OPDIVO® (nivolumab) + YERVOY® (ipilimumab): rethink what’s possible for your HCC patients previously treated with sorafenib*

*Patients who progressed on or were intolerant to sorafenib.†

Checkmate 040 OPDIVO + YERVOY cohort trial design: Checkmate 040 included a phase 1/2, multicenter, open-label trial investigating OPDIVO in combination with YERVOY in patients with HCC who progressed on or were intolerant to sorafenib. Key eligibility criteria included histologic confirmation of HCC and Child-Pugh Class A cirrhosis status. Additional eligibility criteria included those who were infected with active HCV or active HBV or were uninfected. Patients with active autoimmune disease, brain metastasis, a history of hepatic encephalopathy, clinically significant ascites, infection with HIV, or active co-infection with HBV and HCV or HBV and HDV were excluded. Patients with known fibrolamellar HCC, sarcomatoid HCC, and mixed cholangiocarcinoma and HCC were also excluded. Within the OPDIVO + YERVOY cohort, 49 patients were treated with OPDIVO 1 mg/kg IV and YERVOY 3 mg/kg IV every 3 weeks for 4 doses, followed by OPDIVO at 240 mg every 2 weeks.† Treatment was continued until disease progression or unacceptable toxicity. The major efficacy outcome was ORR, as assessed by BICR using RECIST v1.1 and mRECIST. Duration of response was also assessed.‡

An efficacious combination: 33% of patients responded to
OPDIVO + YERVOY†

- ORR based on mRECIST was 35% (17/49; 95% CI: 22.0–50.0)‡
  - CR: 12% (6/49); PR: 22% (11/49)
  - ORR was a major efficacy endpoint
  - Overall responses were observed in both PD-L1 expressors and non- expressors‡

**OPDIVO + YERVOY showed a 17.5 month mDOR**

- Median DOR is a Kaplan-Meier estimate.‡
- Minimum follow-up at time of data cutoff: 28 months
- Percentage of responders with DOR‡:
  - ≥6 months: 88%
  - ≥12 months: 56%
  - ≥24 months: 31%

**Selected safety profile in the OPDIVO + YERVOY cohort‡**

**Serious adverse reactions**
- In Checkmate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with YERVOY (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, diarrhea, anemia, increased AST, adrenal insufficiency, ascites, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis

**Common adverse reactions**
- In Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with YERVOY (n=49), were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (39%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%)

**Treatment discontinuation**
- Treatment was discontinued in 29% of patients and delayed in 65% of patients for an adverse reaction

**INDICATION**

OPDIVO, in combination with YERVOY, is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. 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 the confirmatory trials.

**SELECT IMPORTANT SAFETY INFORMATION**

**WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

YERVOY® (ipilimumab) 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), neuropathy, 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, hepatic, 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.

Summary of Warnings and Precautions
- OPDIVO is associated with the following Warnings and Precautions including immune-mediated: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, endocrinopathy, 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.

Please see additional Important Safety Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY, on page 4, and US Full Prescribing Information for OPDIVO and YERVOY.
**For patients with HCC previously treated with sorafenib**

**Majority** of immune-mediated adverse reactions across most categories were resolved after appropriate management.1

**Incidence and resolution of IMARs seen with OPDIVO® (nivolumab) + YERVOY® (ipilimumab)1-3**

<table>
<thead>
<tr>
<th>IMAR category</th>
<th>Any-grade IMARs</th>
<th>Median time to resolution (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% incidence</td>
<td>% resolution</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>10% (5/49)</td>
<td>80%</td>
</tr>
<tr>
<td>Colitis</td>
<td>10% (5/49)</td>
<td>100%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>20% (10/49)</td>
<td>90%</td>
</tr>
<tr>
<td>Rash</td>
<td>35% (7/49)</td>
<td>82%</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>4% (2/49)</td>
<td>0%</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>18% (9/49)</td>
<td>22%</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>22% (10/49)</td>
<td>46%</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10% (5/49)</td>
<td>80%</td>
</tr>
</tbody>
</table>

**IMAR analyses were limited to subjects who received immune-modulating medication for treatment of the event, with the exception of endocrine events.**

**Resolution was defined as improvement to Grade 0 or baseline grade per investigator assessment for all clustered events in a given category that occurred in a patient.**

OPDIVO can cause skin immune-mediated adverse reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); some cases with fatal outcome.1

Infusion-related reactions occurred in 8% (4/49) of patients. All events resolved. Median time to resolution: 0.4 weeks (range: 0.1–9.1 weeks).1

For recommendations on appropriate AE management, please refer to the dose modifications table in Section 2 and the Warnings and Precautions in Section 5 of the US Full Prescribing Information for OPDIVO and YERVOY.

**SELECT IMPORTANT SAFETY INFORMATION**

**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 greater transaminase elevations. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to >3 and up to 5 times the upper limit of normal (ULN), if AST/ALT is >1 and up to 3 times ULN at baseline and increases to >5 and up to 10 times the ULN, and if AST/ALT is >3 and up to 5 times ULN at baseline and increases to >8 and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to >10 times the ULN or total bilirubin increases >3 times the ULN. In HCC patients receiving OPDIVO 1 mg/kg with YERVOY 3 mg/kg, immune-mediated hepatitis occurred in 20% (10/49) of patients.

Please see additional Important Safety Information for OPDIVO and YERVOY, including **Boxed WARNING** regarding immune-mediated adverse reactions for YERVOY, on page 4, and US Full Prescribing Information for OPDIVO and YERVOY.
For patients with HCC previously treated with sorafenib

Start with OPDIVO® (nivolumab) + YERVOY® (ipilimumab), maintain with OPDIVO monotherapy flexible dosing schedules

Treat until disease progression or unacceptable toxicity.

Based on exploratory dose exposure–response relationships for efficacy and safety, OPDIVO 240 mg q2w and 480 mg q4w are predicted to be similar.

Review the Full Prescribing Information for OPDIVO and YERVOY, including Boxed WARNING for YERVOY, prior to initiation.

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

**SELECT IMPORTANT SAFETY INFORMATION**

**Infusion-Related Reactions**

- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2.
- In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO.

Please see additional Important Safety Information for OPDIVO and YERVOY, including Boxed WARNING regarding immune-mediated adverse reactions for YERVOY, on page 4, and US Full Prescribing Information for OPDIVO and YERVOY.
IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

YERVOR® (ipilimumab) 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 encephalopathy. The severity of these immune-mediated reactions typically manifested during treatment; however, a minority occurred weeks to months after discontinuation of Yervor.

Assess patients for signs and symptoms of enterocolitis, hepatitis, nephropathy, and encephalopathy, 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 Yervor and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.

**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 HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, immune-mediated pneumonitis occurred in 10% (5/49) of patients.

**Immune-Mediated Colitis**

- OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with Yervor, withhold OPDIVO for Grade 2, 3, or 4 colitis. In HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, immune-mediated colitis occurred in 10% (5/49) of patients.

**Immune-Mediated Nephritis and Renal Dysfunction**

- OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine. Administer corticosteroids for Grade 2 or more severe nephritis. Discontinue OPDIVO in patients with Grade 4 increases in creatinine. In HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, immune-mediated nephritis occurred in 20% (10/49) of patients.

**Immune-Mediated Endocrinopathies**

- OPDIVO can cause immune-mediated endocrinopathies, including autoimmune thyroid disorders, Type 1 diabetes mellitus, and hypophysitis. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adenaial insufficiency, thyroid dysfunction, and hyperglicemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

- In HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, hypophysitis occurred in 4% (2/49) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, adrenal insufficiency occurred in 18% (9/49) of patients. In HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, hypothyroidism or thyrotoxicosis resulting in hypothyroidism occurred in 22% (11/49) of patients. Hypothyroidism occurred in 10% (5/49) of patients receiving this dose of OPDIVO with Yervor.

**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.

**Immune-Mediated Skin Adverse Reactions**

- OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold OPDIVO for Grade 3 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 HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, immune-mediated rash occurred in 35% (17/49) of patients.

**Immune-Mediated Encephalitis**

- OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms should include, but not be limited to, consultation with a neurologist, brain MR, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis.

Other Immune-Mediated Adverse Reactions

- Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with Yervor, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, uveitis, iritis, pancreatitis, facial and abducens nerve paresis, dermelynosis, polylymphagia rheumatica, autoimmune nephropathy Guillian-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome with gastroenteritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), motor dysfunction, vasculitis, aplastic anemia, pericarditis, and myasthenic syndrome.

- If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, which has been observed in patients receiving OPDIVO and may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Infusion-Related Reactions

- OPDIVO can cause severe infusion-related reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion-related reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy as a 60-minute infusion, infusion-related reactions occurred in 6.4% (127/1994) of patients. In a separate trial in which patients received OPDIVO monotherapy as a 60-minute infusion or a 30-minute infusion, infusion-related reactions occurred in 2.2% (8/368) and 2.7% (10/369) of patients, respectively. Additionally, 0.5% (2/368) and 1.4% (5/369) of patients, respectively, experienced adverse reactions within 48 hours of infusion that led to dose delay, permanent discontinuation or withholding of OPDIVO. In HCC patients receiving OPDIVO 1 mg/kg with YERVOR 3 mg/kg, infusion-related reactions occurred in 8% (4/49) of patients.

Embryo-Fetal Toxicity

- Based on mechanism of action, OPDIVO and Yervor can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDIVO or Yervor and for at least 5 months after the last dose.

Increased Mortality in Patients with Multiple Myeloma when OPDIVO is Added to a Thalidomide Analogue and Dexamethasone

- In clinical trials in patients with multiple myeloma, the addition of OPDIVO to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Lactation

- It is not known whether OPDIVO or Yervor is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from OPDIVO or Yervor, advise women not to breastfeed during treatment and for at least 5 months after the last dose.

Serious Adverse Reactions

- In CheckMate 040, serious adverse reactions occurred in 59% of patients receiving OPDIVO with Yervor (n=49). Serious adverse reactions reported in ≥4% of patients were pyrexia, anemia, diarrhea, increased AST, adrenal insufficiency, asesthes, esophageal varices hemorrhage, hyponatremia, increased blood bilirubin, and pneumonitis.

Common Adverse Reactions

- In CheckMate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO with Yervor (n=49) were rash (53%), pruritus (53%), musculoskeletal pain (41%), diarrhea (35%), cough (37%), decreased appetite (35%), fatigue (27%), pyrexia (27%), abdominal pain (22%), headache (22%), nausea (20%), dizziness (20%), hypothyroidism (20%), and weight decreased (20%).

Please see additional Important Safety Information for OPDIVO and Yervor, including Boxed WARNING regarding immune-mediated adverse reactions for Yervor, on this page, and US Full Prescribing Information for OPDIVO and Yervor.

References:


