HCC

UNRESECTABLE

# GUIDE TO DOSING AND IMMUNE-MEDIATED ADVERSE REACTIONS

## For patients receiving IMFINZI + IMJUDO for the 1L treatment of unresectable hepatocellular carcinoma (uHCC)

1L=first line.

### Indication:

IMFINZI in combination with IMJUDO is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).

### IMPORTANT SAFETY INFORMATION

There are no contraindications for IMFINZI® (durvalumab) or IMJUDO® (tremelimumab-actl).

**Severe and Fatal Immune-Mediated Adverse Reactions**

Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment or after discontinuation. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function at baseline and before each dose. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold or permanently discontinue IMFINZI and IMJUDO depending on severity. See USPI Dosing and Administration for specific details. In general, if combination of IMFINZI and IMJUDO requires interruption or discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

**Please see additional Important Safety Information throughout and Full Prescribing Information including Medication Guide for IMFINZI and IMJUDO.**

IMFINZI® durvalumab
Injection for Intravenous Use 50 mg/mL

IMJUDO® tremelimumab-actl
Injection for Intravenous Use 20 mg/mL

# STRIDE (Single Tremelimumab Regular Interval Durvalumab): The only approved dual-IO regimen for 1L treatment of uHCC[1-3]

- Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that binds to PD-L1 and blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, without inducing antibody-dependent cell-mediated cytotoxicity (ADCC)[1]
- Tremelimumab-actl is a monoclonal antibody that binds to CTLA-4 and blocks the interaction with its ligands CD80 and CD86, releasing CTLA-4–mediated inhibition of T-cell activation[2]

## STRIDE Regimen: Single priming dose IMJUDO + IMFINZI on Day 1, followed by Q4W IMFINZI[1,2]

**For patients with a body weight of ≥30 kg**

**ON DAY 1**

SINGLE-DOSE **IMJUDO** 300-mg fixed-dose infusion* + **IMFINZI** 1500-mg fixed-dose infusion†

1-hour (60-minute) observation

**EVERY 4 WEEKS**

**IMFINZI**

1500-mg fixed-dose infusion†

Continue until disease progression or unacceptable toxicity

*Patients with a body weight of <30 kg must receive weight-based dosing, equivalent to IMJUDO 4 mg/kg until body weight is ≥30 kg.
†Patients with a body weight of <30 kg must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg until body weight is ≥30 kg.

- The STRIDE Regimen (Single Tremelimumab Regular Interval Durvalumab): A single priming dose of IMJUDO 300 mg followed by IMFINZI 1500 mg on Day 1 of Cycle 1; continue IMFINZI 1500 mg as a single agent every 4 weeks[1,2]
- IMJUDO and IMFINZI are each administered as a 60-minute IV infusion with no premedication required[1,2]
- Administer IMJUDO prior to IMFINZI on Day 1 of treatment[1,2]
- Observe patient for 60 minutes following completion of IMJUDO infusion. Then administer IMFINZI as a separate IV infusion over 60 minutes on the same day[1,2]

**For more information on administering IMFINZI + IMJUDO, visit IMFINZIhcp.com/HCCdosing**

CD80=cluster of differentiation 80; CD86=cluster of differentiation 86; CTLA-4=cytotoxic T-lymphocyte–associated protein 4; IO=immuno-oncology; IV=intravenous; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; Q4W=every 4 weeks.



# Summary of immune-mediated adverse reactions with IMFINZI + IMJUDO in the HIMALAYA study[4,5]

- IMFINZI + IMJUDO may induce immune-mediated adverse reactions. imARs can occur in any organ system or tissue at any time after starting IMFINZI + IMJUDO, including after discontinuation of treatment. imARs may be severe or fatal[1,2]

