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PRODUCT PERSPECTIVES

Biliary Tract Cancers (BTCs) Unveiled: Expert Perspectives on Unique Challenges and Management Considerations

Patient Journey and Current Treatment of Biliary Tract Cancer Roundtable Panel of Experts:
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Biliary tract cancers (BTCs), including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), and gallbladder cancer (GBC), are a heterogeneous group of rare but aggressive malignancies with a very poor prognosis.[1,2] Patients with BTCs often remain asymptomatic or may present with symptoms like jaundice due to tumor-related biliary obstruction.[3] The lack of specific symptoms and asymptomatic progression frequently results in delayed diagnoses, leading to approximately 80% of BTC patients being diagnosed with advanced, unresectable disease with limited treatment options.[2,4,5]

BTCs arise from the biliary tree and are grouped into three subtypes by primary anatomical location (Figure 1).[6] iCCA subtype arises in

Biliary Tract Cancers Are a Group of Rare, Heterogeneous Malignancies That Arise from the Biliary Tree[6,9]

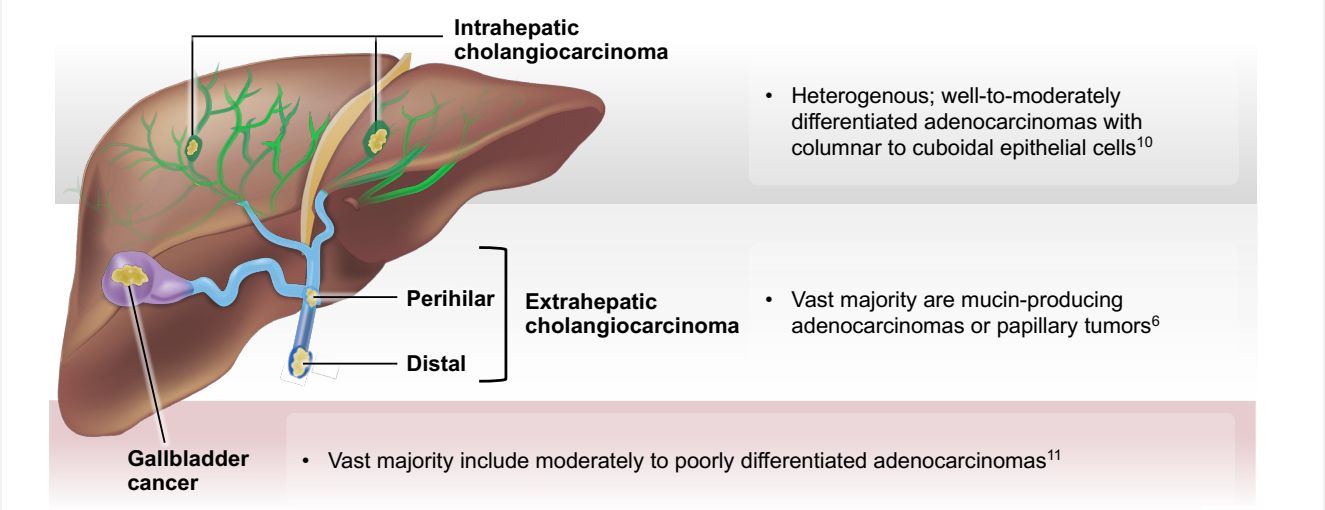

Figure 1. Biliary Tract Cancer Subtypes and Locations

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bile ducts proximal to the second-order ducts and accounts for approximately 10%–20% of all cholangiocarcinoma cases.[7,8] Together, perihilar and distal subtypes constitute eCCAs and arise in the large bile ducts between the second-order bile ducts and the ampulla ofVater.[8] Perihilar cholangiocarcinoma is the most prevalent subtype, accounting for an incidence of approximately 50%-60% of all cases, followed by distal cholangiocarcinoma subtype (involving the extrahepatic bile ducts, distal to the insertion of the cystic duct), which represents about 20%–30% of all cholangiocarcinomas.[7,8] Gallbladder cancer represents about 40% of new cases of BTCs in the United States, and is epithelial in origin, arising from the gallbladder itself or from the cystic duct.[9]

There have been limited to no advancements in the treatment landscape of BTCs for over a decade.[12] However, recent approvals has sparked interest in the broader medical community, prompting the assembly of an expert panel to discuss current challenges and patient management considerations. Their insights and recommendations for oncology stakeholders, including patients, healthcare providers, and payers, are summarized in this report.

The Patient Journey to Diagnosis of BTCs

Navigating the complex diagnostic process, which often results in delays or misdiagnoses, is an intricate journey involving multiple steps toward the eventual treatment of BTCs.

Patients with BTCs may present variably, often asymptomatically in the early stages of advanced disease, complicating timely detection and diagnosis. Nonetheless, when symptoms do emerge, they are generally nonspecific (**Figure 2**).[2,3]

Presentation may be dependent on the type of BTC, either iCCA, eCCA, or GBC. Often, patients with iCCA, for example, may not present for an office visit until the mass is big enough to cause abdominal pain. Perihilar or distal eCCA patients may present with sudden onset of painless jaundice and itching or biliary obstruction (reflected in liver function tests, enzymes) and abdominal pain.[2,3]

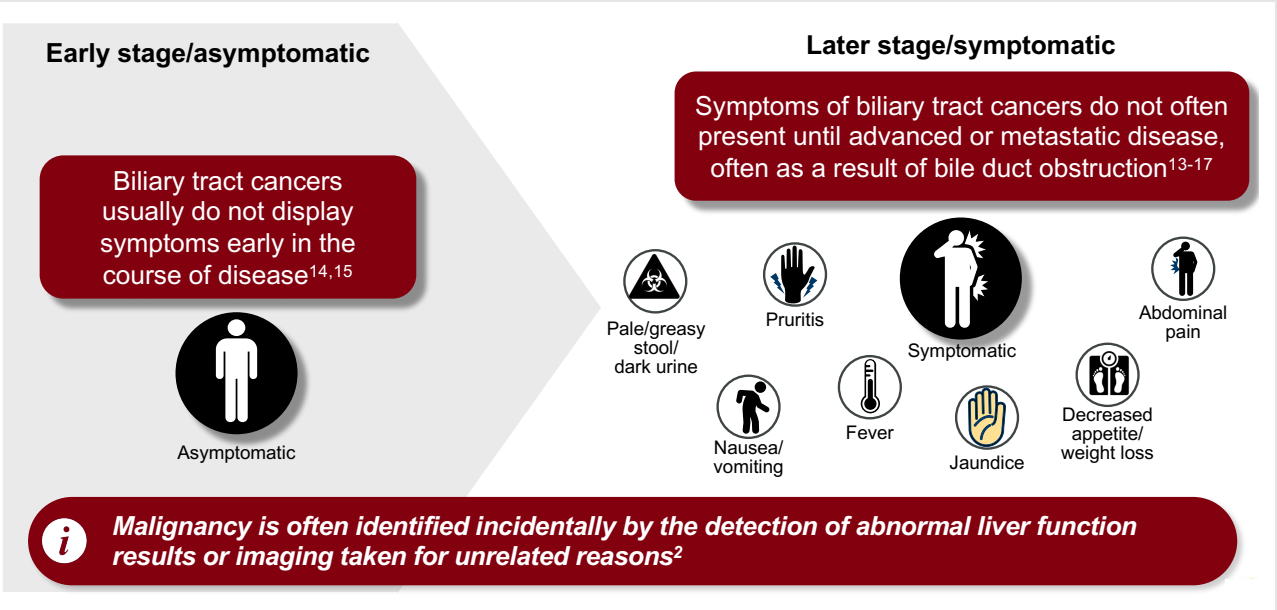

Figure 2. Challenges with Presentation and Diagnosis of BTCs

Indication:

IMFINZI, in combination with gemcitabine and cisplatin, is indicated for the treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC).

DURVALUMAB IMPORTANT SAFETY INFORMATION

There are no contraindications for IMFINZI® (durvalumab).

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

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"It's difficult to treat [eCCA] if you do not get the obstruction resolved. Sometimes it's very difficult, and [the] patient must go through multiple procedures to have the biliary stent drained. Sometimes that takes quite a lot of time before a patient can come to get treatment."

- Dr Ruth He

Intrahepatic cholangiocarcinoma lesions are less likely to cause obstructive complications due to their location along the biliary tree, with patients developing obstructive jaundice and palpable abdominal mass at more advanced stages of the disease.[18,19] Signs and symptoms of obstruction are typically the first clinical presentation of eCCA, with most patients presenting with jaundice due to biliary obstruction.[20] Approximately 30%-60% of patients with GBC show jaundice at the initial presentation.[21] However, a majority of patients are diagnosed incidentally after cholecystectomy for symptomatic gallbladder disease.

Early diagnosis of BTCs is crucial due to the asymptomatic nature of symptoms in the initial stages of the disease.[20] The involvement of healthcare providers (HCPs) during diagnosis varies and may depend on lesion characteristics.[20] Patients with suspected cholangiocarcinoma may be referred by their HCPs to specialized centers for further work-up.[23] Typically, PCPs are frequently involved in the diagnosis of patients with advanced disease presenting with nonspecific abdominal pain.[23]

"Early diagnosis is unfortunately not as common as we'd like it to be."

- Dr Tom Abrams

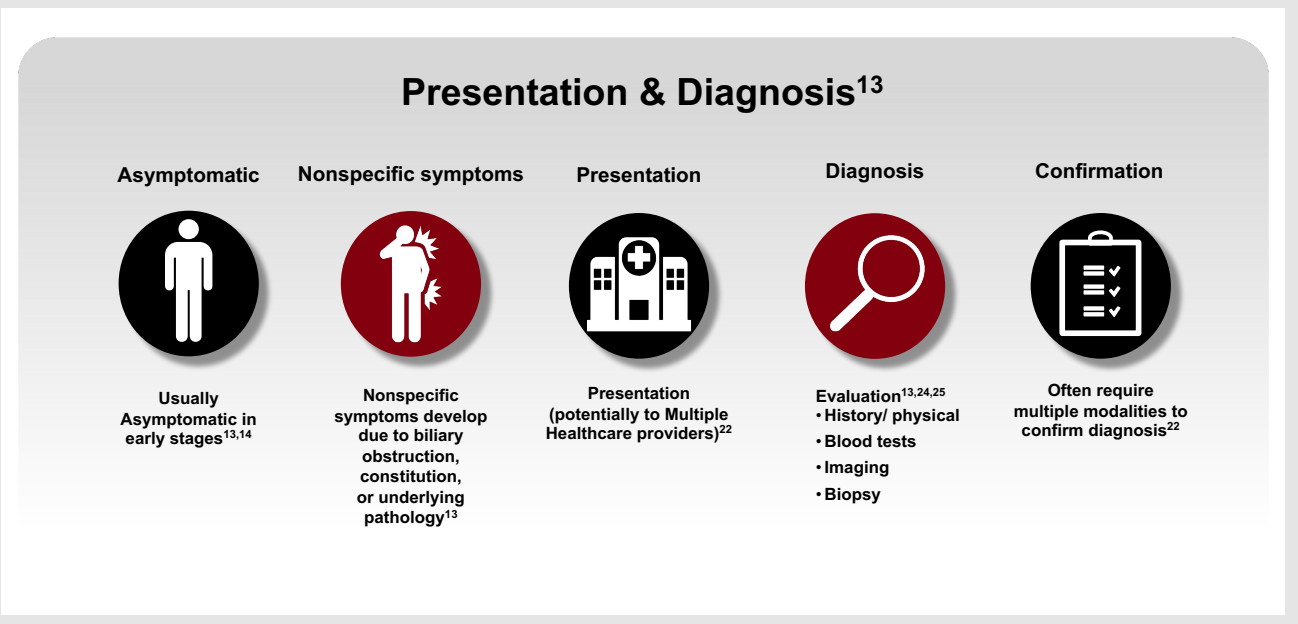

Figure 3. Potential Causes of Delayed Diagnosis of BTCs

DURVALUMAB IMPORTANT SAFETY INFORMATION

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.

