IMFINZI® (durvalumab) injection, for intravenous use

IMFINZI is a programmed death-ligand 1 (PD-L1) blocking antibody indicated for the treatment of patients with:

- Locally advanced or metastatic urothelial carcinoma who:
  - have disease progression during or following platinum-containing chemotherapy. (1.1)
  - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. (1.1)

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1.1)

- Unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. (1.2)

- Stage III NSCLC: 10 mg/kg every 2 weeks. (2.2)
- Urothelial Carcinoma: 10 mg/kg every 2 weeks. (2.1)

- Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial. (3)
- Injection: 120 mg/2.4 mL (50 mg/mL) solution in a single-dose vial. (3)

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**Adverse Reactions**

- Most common adverse reactions (≥15% of patients with urothelial carcinoma) were fatigue, musculoskeletal pain, constipation, decreased appetite, nausea, peripheral edema, and urinary tract infection. (6.1)
- Most common adverse reactions (≥20% of patients with unresectable, Stage III NSCLC) were cough, fatigue, pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash. (6.1)

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**Use in Specific Populations**

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for Patient Counseling Information and Medication Guide

Revised: 02/2018
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Urothelial Carcinoma

IMFINZI is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy;
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [see Clinical Studies (14.1)].

1.2 Non-Small Cell Lung Cancer

IMFINZI is indicated for the treatment of patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Urothelial Carcinoma

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks, until disease progression or unacceptable toxicity.

2.2 Recommended Dosage for NSCLC

The recommended dose of IMFINZI is 10 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression, unacceptable toxicity, or a maximum of 12 months.

2.3 Dosage Modifications for Adverse Reactions

No dose reductions are recommended. Withhold or discontinue IMFINZI to manage adverse reactions as described in Table 1.

Table 1. Recommended Dosage Modifications for Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Dosage Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis [see Warnings and Precautions (5.1)]</td>
<td>Grade 2</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>For ALT or AST greater than 3 times the ULN or Total bilirubin greater than 1.5 but less than or equal to 5 times the ULN</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>ALT or AST greater than 8 times the ULN or Total bilirubin greater than 5 times the ULN or Concurrent ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN with no other cause</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hepatitis [see Warnings and Precautions (5.2)]</td>
<td>Grade 2</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td></td>
<td>For ALT or AST greater than 3 times the ULN or Total bilirubin greater than 1.5 but less than or equal to 5 times the ULN</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>Concurrent ALT or AST greater than 3 times the ULN and total bilirubin greater than 2 times the ULN with no other cause</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Colitis or diarrhea [see Warnings and Precautions (5.3)]</td>
<td>Grade 2</td>
<td>Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent).</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue</td>
</tr>
<tr>
<td>Hyperthyroidism [see Warnings and Precautions (5.4)]</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
</tr>
<tr>
<td>Adrenal insufficiency or Hypophysis/ Hypopituitarism [see Warnings and Precautions (5.4)]</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
</tr>
<tr>
<td>Type 1 Diabetes Mellitus [see Warnings and Precautions (5.4)]</td>
<td>Grade 2-4</td>
<td>Withhold dose until clinically stable</td>
</tr>
</tbody>
</table>

1. National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

2.4 Preparation and Administration

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.
- Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous 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.

Storage of Infusion Solution

- IMFINZI does not contain a preservative.
- Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the total time from vial puncture to the start of the administration should not exceed:
  - 24 hours in a refrigerator at 2°C to 8°C (36°F to 46°F)
  - 4 hours at room temperature up to 25°C (77°F)
- Do not freeze.
- Do not shake.

Administration

- Administer infusion solution intravenously over 60 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.
- Do not co-administer other drugs through the same infusion line.
IMFINZI® (durvalumab) injection, for intravenous use

3 DOSAGE FORMS AND STRENGTHS
Injection: 120 mg/2.4 mL (50 mg/mL) and 500 mg/10 mL (50 mg/mL) clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Immune-Mediated Pneumonitis
IMFINZI can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids. Fatal cases have been reported.

Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent for moderate (Grade 2) pneumonitis or prednisone 1 to 4 mg per kg per day or equivalent for more severe (Grade 3-4) pneumonitis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1)], pneumonitis occurred in 5% of patients, including Grade 3 (0.8%), Grade 4 (< 0.1%) and Grade 5 (0.3%) immune-mediated pneumonitis. The median time to onset was 1.8 months (range: 1 day to 13.9 months) and the median time to resolution was 4.9 months (range: 0 days to 13.7 months).

Pneumonitis led to discontinuation of IMFINZI in 1.5% of the 1889 patients. Pneumonitis resolved in 54% of patients. Systemic corticosteroids were required in 3.5% of the 1889 patients, with 2.5% requiring high-dose corticosteroids (prednisone > 40 mg per day or equivalent) and 0.1% requiring infliximab.

The incidence of pneumonitis (including radiation pneumonitis) was higher in patients in the PACIFIC study who completed treatment with definitive chemoradiation within 42 days prior to initiation of IMFINZI (34%) compared to patients in other clinical studies (2.3%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI.

In the PACIFIC study, the incidence of Grade 3 pneumonitis was 3.4% and the incidence of Grade 5 pneumonitis was 1.1% in the IMFINZI arm. The median time to onset of pneumonitis was 1.8 months and the median duration was 2.1 months (range: 3 days to 18.7 months). Pneumonitis led to discontinuation of IMFINZI in 6% of patients. Pneumonitis resolved in 47% of patients experiencing pneumonitis. Systemic corticosteroids were required in 21% of patients, with 12% requiring high-dose corticosteroids and 0.1% requiring infliximab.

