**Supplementary Appendix**

## Supplementary Results

**OS by baseline PD-L1 expression**

In patients with ≥ 5% programmed cell death (PD)-1 ligand (PD-L1) expression at baseline, median overall survival (OS) was 12.6 months (95% CI, 11.1-16.2) in the NIVO+RT arm and 14.2 months (95% CI, 12.3-17.3) in the TMZ+RT arm (HR, 1.3; 95% CI, 0.9-1.8). Median OS in patients with < 5% PD-L1 expression at baseline was 13.6 months (95% CI, 12.9-14.4) in the NIVO+RT arm and 15.2 months (95% CI, 13.2-16.2) in the TMZ+RT arm (HR, 1.3; 95% CI, 1.0-1.6) (**Figure S1**).

**Investigator-assessed objective response rate**

The median time to response was 2.4 months (range, 2.1-6.9) in the NIVO+RT arm and 2.9 months (range, 2.3-17.8) in the TMZ+RT arm. The median duration of response in all confirmed evaluable responders was 5.3 months (95% CI, 3.3-5.9) in the NIVO+RT arm and 4.5 months (95% CI, 2.1-5.8) in the TMZ+RT arm (**Table S2**).

**Supplemental Tables and Figures**

## Table S1. Baseline Tumor Assessments Summary.

|  |  |  |
| --- | --- | --- |
|  | Nivolumab Plus Radiotherapy  (n = 280) | Temozolomide Plus Radiotherapy  (n = 280) |
| Patients with ≥ 1 lesion — no. (%)a | 280 (100) | 280 (100) |
| Site of lesion*a,b*  Temporal lobe  Frontal lobe  Parietal lobe  Occipital lobe  Corpus callosum  Basal ganglia  Brain stem  Thalamus  Cerebellum  Other | 116 (41.4)  88 (31.4)  57 (20.4)  24 (8.6)  13 (4.6)  2 (0.7)  1 (0.4)  3 (1.1)  0  22 (7.9) | 101 (36.1)  87 (31.1)  59 (21.1)  26 (9.3)  12 (4.3)  5 (1.8)  0  3 (1.1)  2 (0.7)  28 (10.0) |
| Measurable target lesion — no. (%) | 117 (41.8) | 111 (39.6) |
| SPD of measurable target lesions — mm2  No.  Median  Range | 116  515.5  75-3401 | 111  810.3  110-4648 |
| Site of target lesion(s) — no. (%)*b* |  |  |
| Temporal lobe  Frontal lobe  Parietal lobe  Occipital lobe  Corpus callosum  Basal ganglia  Brain stem  Thalamus  Other | 43 (15.4)  38 (13.6)  19 (6.8)  10 (3.6)  8 (2.9)  1 (0.4)  1 (0.4)  0  9 (3.2) | 41 (14.6)  30 (10.7)  21 (7.5)  12 (4.3)  9 (3.2)  4 (1.4)  0  1 (0.4)  8 (2.9) |

SPD, sum of products of perpendicular diameters.  
*a* Includes both measurable and nonmeasurable lesions.

*b* Patients may have lesions at > 1 site.

## Table S2. Response Rates and Duration of Response Per Investigator Assessment.

|  |  |  |
| --- | --- | --- |
|  | Nivolumab Plus Radiotherapy  (n = 116)*a* | Temozolomide Plus Radiotherapy  (n = 111)*a* |
| Objective response rate — no. (%)  (95% CI) | 9 (7.8)  (3.6-14.2) | 8 (7.2)  (3.2-13.7) |
| Best overall response — no. (%)  Complete response  Partial response  Stable disease  Progressive disease  Unable to determine  Death prior to disease assessment  Discontinued early due to toxicity  Other  Not reported | 2 (1.7)  7 (6.0)  66 (56.9)  36 (31.0)  5 (4.3)  4 (3.4)  0  1 (0.9)  0 | 1 (0.9)  7 (6.3)  56 (50.5)  32 (28.8)  10 (9.0)  3 (2.7)  1 (0.9)  6 (5.4)  5 (4.5) |
| Duration of response  Median (95% CI) — mo | 5.3 (3.3-5.9) | 4.5 (2.1-5.8) |

*a* Patients who were evaluable for response.

