KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

PD-1 = programmed death receptor-1.

Dear Health Care Professional,

Merck is pleased to announce the approval of another indication for KEYTRUDA by the US Food and Drug Administration for the treatment of patients with advanced MSI-H/dMMR cancers who have received prior therapy.

KEYTRUDA: Summary of efficacy in patients with advanced MSI-H/dMMR cancers

<table>
<thead>
<tr>
<th>Objective Response Rate</th>
<th>7.4% Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=149</td>
<td>39.6% (95% CI, 31.7–47.9)</td>
</tr>
<tr>
<td></td>
<td>32.2% Partial response</td>
</tr>
</tbody>
</table>

CI = confidence interval.

% With Duration ≥6 Months

Median duration of response (DOR) had not been reached (range: 1.6+ to 22.7+ months).

SELECTED SAFETY INFORMATION

• Immune-mediated adverse reactions occurred with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if appropriate. For more information regarding immune-mediated adverse reactions, please read the additional Selected Safety Information on pages 3 and 5.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on the following pages and the accompanying Prescribing Information. The Medication Guide also is available.

Visit keytruda.com to download resources and register to receive product updates.
The efficacy of KEYTRUDA was evaluated in patients with MSI-H or dMMR, solid tumors enrolled in 1 of 5 uncontrolled, open-label, multicohort, multicenter, single-arm trials. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the 5 trials. Patients received either KEYTRUDA 200 mg every 3 weeks (Q3W) or KEYTRUDA 10 mg/kg every 2 weeks (Q2W) until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status; or a maximum of 24 months. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were objective response rate (ORR) as assessed by blinded independent central radiologists’ review according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and DOR.

The 5 trials were designed as follows:

| KEYNOTE-016 | Six-site prospective, investigator-initiated trial included patients with CRC (n=28) and non-CRC (n=30) who received KEYTRUDA 10 mg/kg Q2W following ≥2 prior regimens for CRC or ≥1 for non-CRC; tested with local PCR or IHC. |
| KEYNOTE-164 | Prospective, international, multicenter trial of patients with CRC (n=61) who received KEYTRUDA 200 mg Q3W following fluoroopyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR monoclonal antibody; tested with local PCR or IHC. |
| KEYNOTE-012 | Retrospectively identified patients (n=6) with PD-L1–positive gastric, bladder, or triple-negative breast cancer who received KEYTRUDA 10 mg/kg Q2W following ≥1 prior regimen; tested with central PCR. |
| KEYNOTE-028 | Retrospectively identified patients (n=5) with PD-L1–positive esophageal, biliary, breast, endometrial, or CRC who received KEYTRUDA 10 mg/kg Q2W following ≥1 prior regimen; tested with central PCR. |
| KEYNOTE-158 | Prospective, international, multicenter enrollment of patients with MSI-H/dMMR non-CRC and retrospectively identified patients who were enrolled in specific rare-tumor non-CRC cohorts (n=18) who received KEYTRUDA 200 mg Q3W following ≥1 prior regimen; tested with local PCR or IHC (central PCR for patients in rare-tumor non-CRC cohorts). |

A total of 149 patients with MSI-H or dMMR cancers were identified across the 5 clinical trials. Among these 149 patients, the baseline characteristics were: median age 55 years (36% age 65 or older); 56% male; 77% White, 19% Asian, 2% Black; and ECOG PS 0 (36%) or 1 (84%). Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was 2. Eighty-four percent of patients had metastatic CRC and 53% of patients with other solid tumors received 2 or more prior lines of therapy.

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed PCR tests for MSI-H status or IHC tests for dMMR. Fourteen of the 149 patients were retrospectively identified as MSI-H by testing tumor samples from a total of 415 patients using a central laboratory-developed PCR test. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests.

CRC = colorectal cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; EGRF = epidermal growth factor receptor; IHC = immunohistochemistry; PCR = polymerase chain reaction; VEGF = vascular endothelial growth factor.