5.2 Immune-Mediated Hepatitis
IMFINZI can cause immune-mediated hepatitis, defined as requiring use of corticosteroids. Fatal cases have been reported.

Monitor patients for signs and symptoms of hepatitis, during and after discontinuation of IMFINZI, including clinical chemistry monitoring. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent, followed by taper for Grade 2 or higher. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1)], hepatitis occurred in 12% of patients, including Grade 3 (4.4%), Grade 4 (0.4%) and Grade 5 (0.2%) immune-mediated hepatitis. The median time to onset was 1.2 months (range: 1 day to 13.6 months). Hepatitis led to discontinuation of IMFINZI in 0.7% of the 1889 patients. Hepatitis resolved in 49% of patients. Systemic corticosteroids were required in 27% of patients, with 17% requiring high-dose corticosteroids and 0.1% requiring mycophenolate.

5.3 Immune-Mediated Colitis
IMFINZI can cause immune-mediated colitis, defined as requiring use of corticosteroids.

Monitor patients for signs and symptoms of diarrhea or colitis. Administer corticosteroids, prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) or more severe (Grade 3-4) colitis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1)], diarrhea or colitis occurred in 18% of patients, including Grade 3 (1%) and Grade 4 (0.1%) immune-mediated colitis. The median time to onset was 1.4 months (range: 1 day to 14 months). Diarrhea or colitis lead to discontinuation of IMFINZI in 0.4% of the 1889 patients. Diarrhea or colitis resolved in 49% of patients. Systemic corticosteroids were required in 19% of patients, with 1% requiring high-dose corticosteroids and 0.1% requiring other immunosuppressants (e.g., infliximab, mycophenolate).

5.4 Immune-Mediated Endocrinopathies
IMFINZI can cause immune-mediated endocrinopathies, including thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus and hypophysitis/hypopituitarism.

Thyroid Disorders: Monitor thyroid function prior to and periodically during treatment with IMFINZI. Initiate hormone replacement therapy or medical management of hyperthyroidism as clinically indicated. Continue IMFINZI for hyperthyroidism and interrupt for hyperthyroidism based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients who received IMFINZI [see Adverse Reactions (6.1)], hypothyroidism occurred in 11% of patients and hyperthyroidism occurred in 7% of patients. Thyroiditis occurred in 0.9% of patients, including Grade 3 (0.1%) thyroiditis. Hypothyroidism was preceded by thyroiditis or hyperthyroidism in 25% of patients.

Adrenal Insufficiency: Monitor patients for clinical signs and symptoms of adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate prednisone 1 to 2 mg per kg per day or equivalent, followed by corticosteroid taper and hormone replacement as clinically indicated. Interrupt IMFINZI based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients who received IMFINZI, adrenal insufficiency occurred in 0.7% of patients, including Grade 3 (0.1%) adrenal insufficiency. Systemic corticosteroids were required in 0.4% of patients, including 0.1% of patients who required high-dose corticosteroids.

Type 1 Diabetes Mellitus: Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Interrupt IMFINZI based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients who received IMFINZI, type 1 diabetes mellitus occurred in < 0.1% of patients. The median time to onset was 1.4 months.

Hypophysitis: For Grade 2 or higher hypophysitis, initiate prednisone 1 to 2 mg per kg per day or equivalent, followed by corticosteroid taper and hormone replacement therapy as clinically indicated. Interrupt IMFINZI based on the severity [see Dosage and Administration (2.3)].

Hypopituitarism leading to adrenal insufficiency and diabetes insipidus occurred in < 0.1% of 1889 patients who received IMFINZI in clinical studies.

5.5 Immune-Mediated Nephritis
IMFINZI can cause immune-mediated nephritis defined as evidence of renal dysfunction, requirement for corticosteroids. Fatal cases have occurred.

Monitor patients for abnormal renal function tests prior to and periodically during treatment with IMFINZI. Initiate prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) or severe (Grade 3-4) nephritis, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients who received IMFINZI, type 1 diabetes mellitus occurred in < 0.1% of patients. The median time to onset was 2 months (range: 1 day to 14.2 months). IMFINZI was discontinued in 0.3% of the 1889 patients. Nephritis resolved in 50% of patients. Systemic corticosteroids were required in 0.6% of patients, with 0.4% receiving high-dose corticosteroids.

5.6 Immune-Mediated Dermatologic Reactions
IMFINZI can cause immune-mediated rash; bullous dermatitis, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) have occurred with other products in this class [see Warnings and Precautions (5.7)].

Monitor for signs and symptoms of rash. Initiate prednisone 1 to 2 mg per kg per day or equivalent, for moderate (Grade 2) rash or dermatitis lasting for more than 1 week or severe (Grade 3-4) rash or dermatitis followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1)], 26% of patients developed rash or dermatitis and 0.4% of the patients developed vitiligo. Rash or dermatitis led to discontinuation of IMFINZI in 0.1% of the 1889 patients. Rash resolved in 62% of patients. Systemic corticosteroids were required in 2.0% of patients, including high-dose corticosteroids in 1% of patients.

5.7 Other Immune-Mediated Adverse Reactions
IMFINZI can cause severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system. While immune-mediated reactions usually manifest during treatment with IMFINZI, immune-mediated adverse reactions can also manifest after discontinuation of IMFINZI.

For suspected Grade 2 immune-mediated adverse reactions, exclude other causes and initiate corticosteroids as clinically indicated. For severe (Grade 3 or 4) adverse reactions, administer corticosteroids, prednisone 1 to 4 mg per kg per day or equivalent, followed by taper. Interrupt or permanently discontinue IMFINZI based on the severity [see Dosage and Administration (2.3)]. If uveitis occurs in combination with other immune-mediated adverse reactions, evaluate for Vogt-Koyanagi-Harada syndrome, which has been observed with other products in this class and may require treatment with systemic steroids to reduce the risk of permanent vision loss.
The following clinically significant, immune-mediated adverse reactions occurred at an incidence of less than 1% each in 1889 patients who received IMFINZI: aseptic meningitis, hemolytic anemia, immune thrombocytopenic purpura, myocarditis, myositis, and ocular inflammatory toxicity, including uveitis and keratitis [see Adverse Reactions (6.1)]. The following clinically significant, immune-mediated adverse reactions have been reported with other products in this class: bullous dermatitis, Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN), pancreatitis, systemic inflammatory response syndrome, rhabdomyolysis, myasthenia gravis, histiocytic necrotizing lymphadenitis, demyelination, vasculitis, hemolytic anemia, iritis, encephalitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome and Vogt-Koyanagi-Harada syndrome.

5.8 Infection
IMFINZI can cause serious infections, including fatal cases. Monitor patients for signs and symptoms of infection. For Grade 3 or higher infections, withhold IMFINZI and resume once clinically stable [see Dosage and Administration (2.3)].

In clinical studies enrolling 1889 patients with various cancers who received IMFINZI [see Adverse Reactions (6.1)], infections occurred in 43% of patients, including Grade 3 (8%), Grade 4 (1.9%), and Grade 5 (1.9%). In the urothelial carcinoma cohort in Study 1108 the most common Grade 3 or higher infection was urinary tract infections, which occurred in 4% of patients. In the PACIFIC study the most common Grade 3 or higher infection was pneumonia, which occurred in 5% of patients. The overall incidence of infections in IMFINZI-treated patients (56%) in the PACIFIC study was higher compared to patients in other studies (38%) in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI.

5.9 Infusion-Related Reactions
IMFINZI 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 based on the severity [see Dosage and Administration (2.3)]. For Grade 1 or 2 infusion-related reactions, consider using pre-medication with subsequent doses.

In clinical studies enrolling 1889 patients with various cancers [see Adverse Reactions (6.1)], infusion-related reactions occurred in 2.2% of patients, including Grade 3 (0.3%).

5.10 Embryo-Fetal Toxicity
Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of durvalumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased premature delivery, fetal loss and premature neonatal death. Advise pregnant females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months after the last dose of IMFINZI [see Use in Specific Populations (8.1, 8.3)].

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Immune-Mediated Pneumonitis [see Warnings and Precautions (5.1)].
- Immune-Mediated Hepatitis [see Warnings and Precautions (5.2)].
- Immune-Mediated Colitis [see Warnings and Precautions (5.3)].
- Immune-Mediated Endocrinopathies [see Warnings and Precautions (5.4)].
- Immune-Mediated Nephritis [see Warnings and Precautions (5.5)].
- Immune-Mediated Dermatologic Reactions [see Warnings and Precautions (5.6)].
- Other Immune-Mediated Adverse Reactions [see Warnings and Precautions (5.7)].
- Infection [see Warnings and Precautions (5.8)].
- Infusion-Related Reactions [see Warnings and Precautions (5.9)].

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the Warnings and Precautions section reflect exposure to IMFINZI in 1889 patients from the PACIFIC study (a randomized, placebo-controlled study that enrolled 475 patients with Stage III NSCLC), Study 1108 (an open-label, single-arm, multicohort study that enrolled 191 patients with urothelial carcinoma and 779 patients with various other solid tumors), and an additional open-label, single-arm trial that enrolled 444 patients with metastatic lung cancer, an indication for which durvalumab is not approved. Across all studies, IMFINZI was administered at a dose of 10 mg/kg intravenously every 2 weeks. Among the 1889 patients, 38% were exposed for 6 months or more and 18% were exposed for 12 months or more.

The data described in this section reflect exposure to IMFINZI in patients with locally advanced or metastatic urothelial carcinoma enrolled in Study 1108 and in patients with Stage III NSCLC enrolled in the PACIFIC study.

Urothelial Carcinoma
The safety data described in Table 2 reflect exposure to IMFINZI in 182 patients with locally advanced or metastatic urothelial carcinoma in the urothelial carcinoma cohort of Study 1108 whose disease has progressed during or after one standard platinum-based regimen. Patients received IMFINZI 10 mg/kg intravenously every 2 weeks [see Clinical Studies (14.1)]. The median duration of exposure was 2.3 months (range: 1 day to 12.1 months).

Thirty-one percent (31%) of patients had a drug delay or interruption for an adverse reaction. The most common (> 2%) were liver injury (4.9%), urinary tract infection (3.3%), acute kidney injury (3.3%), and musculoskeletal pain (2.7%).

The most common adverse reactions (> 15%) were fatigue (39%), musculoskeletal pain (24%), constipation (21%), decreased appetite (19%), nausea (16%), peripheral edema (15%) and urinary tract infection (15%). The most common Grade 3 or 4 adverse reactions (≥ 3%) were fatigue, urinary tract infection, musculoskeletal pain, abdominal pain, dehydration, and general physical health deterioration.