## Table S3. Demographic and Disease Characteristics of Responders.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Response** | **Age/Sex** | **PD-L1 Expression Level (%)** | **RPA Class** | **Surgery Type** | **Corticosteroid Usea** |
| Nivolumab plus radiotherapy | PR | 64/F | 40 | V | Partial resection | > 3 mg/day |
| PR | 62/F | 40 | IV | Partial resection | No |
| PR | 66/F | 40 | IV | Complete resection | No |
| CR | 57/F | 5 | IV | Complete resection | No |
| PR | 65/M | 0 | IV | Partial resection | No |
| PR | 73/M | 0 | V | Partial resection | No |
| PR | 59/M | 0 | IV | Partial resection | ≤ 3 mg/day |
| CR | 49/F | 0 | IV | Partial resection | No |
| PR | 51/F | 0 | IV | Partial resection | No |
| Temozolomide plus radiotherapy | PR | 68/F | 20 | IV | Complete resection | No |
| PR | 69/F | 10 | IV | Partial resection | No |
| PR | 54/M | 1 | IV | Partial resection | No |
| PR | 53/M | 0 | IV | Partial resection | > 3 mg/day |
| CR | 44/M | 0 | IV | Partial resection | ≤ 3 mg/day |
| PR | 70/F | 0 | IV | Partial resection | No |
| PR | 53/F | 0 | IV | Partial resection | ≤ 3 mg/day |
| PR | 67/M | 0 | V | Complete resection | ≤ 3 mg/day |

CR, complete response; PD-L1, programmed cell death ligand 1; PR, partial response; RPA, recursive-partitioning analysis.

*a* Based on average corticosteroid use 5 days before start of dosing or randomization date for patients not treated (in dexamethasone equivalent). Patients enrolled at doses > 3 mg/day were tapered off; treatment did not commence until the dose was ≤ 3mg/day.

## Table S4. Subsequent Therapies.

|  |  |  |
| --- | --- | --- |
| **Patients — no. (%)** | **Nivolumab Plus**  **Radiotherapy**  **(n = 280)** | **Temozolomide Plus Radiotherapy**  **(n = 280)** |
| **Any subsequent therapy** | 178 (63.6) | 150 (53.6) |
| **Surgery** | 76 (27.1) | 44 (15.7) |
| **Radiotherapy** | 26 (9.3) | 24 (8.6) |
| **Systemic therapy** | 148 (52.9) | 129 (46.1) |
| Alkylating agent  Lomustine  Temozolomide  Fotemustine  Carmustine  Procarbazine  Ifosfamide | 115 (41.1)  25 (8.9)  109 (38.9)  4 (1.4)  5 (1.8)  3 (1.1)  1 (0.4) | 86 (30.7)  49 (17.5)  33 (11.8)  12 (4.3)  6 (2.1)  5 (1.8)  0 |
| **Other cytotoxic therapy**  Carboplatin  Etoposide  Irinotecan  Vincristine | 13 (4.6)  6 (2.1)  2 (0.7)  7 (2.5)  1 (0.4) | 29 (10.4)  19 (6.8)  1 (0.4)  9 (3.2)  1 (0.4) |
| **Anti-VEGF**  Bevacizumab | 77 (27.5)  77 (27.5) | 81 (28.9)  81 (28.9) |
| **Immunotherapy**  Anti–PD-1  Nivolumab  Pembrolizumab  Oncolytic virus therapy  Vocimagene amiretrorepvec  Other immunotherapy  Investigational immunotherapy | 3 (1.1)  2 (0.7)  2 (0.7)  0  1 (0.4)  1 (0.4)  0  0 | 7 (2.5)  6 (2.1)  4 (1.4)  2 (0.7)  0  0  1 (0.4)  1 (0.4) |
| **Cytotoxic free-radical – photodynamic therapy**  Aminolevulinic acid  Talaporfin | 4 (1.4)  1 (0.4)  3 (1.1) | 0  0  0 |
| **Mitosis inhibitor (microtubilin) – chemotherapy**  Carboplatin/paclitaxel | 2 (0.7)  2 (0.7) | 0  0 |
| **DNA cross-linker – chemotherapy**  Cyclophosphamide | 1 (0.4)  1 (0.4) | 2 (0.7)  2 (0.7) |
| **CDK4 and CDK6 inhibitors – chemotherapy**  Palbociclib | 1 (0.4)  1 (0.4) | 0  0 |
| **VEGFR2 – TIE2 inhibitors – tyrosine kinase inhibitor**  Regorafenib | 0  0 | 1 (0.4)  1 (0.4) |
| **MEK1 and MEK2 inhibitors – MEK inhibitors**  Trametinib | 1 (0.4)  1 (0.4) | 1 (0.4)  1 (0.4) |
| **Other**  Antineoplastic/investigational drug  Investigational drug | 10 (3.6)  5 (1.8)  4 (1.4)  1 (0.4) | 7 (2.5)  0  4 (1.4)  3 (1.1) |