Barriers to Early Diagnosis

Delays with early diagnosis may be the result of various factors (**Figure 3**). Detecting early-stage disease is challenging, and BTCs lack a singular identifying tool.[22] Instead, diagnosis currently relies on a combination of clinical, biochemical, radiologic, and histologic techniques.[22] For some diagnostic techniques, such as fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS), HCPs or centers may lack sufficient experience with BTCs or with these modalities, and often refer patients to specialists for further testing.[23]

Dr Abrams shared that at the Dana-Farber Cancer Institute, for example, NGS testing is done on tumor samples or blood, and a standard genetic panel is obtained for every patient. Some biomarkers, however, are not routinely tested for but would be helpful, especially for cases where biopsy samples are sometimes insufficient. The results gleaned from these biomarker tests could provide valuable insights for payers. As diagnostic technologies continue to improve, the assessment and monitoring of cancer at the molecular level could potentially transform patient care and lower healthcare costs to the system for both patients and payers.[26] However, some health plans may be willing to only offer coverage for an individual tissue biomarker and are hesitant to pay for a full biomarker panel.[27] Some community settings, however, may rely on circulating tumor DNA (ctDNA) results and may not have the capability to obtain the whole biomarker panel. Other community settings, however, do appear to sequence mutations as the standard approach. ctDNA has great potential, serving as a non-invasive tool to identify actionable mutations for treatment decisions and monitoring of tumor mutational profile during treatment.[28] However, this has not yet been validated in BTCs.

NGS enables the profiling of multiple genes, revealing molecular subsets and genomic differences between BTC types.[28] The growth of NGS testing in clinical practice has helped to facilitate the detection of recurring genomic changes in BTCs as well as improve the understanding of the disease.[28] The 2023 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend molecular testing, in patients with unresectable or metastatic BTCs.[29] Implementing routine genomic profiling may provide valuable insights into the tumor biology of BTCs.[28]

Vague presentation of cholangiocarcinomas may make it difficult for radiologists to recognize the disease, delaying diagnosis.[17] Perihilar cholangiocarcinomas in particular are very difficult to diagnose at an early stage. The prognosis of perihilar and distal extrahepatic cholangiocarcinomas is poor and is due in part to the challenges with early diagnosis.[30]

In solid organ tumors, including perihilar disease, biopsies are crucial and required to confirm a diagnosis, as well as to assess suitable treatment options, including the possibility of a liver transplant. For hypocellular tumors, with a big stromal component and not as many cancer cells, the sensitivity of cytology is subpar (around 20%-30%). Compared to conventional or brush cytology with low sensitivity between 20%-40%, FISH may help to increase the sensitivity in addition to conventional cytology while maintaining high specificity.[31] Combining FISH with conventional cytology study is beneficial because it helps with the detection of chromosomal abnormalities, especially in more differentiated cells.[31]

Cancer of unknown primary (CUP) is diagnosed less frequently due to increased awareness and detection of BTCs. However, poor imaging quality and delays in the identification of the tumor remain as challenges.[32] Recent advances in identifying the origin of tissue and possible primary site by using tools such as gene expression arrays and immunohistochemistry from the biopsy site have helped with the identification of primary cancers, particularly those attributable to BTCs.[32]

Addressing delays in the diagnosis of BTCs requires proactive solutions to streamline the diagnostic process and improve diagnostic accuracy. One potential solution involves integrating onsite cytopathology as a standard of care practice. By doing so, medical professionals can promptly confirm the adequacy of tissue samples collected for molecular testing, thus expediting the diagnostic phase of the patient journey. Additionally, enhancing the quality of biopsies and refining the techniques employed by interventional radiologists during tissue collection is crucial. This approach ensures that sufficient tissue sample is obtained, increasing the likelihood of an accurate diagnosis. These measures, emphasized by the panelists, are vital in reducing diagnostic delays, facilitating timely intervention, and ultimately improving the outcomes for patients with BTCs.

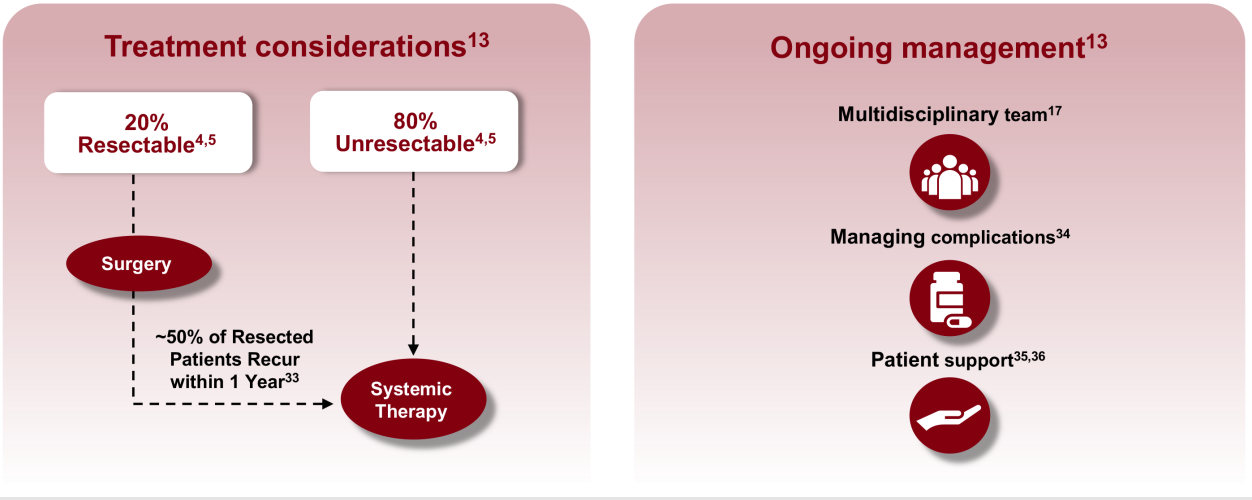

Figure 4. Treatment Journey for Patients with BTCs

The Patient's Journey to Treatment for BTCs

Early diagnosis of BTCs allows the opportunity for surgical consideration, which may be the only potentially curative modality, but feasibility varies among patients.[4] Less than 20% of patients may present as resectable, while the remaining 80% would likely be referred for a medical oncology consult (**Figure 4**).[4,5]

After resection, however, it is estimated that up to 50% of patients will experience recurrence.[37]

Patients and their caregivers may face several challenges during different steps in BTC care.

Key insights from our panelists regarding BTC care have been outlined here by the panel.

- **Q: What are some challenges that patients and caregivers may encounter at different stages of BTC care?**

  A: Patients and caregivers often encounter financial challenges related to BTC care, including seeking financial assistance for deductibles, copays, and coinsurance costs.

  A: The initial diagnosis of BTC can be overwhelming, leading to anxiety, fear, and emotional distress for patients and their families. Patients and caregivers may struggle to understand complex medical information and treatment options.
- **Q: What questions might patients ask about available therapies regarding BTC care?**

  A: Well-informed patients may inquire about their candidacy for approved therapies, or if they are eligible for clinical trials.
- **Q: What challenges do third-party payers, such as insurance companies, encounter in the context of BTC care?**

  A: From the perspective of third-party payers, there can be distinct challenges. These challenges may arise from a payer's lack of knowledge or familiarity with different diagnostic approaches and treatment options, as observed by the panel members in practice.
- **Q: How are side effects and adverse events managed in the context of BTC care?**

  A: Side effects and adverse events in BTCs are managed through a multidisciplinary approach, which may involve close monitoring, patient education, and the use of specific assessment tools to address and mitigate these treatment-related challenges.[35]

Patients with BTC undergoing treatment, particularly chemotherapy, require multidisciplinary guidance for the effective management of chemotherapy-related side effects. Such guidance may focus on educating patients and caregivers about treatment aspects, recognizing and addressing common adverse effects, and implementing preventive measures. Additionally, management strategies may include[35]:

- Documenting of patient allergies and history of hypersensitivity reactions
- Educating patients about their treatments and other associated supportive care
- Assessing and addressing psychosocial concerns that may arise during treatment
- Monitoring patients for common side effects associated with their treatment
- Evaluating patient condition using specific chemotherapy management assessment tools
- Actively listening to patient reports of manageable side effects

The benefit of multidisciplinary management strategies or teams in improving clinical outcomes in BTCs is still not clearly understood, however, some data shows that patients discussed at multidisciplinary meetings are more likely to receive more accurate staging and therapy[38]

Composition and Coordination of a Hepatobiliary Multidisciplinary Care Team (MDT)

BTCs are complex diseases requiring a multidisciplinary approach to ensure that the best care is provided at all steps of care throughout the patient journey.[38] A hepatobiliary multidisciplinary care team (MDT) may be implemented regardless of the clinical practice setting and may involve several HCPs.[39]

Medical oncologists play a crucial role in the care of patients with BTCs, working in partnership with hepatologists, and other specialties to provide comprehensive and individualized care for patients.[39]

In some instances, a medical oncologist may be the first specialist the patient diagnosed with hepatobiliary cancer sees, followed by a hepatologist.[39]

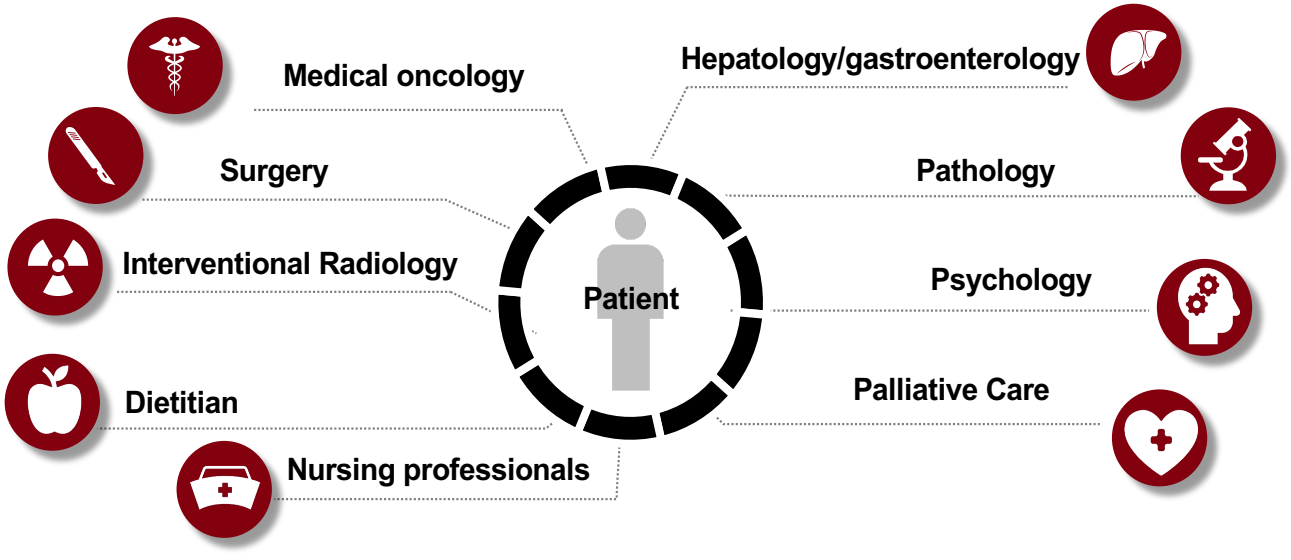

Figure 5.[39] Potential Members of the Multidisciplinary Care Team for a Patient with Biliary Tract Cancer

DURVALUMAB IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Pneumonitis

IMFINZI can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. In patients who did not receive recent prior radiation, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (<0.1%), and Grade 3-4 (0.4%) adverse reactions.

