The first and only I-O + I-O combination for MSI-H/dMMR mCRC patients with progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan1

INDICATION

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of adults and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO (3 mg/kg) and YERVOY (1 mg/kg) are administered as intravenous infusions over 30 minutes, on the same day, every 3 weeks for 4 doses. After completing 4 doses of the combination, administer OPDIVO as a single agent, either 240 mg every 2 weeks or 480 mg every 4 weeks as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity.

The first dose of OPDIVO monotherapy should be administered after completing 4 doses of the combination.

Based on exploratory dose exposure-response relationships for efficacy and safety, OPDIVO 240 mg q4w and 480 mg q4w are predicted to be similar.

The median duration of response was not yet reached1 in the combination cohort, and median overall survival has not been reached.4

OPDIVO + YERVOY combination1

INDUCTION DOSING

OPDIVO® + YERVOY® delivered an ORR of 46% (95% CI: 35–58) and mDOR not yet reached1,3†

86% of patients (102/119) received all 4 doses of OPDIVO + YERVOY in the combination cohort6

SELECT IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), nephropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.

Assess patients for signs and symptoms of enterocolitis, dermatitis, nephropathy, and endocrinopathy, and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotropic hormone (ACTH) level, and thyroid function tests, at baseline and before each dose.

Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, dermatitis, nephritis and renal dysfunction, skin adverse reactions, encephalitis, other adverse reactions; infusion-related reactions; embryo-fetal toxicity; and increased mortality in patients with multiple myeloma when OPDIVO is added to a thalidomide analogue and dexamethasone, which is not recommended outside of controlled clinical trials.

Serious Adverse Reactions

In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions reported in ≥2% of patients were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration.

Common Adverse Reactions

In Checkmate 142 in MSI-H/dMMR mCRC patients receiving OPDIVO with YERVOY, the most common adverse reactions (≥20%) were fatigue (49%), diarrhea (45%), pyrexia (34%), musculoskeletal pain (36%), abdominal pain (30%), pruritus (28%), nausea (26%), rash (25%), decreased appetite (20%), and vomiting (20%).

Treatment discontinuation

OPDIVO was discontinued in 13% of patients and delayed in 45% of patients for an adverse reaction.

Please see additional Important Safety Information for OPDIVO and YERVOY on following page, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY, and U.S. Full Prescribing Information for OPDIVO and YERVOY.

Checkmate 142 trial design: Checkmate 142 was a multicenter, non-randomized, multiple parallel-cohort, open-label trial, which included a single-arm cohort investigating OPDIVO in combination with YERVOY in patients with locally determined MSI-H/dMMR mCRC (N=119) who had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy. Select key eligibility criteria included at least 1 prior line of treatment for metastatic disease; ECOG PS 0 or 1; and absence of the following: active brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression. Patients enrolled in the OPDIVO + YERVOY MSI-H/dMMR mCRC cohort received OPDIVO 3 mg/kg and YERVOY 1 mg/kg IV every 3 weeks for 4 doses, followed by OPDIVO 3 mg/kg IV as a single agent every 2 weeks.2 Treatment was continued until unacceptable toxicity or radiographic progression. Across 119 patients, 69% had received prior treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Efficacy outcome measures included ORR and DOR, as assessed by IRCs using Response Evaluation Criteria In Solid Tumors v1.1.1

In the entire combination cohort in Checkmate 142, OPDIVO + YERVOY demonstrated an ORR of 49% (95% CI: 39–58), a CR of 4.2% (5/119), and a PR of 45% (53/119). Median DOR was not reached (range: 1.9 to 23.2+ months). The proportion with ≥6 months response duration was 83%. The proportion with ≥12 months response duration was 19%1,3,4

In the combination cohort, 78% of the 51 patients with ongoing responses were followed <12 months from the date of onset of response1

In patients who had disease progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, median TTR was 3.3 months (range: 1.3 to 11.1 months).4
Immune-Mediated Pneumonitis
- OPDIVO (nivolumab) can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated pneumonitis occurred in 1.7% (2/119) of patients.

Immune-Mediated Nephritis and Renal Dysfunction
- OPDIVO can cause immune-mediated nephritis and renal dysfunction. Monitor patients for signs and symptoms of nephritis. Administer corticosteroids for Grade 2 or more severe nephritis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 1.5% (2/119) of patients.

Immune-Mediated Colitis
- OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or more severe colitis. Allow corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered in corticosteroid-refractory immune-mediated colitis if other causes are excluded.

Immune-Mediated Hepatitis
- OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or more severe hepatitis. Administer corticosteroids for Grade 3 or more severe hepatitis. Temporarily discontinue for Grade 4 hepatitis. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hepatitis occurred in 8% (10/119) of patients.

Immune-Mediated Endocrinopathies
- OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer corticosteroids as clinically indicated and corticosteroids for Grade 2 or more severe hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or more severe adrenal insufficiency. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 adrenal insufficiency. Administer corticosteroids for Grade 3 or more severe hypophysitis or adrenal insufficiency. Initiate medical management for control of hypophysitis. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hypophysitis. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated hypophysitis occurred in 3.4% (4/119) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, adrenal insufficiency occurred in 5.9% (7/119) of patients. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, hypophysitis or thyroiditis resulting in hypophysitis occurred in 15% (18/119) of patients. Hypothyroidism occurred in 12% (14/119) of patients.

Immune-Mediated Nephritis and Renal Dysfunction
- OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2–4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated nephritis and renal dysfunction occurred in 1.7% (2/119) of patients.

Immune-Mediated Skin Adverse Reactions
- OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). In some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 2 and permanently discontinue for Grade 4 rash. For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In MSI-H/dMMR mCRC patients receiving OPDIVO 3 mg/kg with YERVOY 1 mg/kg, immune-mediated rash occurred in 14% (17/119) of patients.

IMPORTANT SAFETY INFORMATION

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OPDIVO (nivolumab)

OPDIVO® and YERVOY® (ipilimumab)

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For OPDIVO and YERVOY®, please see Important Safety Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY, above, and U.S. Full Prescribing Information for OPDIVO and YERVOY.