CDK, cyclin-dependent kinase; MEK, mitogen-activated protein kinase; PD-1, programmed cell death 1 protein; TIE2, tunica interna endothelial cell kinase 2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

## Table S5. Treatment-Related Adverse Events.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Nivolumab Plus Radiotherapy  (n = 278) | | | Temozolomide Plus Radiotherapy  (n = 275) | | |
| Treatment-Related Adverse Event — no. (%) | **Any**  **Grade** | **Grade**  **3/4** | **Grade**  **5** | **Any**  **Grade** | **Grade**  **3/4** | **Grade 5** |

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Table S5. Treatment-Related Adverse Events (cont).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Nivolumab Plus Radiotherapy  (n = 278) | | | Temozolomide Plus Radiotherapy  (n = 275) | | |
| Treatment-Related Adverse Event — no. (%) | **Any**  **Grade** | **Grade**  **3/4** | **Grade**  **5** | **Any**  **Grade** | **Grade**  **3/4** | **Grade 5** |

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Table S5. Treatment-Related Adverse Events (cont).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Nivolumab Plus Radiotherapy  (n = 278) | | | Temozolomide Plus Radiotherapy  (n = 275) | | |
| Treatment-Related Adverse Event — no. (%) | **Any**  **Grade** | **Grade**  **3/4** | **Grade**  **5** | **Any**  **Grade** | **Grade**  **3/4** | **Grade 5** |

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Table S5. Treatment-Related Adverse Events (cont).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Nivolumab Plus Radiotherapy  (n = 278) | | | Temozolomide Plus Radiotherapy  (n = 275) | | |
| Treatment-Related Adverse Event — no. (%) | **Any**  **Grade** | **Grade**  **3/4** | **Grade**  **5** | **Any**  **Grade** | **Grade**  **3/4** | **Grade 5** |

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Table S5. Treatment-Related Adverse Events (cont).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Nivolumab Plus Radiotherapy  (n = 278) | | | Temozolomide Plus Radiotherapy  (n = 275) | | |
| Treatment-Related Adverse Event — no. (%) | **Any**  **Grade** | **Grade**  **3/4** | **Grade**  **5** | **Any**  **Grade** | **Grade**  **3/4** | **Grade 5** |

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Data are based on a March 21, 2019, database lock. The safety analysis included all patients who received ≥ 1 dose of study drug. Some patients had > 1 adverse event. Includes events reported between first dose and 30 days after last dose of study therapy. Three treatment-related deaths were reported in the NIVO+RT arm due to vasogenic cerebral edema, sudden death, and respiratory failure (1 each); no treatment-related deaths were reported in the TMZ+RT arm.