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Implementing MDT care in BTCs varies across institutions with distinct models. Some of the models in BTC care include a pre-visit model, a virtual MDT, tumor board reviews, and an integrated clinic (see Sidebar Case Vignettes for examples of two distinct models).

MDT Model Case Vignettes

MDT Model at Mayo Clinic

Overview (from Dr. Sumera Ilyas)

- At the Mayo Clinic, hepatobiliary malignancies come through the Hepatobiliary Neoplasia Clinic, a form of an integrated clinic model, that is staffed by hepatology. Here, only the patients who have biopsy-proven and clearly metastatic disease directly go to medical oncology. In addition, coordination of meetings with patients and members of the multidisciplinary care team for an office visit occurs through a pre-visit model, where nurses will pre-schedule appointments with surgery and medical oncology as needed

Patient Pathways

- Patients with hepatobiliary malignancies, including BTCs, primarily go through the Hepatobiliary Neoplasia Clinic, which is staffed by hepatologists
- Patients directly sent to medical oncology typically have biopsy-proven, clearly metastatic disease or extrahepatic metastasis
- Collaboration with other specialties such as transplant surgery, radiation oncology, and interventional radiology occurs based on the patient's condition and staging

MDT meetings

- Tumor board meetings occur weekly, especially to discuss unique cases and to ensure a collective understanding of complex patient scenarios with follow-up meetings in a few weeks' time
- Tumor board meetings are held in a hybrid format, with a preference for in-person attendance
- Multidisciplinary discussions at the tumor board meetings guide the choice of treatment modality
- Coordination for specialized treatments such as transplant surgery is spearheaded by hepatologists in collaboration with the surgeon

MDT Model at Georgetown University Hospital

Overview (from Dr. Ruth He)

- At Georgetown, nurse navigators may be involved in the initial screening of patients; however, this model may not be feasible in all institutions. At Georgetown, patients with confirmed extrahepatic BTCs will be directed to medical oncology. However, cancer that is localized in the liver will be managed by a tumor board, which may hold multiple meetings in a week to review and discuss treatment plans and modalities. In such cases, surgeons are involved in the MDT care of patients who have surgically amenable diseases. In most cases, patients with early-stage hepatobiliary cancers are evaluated in an MDT clinic where all the specialties will be present

Patient Pathways

- Patients with extrahepatic disease are seen by medical oncology
- Localized liver cases undergo evaluation for potential downstaging using multimodality treatment, combining chemotherapy and local-regional therapy with interventional radiology and radiation oncology.
- A protocol exists for perihilar cholangiocarcinoma patients
- Genetic testing is conducted for each patient to identify potential therapeutics based on mutational profiles. There is an emphasis on connecting mutations to available drugs or clinical trials as a secondary treatment option
- The practice groups employ care coordinators, including nurse navigators and surgeons who assess the number of required appointments for patients

MDT meetings

- Tumor board meetings occur twice weekly where cases may be re-presented to ensure a collective understanding of complex patient scenarios
- There are also monthly tumor board meetings to review all the cases including patients with the potential for transplant surgery
- Gastrointestinal (GI) Tumor Board meetings are typically run by medical oncology once a week usually on Wednesdays and a Hepatobiliary Tumor Board meeting is led by surgeons the same week usually occurring on Fridays.
- Active participation in both GI tumor board and Hepatobiliary Tumor board meetings is encouraged

Patients with advanced BTC may have malnutrition caused by symptoms such as nausea, vomiting, loss of appetite or weight loss, or nutritional deficiencies due to biliary obstruction.[40] In such cases, nutritionists play a valuable role in managing these patients. In cases where patients may be experiencing a lot of pain due to metastases into the bone, palliative care plays a pivotal role in managing their condition. Partnering with nursing professionals and social workers is crucial to providing optimal care. The team should work together to coordinate care and provide education and aid in addressing the emotional, logistical, and financial aspects of care.[39]

The MDT has the potential to optimize diagnosis and care for BTCs.[41] For example, **Figure 6** summarizes results from a retrospective study of 76 patients diagnosed with BTCs at Johns Hopkins Hospital, where 8% of diagnoses changed after multidisciplinary review (n=6/76) and 31% of treatment recommendations changed for patients presenting for a second opinion (n=9/29).[41] The 8% of diagnoses that changed included a change from metastatic disease to lung sarcoidosis and identification of synchronous cholangiocarcinoma.[41] The 31% change in treatment recommendations included a recommendation for hospice for 1 patient, a change in the systemic agent used for 4 patients, and a change to a multimodal treatment for 4 patients.[41] The team consisted of hepatologists, interventional radiologists, medical oncologists, palliative care, pathologists, radiation oncologists, radiologists, and hepatobiliary surgical oncologists.[41] Consequently, in this study, a weekly multidisciplinary clinic was established to manage patients with hepatocellular carcinoma, cholangiocarcinoma, or gallbladder cancer.[41]

Establishing standardized approaches for staging, diagnosis, and treatment of BTCs through MDT may help to engage specialists within the team for any new treatment approaches and decisions.[42] This is increasingly important as recent advances in BTC care promote innovative, personalized treatment options, making complex cases more common and highlighting the essential role of MDTs. Moreover, MDTs foster the education of the respective specialties, especially since new developments in techniques and approaches are making treatments more feasible for patients, such as those who may not have been candidates for such advanced treatments two years prior.

When feasible, MDT meetings may help in other areas such as addressing challenges associated with the coordination of BTC care. A unique challenge that can be overcome through MDTs is having representation of specialists from each discipline, with at least one person from at least eight disciplines identified to attend regular meetings. Another challenge may involve proper documentation following a formal presentation at the MDT meeting and capturing the meeting notes in an electronic medical record (EMR) with follow-up consensus.

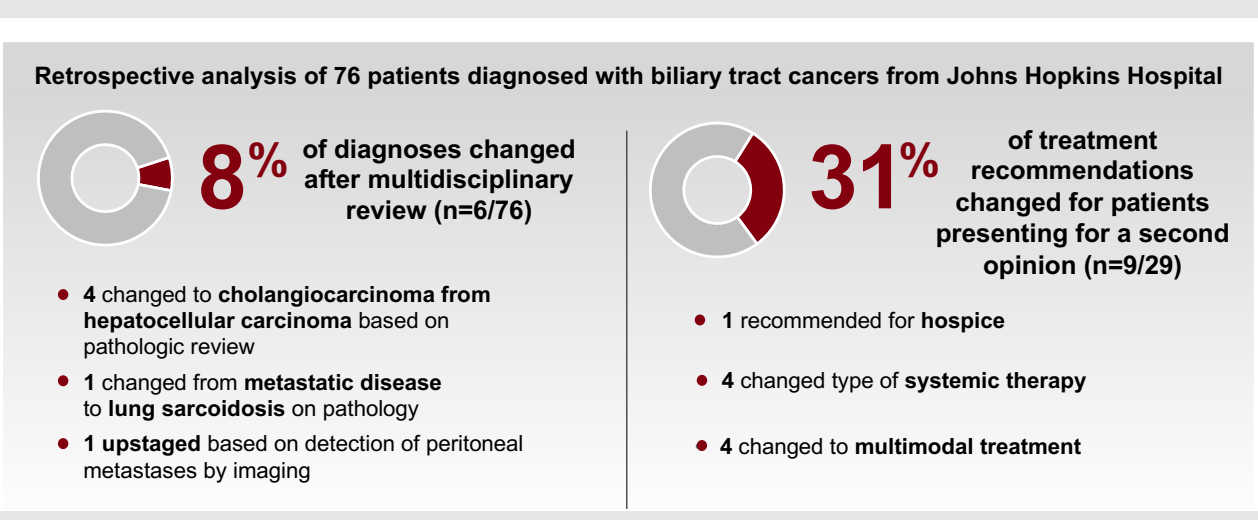

Figure 6.[41] Retrospective Analysis Demonstrating the Potential for an MDT to Optimize Diagnosis and Care for BTCs

DURVALUMAB IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Pneumonitis

The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar in patients who received IMFINZI as a single agent or with ES-SCLC or BTC when given in combination with chemotherapy.

"Communication between the specialties is critical, and I think without that, it's impossible to treat the patient effectively. In order to really get the benefit of a multidisciplinary team, we must be sharing our opinions and coming to conclusions with respect to treatment together. I think that's really what a lot of these multidisciplinary conferences and these teams, these approaches have shown us is that this is a system that really works, and it is to the benefit of patients when specialties are working in concert with each other to develop treatment plans."