KEYNOTE-016: STUDY DESIGN IN MSI-H/dMMR CANCERS ACROSS 5 CLINICAL TRIALS

| SELECTED SAFETY INFORMATION |

- **KEYTRUDA can cause immune-mediated pneumonitis**, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (8.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%) pneumonitis, and occurred more frequently in patients with a history of prior thoracic radiation (6.8%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

- **KEYTRUDA can cause immune-mediated colitis.** Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), 3 (1.1%), and 4 (0.1%) colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.

- **KEYTRUDA can cause immune-mediated hepatitis.** Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (0.1%) hepatitis. Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

- **KEYTRUDA can cause hypophysitis.** Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), 3 (0.3%), and 4 (0.1%) hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2; withhold or discontinue for Grade 3 or 4 hypophysitis.

- **KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis.** Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and 3 (0.1%) hyperthyroidism. Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and 3 (0.1%) hypothyroidism. Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hyperthyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or 4 hyperthyroidism.

- **KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients.** Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.

- **KEYTRUDA can cause immune-mediated nephritis.** Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (0.1%) nephritis. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 nephritis.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available.
The efficacy of KEYTRUDA was evaluated in patients with MSI-H or dMMR, solid tumors enrolled in 1 of 5 clinical trials. KEYNOTE-028, an open-label, multicenter, non-randomized, phase 2 trial, evaluated KEYTRUDA 2 mg/kg every 2 weeks (Q2W) versus placebo in patients with advanced esophageal or gastroesophageal adenocarcinoma. Treatment with KEYTRUDA for ≥20% of patients) were fatigue, pruritus, cough, dyspnea, musculoskeletal pain, arthralgia, nausea, vomiting, hypotension, hypoxemia, and fever. For Grade 3 and 4 infusion-related reactions, including hypotension, asthma, and anaphylaxis, patients should be treated with corticosteroids and epinephrine. For Grade 3 and 4 infusion-related reactions, including hypotension, asthma, and anaphylaxis, patients should be treated with corticosteroids and epinephrine.
KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) • solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or • colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

### SELECTED SAFETY INFORMATION (continued)

- Immune-mediated adverse reactions occurred with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if appropriate. For more information regarding immune-mediated adverse reactions, please read the additional Selected Safety Information on pages 3 and 5.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available. For additional copies of the Prescribing Information, please call 800-672-6372, visit keytruda.com, or contact your Merck representative.

### Test for MSI or MMR Status

Request MSI or MMR testing in advanced cancers. Visit keytruda.com for more information on advanced MSI-H/dMMR cancers.

MSI = microsatellite instability-high; MMR = mismatch repair.

**Treat with KEYTRUDA in previously treated adult patients with advanced MSI-H/dMMR cancers**

| 200-mg fixed dose administered intravenously | over 30 minutes | every 3 weeks |

- Treatment should continue until disease progression, unacceptable toxicity, or for up to 24 months in patients without disease progression.

### The Merck Access Program

Visit merckaccessprogram-keytruda.com or call 855-257-3932 Monday to Friday, between 8 AM and 8 PM ET.

---

**Test for MSI OR MMR STATUS IN ADVANCED CANCERS. TREAT WITH KEYTRUDA.**

---

**Test for MSI or MMR Status**

Request MSI or MMR testing in advanced cancers. Visit keytruda.com for more information on advanced MSI-H/dMMR cancers.

MSI = microsatellite instability-high; MMR = mismatch repair.

**Treat with KEYTRUDA in previously treated adult patients with advanced MSI-H/dMMR cancers**

| 200-mg fixed dose administered intravenously | over 30 minutes | every 3 weeks |

- Treatment should continue until disease progression, unacceptable toxicity, or for up to 24 months in patients without disease progression.

### SELECTED SAFETY INFORMATION (continued)

- Immune-mediated adverse reactions occurred with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if appropriate. For more information regarding immune-mediated adverse reactions, please read the additional Selected Safety Information on pages 3 and 5.

Before prescribing KEYTRUDA, please read the accompanying Prescribing Information. The Medication Guide also is available. For additional copies of the Prescribing Information, please call 800-672-6372, visit keytruda.com, or contact your Merck representative.

### The Merck Access Program

Visit merckaccessprogram-keytruda.com or call 855-257-3932 Monday to Friday, between 8 AM and 8 PM ET.