Eight patients (4.4%) who were treated with IMFINZI experienced Grade 5 adverse reactions of cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis, or immune-mediated hepatitis. Three additional patients were experiencing infection and disease progression at the time of death. IMFINZI was discontinued for adverse reactions in 3.3% of patients. Serious adverse reactions occurred in 46% of patients. The most frequent serious adverse reactions (> 2%) were acute kidney injury (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver injury (3.3%), general physical health deterioration (3.3%), sepsis, abdominal pain and pyrexia/tumor associated fever (2.7% each).

Table 2 summarizes the adverse reactions that occurred in ≥ 10% of patients, while Table 3 summarizes the Grade 3 - 4 laboratory abnormalities that occurred in ≥ 1% of patients treated with IMFINZI in the urothelial carcinoma cohort of Study 1108.

Table 2. Adverse Reactions in ≥ 10% of Patients in Study 1108 Urothelial Carcinoma Cohort

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMFINZI N=182</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades (%)</td>
<td>Grades 3 - 4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea/Colitis</td>
<td>13</td>
</tr>
<tr>
<td>General Disorders and Administration</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>39</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>15</td>
</tr>
<tr>
<td>Pyrexia/Tumor associated fever</td>
<td>14</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite/Hypophagia</td>
<td>19</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>24</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnea/Exertional Dyspnea</td>
<td>13</td>
</tr>
<tr>
<td>Cough/Productive Cough</td>
<td>10</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>11</td>
</tr>
</tbody>
</table>

1 Includes abdominal pain upper, abdominal pain lower and flank pain
2 Includes asthenia, lethargy, and malaise
3 Includes edema, localized edema, edema peripheral, lymphedema, peripheral swelling, scrotal edema, and scrotal swelling
4 Includes cystitis, candiduria and urorpusis
5 Includes back pain, musculoskeletal chest pain, musculoskeletal pain and discomfort, myalgia, and neck pain
6 Includes dermatitis, dermatitis aciform, dermatitis psoriasisform, psoriasis, rash maculo-papular, rash pruritic, rash papular, rash pustular, skin toxicity, eczema, erythema, erythema multiforme, rash erythematous, acne, and lichen planus
The safety of IMFINZI in patients with Stage III NSCLC who completed concurrent platinum-based chemoradiotherapy within 42 days prior to initiation of study drug was evaluated in the PACIFIC study, a multicenter, randomized, double-blind, placebo-controlled study. A total of 475 patients received IMFINZI 10 mg/kg intravenously every 2 weeks. The study excluded patients who had disease progression following chemoradiation, with active or prior autoimmune disease within 2 years of initiation of the study or with medical conditions that required systemic immunosuppression [see Clinical Studies (14.2)].

The study population characteristics were: median age of 64 years (range: 23 to 90), 45% age 65 years or older, 70% male, 69% White, 27% Asian, 75% former smoker, 45% age 65 years or older, 70% male, 69% White, 27% Asian, 75% former smoker, 51% had WHO performance status of 1. All patients received definitive radiotherapy as per protocol, of which 92% received a total radiation dose of 54 Gy to 66 Gy. The median duration of exposure to IMFINZI was 10 months (range: 0.2 to 12.6).

IMFINZI was discontinued due to adverse reactions in 15% of patients. The most common adverse reactions leading to IMFINZI discontinuation were pneumonitis or radiation pneumonitis in 6% of patients. Serious adverse reactions occurred in 29% of patients receiving IMFINZI. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in < 2% of patients and were similar across arms. The most common adverse reactions (occurring in ≥ 20% of patients) were cough, fatigue, pneumonitis or radiation pneumonitis, upper respiratory tract infections, dyspnea and rash. The most frequent serious adverse reactions leading to IMFINZI discontinuation were pneumonitis or radiation pneumonitis in 6% of patients. The most common adverse reactions occurring in ≥ 20% of patients were cough, fatigue, pneumonitis or radiation pneumonitis, upper respiratory tract infections, dyspnea and rash. Other adverse reactions occurring in less than 10% of patients treated with IMFINZI were dysphonia, dysuria, night sweats, peripheral edema, and increased susceptibility to infections.

Table 3. Grade 3-4 Laboratory Abnormalities Worsened from Baseline Occurring in ≥ 1% Patients in Study 1108 Urothelial Carcinoma Cohort

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Increased alkaline phosphatase</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Increased AST</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Increased ALT</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>46</td>
<td>0.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>39</td>
<td>2.3</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>36</td>
<td>2.8</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>33</td>
<td>3.6</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>32</td>
<td>1.1</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>24</td>
<td>3.4</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>43</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 4. Adverse Reactions Occurring in ≥ 10% Patients in the PACIFIC Study

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>IMFINZI N=475</th>
<th>Placebo N=234</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough/Productive Cough</td>
<td>40</td>
<td>0.6</td>
</tr>
<tr>
<td>Pneumonitis/Radiation Pneumonitis</td>
<td>34</td>
<td>3.4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>25</td>
<td>1.5</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>0.4</td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>23</td>
<td>0.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>0.0</td>
</tr>
<tr>
<td>General Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>34</td>
<td>0.8</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15</td>
<td>0.2</td>
</tr>
<tr>
<td>Infecions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>26</td>
<td>0.4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>

1 The PACIFIC study was not designed to demonstrate statistically significant difference in adverse reaction rates for IMFINZI, as compared to placebo, for any specific adverse reaction listed in Table 4.
2 Includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis.
3 Includes dyspnea and exertional dyspnea.
4 Includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain.
5 Includes autoimmune hypothyroidism and hypothyroidism.
6 Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash purpuric, rash purpural, erythema, eczema, rash and dermatitis.
7 Includes pruritus generalized and pruritus.
8 Includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection.
9 Includes laryngitis, pneumonitis, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia klebsiella, pneumonia necrotising, pneumonia pneumococcal, and pneumonia streptococcal.