- Dr Tom Abrams

Considerations for a Successful Multidisciplinary Team

Some general principles of an MDT may include:

- Maintaining a dedicated hepatobiliary cancer-specific multidisciplinary team that meets weekly to manage patient cases.[39,42]
  - For example, an MDT case study at Oregon Health and Science University spanning a period of 3 years revealed a perceived benefit by the 10 to 15 members of the MDT team who averaged approximately 550 case presentations per year during their weekly meetings lasting about 1 to 2 hours.[42] During that time, the data also revealed that about 25% of the cases were new cases, while 40% were repeat cases for which there was ongoing management.[42]
- Involving all the appropriate specialties, regardless of location, whether through in-person or virtual tumor board meetings in order to provide individualized treatments to patients.[39,42] Sometimes, virtual tumor boards that connect providers may be located across various geographic locations and institutions.[39]
  - By coordinating resources from multiple specialties and minimizing communication failures among the members of the team, MDTs are able to quickly and efficiently appropriate therapeutic regimens in patients thereby helping to optimize outcomes.[42]
- Establishing a standardized approach for screening of hepatobiliary cancers.[42]
  - An MDT utilizing standardized screening procedures may facilitate timely diagnosis.[42] Additionally, an MDT can greatly enhance the number of patients screened and suitable for curative or palliative treatment, thanks to improved screening methods, heightened awareness of at-risk patients among clinicians, and enhanced communication across specialties.[42]
- Defining approaches for early identification and management of adverse events or immune-mediated adverse reactions including continuous monitoring, treatment of the adverse event, withholding treatment, and patient referral to a specialist, is crucial for a successful outcome.[43]
- Partnering with nursing professionals and social workers to provide patient education and resources to help address emotional, logistical, and financial challenges.[39]
  - Nurse navigators may guide patients through the hospital or clinic and social service processes, provide psychosocial support, offer insurance and social referral assistance, address transportation needs, document tumor board discussions, arrange culturally competent care, and maintain close communication with the patient across the care continuum.[39]

DURVALUMAB IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Colitis

IMFINZI 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 occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (<0.1%) and Grade 3 (0.4%) adverse reactions.

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Some considerations and benefits of regular MDT meetings may involve:

- Ensuring a good flow of communication between the specialties, especially across multiple facilities through regular MDT meetings
  - Having regular meetings may minimize communication errors between providers and delays in treatment due to miscommunication, and ensure that providers from multiple specialties who may not have otherwise been consulted, have input on each case.[42]
- A clear communication pathway between the patient, their family and the provider
- Fostering team knowledge and education among all the specialties (eg, updates on clinical trials and results).
  - Having regular MDT meetings significantly increases provider awareness about new research in related fields. For example, the hepatologist in an MDT may keep the group updated on the latest hepatology research relevant to the treatment, while an interventional radiologist may keep the group abreast on specific treatment methodologies, and a medical oncologist may update the group on available clinical trials with new medications.[42]
  - Having regular MDT meetings helps foster the development of a comprehensive treatment plan involving multiple providers, which may be a difficult and time-consuming task in the absence of regular meetings.[42] In addition, such meetings can help cultivate uniformity in the treatment approach over time.[42]
- Respecting and understanding the needs of each discipline
- Ensuring protected time to attend MDT meetings (eg, integrating meetings into the clinical calendar), as well as protected time for diagnostic radiology to review the images beforehand
- Expeditious handling of the patient case review, especially because these can be aggressive conditions
  - Having regular MDT meetings presents an opportunity to tackle and address difficult questions arising from patient cases in a group setting where consensus recommendation can strengthen patient and provider confidence in the management plan.[42]
  - Through an MDT meeting, providers may be able to expedite some straightforward cases without the need for a formal presentation to the group, especially because members of the team are regular attendees and are familiar with group practice, current research, and patient cases.[44] Such expediency may be necessary to accommodate the increasingly large number of patients.[42]
- Recognition of individualized patient care and allowing for flexibility, particularly for patients who may not fit a textbook condition, where protocol may be followed algorithmically
- Ensuring that a designated person from each discipline carries out the recommendations discussed at the tumor board meeting

The benefits of regular MDT meetings discussed here are unlikely to be realized through traditional provider-to-provider communication when caring for a specific patient. Due to the complexity of management, it is recommended that every patient be initially presented to the MDT to establish a comprehensive management plan.[42]

Some challenges and recommendations with establishing an MDT

- Lack of access to specialized care especially in underserved areas is a significant barrier to implementing MDTs for cancer patients, hindering the goal of equal access to standardized care.[42]
  - To address this access barrier, many MDTs are incorporating telemedicine and teleconferencing, enabling the virtual participation of healthcare providers in case discussions.[42]
  - Telemedicine technology connects various sites, allowing MDT members to engage in real-time videoconferencing for sharing knowledge and important medical images such as pathology slides and radiologic scans.[42]
  - Telehealth technology provides a means for centers with limited resources to communicate with specialists who may not be available locally.
  - To overcome the logistical challenges associated with traditional in-person face-to-face meetings, a potential solution may be transitioning to virtual MDTs.[42]
- Characteristics of a virtual MDT meeting may involve asynchronous participation of attendees, who may join and leave discussions as needed, a variable composition that allows for members to join temporarily as required for specific cases, not bound by geographic limitation, and diversified platform capabilities including video clips, notes, images, and virtual imaging.[42]
- However, despite the advantages of virtual MDT meetings, replacing traditional face-to-face meetings in cancer management may be unlikely due to various challenges such as acquiring quality equipment, coordinating the appropriate personnel, and establishing a reimbursement structure.[42]

DURVALUMAB IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Hepatitis

IMFINZI can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 3 (1.4%) adverse reactions.

Considerations for a successful MDT in cancer care involve maintaining a dedicated team, involving all the specialties regardless of location, standardizing screening, addressing adverse events, and partnering with nursing professionals and social workers for a holistic approach. Regular MDT meetings promote communication, knowledge sharing, and expedited case reviews. Challenges in establishing MDTs include limited access to specialized care, which can be mitigated through telemedicine and teleconferencing. Virtual MDTs offer flexibility but may present challenges in acquiring equipment, coordinating appropriate personnel, and reimbursing structures. These collaborative efforts via regular MDT meetings aim to enhance patient outcomes, particularly due to the persistent challenge of low median overall survival (OS) rates in BTC care, highlighting the need for newer and effective treatments.[12]

Current Treatment of Locally Advanced or Metastatic Biliary Tract Cancers (BTCs) - Cholangiocarcinoma and Gallbladder Cancer

Given the unmet needs and poor prognosis in Locally Advanced or Metastatic BTCs, there has been a long-awaited anticipation for advancements and progress in treatment options.[47]

TOPAZ-1 was the first global phase 3 trial of a first-line treatment for advanced BTCs to demonstrate positive results since ABC-02 (2010) established gemcitabine and cisplatin (gem-cis) as the original standard of care.[12] IMFINZI, in combination with gemcitabine and cisplatin, is indicated for the treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC).[47]

TOPAZ-1 was a phase 3, randomized, double-blind, placebo-controlled global study, where patients were randomized in a 1:1 ratio to receive either durvalumab in combination with gemcitabine and cisplatin or placebo in combination with gemcitabine and cisplatin.[12] Randomization was stratified based on disease status, (initially unresectable vs recurrent), and primary tumor site (iCCA vs eCCA vs GBC).[12] In all, 685 patients were randomly assigned to durvalumab (n=341) or placebo (n=344) in combination with gem-cis.[12]

The primary endpoint of the trial was OS, which was defined as the time between randomization and death due to any cause, in the durvalumab vs placebo group. Secondary endpoints included progression-free survival (PFS) and objective response rates (ORR). PFS was defined as the time from the date of randomization until the date of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 defined imaging disease progression or death.[12,45] ORR was defined as the sum of the rate of complete responses and partial responses in patients with measurable disease.[12] Safety and adverse events were assessed for the durvalumab and placebo groups.[12]

Results from the study showed that the hazard ratio for overall survival was 0.80 (95% confidence interval [CI], 0.66-0.97; P=0.021).[12] The median OS was 12.8 months (95% CI, 11.1-14.0) with durvalumab + gem-cis vs 11.5 months (95% CI, 10.1-12.5) with gem-cis.[12] In TOPAZ-1, durvalumab plus gem-cis, was also the first and only immunotherapy-based regimen to demonstrate significant improvement in overall survival and PFS vs gemcitabine plus cisplatin in locally advanced or metastatic BTCs and is a standard of care.[12] The hazard ratio for progression-free survival was 0.75 (95% CI, 0.63-0.89; P=0.001).[12] The median PFS with durvalumab + gem-cis was 7.2 months (95% CI, 6.7-7.4) vs 5.7 months (95% CI, 5.6-6.7) with placebo.[12] ORR was 26.7% with durvalumab + gem-cis and 18.7% with placebo + gem-cis.[12] The incidences of grade 3 or 4 adverse events were 75.7% and 77.8% with durvalumab plus gemcitabine and cisplatin regimen vs placebo, respectively.[12]

In an updated OS analysis post-primary finding with 6.5 months of additional follow-up, the estimated 24-month OS rate was 23.6% (95% CI, 18.7-28.9) for durvalumab plus gem-cis and 11.5% (95% CI, 7.6-16.2) for gem-cis.[46] The updated OS analysis was not formally tested for statistical significance.

Serious adverse reactions occurred in 47% of patients receiving

DURVALUMAB IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Endocrinopathies

Adrenal Insufficiency: IMFINZI 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 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

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2022

JAN

TOPAZ-1 Overall Survival Primary Final Analysis[12,47,48]

JUNE

Patient-Reported Outcomes (PROs) in Prespecified Analyses from TOPAZ-1[45]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

Overall Survival Subgroup Analysis by Geographic Region[49]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

Overall Survival Subgroup Analysis by Primary Tumor Location[50]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

Overall Survival Subgroup Analysis by Disease State At Baseline[51]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

SEPT

Update Overall Survival With 6.5 months of Additional Follow-Up[48]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

Immune-Mediated Adverse Events (imAEs) Analysis[52]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

Panel Perspective:
The updated overall survival results provide more data in the regimen. Dr Sumera Ilyas

DEC

Exploratory Analysis of Mutational Status in TOPAZ-1[53]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

2023

JAN

Outcomes by Antibiotics Use[54]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

Long-Term Survivor Analysis TOPAZ-1[55]

This exploratory subgroup analysis was not powered to show differences between or within individual subgroups and was not formally tested for statistical significance.

DURVALUMAB IMPORTANT SAFETY INFORMATION

Immune-Mediated Endocrinopathies

Hypophysitis: IMFINZI 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. Grade 3 hypophysitis/hypopituitarism occurred in <0.1% (1/1889) of patients who received IMFINZI.

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durvalumab + gem-cis.[47] The most frequent serious adverse reactions ≥ 2% of patients were cholangitis (7%), pyrexia (3.8%), anemia (3.6%), sepsis (3.3%), and acute kidney injury (2.4%).[47] Fatal adverse reactions occurred in 3.6% of patients receiving durvalumab + gem-cis and included ischemic or hemorrhagic stroke (reported in 4 patients), sepsis, and upper gastrointestinal hemorrhage (reported in 2 patients each).[47] The most common adverse reactions (≥ 20% of patients) with IMFINZI + gem-cis were fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia.[47]

The TOPAZ-1 study is a treatment option for patients with locally advanced or metastatic BTCs and is considered a standard of care for our panelists. The panelists also added that, the TOPAZ-1 study highlighted the durvalumab plus chemotherapy doublet vs chemotherapy doublet alone, which has been in use for more than a decade.[12] As a result, durvalumab + gemcitabine and cisplatin is [an] [NCCN Guidelines® Version 3.2023] Category 1, preferred primary systemic therapy option for unresectable or metastatic biliary tract cancers.[29]

The TOPAZ-1 study, initially presented at ASCO GI in January 2022, sparked additional analyses of the study conducted until January 2023 addressing key questions. According to our panelists, these additional analyses were instrumental in providing more data for durvalumab plus gemcitabine and cisplatin across patients with locally advanced or metastatic BTCs. A timeline of these additional analyses have been outlined here.