**IMMUNE-MEDIATED ADVERSE REACTIONS OBSERVED WITH IMFINZI + IMJUDO IN THE HIMALAYA STUDY[4,5]**

| | IMFINZI + IMJUDO (n=388) | | |
|---|---|---|---|
| **imARs** | **All grades (%)** | **Grade 3-4 (%)** | **Patients discontinuing due to imARs (%)** |
| Any | **35.8** | **12.6** | **5.7** |
| Hepatic events | **7.5** | **4.1** | **2.3** |
| Diarrhea/colitis‡ | **5.9** | **3.6** | **1.3** |
| Dermatitis/rash§ | **4.9** | **1.8** | **0.5** |
| Pancreatic events | **2.3** | **1.8** | **0** |
| Renal events | **1** | **0.5** | **0.5** |
| Adrenal insufficiency | **1.5** | **0.3** | **0** |
| Hyperthyroid events | **4.6** | **0.3** | **0** |
| Hypothyroid events | **10.8** | **0** | **0** |
| Pneumonitis | **1.3** | **0** | **0.3** |

Includes adverse events with onset or increase in severity on or after the date of first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.
‡Immune-mediated diarrhea/colitis was reported as a grouped term within the HIMALAYA study.
§Immune-mediated dermatitis/rash was reported as a grouped term within the HIMALAYA study.
imARs=immune-mediated adverse reactions.

- 20.1% of patients treated with IMFINZI + IMJUDO required corticosteroids dosed at ≥40 mg prednisone or equivalent per day for the management of imARs[4]
- 5.7% of patients treated with IMFINZI + IMJUDO discontinued due to imARs[4]
- Treatment-emergent fatal imARs occurred in 6 patients (1.5%) treated with IMFINZI + IMJUDO[4]

## IMPORTANT SAFETY INFORMATION (continued)

**Immune-Mediated Pneumonitis**

IMFINZI in combination with IMJUDO can cause immune-mediated pneumonitis, which may be fatal. Immune-mediated pneumonitis occurred in 1.3% (5/388) of patients receiving IMFINZI and IMJUDO, including fatal (0.3%) and Grade 3 (0.2%) adverse reactions.

**Please see additional Important Safety Information throughout and Full Prescribing Information including Medication Guide for IMFINZI and IMJUDO.**

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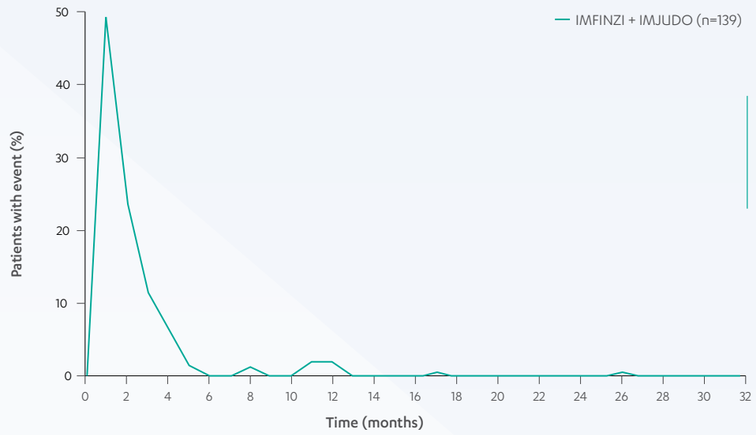
# Frequency of events in patients experiencing imARs with IMFINZI + IMJUDO in the HIMALAYA study (exploratory post-hoc analysis)[6]

For patients who experienced an imAR with IMFINZI + IMJUDO, most events occurred within the first 3 months of treatment

**OVERALL FREQUENCY OF ANY imAR BY TIME IN PATIENTS WHO EXPERIENCED AN imAR (n/N=139/388)***




**Pattern of occurrence** for the 35.8% of patients treated with IMFINZI + IMJUDO who experienced an imAR (n/N=139/388)[5,6]

*The percentage of patients with a reaction is the number of patients who experienced ≥1 imAR at each time interval divided by the number of patients who experienced ≥1 imAR at any time; includes first imARs only, regardless of grade.