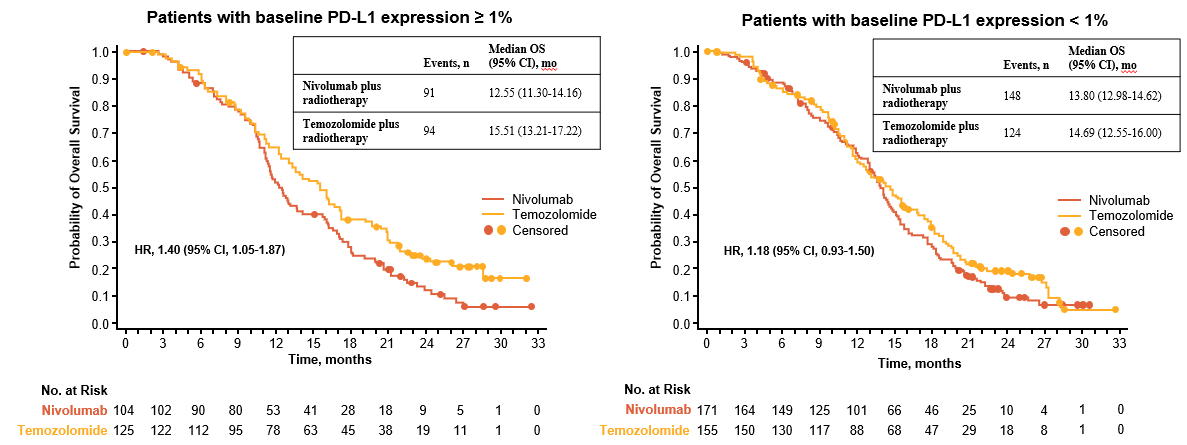
## Table S6. Immune-Mediated Select Adverse Events by Category.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Nivolumab Plus**  **Radiotherapy**  **(n = 278)** | | **Temozolomide Plus  Radiotherapy**  **(n = 275)** | |
|  | **Any Grade** | **Grade 3/4** | **Any Grade** | **Grade 3/4** |
| **Treatment-related select AEs by category**  **Patients — no. (%)** | | | | |
| Endocrine | 25 (9.0) | 4 (1.4) | 0 | 0 |
| Gastrointestinal | 22 (7.9) | 2 (0.7) | 8 (2.9) | 0 |
| Hepatic | 24 (8.6) | 11 (4.0) | 17 (6.2) | 6 (2.2) |
| Pulmonary | 2 (0.7) | 0 | 0 | 0 |
| Renal | 2 (0.7) | 1 (0.4) | 1 (0.4) | 0 |
| Dermal | 54 (19.4) | 12 (4.3) | 31 (11.3) | 5 (1.8) |
| Hypersensitivity/infusion reaction | 12 (4.3) | 1 (0.4) | 0 | 0 |

AE, adverse event.