Adverse Event Management During Systemic Treatment for BTCs

Consistent with TOPAZ-1 data, our panelists most commonly see adverse reactions associated with the durvalumab and gemcitabine-cisplatin regimen, such as fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia.[47]

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, and solid organ transplant rejection.[47] Durvalumab can cause severe or life-threatening infusion-related reactions. Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a programmed cell death-1/programmed cell death-ligand 1 blocking antibody.[47]

Adverse event management during systemic treatment for locally advanced or metastatic BTC is challenging due to complications such as immune-related liver injury.[56] Adverse events such as immune-related liver injury are associated with increased use of immune checkpoint inhibitors for locally advanced or metastatic BTC treatment.[56] Patients with locally advanced or metastatic BTC and concomitant biliary obstruction or poor liver function, may be at an increased risk of adverse reactions.[56] Immune-related liver injury may be higher in patients with cholangiocarcinoma than in those with gastric cancer.[56] Therefore it is recommended that in patients with locally advanced or metastatic BTC, liver function should be monitored more closely when administering immunotherapy.[56] The clinical manifestation of immune-related cholestatic hepatitis and cholangitis can be difficult to diagnose, often requiring a combination of histological examination and imaging tests to differentiate from tumor progression.[56] Corticosteroid therapy, traditionally used for immune-related adverse events, may be less effective for cholestasis-type liver injury.[56] Managing immune-related adverse events in locally advanced or metastatic BTC requires careful monitoring of several organs including liver function, a timely differential diagnosis, and a tailored approach.[56] IMFINZI Prescribing Information has additional information for dosage modification and management specific to adverse reactions.

DURVALUMAB IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Endocrinopathies

Thyroid Disorders: IMFINZI 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.

Thyroiditis: Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

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Key Takeaways

Our panelists are familiar with the TOPAZ-1 data, and community oncologists have widely adopted this triplet regimen for locally advanced or metastatic BTCs. TOPAZ-1 has demonstrated this regimen as a standard of care amid a rapidly evolving immunotherapy landscape.[57] The future for locally advanced or metastatic BTC care is promising with the impact of the TOPAZ-1 study as a recent advancement.[57] This pivotal trial has sparked increased interest and hope in treating locally advanced or metastatic BTCs.[57] As a result of the TOPAZ-1 study, [durvalumab plus gemcitabine-cisplatin is a category 1, preferred primary systemic treatment option for patients with unresectable and metastatic locally advanced or metastatic BTCs in the updated NCCN Guidelines for Biliary Tract Cancers Version 3.2023.[29]]

Conclusion

Biliary tract cancers comprising iCCA, eCCA, and GBC, are rare yet aggressive malignancies notorious for their poor prognosis.[1,2] The asymptomatic progression of the disease and challenges with diagnosis often results in delayed diagnosis, with around 80% of BTC patients presenting with advanced, unresectable disease.[2,4,5] Timely detection and diagnosis of BTCs is crucial but challenging.[2,3] The disease lacks a singular identifying tool, requiring a blend of clinical, biochemical, radiologic, and histologic techniques for diagnosis.[22] Approaches such as FISH and NGS testing are sometimes underutilized due to feasibility in some settings and lack of expertise.[23] Next-generation sequencing, which offer insight into the genomic profile and differences between biliary tract cancer types, is increasingly being adopted in clinical practice.[28] Implementing routine genomic profiling may facilitate treatment decisions in the future.[28] Addressing the challenges of timely diagnosis requires integrated solutions such as onsite cytopathology, enhanced biopsy techniques, and streamlining the diagnostic process. Early diagnosis may be able to enable surgical intervention, the potentially only curative modality for BTCs.[4]

Patients and caregivers encounter various hurdles, including financial constraints and challenges with understanding and adhering to treatment recommendations. Navigating the complexities of the BTC patient journey can be a daunting task for patients grappling with the uncertainty of long-term outcomes, lifelong systemic therapy, availability of effective treatments, and the logistical challenges of hospital visits. Due to the complexity of BTCs, a multidisciplinary approach involving various healthcare professionals is essential.[38] A hepatobiliary MDT that includes various specialties: medical oncology, hepatology/gastroenterology, interventional radiology, nursing, surgical oncology, nutrition, pathology, psychology, and social work, among others, promises comprehensive patient care via a holistic approach.[39] The composition, coordination, and models of MDT differs across institutions. Principles guiding an MDT include regular meetings, involvement of all relevant specialties, and establishing standardized screening procedures.[42] Studies have shown that MDTs have the potential to optimize diagnosis and treatment recommendations for BTC patients.[41]

The TOPAZ-1 trial evaluated the durvalumab plus gemcitabine and cisplatin regimen, marking a development with triplet therapy, which has been cemented as a standard of care.[57] Clinical pathways adapting to recent approvals may consider integrating durvalumab in combination with gemcitabine and cisplatin as a potential option in the evolving standard of care for advanced and metastatic BTCs. By adopting these recommendations, clinicians and healthcare professionals can work to advance the care of BTCs.

Various resources are available for HCPs, patients, and their caregivers seeking more information and support for BTCs. Medical professionals can access the latest information and treatment guidelines via the NCCN Guidelines, medical journals, and clinical trial updates, including supplements such as *The Journal of Clinical Pathways.* Patients and caregivers can benefit from patient advocacy groups, online communities, and support networks dedicated to BTCs providing valuable insights and emotional support.

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DURVALUMAB IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Nephritis with Renal Dysfunction

IMFINZI can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.

Immune-Mediated Dermatology Reactions

IMFINZI 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 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 1.8% (34/1889) of patients receiving IMFINZI, including Grade 3 (0.4%) 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 or were reported with the use of other PD-1/PD-L1 blocking antibodies.

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: Pancreatitis including increases in serum amylase and lipase levels, 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.

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 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 2.2% (42/1889) of patients receiving IMFINZI, including Grade 3 (0.3%) adverse reactions.

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 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 advise them to use effective contraception during treatment with IMFINZI and for 3 months after the last dose of IMFINZI.

Lactation

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

Adverse Reactions

In patients with locally advanced or metastatic BTC in the TOPAZ-1 study receiving IMFINZI (n=338), the most common adverse reactions (occurring in ≥20% of patients) were fatigue (42%), nausea (40%), constipation (32%), decreased appetite (26%), abdominal pain (24%), rash (23%), and pyrexia (20%). In patients with locally advanced or metastatic BTC in the TOPAZ-1 study receiving IMFINZI (n=338), discontinuation due to adverse reactions occurred in 6% of the patients receiving IMFINZI plus chemotherapy.

Serious adverse reactions occurred in 47% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 2% of patients were cholangitis (7%), pyrexia (3.8%), anemia (3.6%), sepsis (3.3%) and acute kidney injury (2.4%). Fatal adverse reactions occurred in 3.6% of patients receiving IMFINZI plus chemotherapy. These include ischemic or hemorrhagic stroke (4 patients), sepsis (2 patients), and upper gastrointestinal hemorrhage (2 patients). The safety and effectiveness of IMFINZI have not been established in pediatric patients.

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NCCN=National Comprehensive Cancer Network® (NCCN®)

Please see full Prescribing Information after page 17

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IMFINZI safely and effectively. See full prescribing information for IMFINZI.

IMFINZI® (durvalumab) injection, for intravenous use
Initial U.S. Approval: 2017

---------- RECENT MAJOR CHANGES----------

Indications and Usage (1.3)	09/2022
Indications and Usage (1.4)	10/2022
Indications and Usage (1.1)	11/2022
Dosage and Administration (2.1)	09/2022
Dosage and Administration (2.1, 2.2, 2.3)	10/2022
Dosage and Administration (2.1, 2.3)	11/2022
Warnings and Precautions (5.1, 5.2)	10/2022
Warnings and Precautions (5.1, 5.2)	11/2022

---------- INDICATIONS AND USAGE ----------

IMFINZI is a programmed death-ligand 1 (PD-L1) blocking antibody indicated:

- for the treatment of adult patients with unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. (1.1)
- in combination with tremelimumab-actl and platinum-based chemotherapy, for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. (1.1)
- in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). (1.2)
- in combination with gemcitabine and cisplatin, as treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC). (1.3)
- in combination with tremelimumab-actl, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC). (1.4)

---------- DOSAGE AND ADMINISTRATION ----------

- Administer IMFINZI as an intravenous infusion over 60 minutes after dilution. (2.3)
- Stage III NSCLC:
  - Weight ≥ 30 kg: 10 mg/kg every 2 weeks or 1,500 mg every 4 weeks (2.1)
  - Weight < 30 kg: 10 mg/kg every 2 weeks (2.1)
- Metastatic NSCLC:
  - Weight ≥ 30 kg: 1,500 mg every 3 weeks in combination with tremelimumab-actl 75 mg and platinum-based chemotherapy for 4 cycles, and then administer IMFINZI 1,500 mg every 4 weeks as a single agent with histology-based pemetrexed maintenance therapy every 4 weeks, and a fifth dose of tremelimumab-actl 75 mg in combination with IMFINZI dose 6 at week 16 (2.1)
  - Weight < 30 kg: 20 mg/kg every 3 weeks in combination with tremelimumab-actl 1 mg/kg and platinum-based chemotherapy, and then administer IMFINZI 20 mg/kg every 4 weeks as a single agent with histology-based pemetrexed therapy every 4 weeks, and a fifth dose of tremelimumab-actl 1 mg/kg in combination with IMFINZI dose 6 at week 16 (2.1)
- ES-SCLC:
  - Weight ≥ 30 kg: With etoposide and either carboplatin or cisplatin, administer IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy, and then 1,500 mg every 4 weeks as a single agent (2.1)
  - Weight < 30 kg: With etoposide and either carboplatin or cisplatin, administer IMFINZI 20 mg/kg every 3 weeks in combination with chemotherapy, and then 10 mg/kg every 2 weeks as a single agent (2.1)
- BTC:
  - Weight ≥ 30 kg: administer IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy, and then 1,500 mg every 4 weeks as a single agent (2.1)
  - Weight < 30 kg: administer IMFINZI 20 mg/kg every 3 weeks in combination with chemotherapy, and then 20 mg/kg every 4 weeks as a single agent (2.1)
- uHCC:
  - Weight ≥ 30 kg: IMFINZI 1,500 mg in combination with tremelimumab-actl 300 mg as a single dose at Cycle 1/Day 1, followed by IMFINZI as a single agent every 4 weeks (2.1)
  - Weight < 30 kg: IMFINZI 20 mg/kg in combination with tremelimumab-actl 4 mg/kg as a single dose at Cycle 1/Day 1, followed by IMFINZI as a single agent every 4 weeks (2.1)
- See full Prescribing Information for preparation and administration instructions and dosage modifications for adverse reactions.

---------- DOSAGE FORMS AND STRENGTHS ----------

- 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)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Immune-Mediated Adverse Reactions (5.1)
  - 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 dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, solid organ transplant rejection, and immune-mediated pancreatitis.
    - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
    - Withhold or permanently discontinue based on severity and type of reaction.
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue IMFINZI based on the severity of the reaction. (5.2)
- Complications of Allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

IMFINZI as a Single Agent

- Most common adverse reactions (≥ 20% of patients with unresectable, Stage III NSCLC) are cough, fatigue, pneumonitis/radiation pneumonitis, upper respiratory tract infections, dyspnea, and rash. (6.1)

IMFINZI in Combination with Platinum-Based Chemotherapy

- Most common adverse reactions (≥ 20% of patients with extensive-stage SCLC) are nausea, fatigue/asthenia, and alopecia. (6.1)

IMFINZI in Combination with gemcitabine and cisplatin

- Most common adverse reactions (≥ 20% of patients with BTC) are fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia. (6.1)

IMFINZI in Combination with Tremelimumab-actl

- Most common adverse reactions (≥ 20%) of patients with uHCC are rash, diarrhea, fatigue, pruritis, musculoskeletal pain, and abdominal pain. (6.1)

IMFINZI in Combination with Tremelimumab-actl and Platinum-Based Chemotherapy

- Most common adverse reactions (≥ 20% of patients with metastatic NSCLC) were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer

- IMFINZI is indicated for the treatment of adult patients with unresectable Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- IMFINZI, in combination with tremelimumab-actl and platinum-based chemotherapy, is indicated for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

1.2 Small Cell Lung Cancer

IMFINZI, in combination with etoposide and either carboplatin or cisplatin, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).

1.3 Biliary Tract Cancers

IMFINZI, in combination with gemcitabine and cisplatin, is indicated for the treatment of adult patients with locally advanced or metastatic biliary tract cancer (BTC).

1.4 Hepatocellular Carcinoma

IMFINZI, in combination with tremelimumab-actl, is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosages for IMFINZI as a single agent and IMFINZI in combination with other therapeutic agents are presented in Tables 1, 2 and 3.

Administer IMFINZI as an intravenous infusion after dilution as recommended *[see Dosage and Administration (2.3)]*.

Table 1. Recommended Dosages of IMFINZI

Indication	Recommended IMFINZI Dosage	Duration of Therapy
Single Agent		
Unresectable stage III NSCLC	Patients with a body weight of ≥ 30 kg: 10 mg/kg every 2 weeks or 1,500 mg every 4 weeks Patients with a body weight of < 30 kg: 10 mg/kg every 2 weeks	Until disease progression, unacceptable toxicity, or a maximum of 12 months
Combination with Other Therapeutic Agents		
ES-SCLC	Patients with a body weight of ≥ 30 kg: 1,500 mg in combination with chemotherapy* every 3 weeks (21 days) for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent Patients with a body weight of < 30 kg: 20 mg/kg in combination with chemotherapy* every 3 weeks (21 days) for 4 cycles, followed by 10 mg/kg every 2 weeks as a single agent	Until disease progression or unacceptable toxicity

Table 1. Recommended Dosages of IMFINZI (cont'd)

Indication	Recommended IMFINZI Dosage	Duration of Therapy
BTC	Patients with a body weight of ≥ 30 kg: 1,500 mg in combination with chemotherapy* every 3 weeks (21 days) up to 8 cycles followed by 1,500 mg every 4 weeks as a single agent Patients with a body weight of < 30 kg: 20 mg/kg in combination with chemotherapy* every 3 weeks (21 days) up to 8 cycles followed by 20 mg/kg every 4 weeks as a single agent	Until disease progression or until unacceptable toxicity
uHCC	Patients with a body weight of ≥ 30 kg: • IMFINZI 1,500 mg following a single dose of tremelimumab-actl[$] 300 mg at Day 1 of Cycle 1; • Continue IMFINZI 1,500 mg as a single agent every 4 weeks Patients with a body weight of < 30 kg: • IMFINZI 20 mg/kg following a single dose of tremelimumab-actl[$] 4 mg/kg at Day 1 of Cycle 1; • Continue IMFINZI 20 mg/kg as a single agent every 4 weeks	After Cycle 1 of combination therapy, administer IMFINZI as a single agent every 4 weeks until disease progression or unacceptable toxicity

* Administer IMFINZI prior to chemotherapy on the same day. Refer to the Prescribing Information for the agent administered in combination with IMFINZI for recommended dosage information, as appropriate.

$ Administer tremelimumab-actl prior to IMFINZI on the same day. When tremelimumab-actl is administered in combination with IMFINZI, refer to the Prescribing Information for tremelimumab-actl dosing information.

IMFINZI in Combination with Tremelimumab-actl and Platinum-Based Chemotherapy

The recommended dosage schedule and regimens for IMFINZI for the treatment of metastatic non-small cell lung cancer (NSCLC) are provided in Tables 2 and 3.

Weigh patients prior to each infusion.

Calculate the appropriate dose using Table 3 below based on the patient's weight and tumor histology.

Table 2: Recommended Dosage Schedule

	Week*,$																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Cycle:	1			2			3			4			5				6				7				8
IMFINZI*,¶	X			X			X			X			X				X				X				X
Tremelimumab-actl¶,#	X			X			X			X							X								
Chemotherapy	X			X			X			X			X[P]				X[P]				X[P]				X[P]

* continue IMFINZI until disease progression or intolerable toxicity.

$ Note the dosing interval change from every 3 weeks to every 4 weeks starting at cycle 5.

¶ intravenous infusion over 60 minutes *[see Dosage and Administration (2.3)]*.

if patients receive fewer than 4 cycles of platinum-based chemotherapy, the remaining cycles of tremelimumab-actl (up to a total of 5) should be given after the platinum-based chemotherapy phase, in combination with IMFINZI, every 4 weeks.

P optional pemetrexed therapy from week 12 until disease progression or intolerable toxicity for patients with non-squamous disease who received treatment with pemetrexed and carboplatin/cisplatin.

Table 3: Recommended Regimen and Dosage

Tumor Histology	Patient Weight	IMFINZI Dosage	Tremelimumab-actl Dosage*	Platinum-based Chemotherapy Regimen*
Non-Squamous	≥ 30kg	1,500 mg	75 mg	• carboplatin & nab-paclitaxel OR • carboplatin or cisplatin & pemetrexed
	< 30kg	20 mg/kg	1 mg/kg	
Squamous	≥ 30kg	1,500 mg	75 mg	• carboplatin & nab-paclitaxel OR • carboplatin or cisplatin & gemcitabine
	< 30kg	20 mg/kg	1 mg/kg	

* Refer to the Prescribing Information for dosing information.

2.2 Dosage Modifications for Adverse Reactions

No dose reduction for IMFINZI is recommended. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Dosage modifications for IMFINZI or IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy for adverse reactions that require management different from these general guidelines are summarized in Table 4.

Table 4. Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2	Withhold†
	Grade 3	Withhold† or permanently discontinue‡
	Grade 4	Permanently discontinue
Intestinal perforation	Any grade	Permanently discontinue
Hepatitis with no tumor involvement of the liver	ALT or AST increases to more than 3 and up to 8 times the ULN or total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	ALT or AST increases to more than 8 times ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver§	AST or ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN or AST or ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN	Withhold†
	AST or ALT increases to more than 10 times ULN or total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
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
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue

Table 4. Recommended Dosage Modifications for Adverse Reactions (cont'd)

Adverse Reaction	Severity*	Dosage Modification
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal.

* Based on National Cancer Institute Common Terminology Criteria for Adverse Events, 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 an inability to reduce corticosteroid dose to 10 mg of prednisone or less per day (or equivalent) within 12 weeks of initiating corticosteroids.

‡ Permanently discontinue IMFINZI for Grade 3 colitis when administered as part of a tremelimumab-actl containing regimen.

§ 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.

2.3 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 the infusion solution is not administered immediately and needs to be stored, the time from preparation until the completion of the infusion should not exceed:
  - 28 days in a refrigerator at 2°C to 8°C (36°F to 46°F)
  - 8 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.
- Use separate infusion bags and filters for each drug product.

IMFINZI in Combination with Other Products

- Administer all drug products as separate intravenous infusions.
- Do not co-administer other drugs through the same infusion line.
- For platinum-based chemotherapy, refer to Prescribing Information for administration information.
- For pemetrexed therapy, refer to Prescribing Information for administration information.

Combination Regimens: Order of Infusions

IMFINZI in Combination with Tremelimumab-actl

- Infuse tremelimumab-actl first, followed by IMFINZI on the same day of dosing.

IMFINZI in Combination with Tremelimumab-actl and Platinum-Based Chemotherapy

- Infuse tremelimumab-actl first, followed by IMFINZI and then platinum-based chemotherapy on the day of dosing.

IMFINZI in Combination with Tremelimumab-actl and Pemetrexed Therapy

- Infuse tremelimumab-actl first, followed by IMFINZI and then pemetrexed therapy on the day of dosing.

Combination Regimens: Infusion Instructions

IMFINZI in Combination with Tremelimumab-actl

- Administer tremelimumab-actl over 60 minutes followed by a 60 minute observation period. Then administer IMFINZI as a separate intravenous infusion over 60 minutes.

IMFINZI in Combination with Tremelimumab-actl and Platinum-Based Chemotherapy/ Pemetrexed Therapy

Cycle 1

- Infuse tremelimumab-actl over 1 hour. One to two hours after completion of tremelimumab-actl infusion, infuse IMFINZI over 1 hour. One to two hours after completion of IMFINZI infusion, administer platinum-based chemotherapy.

Subsequent Cycles

- If there are no infusion reactions during cycle 1, subsequent cycles of IMFINZI can be given immediately after tremelimumab-actl. The time between the end of the IMFINZI infusion and the start of chemotherapy can be reduced to 30 minutes.

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 Adverse Reactions

IMFINZI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing 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.

The incidence and severity of immune-mediated adverse reactions were similar when IMFINZI was administered as a single agent or in combination with chemotherapy or in combination with tremelimumab-actl and platinum-based chemotherapy, unless otherwise noted.

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 with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. 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 depending on severity *[see Dosage and Administration (2.2)]*. In general, if IMFINZI 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.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

IMFINZI can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

IMFINZI as a Single Agent

In Patients Who Did Not Receive Recent Prior Radiation

In patients who received IMFINZI on clinical trials in which radiation therapy was generally not administered immediately prior to initiation of IMFINZI, the incidence of immune-mediated pneumonitis was 2.4% (34/1414), including fatal (< 0.1%), and Grade 3-4 (0.4%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 5 patients. Systemic corticosteroids were required in 19 patients (19/34) with pneumonitis who did not receive chemoradiation prior to initiation of IMFINZI.

In Patients Who Received Recent Prior Radiation

The incidence of pneumonitis (including radiation pneumonitis) in patients with unresectable Stage III NSCLC following definitive chemoradiation within 42 days prior to initiation of IMFINZI in PACIFIC was 18.3% (87/475) in patients receiving IMFINZI and 12.8% (30/234) in patients receiving placebo. Of the patients who received IMFINZI (475) 1.1% were fatal and 2.7% were Grade 3 adverse reactions. Events resolved in 50 of the 87 patients and resulted in permanent discontinuation in 27 patients.

Systemic corticosteroids were required in 64 patients (64/87) with pneumonitis who had received chemoradiation prior to initiation of IMFINZI, while 2 patients required use of infliximab with high-dose steroids.

The frequency and severity of immune-mediated pneumonitis in patients who did not receive definitive chemoradiation prior to IMFINZI were similar whether IMFINZI was given as a single agent in patients with various cancers in a pooled data set or in patients with ES-SCLC or BTC when given in combination with chemotherapy.

IMFINZI with Tremelimumab-actl

Immune-mediated pneumonitis occurred in 1.3% (5/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including fatal (0.3%) and Grade 3 (0.2%) adverse reactions. Events resolved in 3 of the 5 patients and resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in all patients; of these, 4 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient (1/5) required other immunosuppressants.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated pneumonitis occurred in 3.5% (21/596) of patients receiving IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy, including fatal (0.5%), and Grade 3 (1%) adverse reactions. Events resolved in 11 of the 21 patients and resulted in permanent discontinuation in 7 patients. Systemic corticosteroids were required in all patients with immune-mediated pneumonitis, while 1 patient (1/21) required other immunosuppressants.

Immune-Mediated Colitis

IMFINZI 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.

IMFINZI as a Single Agent

Immune-mediated colitis occurred in 2% (37/1889) of patients receiving IMFINZI, including Grade 4 (< 0.1%) and Grade 3 (0.4%) adverse reactions. Events resolved in 27 of the 37 patients and resulted in permanent discontinuation in 8 patients. Systemic corticosteroids were required in all patients with immune-mediated colitis, while 2 patients (2/37) required other immunosuppressants (e.g., infliximab, mycophenolate).

IMFINZI with Tremelimumab-actl

Immune-mediated colitis or diarrhea occurred in 6% (23/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (3.6%) adverse reactions. Events resolved in 22 of the 23 patients and resulted in permanent discontinuation in 5 patients. All patients received systemic corticosteroids, and 20 of the 23 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also received other immunosuppressants.

Intestinal perforation has been observed in other studies of IMFINZI in combination with tremelimumab-actl.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated colitis occurred in 6.5% (39/596) of patients receiving IMFINZI in combination with tremelimumab-actl including fatal (0.2%) and Grade 3 (2.5%) adverse reactions. Events resolved in 33 of 39 patients and resulted in permanent discontinuation in 11 patients. Systemic corticosteroids were required in all patients with immune-mediated colitis, while 4 patients (4/39) required other corticosteroids.

Intestinal perforation and large intestine perforation were reported in 0.1% of patients receiving IMFINZI in combination with tremelimumab-actl.

Immune-Mediated Hepatitis

IMFINZI can cause immune-mediated hepatitis.

IMFINZI as a Single Agent

Immune-mediated hepatitis occurred in 2.8% (52/1889) of patients receiving IMFINZI, including fatal (0.2%), Grade 4 (0.3%) and Grade 3 (1.4%) adverse reactions. Events resolved in 21 of the 52 patients and resulted in permanent discontinuation of IMFINZI in 6 patients. Systemic corticosteroids were required in all patients with immune-mediated hepatitis, while 2 patients (2/52) required use of mycophenolate with high-dose steroids.

IMFINZI with Tremelimumab-actl

Immune-mediated hepatitis occurred in 7.5% (29/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including fatal (0.8%), Grade 4 (0.3%), and Grade 3 (4.1%) adverse reactions. Events resolved in 12 of the 29 patients and resulted in permanent discontinuation in 9 patients. Systemic corticosteroids were required in all 29 patients and all 29 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eight patients (8/29) required other immunosuppressants.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated hepatitis occurred in 3.9% (23/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including fatal (0.3%), Grade 4 (0.5%), and Grade 3 (2.0%) adverse reactions. Events resolved in 12 of the 23 patients and resulted in permanent discontinuation in 10 patients. Systemic corticosteroids were required in all patients with immune-mediated hepatitis, while 2 patients (2/23) required use of other immunosuppressants.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

IMFINZI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold or permanently discontinue IMFINZI based on the severity *[see Dosage and Administration (2.2)]*.

IMFINZI as a Single Agent

Immune-mediated adrenal insufficiency occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (< 0.1%) adverse reactions. Events resolved in 1 of the 9 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in all patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids.

IMFINZI with Tremelimumab-actl

Immune-mediated adrenal insufficiency occurred in 1.5% (6/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.3%) adverse reactions. Events resolved in 2 of the 6 patients. Systemic corticosteroids were required in all 6 patients, and of these, 1 patient required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated adrenal insufficiency occurred in 2.2% (13/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.8%) adverse reactions. Events resolved in 2 of the 13 patients and resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in all patients with adrenal insufficiency. One patient also required endocrine therapy.

Hypophysitis

IMFINZI 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. Withhold or permanently discontinue IMFINZI depending on severity *[see Dosage and Administration (2.2)]*.

IMFINZI as a Single Agent

Grade 3 hypophysitis/hypopituitarism occurred in < 0.1% (1/1889) of patients who received IMFINZI. Treatment with systemic corticosteroids was administered in this patient. The event did not lead to permanent discontinuation of IMFINZI.

IMFINZI with Tremelimumab-actl

Immune-mediated hypophysitis/hypopituitarism occurred in 1% (4/388) of patients receiving IMFINZI in combination with tremelimumab-actl. Events resolved in 2 of the 4 patients. Systemic corticosteroids were required in 3 patients, and of these, 1 patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Two patients also required endocrine therapy.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated hypophysitis occurred in 1.3% (8/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.5%) adverse reactions. Events resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in 6 patients with immune-mediated hypophysitis; of these, 2 of the 8 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also required endocrine therapy.

Thyroid Disorders

IMFINZI 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. Withhold or discontinue IMFINZI based on the severity *[see Dosage and Administration (2.2)]*.

Thyroiditis

IMFINZI as a Single Agent

Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (< 0.1%) adverse reactions. Events resolved in 4 of the 9 patients and resulted in permanent discontinuation in 1 patient. Systemic corticosteroids were required in 3 patients (3/9) with immune-mediated thyroiditis, while 8 patients (8/9) required endocrine therapy.

IMFINZI with Tremelimumab-actl

Immune-mediated thyroiditis occurred in 1.5% (6/388) of patients receiving IMFINZI in combination with tremelimumab-actl. Events resolved in 2 of the 6 patients. Systemic corticosteroids were required in 2 patients (2/6) with immune-mediated thyroiditis; of these, 1 patient required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated thyroiditis occurred in 1.2% (7/596) of patients receiving IMFINZI in combination with tremelimumab-actl. Events resolved in 2 of the 7 patients and one resulted in permanent discontinuation. Systemic corticosteroids were required in 2 patients (2/7) with immune-mediated thyroiditis, while all patients required endocrine therapy.

Hyperthyroidism

IMFINZI as a Single Agent

Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI. Events resolved in 30 of the 39 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in 9 patients (9/39) with immune-mediated hyperthyroidism, while 35 patients (35/39) required endocrine therapy.

IMFINZI with Tremelimumab-actl

Immune-mediated hyperthyroidism occurred in 4.6% (18/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.3%) adverse reactions. Events resolved in 15 of the 18 patients. Two patients (2/18) required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seventeen patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker).

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated hyperthyroidism occurred in 5% (30/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.2%) adverse reactions. Events resolved in 21 of the 30 patients. Systemic corticosteroids were required in 5 patients (5/30) with immune-mediated hyperthyroidism, while 28 patients (28/30) required endocrine therapy.

Hypothyroidism

IMFINZI as a Single Agent

Immune-mediated hypothyroidism occurred in 8.3% (156/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions. Events resolved in 31 of the 156 patients and did not lead to permanent discontinuation of IMFINZI in any patients. Systemic corticosteroids were required in 11 patients (11/156) and the majority of patients (152/156) required long-term thyroid hormone replacement.

IMFINZI with Tremelimumab-actl

Immune-mediated hypothyroidism occurred in 11% (42/388) of patients receiving IMFINZI in combination with tremelimumab-actl. Events resolved in 5 of the 42 patients. One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker).

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated hypothyroidism occurred in 8.6% (51/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.5%) adverse reactions. Systemic corticosteroids were required in 2 patients (2/51) and all patients required endocrine therapy.

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. Withhold or permanently discontinue IMFINZI based on the severity *[see Dosage and Administration (2.2)]*.

IMFINZI as a Single Agent

Grade 3 immune-mediated type 1 diabetes mellitus occurred in < 0.1% (1/1889) of patients receiving IMFINZI. This patient required long-term insulin therapy and IMFINZI was permanently discontinued. Two additional patients (0.1%, 2/1889) had events of hyperglycemia requiring insulin therapy that did not resolve at the time of reporting.

IMFINZI with Tremelimumab-actl

Two patients (0.5%, 2/388) had events of hyperglycemia requiring insulin therapy that had not resolved at last follow-up.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated Type 1 diabetes mellitus occurred in 0.5% (3/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.3%) adverse reactions. All patients required endocrine therapy.

Immune-Mediated Nephritis with Renal Dysfunction

IMFINZI can cause immune-mediated nephritis.

IMFINZI as a Single Agent

Immune-mediated nephritis occurred in 0.5% (10/1889) of patients receiving IMFINZI, including Grade 3 (< 0.1%) adverse reactions. Events resolved in 5 of the 10 patients and resulted in permanent discontinuation in 3 patients. Systemic corticosteroids were required in all patients with immune-mediated nephritis.

IMFINZI with Tremelimumab-actl

Immune-mediated nephritis occurred in 1% (4/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.5%) adverse reactions. Events resolved in 3 of the 4 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated nephritis; of these, 3 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated nephritis occurred in 0.7% (4/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.2%) adverse reactions. Events resolved in 1 of the 4 patients and resulted in permanent discontinuation in 3 patients. Systemic corticosteroids were required in all patients with immune-mediated nephritis.

Immune-Mediated Dermatology Reactions

IMFINZI 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 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue IMFINZI depending on severity *[see Dosage and Administration (2.2)]*.

IMFINZI as a Single Agent

Immune-mediated rash or dermatitis occurred in 1.8% (34/1889) of patients receiving IMFINZI, including Grade 3 (0.4%) adverse reactions. Events resolved in 19 of the 34 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated rash or dermatitis.

IMFINZI with Tremelimumab-actl

Immune-mediated rash or dermatitis occurred in 4.9% (19/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions. Events resolved in 13 of the 19 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated rash or dermatitis; of these, 12 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Immune-mediated rash or dermatitis occurred in 7.2% (43/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.3%) adverse reactions. Events resolved in 32 of the 43 patients and resulted in permanent discontinuation in 2 patients. Systemic corticosteroids were required in all patients with immune-mediated rash or dermatitis.

Immune-Mediated Pancreatitis

IMFINZI in combination with tremelimumab-actl can cause immune-mediated pancreatitis.