- This exploratory post-hoc analysis assessed temporal patterns of imARs in patients with uHCC treated with IMFINZI + IMJUDO in the HIMALAYA study (n=388). Data cutoff: August 27, 2021[6]
- Median total duration of IMFINZI treatment was 5.5 months (range: 0.4-42.7) for IMFINZI + IMJUDO (n=388)[4]

**imARs, which may be severe or fatal, can occur in any organ system or tissue. imARs can occur at any time after starting treatment or after discontinuation[1,2]**

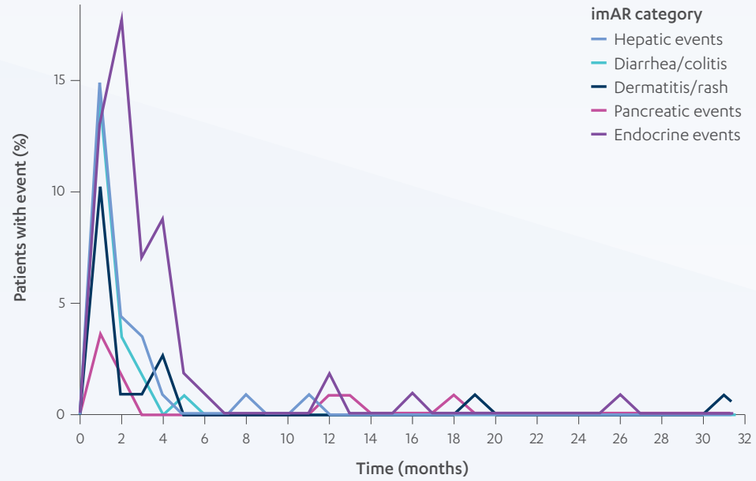
## IMPORTANT SAFETY INFORMATION (continued)

**Immune-Mediated Colitis**

IMFINZI in combination with IMJUDO can cause immune-mediated colitis that is frequently associated with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis or diarrhea occurred in 6% (23/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (3.6%) adverse reactions. Intestinal perforation has been observed in other studies of IMFINZI and IMJUDO.

# Frequency of most common imARs with IMFINZI + IMJUDO by category[6]

**FREQUENCY OF MOST COMMON imARs BY TIME IN PATIENTS WITH AN imAR†**




†The percentage of patients with a reaction is the number of patients who experienced ≥1 imAR at each time interval divided by the number of patients who experienced ≥1 imAR at any time; includes the first imARs only, regardless of grade.

- Most common imARs shown include those that occurred in ≥2.0% of patients in the IMFINZI + IMJUDO treatment arm[5,6]
- The most common imARs observed with IMFINZI + IMJUDO in the HIMALAYA study (all grades) were hepatic events (7.5%), diarrhea/colitis (5.9%), dermatitis/rash (4.9%), pancreatic events (2.3%), adrenal insufficiency (1.5%), hyperthyroid events (4.6%), hypothyroid events (10.8%), pneumonitis (1.3%), and renal events (1.0%)[5]
- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated dermatologic reactions, immune-mediated pancreatitis, solid organ transplant rejection, and other transplant (including corneal graft) rejection[1,2]

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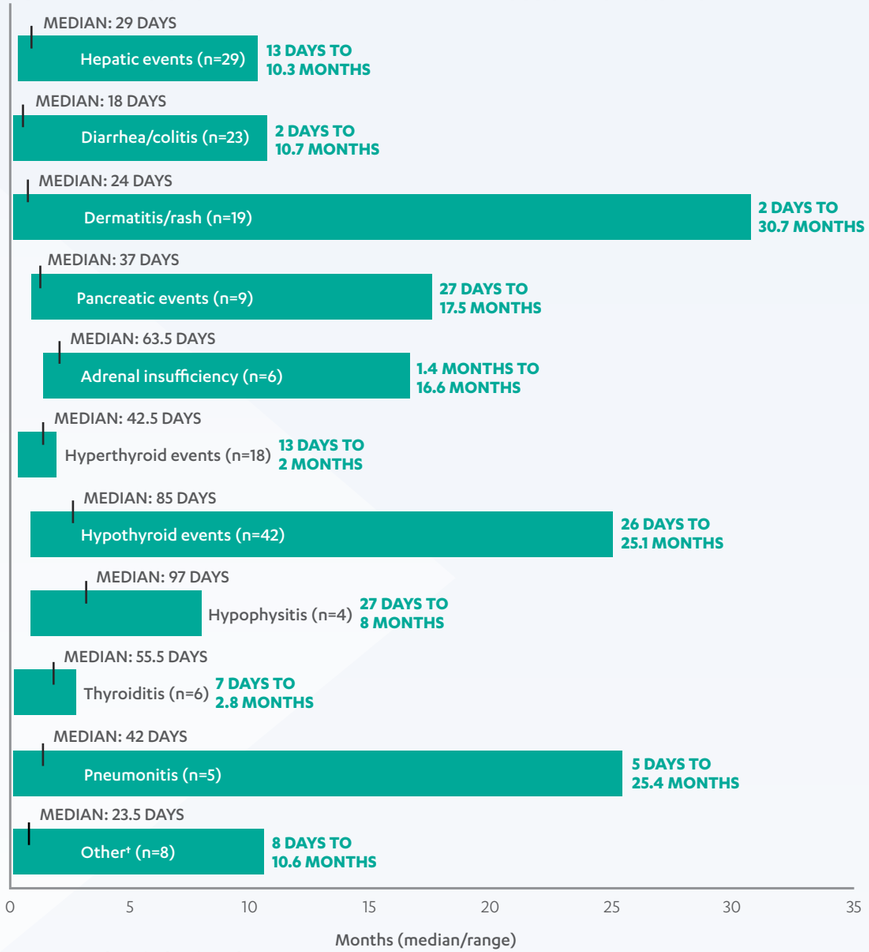
# Time to onset and general guidance for managing imARs with IMFINZI + IMJUDO

**Immune-mediated adverse reactions can occur at any time during or after treatment with IMFINZI + IMJUDO.[1,2]**

**MEDIAN TIME TO ONSET OF imARs WITH IMFINZI + IMJUDO WAS <90 DAYS[4,7]***




*Time to onset was from the first dose of treatment.
†Arthralgia (n=4), polymyalgia rheumatica (n=3), vasculitis (n=1).

## General guidance for managing imARs with IMFINZI + IMJUDO[1,2]

**No dose reduction for IMFINZI or IMJUDO is recommended. Withholding or permanently discontinuing the treatment regimen due to adverse reactions may be required**

- Withhold the treatment regimen for severe (Grade 3) imARs
- Permanently discontinue the treatment regimen for life-threatening (Grade 4) imARs
- Permanently discontinue the treatment regimen for recurrent severe (Grade 3) imARs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to ≤10 mg prednisone or equivalent per day within 12 weeks of initiating corticosteroids



# Treatment modifications for IMFINZI + IMJUDO[1,2]

## General guidance for managing imARs with IMFINZI + IMJUDO[1,2] (continued)

- If the treatment regimen requires interruption or permanent discontinuation, administer systemic corticosteroid therapy (1 mg to 2 mg/kg/day prednisone or equivalent) until improvement to Grade ≤1
- Upon improvement to Grade ≤1, initiate corticosteroid taper and continue to taper over at least 1 month. Resume treatment in patients after complete or partial resolution and taper