## Figure S1. OS by PD-L1 Expression.

**A B**



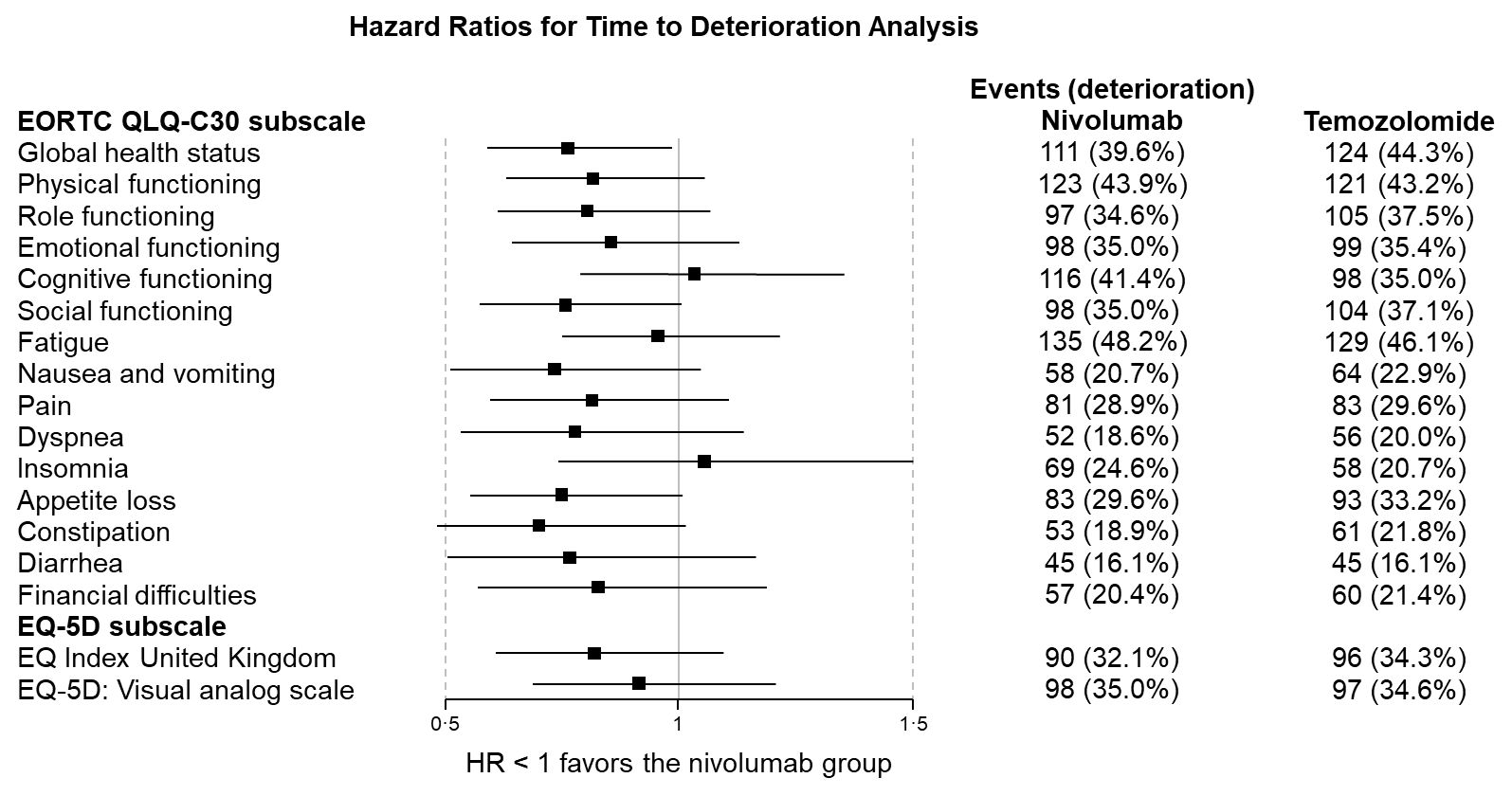
**C D**

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**Figure S1. OS by PD-L1 Expression.** Number of events, median OS, and Kaplan-Meier curves for OS in patients treated with nivolumab plus radiotherapy or temozolomide plus radiotherapy with baseline PD-L1 expression ≥ 1% (A), < 1% (B), ≥ 5% (C), and < 5% (D). Symbols indicate censored observations. Hazard ratios (HRs) and 95% CIs were estimated using a Cox proportional hazards model. OS, overall survival; PD-L1, programmed cell death ligand 1.

## Figure S2. Time to Deterioration in Patient-Reported Outcome Analyses.

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**Figure S2.** **Time to Deterioration in Patient-Reported Outcome Analyses.** Forest plot of hazard ratios for time to deterioration analyses in domains of health-related quality of life and for general health utilities (EQ-5D-3L index and visual analog scale). EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio.