TIB (N=12) | SOC (N=37) |
| Cause of death | | | | | |
| Disease progression | 4  (50%) | 5  (71.4%) | 9  (75%) | 8  (66.7%) | 21  (56.8%) |
| Aspiration pneumonia | 3  (37.5%) | 1  (14.3%) | 5  (41.7%) | 7  (58.3%) | 20  (54.1%) |
| Cardiovascular complications | 2  (25%) | 1  (14.3%) | 3  (25%) | 4  (33.3%) | 11  (29.7%) |
| PE/DVT | 0 | 0 | 2  (16.7%) | 1 | 5  (13.5%) |
| Sepsis | 2  (25%) | 0 | 1  (8.3%) | 2  (16.7%) | 4  (10.8%) |
| Perforated Diverticulitis | 0 | 0 | 0 | 0 | 1  (2.7%) |
| Multi-organ failure | 5  (62.5%) | 0 | 3  (25%) | 0 | 4  (10.8%) |
| Prolonged seizure | 0 | 0 | 0 | 0 | 3  (10.8%) |
| Brain Hemorrhage | 4  (50%) | 0 | 0 | 0 | 0 |
| ARDS | 2  (25%) | 0 | 2  (16.7%) | 0 | 1  (2.7%) |
| Autopsy gross and microscopic findings | | | | | |
| PE/DVT | 0 | 2  (28.6%) | 3  (25%) | 1  (8.3%) | 9  (24.3%) |
| Brain herniation | 1  (12.5%) | 2  (28.6%) | 4  (33.3%) | 2  (16.7%) | 3  (8.1%) |
| Hemorrhage within brain | 4  (50%) | 1  (14.3%) | 3  (25%) | 0 | 2  (5.4%) |
| Bone marrow suppression\* | 4#/7 | 0/2 | 2/6 | 0/5 | 3/19 |

PE Pulmonary Embolism; DVT: Deep vein thrombosis; ARDS: acute respiratory distress syndrome. \*Thirty-nine cases reported bone marrow examinations. Data is presented as confirmed result over available cases. #Presence of large clusters of blasts cells in bone marrow biopsy from a decedent of chronic myeloid leukemia with brain mets.



Supplement Figure 1: Gross, microscopic and EM study of kidney from subject #22, who received 5X TMZ in total; 9X BEV and 2X IRI were counted as part of TIB cycles for her rGBM. A) Gross autopsy pictures of left (L) kidney were taken 20 hours postmortem. Corticomedullary junction was sharp in both kidneys upon section. Except a cyst (1.5 x 1.5 cm) presented at the posterior upper pole of the left kidney, there was no other gross pathologic abnormality. B) H&E staining demonstrated autolytic changes including diffuse loss or proximal tubular epithelial nuclei; diffuse pyknosis of glomerular and collecting duct nuclei; and variable detachment of epithelial cells from tubular basement membranes. Scale bar=50µm. C) Essentially normal tissues from a fresh nephrectomy specimen, not related to this study, is provided as a control to B). D) Ultrastructure of glomerulus from tissues collected 3 hours postmortem through kidney biopsy showed early TMA in addition to autolytic artifacts. The diagnosis of TMA was based on the deposition of slightly electron-dense matrix in the zone of subendothelial rarefication that was resistant to autolysis and could be identified along with autolyzed cellular debris, as cellular (“mesangial”) interpositioning. Scale bar=1 µm. E) Ultrastructure of glomerulus picture from a patient who was treated with BEV and developed TMA as a comparison to D), there was no autolytic changes because tissue was obtained through a renal biopsy specimen. This patient was not related to current study. For C) and E), UTHealth CPHS allows researchers to study 1-3 cases for research purpose without a formal study application.