**TREATMENT MODIFICATIONS FOR ADVERSE REACTIONS[1,2]**

| Adverse reaction | Severity‡ | Treatment modification |
|---|---|---|
| **imARs** | | |
| **Pulmonary** Pneumonitis | Grade 2 | Withhold§ |
| | Grade 3 or 4 | Permanently discontinue |
| **Gastrointestinal** Colitis | Grade 2 | Withhold§ |
| | Grade 3 or 4 | Permanently discontinue |
| **Gastrointestinal** Intestinal perforation | Any grade | Permanently discontinue |
| **Hepatic** Hepatitis with no tumor involvement of the liver | AST or ALT increases to >3 and up to 8 × ULN or total bilirubin increases to >1.5 and up to 3 × ULN | Withhold§ |
| | AST or ALT increases to >8 × ULN or total bilirubin increases to >3 × ULN | Permanently discontinue |
| **Hepatic** Hepatitis with tumor involvement of the liver‖ | AST or ALT is >1 and up to 3 × ULN at baseline and increases to >5 and up to 10 × ULN or AST or ALT is >3 and up to 5 × ULN at baseline and increases to >8 and up to 10 × ULN | Withhold§ |
| | AST or ALT increases to >10 × ULN or total bilirubin increases to >3 × ULN | Permanently discontinue |
| **Endocrine** Endocrinopathies | Grade 3 or 4 | Withhold until clinically stable or permanently discontinue depending on severity |
| **Renal** Nephritis with renal dysfunction | Grade 2 or 3 increased blood creatinine | Withhold§ |
| | Grade 4 increased blood creatinine | Permanently discontinue |
| **Exfoliative dermatologic conditions** | Suspected SJS, TEN, or DRESS | Withhold§ |
| | Confirmed SJS, TEN, or DRESS | Permanently discontinue |
| **Cardiac** Myocarditis | Grade 2, 3, or 4 | Permanently discontinue |
| **Neurological toxicities** | Grade 2 | Withhold§ |
| | Grade 3 or 4 | Permanently discontinue |
| **Other adverse reactions** | | |
| **Infusion-related reactions** | Grade 1 or 2 | Interrupt or slow the rate of infusion |
| | Grade 3 or 4 | Permanently discontinue |

‡Based on NCI CTCAE, version 4.03.
§Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce corticosteroid dose to 10 mg of prednisone or less per day (or equivalent) within 12 weeks of initiating corticosteroids.
‖If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue IMFINZI based on recommendations for hepatitis with no liver involvement.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; DRESS=Drug Rash with Eosinophilia and Systemic Symptoms; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; SJS=Stevens-Johnson Syndrome; TEN=toxic epidermal necrolysis; ULN=upper limit of normal.

**Prescribing Information has additional information for dosage modification and management specific to adverse reactions.**

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# IMFINZI preparation, administration, and storage[1]

## Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed

Withdraw the required volume from the vial(s) of IMFINZI and transfer into an IV bag containing 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL

Discard partially used or empty vials of IMFINZI

Do not shake the vial

## Administration

Administer infusion solution intravenously over 60 minutes through an IV line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter

For combination therapy, administer all drug products as separate IV infusions. Use separate infusion bags and filters for each drug product

## Storage

IMFINZI does not contain a preservative.
The time from preparation until completion of the infusion should not exceed:

28 days in a refrigerator at 2°C to 8°C (36°F to 46°F)

Do not freeze

8 hours at room temperature up to 25°C (77°F)

Do not shake

IMFINZI is supplied as single-use vials that contain:

- 120 mg/2.4 mL (50 mg/mL)
- 500 mg/10 mL (50 mg/mL)


Vials are not shown to actual size or scale.

**Please see additional Important Safety Information throughout and Full Prescribing Information including Medication Guide for IMFINZI and IMJUDO.**



# IMJUDO preparation, administration, and storage[2]

## Preparation

Visually inspect drug product for particulate matter and discoloration prior to administration whenever solution and container permit. Discard the vial if the solution is cloudy, discolored, or visible particles are observed

Withdraw the required volume from the vial(s) of IMJUDO and transfer into an IV bag containing 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake the solution. The final concentration of the diluted solution should not exceed 10 mg/mL

Discard partially used or empty vials of IMJUDO

Do not shake the vial

## Administration

Administer infusion solution intravenously over 60 minutes through an IV line containing a sterile, low-protein binding 0.2 or 0.22 micron filter

Do not co-administer other drugs through the same infusion line. Use separate infusion bags and filters for each drug product

## Storage

IMJUDO does not contain a preservative.
The total time from preparation to the start of administration should not exceed:

24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F)

Do not freeze

24 hours at room temperature up to 30°C (86°F)

Do not shake

IMJUDO is supplied as single-use vials that contain:

- 25 mg/1.25 mL (20 mg/mL)
- 300 mg/15 mL (20 mg/mL)


Vials are not shown to actual size or scale.