Other adverse reactions occurring in less than 10% of patients treated with IMFINZI were dysphonia, dysuria, night sweats, peripheral edema, and increased susceptibility to infections.

Table 5 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI.

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>52</td>
<td>8</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>46</td>
<td>0.2</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>39</td>
<td>2.3</td>
</tr>
<tr>
<td>Increased AST</td>
<td>36</td>
<td>2.8</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>33</td>
<td>3.6</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>32</td>
<td>1.1</td>
</tr>
<tr>
<td>Increased GGT</td>
<td>24</td>
<td>3.4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>43</td>
<td>17</td>
</tr>
</tbody>
</table>

1 Graded according to NCI CTCAE version 4.0
2 Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI (range: 464 to 470) and placebo (range: 224 to 229)
6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to durvalumab to the incidence of antibodies to other products may be misleading.

Due to the limitations in assay performance, the incidence of antibody development in patients receiving IMFINZI may be underestimated. Of 1570 patients who were treated with IMFINZI 10 mg/kg every 2 weeks and evaluable for the presence of anti-drug antibodies (ADAs), 45 (2.9%) patients tested positive for treatment-emergent ADAs. The development of treatment-emergent ADA against durvalumab appears to have no clinically relevant effect on its pharmacokinetic profile. There are insufficient numbers of patients with ADA to determine whether ADA alters the safety or efficacy of durvalumab.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk summary
Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no data on the use of IMFINZI in pregnant women.

In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys from the confirmation of pregnancy through delivery resulted in an increase in premature delivery, fetal loss and premature neonatal death (see Data). Human immunoglobulin G1 (IgG1) is known to cross the placental barrier; therefore, durvalumab has the potential to be transmitted from the mother to the developing fetus. Apprise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the fetus. In mouse allogeneic pregnancy models, disruption of PD-L1 signaling was shown to result in an increase in fetal loss. The effects of durvalumab on prenatatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab was administered from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature delivery, fetal loss (abortion and stillbirth) and increase in neonatal deaths. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, fetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

8.2 Lactation
Risk Summary
There is no information regarding the presence of durvalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG1 is excreted in human milk. Durvalumab was present in the milk of lactating cynomolgus monkeys and was associated with premature neonatal death (see Data).

Because of the potential for adverse reactions in breastfed infants, advise women not to breastfeed during treatment with IMFINZI and for at least 3 months after the last dose.

Data
In lactating cynomolgus monkeys, durvalumab was present in breast milk at about 0.15% of maternal serum concentrations after administration of durvalumab from the confirmation of pregnancy through delivery at exposure levels approximately 6 to 20 times higher than those observed at the recommended clinical dose of 10 mg/kg (based on AUC). Administration of durvalumab resulted in premature neonatal death.

8.8 Females and Males of Reproductive Potential
Contraception
Females
Based on its mechanism of action and data from animal studies, IMFINZI can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for at least 3 months following the last dose of IMFINZI.

8.4 Pediatric Use
The safety and effectiveness of IMFINZI have not been established in pediatric patients.

8.5 Geriatric Use
Of the 182 patients treated with IMFINZI in patients with urothelial carcinoma, 112 patients were 65 years or older and 34 patients were 75 years or older. The overall response rate in patients 65 years or older was 15% (17/112) and was 12% (4/34) in patients 75 years or older. Grade 3 or 4 adverse reactions occurred in 38% (42/112) of patients 65 years or older and 35% (12/34) of patients 75 years or older.

Of the 476 patients treated with IMFINZI in the PACIFIC study, 45% were 65 years or older, while 7.6% were 75 years or older. No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients. The PACIFIC study did not include sufficient numbers of patients aged 75 years and over to determine whether they respond differently from younger patients.

10 OVERDOSAGE
There is no information on overdose with IMFINZI.

11 DESCRIPTION
Durvalumab is a programmed cell death ligand 1 (PD-L1) blocking antibody. Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that is produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cell suspension culture. IMFINZI (durvalumab) Injection for intravenous use is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

Each 500 mg vial of IMFINZI contains 500 mg of durvalumab in 10 mL solution. Each mL contains durvalumab, 50 mg, L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α′-trehalose dihydrate (104 mg), Polysorbate 80 (0.2 mg), and Water for Injection, USP.

Each 120 mg vial of IMFINZI contains 120 mg of durvalumab in 2.4 mL solution. Each mL contains durvalumab, 50 mg, L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α′-trehalose dihydrate (104 mg), Polysorbate 80 (0.2 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Expression of programmed cell death ligand-1 (PD-L1) can be induced by inflammatory signals (e.g., IFN-gamma) and can be expressed on both tumor cells and tumor-associated immune cells in the tumor microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.

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).

PD-L1 blockade with durvalumab led to increased T-cell activation in vitro and decreased tumor size in co-engrafted human tumor and immune cell xenograft mouse models.

12.3 Pharmacokinetics
The pharmacokinetics of durvalumab was studied in 1902 patients with doses ranging from 0.1 mg/kg (0.01 times the approved recommended dosage) to 20 mg/kg (2 times the approved recommended dosage) administered once every two, three or four weeks.

PK exposure increased more than dose-proportionally at doses < 3 mg/kg (0.3 times the approved recommended dosage) and dose proportionally at doses ≥ 3 mg/kg every 2 weeks. Steady state was achieved at approximately 16 weeks.

Distribution
The geometric mean (% coefficient of variation [CV%]) steady state volume of distribution was 5.6 (18%) L.

Elimination
Durvalumab clearance decreases over time, with a mean maximal reduction (CV%) from baseline values of approximately 23% (57%) resulting in a geometric mean (CV%) steady state clearance (CLss) of 8.2 mL/h (39%) at day 365; the decrease in CLss is not considered clinically relevant. The geometric mean (CV%) terminal half-life, based on baseline CL was approximately 18 (24%) days.

Specific Populations
Age (19–96 years), body weight (34-149 kg), sex, albumin levels, lactate dehydrogenase (LDH) levels, creatinine levels, soluble PD-L1, tumor type, race, mild renal impairment (creatinine clearance (CLcr) 60 to 89 mL/min), moderate renal impairment (CLcr 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and...
AST > ULN or bilirubin > 1 to 1.5x ULN and any AST), or ECOG/WHO performance status had no clinically significant effect on the pharmacokinetics of durvalumab. The effect of severe renal impairment (C\text{Creat} 15 to 29 mL/min) or moderate hepatic impairment (bilirubin > 1.5 to 3x ULN and any AST) or severe hepatic impairment (bilirubin > 3x ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

**13 NONCLINICAL TOXICITY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

The carcinogenic and genotoxic potential of durvalumab have not been evaluated. Animal fertility studies have not been conducted with durvalumab. In repeat-dose toxicity studies with durvalumab in sexually mature cynomolgus monkeys of up to 3 months duration, there were no notable effects on the male and female reproductive organs.

**13.2 Animal Toxicology and/or Pharmacology**

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. M. tuberculosis-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-L1 and PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

**14 CLINICAL STUDIES**

**14.1 Urothelial Carcinoma**

The efficacy of IMFINZI was evaluated in the urothelial carcinoma cohort of Study 1108 (NCT01693562), a multicenter, multi-cohort, open-label clinical trial. In Study 1108, 182 patients with locally advanced or metastatic urothelial carcinoma were enrolled. Patients had progressed while on or after a platinum-based therapy, including those who progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. These patients had initiated IMFINZI at least 13 weeks prior to the data cutoff date. The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression (not to exceed 10 mg per day of prednisone or equivalent); history of severe autoimmune disease: untreated CNS metastases (except cerebral edema); active tuberculosis, or hepatitis B or C; and patients who received IMFINZI 10 mg/kg intravenously every 2 weeks for up to 12 months or until unacceptable toxicity or disease progression. Tumor assessments were performed at Weeks 6, 12, and 16, and then every 8 weeks for the first year and every 12 weeks thereafter. The major efficacy outcome measures were confirmed Overall Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR), and duration of response (DoR).

The median age was 67 years (range: 34 to 88), 72% were male, 64% were White. Sixty-six percent (66%) of patients had visceral metastasis (bone, liver, or lung), including 34% with liver metastasis. Lymph node only metastasis were present in 13% of patients. Sixty-six percent (66%) of patients had ECOG score of 1 and 41% of patients had a baseline creatinine clearance < 60 mL/min. The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 23%, 1 in 38%, 2 in 29%, and 3 in 9% of patients. Twenty percent (20%) of patients had a baseline creatinine clearance < 60 mL/min. The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 23%, 1 in 38%, 2 in 29%, and 3 in 9% of patients. Twenty percent (20%) of patients had a baseline creatinine clearance < 60 mL/min. The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 23%, 1 in 38%, 2 in 29%, and 3 in 9% of patients. Twenty percent (20%) of patients had a baseline creatinine clearance < 60 mL/min. The Bellmunt risk score (which includes ECOG score, baseline hemoglobin, and liver metastases) was 0 in 23%, 1 in 38%, 2 in 29%, and 3 in 9% of patients.

Table 6. Efficacy Results for Study 1108 Urothelial Carcinoma Cohort

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>All Patients</th>
<th>PD-L1 High</th>
<th>PD-L1 Low/Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Duration of Response (months)</td>
<td>16.8 (13.18, 18.1)</td>
<td>5.6 (4.6, 7.8)</td>
<td>3.1 (2.8, 3.4)</td>
</tr>
<tr>
<td>Median Duration of Response (months)</td>
<td>NR (0.9, 19.9)</td>
<td>NR (0.9, 19.9)</td>
<td>12.3 (1.9, 12.3)</td>
</tr>
<tr>
<td>Overall Response Rate by BICR n (%)</td>
<td>31 (17%)</td>
<td>25 (26%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Favored Treatment</td>
<td>IMFINZI</td>
<td>IMFINZI</td>
<td>Placebo</td>
</tr>
<tr>
<td>Complete Response</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Partial Response</td>
<td>26</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Failure Rate</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>
| BICR = Blinded Independent Central Review; NE = Not Evaluable; NR = Not Reached, * denotes a censored value

**14.2 Non-Small Cell Lung Cancer (NSCLC)**

The efficacy of IMFINZI was evaluated in the PACIFIC study (NCT02125461), a multicenter, randomized, double-blind, placebo-controlled study in patients with unresectable Stage III NSCLC who completed at least 2 cycles of concurrent platinum-based chemotherapy and definitive radiation within 42 days prior to initiation of the study drug and had a WHO performance status of 0 or 1. The study excluded patients who had progressed following concurrent chemoradiation, patients with active or prior documented autoimmune disease within 2 years of initiation of the study or patients with medical conditions that required systemic immunosuppression. Randomization was stratified by sex, age (≥65 years vs. < 65 years) and smoking history (smoker vs. non-smoker). Patients were randomized 2:1 to receive IMFINZI 10 mg/kg or placebo intravenously every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed RECIST 1.1-defined progression. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were progression-free survival (PFS) as assessed by a BICR RECIST 1.1 and overall survival (OS). Additional efficacy outcome measures included ORR assessed by BICR.

A total of 713 patients were randomized: 476 patients to the IMFINZI arm and 237 to the placebo arm. The study population characteristics were: median age of 64 years (range: 23 to 90); 70% male; 69% White and 27% Asian; 16% current smokers, 75% former smokers and 9% never smokers; 51% WHO performance status of 1; 53% with Stage IIIA and 45% were Stage IIIB; 46% with squamous and 54% with non-squamous histology. All patients received definitive radiotherapy as per protocol, of which 92% received a total radiation dose of 54 Gy to 66 Gy; 99% of patients received concomitant platinum-based chemotherapy (55% cisplatin-based, 42% carboplatin-based chemotherapy and 2% switched between cisplatin and carboplatin).

The pre-specified interim PFS analysis based on 371 events (81% of total planned events) demonstrated a statistically significant improvement in PFS in patients randomized to IMFINZI compared to placebo. Results are presented in Table 7 and Figure 1. OS data were not mature at the time of the interim PFS analysis.

Table 7. Efficacy Results for the PACIFIC Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>IMFINZI (N=478)</th>
<th>Placebo (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-Free Survival (PFS) (%)</td>
<td>214 (45%)</td>
<td>157 (66%)</td>
</tr>
<tr>
<td>Median in months (95% CI)</td>
<td>16.8 (13.18, 18.1)</td>
<td>5.6 (4.6, 7.8)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI) *</td>
<td>0.52 (0.42, 0.65)</td>
<td>~&lt;0.0001</td>
</tr>
<tr>
<td>Overall Response Rate (ORR) (%)</td>
<td>26% (23, 31)</td>
<td>14% (10, 19)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>25%</td>
<td>14%</td>
</tr>
</tbody>
</table>

1 Among the ITT population, 7% in the IMFINZI arm and 10% in the placebo arm had non-measurable disease as assessed by BICR according to RECIST v1.1
2 Stratified by sex, age, and smoking history
3 Compared with allocated c of 0.0104 (Lan DeMets spending function approximating O’Brien Fleming boundary) for interim analysis
**IMFINZI (durvalumab) injection, for intravenous use**

**17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of IMFINZI, including:

- **Pneumonitis:** Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath [see Warnings and Precautions (5.1)].
- **Hepatitis:** Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding [see Warnings and Precautions (5.2)].
- **Colitis:** Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain [see Warnings and Precautions (5.3)].
- **Endocrinopathies:** Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, or hypophysitis [see Warnings and Precautions (5.4)].
- **Nephritis:** Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis [see Warnings and Precautions (5.5)].
- **Dermatological Reactions:** Advise patients to contact their healthcare provider immediately for signs or symptoms of severe dermatological reactions [see Warnings and Precautions (5.6)].
- **Other Immune-Mediated Adverse Reactions:** Advise patients to contact their healthcare provider immediately for signs or symptoms of aseptic meningitis, thrombocytopenic purpura, myocarditis, hemolytic anemia, myositis, uveitis and keratitis [see Warnings and Precautions (5.7)].
- **Infection:** Advise patients to contact their healthcare provider immediately for infection [see Warnings and Precautions (5.8)].
- **Infusion-Related Reactions:** Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions [see Warnings and Precautions (5.9)].
- **Embryo-Fetal Toxicity:** Advise females of reproductive potential that IMFINZI can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.10) and Use in Specific Populations (8.1, 8.3)].
- **Lactation:** Advise female patients not to breastfeed while taking IMFINZI and for at least 3 months after the last dose [see Warnings and Precautions (5.10) and Use in Specific Populations (8.2)].

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

By: AstraZeneca UK Limited
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Cambridge, England CB2 0AA
US License No. 2043

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**Figure 1 Kaplan-Meier Curves of Progression-Free Survival in the PACIFIC Study**

![Kaplan-Meier Curves](image)

**Number of patients at risk**

<table>
<thead>
<tr>
<th>Month</th>
<th>IMFINZI</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>476</td>
<td>237</td>
</tr>
<tr>
<td>3</td>
<td>377</td>
<td>163</td>
</tr>
<tr>
<td>6</td>
<td>301</td>
<td>106</td>
</tr>
<tr>
<td>9</td>
<td>264</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>159</td>
<td>52</td>
</tr>
<tr>
<td>15</td>
<td>86</td>
<td>28</td>
</tr>
<tr>
<td>18</td>
<td>44</td>
<td>15</td>
</tr>
<tr>
<td>21</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Probability of PFS**

- **IMFINZI**
- **Placebo**

**Time from randomization (months)**

- 0
- 3
- 6
- 9
- 12
- 15
- 18
- 21
- 24
- 27

**Probability of PFS**

- 1.0
- 0.9
- 0.8
- 0.7
- 0.6
- 0.5
- 0.4
- 0.3
- 0.2
- 0.1
- 0.0

**16 HOW SUPPLIED/STORAGE AND HANDLING**

IMFINZI (durvalumab) Injection is a clear to opalescent, colorless to slightly yellow solution supplied in a carton containing one single-dose vial either as:

- **500 mg/10 mL (NDC 0310-4611-50)**
- **120 mg/2.4 mL (NDC 0310-4500-12)**

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.

Do not freeze. Do not shake.
**IMFINZI® (durvalumab) injection, for intravenous use**

**MEDICATION GUIDE**

**IMFINZI® (im-FIN-zee)**

**(durvalumab)**

*Injection*

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**What is the most important information I should know about IMFINZI?**

IMFINZI is a medicine that may treat a type of cancer in the bladder and urinary tract or a type of lung cancer by working with your immune system.

IMFINZI can cause your immune system to attack normal organs and tissues and can affect the way they work. These problems can sometimes become serious or life-threatening and can lead to death.

**Call or see your healthcare provider right away if you develop any symptoms of the following problems or these symptoms get worse:**

**Lung problems (pneumonitis).** Signs and symptoms of pneumonitis may include:

- new or worsening cough
- shortness of breath
- chest pain

**Liver problems (hepatitis).** Signs and symptoms of hepatitis may include:

- yellowing of your skin or the whites of your eyes
- dark urine (tea colored)
- severe nausea or vomiting
- bleeding or bruising more easily than normal
- pain on the right side of your stomach area (abdomen)
- feeling less hungry than usual
- drowsiness

**Intestinal problems (colitis).** Signs and symptoms of colitis may include:

- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach area (abdomen) pain or tenderness

**Hormone gland problems (especially the thyroid, adrenals, pituitary and pancreas).** Signs and symptoms that your hormone glands are not working properly may include:

- headaches that will not go away or unusual headaches
- feeling cold
- extremely tiredness
- weight gain or weight loss
- constipation
- dizziness or fainting
- your voice gets deeper
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- nausea or vomiting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness
- stomach area (abdomen) pain
- skin loss
- urinary problems
- irritability
- changes in mood or behavior
- changes in mood or behavior
- changes in mood or behavior

**Kidney problems, including nephritis and kidney failure.** Signs of kidney problems may include:

- decrease in the amount of urine
- swelling of your ankles
- blood in your urine
- loss of appetite

**Skin problems.** Signs of these problems may include:

- rash
- skin blistering
- itching
Problems in other organs. Signs and symptoms may include:

- neck stiffness
- headache
- confusion
- fever
- chest pain, shortness of breath, or irregular heartbeat (myocarditis)
- changes in mood or behavior
- low red blood cells (anemia)
- excessive bleeding or bruising
- muscle weakness or muscle pain
- blurry vision, double vision, or other vision problem
- eye pain or redness

Severe Infections. Signs and symptoms may include:

- fever
- cough
- frequent urination
- pain when urinating
- flu-like symptoms

Severe infusion reactions. Signs and symptoms of severe infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- fever
- feel like passing out
- back or neck pain
- facial swelling

Getting medical treatment right away may help keep these problems from becoming more serious. Your healthcare provider will check you for these problems during your treatment with IMFINZI. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may delay or completely stop treatment with IMFINZI, if you have severe side effects.

What is IMFINZI?
IMFINZI is a prescription medicine used to treat:

- a type of cancer in the bladder and urinary tract called urothelial carcinoma. IMFINZI may be used when your urothelial carcinoma:
  - has spread or cannot be removed by surgery and,
  - you have tried chemotherapy that contains platinum, and it did not work or is no longer working.
- a type of lung cancer called non-small cell lung cancer (NSCLC). IMFINZI may be used when your NSCLC:
  - has not spread outside your chest
  - cannot be removed by surgery, and
  - has responded or stabilized with initial treatment with chemotherapy that contains platinum, given at the same time as radiation therapy.

It is not known if IMFINZI is safe and effective in children.

Before you receive IMFINZI, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems such as Crohn’s disease, ulcerative colitis, or lupus
- have had an organ transplant
- have lung or breathing problems
- have liver problems
- are being treated for an infection
- are pregnant or plan to become pregnant. IMFINZI can harm your unborn baby. If you are able to become pregnant, you should use an effective method of birth control during your treatment and for at least 3 months after the last dose of IMFINZI. Talk to your healthcare provider about birth control methods that you can use during this time. Tell your healthcare provider right away if you become pregnant during treatment with IMFINZI.
- are breastfeeding or plan to breastfeed. It is not known if IMFINZI passes into your breast milk. Do not breastfeed during treatment and for at least 3 months after the last dose of IMFINZI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
How will I receive IMFINZI?
• Your healthcare provider will give you IMFINZI into your vein through an intravenous (IV) line over 60 minutes.
• IMFINZI is usually given every 2 weeks.
• Your healthcare provider will decide how many treatments you need.
• Your healthcare provider will test your blood to check you for certain side effects.
• If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of IMFINZI?
IMFINZI can cause serious side effects, including:
See “What is the most important information I should know about IMFINZI?”
The most common side effects of IMFINZI in people with urothelial carcinoma include:
• feeling tired
• muscle or bone pain
• constipation
• decreased appetite

The most common side effects of IMFINZI in people with NSCLC include:
• cough
• feeling tired
• inflammation in the lungs (pneumonitis)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of IMFINZI. Ask your healthcare provider or pharmacist for more information. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of IMFINZI.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about IMFINZI, talk with your healthcare provider. You can ask your healthcare provider for information about IMFINZI that is written for health professionals.

What are the ingredients in IMFINZI?
Active ingredient: durvalumab
Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, polysorbate 80, water for injection, USP.

Manufactured for: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850
By: AstraZeneca UK Limited
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For more information, call 1-800-236-9933 or go to www.IMFINZI.com
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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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