### GLIO-3 and GLIO-4

**External request:**

Submission from Novocure Inc. (12/19/17 and 9/7/17) Please consider adding tumor treating fields in combination with temozolomide for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma as a category 1 recommendation.

Based on the discussion and noted references, there was uniform panel consensus that the following regimen is supported by high-level evidence as an option for postoperative treatment for newly-diagnosed glioblastoma in patients with good performance status (KPS≥60):

**Standard RT + concurrent and adjuvant TMZ + alternating electric field therapy**

This regimen is now a category 1 recommended option in all of the following pathways:

- **Age ≤70 y and MGMT promoter methylated (GLIO-3, top pathway)**
  - YES: 23, NO: 2, ABSTAIN: 1, ABSENT: 1

- **Age ≤70 y and MGMT promoter unmethylated or indeterminate (GLIO-3, second pathway)**
  - YES: 22, NO: 3, ABSTAIN: 1, ABSENT: 1

- **Age >70 y and MGMT promoter methylated (GLIO-4, top pathway)**
  - YES: 23, NO: 2, ABSTAIN: 1, ABSENT: 1

- **Age >70 y and MGMT promoter unmethylated or indeterminate (GLIO-4, second pathway)**
  - YES: 22, NO: 3, ABSTAIN: 1, ABSENT: 1

**Supporting references:**


### GLIO-4

**Internal request:**

For postoperative treatment of newly-diagnosed glioblastoma in patients with good performance status (KPS≥60), age >70, request to change “Hypofractionated brain RT alone” from category 1 to category 2A, and to list

Based on the discussion and noted reference, there was uniform panel consensus that “**Hypofractionated RT + concurrent and adjuvant temozolomide**” is supported by high-level evidence for postoperative adjuvant treatment of newly-diagnosed glioma in patients age >70 with good performance status (KPS ≥60) and MGMT promoter methylation (GLIO-4, top pathway).

This is a category 1 recommendation.

<table>
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<tr>
<th>Institution Vote</th>
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<tbody>
<tr>
<td>GLIO-4</td>
<td>24</td>
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### Guideline Page and Request

**“Hypofractionated brain RT + concurrent and adjuvant temozolomide” as a category 1 option.**

Based on the discussion and noted reference, there was not uniform consensus among the panel that “Hypofractionated RT + concurrent and adjuvant temozolomide” is supported by high-level evidence for postoperative adjuvant treatment of newly-diagnosed glioblastoma in patients age >70, with good performance status (KPS ≥60), and with MGMT promoter unmethylated or indeterminate (GLIO-4, second pathway). This is a category 2A recommendation.

**Supporting reference:**

### PCNS-3

**Internal request:**
For induction therapy and consolidation therapy for newly-diagnosed primary CNS lymphoma (PCNS-2) and treatment for relapsed or refractory primary CNS lymphoma (PCNS-3), the PCNSL subcommittee revised the recommendations, including changes to the systemic therapy options on BRAIN-D 3 of 8 and 4 of 8.

Based on the discussion, there was uniform panel consensus supporting the changes made to PCNS-2, PCNS-3, and BRAIN-D 3 of 8 and 4 of 8.

**Supporting references were added to the reference section of BRAIN-D.**

<table>
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### MENI-2 and BRAIN-D 3 of 8

**Internal request:**
Request to add bevacizumab + everolimus as a systemic therapy option for meningiomas. (BRAIN-D, 3 of 8)

Based on the discussion and noted reference, nonuniform panel consensus supported the inclusion of “bevacizumab + everolimus” as a systemic therapy option for recurrent or progressive meningiomas that are not surgically resectable and RT not possible (MENI-2, third pathway and BRAIN-D 3 of 8).

This is a category 2B recommendation.

**Supporting reference:**
**Panel Discussion/References**

Based on the discussion and noted reference, uniform panel consensus supported the inclusion of dabrafenib/trametinib combination as a systemic therapy option for patients with newly diagnosed melanoma brain metastases (LTD-1, LTD-2, and BRAIN-D). This is a category 2A recommendation.

Based on the discussion and noted reference, uniform panel consensus supported the inclusion of dabrafenib/trametinib combination as a systemic therapy option for patients with recurrent melanoma brain metastases (LTD-3, MU-2, and BRAIN-D). This is a category 2A recommendation.

**Supporting reference:**

For patients with newly-diagnosed brain metastases, request to include the following regimens as options for a systemic therapy:
- Vemurafenib/cobimetinib combination therapy (melanoma)
- Pembrolizumab monotherapy (melanoma or NSCLC)
- Alectinib (ALK rearrangement-positive NSCLC)

Based on the discussion and noted reference, nonuniform panel consensus supported the addition of vemurafenib/cobimetinib combination as a systemic therapy option for newly-diagnosed melanoma brain metastases. This is a category 2B recommendation.

Supporting reference:

Based on the discussion and noted reference, uniform panel consensus supported the addition of pembrolizumab monotherapy as a systemic therapy option for newly-diagnosed brain metastases from melanoma or NSCLC. This is a category 2A recommendation.

Supporting reference:

Based on the discussion and noted reference, uniform panel consensus supported the addition of alectinib as a systemic therapy option for newly-diagnosed brain metastases from ALK rearrangement-positive NSCLC. This is a category 2A recommendation.

Supporting reference:
For patients with recurrent brain metastases (LTD-3, MU-2) request to include the following systemic therapy options (BRAIN-D 4 of 8):

- Vemurafenib/cobimetinib combination for patients with melanoma
- Brigatinib for patients with ALK rearrangement-positive NSCLC

**Panel Discussion/References**

Uniform panel consensus supported the addition of vemurafenib/cobimetinib combination as a systemic therapy option for patients with recurrent melanoma brain metastases. This is a category 2A recommendation.

**Supporting references:**

Based on the discussion and noted reference, uniform panel consensus supported the addition of brigatinib as a systemic therapy option for recurrent brain metastases in patients with ALK rearrangement-positive NSCLC. This is a category 2A recommendation.

**Supporting reference:**

<table>
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<th>Institution Vote</th>
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| LTD-3, MU-2, and BRAIN-D 4 of 8 | Uniform panel consensus supported the addition of vemurafenib/cobimetinib combination as a systemic therapy option for patients with recurrent melanoma brain metastases. This is a category 2A recommendation. **Supporting references:**
<table>
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<tr>
<td>BRAIN-D 4 of 8</td>
<td>Based on the discussion and noted references, uniform panel consensus supported the inclusion of ipilimumab/nivolumab for patients with newly diagnosed brain metastases from melanoma (LTD-1, LTD-2, BRAIN-D). This is a category 2A recommendation. Supporting references:</td>
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<td>Panel Discussion/References</td>
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