## IMPORTANT SAFETY INFORMATION (continued)

**Immune-Mediated Hepatitis**

IMFINZI in combination with IMJUDO can cause immune-mediated hepatitis, which may be fatal. Immune-mediated hepatitis occurred in 7.5% (29/388) of patients receiving IMFINZI and IMJUDO, including fatal (0.8%), Grade 4 (0.3%) and Grade 3 (4.1%) adverse reactions.

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# Check patients for immune-mediated adverse reactions at each visit[1,2]

Monitoring your patients who are being treated with IMFINZI + IMJUDO at every infusion and office visit can aid in early identification and interventions for imARs. This is important to help ensure the safety of your patients as they continue treatment.

Consult with the care team right away if patients present any new or worsening signs or symptoms, including the below.

### Pulmonary

- Cough
- Shortness of breath
- Chest pain

### Gastrointestinal

- Diarrhea (loose stools) or more frequent bowel movements than usual
- Stools that are black, tarry, sticky, or have blood or mucus
- Severe abdominal pain or tenderness

### Hepatic

- Yellowing of the skin or whites of the eyes
- Severe nausea or vomiting
- Pain on the right side of abdomen
- Dark urine (tea colored)
- Bleeding or bruising more easily than normal

### Endocrine

- Headaches that will not go away or unusual headaches
- Eye sensitivity to light
- Eye problems
- Rapid heartbeat
- Increased sweating
- Extreme tiredness
- Weight gain or weight loss
- Feeling more hungry or thirsty than usual
- Urinating more often than usual
- Hair loss
- Feeling cold
- Constipation
- Voice gets deeper
- Dizziness or fainting
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

### Renal

- Decrease in amount of urine
- Blood in urine
- Swelling of ankles
- Loss of appetite

### Skin

- Rash
- Itching
- Skin blistering or peeling
- Painful sores or ulcers in mouth or nose, throat, or genital area
- Fever or flu-like symptoms
- Swollen lymph nodes

### Pancreatic

- Pain in the upper abdomen
- Severe nausea or vomiting
- Loss of appetite

### Other

- Chest pain, irregular heartbeats, shortness of breath, or swelling of ankles
- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Persistent or severe muscle pain or weakness, muscle cramps
- Low red blood cells, bruising

**For more information on managing immune-mediated adverse reactions with IMFINZI + IMJUDO, visit IMFINZIhcp.com/HCCimARs**

**References: 1.** IMFINZI® (durvalumab) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2024. **2.** IMJUDO® (tremelimumab-actl) [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. **3.** Oncology (cancer)/hematologic malignancies approval notifications. US Food and Drug Administration. Updated April 29, 2024. Accessed May 8, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications **4.** Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1(8). doi:10.1056/EVIDoa2100070. **5.** Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab and durvalumab as first-line therapy in patients with unresectable hepatocellular carcinoma: HIMALAYA. Presented at: ASCO Gastrointestinal Cancers Symposium; January 20-22, 2022; San Francisco, CA. **6.** Lau G, Sangro B, Crysler OV, et al. Temporal patterns of immune-mediated adverse events with tremelimumab plus durvalumab in the phase 3 HIMALAYA study in unresectable hepatocellular carcinoma. Poster presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, IL. **7.** Sangro B, Chan SL, Kudo M, et al. Adverse event profiles and time to onset and resolution with tremelimumab plus durvalumab in patients with unresectable hepatocellular carcinoma in the Phase 3 HIMALAYA trial. Presented at: International Liver Cancer Association Annual Conference; September 1-4, 2022; Madrid, Spain. **8.** Wiley K, LeFebvre KB, Wall L, et al. Immunotherapy administration: Oncology Nursing Society recommendations. *Clin J Oncol Nurs*. 2017;21(suppl 2):5-7. **9.** Bayer V, Amaya B, Baniewicz D, Callahan C, Marsh L, McCoy AS. Cancer immunotherapy: an evidence-based overview and implications for practice. *Clin J Oncol Nurs*. 2017;21(suppl 2):13-21. **10.** Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol*. 2016;2(10):1346-1353. **11.** Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13(8):473-486. **12.** Wood LS, Moldawer NP, Lewis C. Immune checkpoint inhibitor therapy: key principles when educating patients. *Clin J Oncol Nurs*. 2019;23(3):271-280.

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# IMPORTANT SAFETY INFORMATION (continued)

**Immune-Mediated Endocrinopathies**

- ***Adrenal Insufficiency***: IMFINZI in combination with IMJUDO can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Immune-mediated adrenal insufficiency occurred in 1.5% (6/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (0.3%) adverse reactions.
- ***Hypophysitis***: IMFINZI in combination with IMJUDO can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field cuts. Hypophysitis can cause hypopituitarism. Initiate symptomatic treatment including hormone replacement as clinically indicated. Immune-mediated hypophysitis/hypopituitarism occurred in 1% (4/388) of patients receiving IMFINZI and IMJUDO.
- ***Thyroid Disorders (Thyroiditis, Hyperthyroidism, and Hypothyroidism)***: IMFINZI in combination with IMJUDO can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement therapy for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated.
  - Immune-mediated thyroiditis occurred in 1.5% (6/388) of patients receiving IMFINZI and IMJUDO.
  - Immune-mediated hyperthyroidism occurred in 4.6% (18/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (0.3%) adverse reactions.
  - Immune-mediated hypothyroidism occurred in 11% (42/388) of patients receiving IMFINZI and IMJUDO.
- ***Type 1 Diabetes Mellitus, which can present with diabetic ketoacidosis***: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Two patients 0.5% (2/388) had events of hyperglycemia requiring insulin therapy that had not resolved at last follow-up.

**Immune-Mediated Nephritis with Renal Dysfunction**

IMFINZI in combination with IMJUDO can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 1% (4/388) of patients receiving IMFINZI and IMJUDO, including Grade 3 (0.5%) adverse reactions.

**Immune-Mediated Dermatology Reactions**

IMFINZI in combination with IMJUDO can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson Syndrome (SJS), drug rash with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TEN), has occurred with PD-1/L-1 and CTLA-4 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Immune-mediated rash or dermatitis occurred in 4.9% (19/388) of patients receiving IMFINZI and IMJUDO, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions.

**Immune-Mediated Pancreatitis**

IMFINZI in combination with IMJUDO can cause immune-mediated pancreatitis. Immune-mediated pancreatitis occurred in 2.3% (9/388) of patients receiving IMFINZI and IMJUDO, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions.

**Other Immune-Mediated Adverse Reactions**

The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in patients who received IMFINZI in combination with IMJUDO or were reported with the use of other immune-checkpoint inhibitors.

- ***Cardiac/vascular***: Myocarditis, pericarditis, vasculitis.
- ***Nervous system***: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.
- ***Ocular***: Uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.
- ***Gastrointestinal***: Gastritis, duodenitis.
- ***Musculoskeletal and connective tissue disorders***: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatic.
- ***Endocrine***: Hypoparathyroidism.
- ***Other (hematologic/immune)***: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection, other transplant (including corneal graft) rejection.

**Infusion-Related Reactions**

IMFINZI and IMJUDO can cause severe or life-threatening infusion-related reactions. Monitor for signs and symptoms of infusion-related reactions. Interrupt, slow the rate of, or permanently discontinue IMFINZI and IMJUDO based on the severity. See USPI Dosing and Administration for specific details. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses. Infusion-related reactions occurred in 10 (2.6%) patients receiving IMFINZI and IMJUDO.

**Complications of Allogeneic HSCT after IMFINZI**

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/L-1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/L-1 blockade and allogeneic HSCT. Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/L-1 blocking antibody prior to or after an allogeneic HSCT.

**Embryo-Fetal Toxicity**

Based on its mechanism of action and data from animal studies, IMFINZI and IMJUDO can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. In females of reproductive potential, verify pregnancy status prior to initiating IMFINZI and IMJUDO and advise them to use effective contraception during treatment with IMFINZI and IMJUDO and for 3 months after the last dose of IMFINZI and IMJUDO.

**Lactation**

There is no information regarding the presence of either IMFINZI or IMJUDO in human milk; however, because of the potential for serious adverse reactions in breastfed infants from IMFINZI and IMJUDO, advise women not to breastfeed during treatment and for 3 months after the last dose.

**Adverse Reactions**

- In patients with unresectable HCC in the HIMALAYA study receiving IMFINZI and IMJUDO (n=388), the most common adverse reactions (occurring in ≥20% of patients) were rash (32%), diarrhea (27%), fatigue (26%), pruritus (23%), musculoskeletal pain (22%), and abdominal pain (20%).
- In patients with unresectable HCC in the HIMALAYA study receiving IMFINZI and IMJUDO (n=388), serious adverse reactions occurred in 41% of patients. Serious adverse reactions in >1% of patients included hemorrhage (6%), diarrhea (4%), sepsis (2.1%), pneumonia (2.1%), rash (1.5%), vomiting (1.3%), acute kidney injury (1.3%), and anemia (1.3%). Fatal adverse reactions occurred in 8% of patients who received IMFINZI and IMJUDO, including death (1%), hemorrhage intracranial (0.5%), cardiac arrest (0.5%), pneumonitis (0.5%), hepatic failure (0.5%), and immune-mediated hepatitis (0.5%). Permanent discontinuation of treatment regimen due to an adverse reaction occurred in 14% of patients.

The safety and effectiveness of IMFINZI and IMJUDO have not been established in pediatric patients.

*You may report side effects related to AstraZeneca products.*

**Please see additional Important Safety Information throughout and Full Prescribing Information including Medication Guide for IMFINZI and IMJUDO.**

IMFINZI® durvalumab Injection for Intravenous Use 50 mg/mL

IMJUDO® tremelimumab-actl Injection for Intravenous Use 20 mg/mL

# Key takeaways

- Immunotherapies come with a unique set of adverse reactions, termed immune-mediated adverse reactions, which differ from those associated with other anticancer approaches[8-10]
- Adverse reactions can develop at any time during the patient's clinical course, even after the end of therapy[11,12]
- Prompt intervention is critical in the management of imARs[12]
- Corticosteroids are the backbone of most imAR treatment[10]

## Help your patients during treatment

Immune-mediated adverse reactions can be different than what is expected with chemotherapy. It is important to understand the safety profiles of IMFINZI and IMJUDO and encourage your patients to track any signs and symptoms they may experience.

## Educate your patients

**Make sure your patients:**

- Understand the signs and symptoms of imARs
- Immediately report unusual signs and symptoms
- Go directly to the oncologist's office for evaluation/treatment
- Go directly to the emergency room if experiencing severe shortness of breath or a life-threatening emergency

## Monitor their health

- Blood tests*
- Schedule patients for regular visits for blood tests and monitoring of signs and symptoms
- Encourage patients to use their symptom tracker

## Create an action plan

- Follow a clear management algorithm for all grades of toxicities
- Understand when a specialist should be contacted to help manage imARs

**Offer your patients receiving IMFINZI + IMJUDO an information card for visits to doctors not on their regular care team or to the emergency room by clicking here**

*Please see complete Prescribing Information for specific blood tests for IMFINZI + IMJUDO.

**Please see Important Safety Information throughout and Full Prescribing Information including Medication Guide for IMFINZI and IMJUDO.**

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