IMFINZI with Tremelimumab-actl

Immune-mediated pancreatitis occurred in 2.3% (9/388) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 4 (0.3%) and Grade 3 (1.5%) adverse reactions. Events resolved in 6 of the 9 patients. Systemic corticosteroids were required in all 9 patients and of these 7 patients required high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day).

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 or IMFINZI in combination with tremelimumab-actl, or were reported with the use of other PD-1/PD-L1 blocking antibodies.

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: Pancreatitis including increases in serum amylase and lipase levels, 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.

5.2 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 (2.2)]*. For Grade 1 or 2 infusion-related reactions, consider using pre-medications with subsequent doses.

IMFINZI as a Single Agent

Infusion-related reactions occurred in 2.2% (42/1889) of patients receiving IMFINZI, including Grade 3 (0.3%) adverse reactions.

IMFINZI in Combination with Tremelimumab-actl

Infusion-related reactions occurred in 10 (2.6%) patients receiving IMFINZI in combination with tremelimumab-actl.

IMFINZI with Tremelimumab-actl and Platinum-Based Chemotherapy

Infusion-related reactions occurred in 2.9% (17/596) of patients receiving IMFINZI in combination with tremelimumab-actl, including Grade 3 (0.3%) adverse reactions.

5.3 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.

5.4 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 women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IMFINZI and for 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 Adverse Reactions *[see Warnings and Precautions (5.1)]*.
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*.

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 as a single agent in a total of 1889 patients enrolled in 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 970 patients with advanced solid tumors), and an additional open-label, single-arm trial (ATLANTIC Study) that enrolled 444 patients with advanced solid tumors, including NSCLC. In these trials, IMFINZI was administered at a dose of 10 mg/kg 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 also reflect exposure to IMFINZI in combination with chemotherapy in 265 patients from the CASPIAN study (a randomized, open-label study in patients with ES-SCLC), in 338 patients from the TOPAZ-1 study (a randomized, double-blind

study in patients with BTC). In the CASPIAN and TOPAZ-1 studies, IMFINZI was administered at a dose of 1,500 mg every 3 or 4 weeks.

The data described in the Warnings and Precautions also reflect exposure to IMFINZI 1,500 mg in combination with tremelimumab-actl 300 mg in 388 patients in HIMALAYA. In the HIMALAYA study patients received IMFINZI 1,500 mg in combination with tremelimumab-actl as a single intravenous infusion of 300 mg, followed by IMFINZI 1,500 mg every 4 weeks. The pooled safety population (N = 596) described in the Warnings and Precautions section reflect exposure to IMFINZI 1,500 mg in combination with tremelimumab-actl 75 mg and histology-based platinum chemotherapy regimens in 330 patients in POSEIDON *[see Clinical Studies (14.1)]* and 266 patients with ES-SCLC in CASPIAN who received up to four cycles of platinum-etoposide plus IMFINZI 1,500 mg with tremelimumab-actl 75 mg every 3 weeks followed by IMFINZI 1,500 mg every 4 weeks (an unapproved regimen for extensive stage small cell lung cancer). Among the 596 patients, 55% were exposed to IMFINZI for 6 months or more and 24% were exposed for 12 months or more.

The data described in this section reflect exposure to IMFINZI in patients with Stage III NSCLC enrolled in the PACIFIC study, in patients with metastatic NSCLC enrolled in the POSEIDON study, in patients with ES-SCLC enrolled in the CASPIAN study, in patients with BTC enrolled in the TOPAZ-1 study and in patients with uHCC included in the HIMALAYA study.

Non-Small Cell Lung Cancer

Stage III NSCLC - PACIFIC

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 (14.1)]*.

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, 16% current smoker, and 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.

Table 5 summarizes the adverse reactions that occurred in at least 10% of patients treated with IMFINZI.

Table 5. Adverse Reactions Occurring in ≥ 10% of Patients in the PACIFIC Study

	IMFINZI N = 475		Placebo N = 234	
Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Respiratory, Thoracic, and Mediastinal Disorders				
Cough/Productive Cough	40	0.6	30	0.4
Pneumonitis*/Radiation Pneumonitis	34	3.4	25	3
Dyspnea†	25	1.5	25	2.6
Gastrointestinal Disorders				
Diarrhea	18	0.6	19	1.3
Abdominal pain‡	10	0.4	6	0.4
Endocrine Disorders				
Hypothyroidism§	12	0.2	1.7	0
Skin and Subcutaneous Tissue Disorders				
Rash¶	23	0.6	12	0
Pruritus#	12	0	6	0
General Disorders				
Fatigueᵖ	34	0.8	32	1.3
Pyrexia	15	0.2	9	0
Infections				
Upper respiratory tract infectionsᵝ	26	0.4	19	0
Pneumoniaà	17	7	12	6

* Includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis.
† Includes dyspnea, and exertional dyspnea.
‡ Includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain.
§ Includes autoimmune hypothyroidism and hypothyroidism.
¶ Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash, and dermatitis.
# Includes pruritus generalized and pruritus.
ᵖ Includes asthenia and fatigue.
ᵝ Includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection.
à Includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia klebsiella, pneumonia necrotizing, 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 6 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI.

Table 6. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the PACIFIC Study

	IMFINZI		Placebo	
Laboratory Abnormality	**All Grades* (%)†**	**Grade 3 or 4 (%)**	**All Grades* (%)†**	**Grade 3 or 4 (%)**
Chemistry				
Hyperglycemia	52	8	51	8
Hypocalcemia	46	0.2	41	0
Increased ALT	39	2.3	22	0.4
Increased AST	36	2.8	21	0.4
Hyponatremia	33	3.6	30	3.1
Hyperkalemia	32	1.1	29	1.8
Increased GGT	24	3.4	22	1.7
Hematology				
Lymphopenia	43	17	39	18

* Graded according to NCI CTCAE version 4.0.
† 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 228).

Metastatic NSCLC - POSEIDON

The safety of IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy in patients with metastatic NSCLC was evaluated in POSEIDON (NCT03164616), a randomized, open-label, multicenter, active-controlled trial. A total of 330 patients received IMFINZI 1,500 mg in combination with tremelimumab-actl (≥ 30 kg body weight received 75 mg and < 30 kg body weight received 1 mg/kg) and histology-based platinum chemotherapy regimens *[see Clinical Studies (14.1)]*. Of these patients, 66% received the maximum 5 doses of tremelimumab-actl and 79% received at least 4 doses. Treatment was continued with IMFINZI as a single agent (or with IMFINZI and histologically-based pemetrexed for non-squamous patients based on the investigator's decision) until disease progression or unacceptable toxicity. The trial excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids or immunosuppressants *[see Clinical Studies (14.1)]*.

The median age of patients who received IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy was 63 years (range: 27 to 87); 80% male; 61% White, 29% Asian, 58% former smoker, 25% current smoker, and 68% ECOG performance of 1.

Serious adverse reactions occurred in 44% of patients receiving IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia (11%), anemia (5%), diarrhea (2.4%), thrombocytopenia (2.4%), pyrexia (2.4%), and febrile neutropenia (2.1%). Fatal adverse reactions occurred in a total of 4.2% of patients receiving IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy. These include hepatitis, nephritis, myocarditis, pancreatitis (all in the same patient), death (2 patients), sepsis (2 patients), pneumonitis (2 patients), acute kidney injury (2 patients), febrile neutropenia (1 patient), chronic obstructive pulmonary disease (1 patient), dyspnea (1 patient), sudden death (1 patient), and ischemic stroke (1 patient).

Permanent discontinuation of IMFINZI or tremelimumab-actl due to an adverse reaction occurred in 17% of the patients. Adverse reactions which resulted in permanent discontinuation of IMFINZI or tremelimumab-actl in > 2% of patients included pneumonia.

Dosage interruption or delay of IMFINZI and tremelimumab-actl due to an adverse reaction occurred in 41% of patients. Adverse reactions which required dosage interruption or delay of IMFINZI and tremelimumab-actl in > 1% of patients included anemia, leukopenia/white blood cell count decreased, pneumonia, pneumonitis, colitis, diarrhea, hepatitis, rash, asthenia, amylase increased, alanine aminotransferase increased, aspartate aminotransferase increased, lipase increased, neutropenia/neutrophil count decreased, and thrombocytopenia/platelet count decreased.

The most common adverse reactions (occurring in ≥ 20% of patients) were nausea, fatigue, musculoskeletal pain, decreased appetite, rash, and diarrhea. Grade 3 or 4 laboratory abnormalities (≥ 10%) were neutropenia, anemia, leukopenia, lymphocytopenia, lipase increased, hyponatremia and thrombocytopenia.

Table 7 summarizes the adverse reactions in POSEIDON.

Table 7. Adverse Reactions (≥ 10%) in Patients with NSCLC Who Received IMFINZI in the POSEIDON Study

	IMFINZI with tremelimumab-actl and platinum-based chemotherapy N = 330		Platinum-based chemotherapy N = 333	
Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Respiratory, thoracic and mediastinal disorders				
Cough/ Productive Cough*	12	0	8	0.3
Gastrointestinal disorders				
Nausea	42	1.8	37	2.1
Diarrhea	22	1.5	15	1.5
Constipation	19	0	24	0.6
Vomiting	18	1.2	14	1.5
Stomatitis†	10	0	6	0.3
Endocrine disorders				
Hypothyroidism‡	13	0	2.1	0
Skin and subcutaneous tissue disorders				
Rash§	27	2.4	10	0.6
Alopecia	10	0	6	0
Pruritus	11	0	4.5	0
General disorders and administration site conditions				
Fatigue/Asthenia¶	36	5	32	4.5
Pyrexia#	19	0	8	0
Edemaᵖ	10	0	10	0.6
Musculoskeletal and connective tissue disorders				
Musculoskeletal Painᵍ	29	0.6	22	1.5
Metabolism and nutrition disorders				
Decreased appetite	28	1.5	25	1.2
Infections and Infestations				
Pneumonia à	17	8	12	4.2
Upper respiratory tract infectionsè	15	0.6	9	0.9
Nervous system disorders				
Headacheð	11	0	8	0.6

* Includes cough and productive cough.
† Includes mucosal inflammation and stomatitis.
‡ Includes blood thyroid stimulating hormone increased and hypothyroidism.
§ Includes eczema, erythema, dermatitis, drug eruption, erythema multiforme, pemphigoid, rash, rash maculo-papular, rash papular, rash pruritic, and rash pustular.
¶ Includes asthenia and fatigue.
# Includes body temperature increased, hyperpyrexia, hyperthermia, and pyrexia.
ᵖ Includes face edema, localized edema, and edema peripheral.
ᵍ Includes arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and spinal pain.
à Includes lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia aspiration, and pneumonia bacterial.
è Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.
ð Includes headache and migraine.

Table 8 summarizes the laboratory abnormalities in POSEIDON.

Table 8. Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients with NSCLC Who Received IMFINZI in the POSEIDON Study

Laboratory Abnormality*	IMFINZI with tremelimumab-actl and platinum-based chemotherapy†		Platinum-based chemotherapy§	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Chemistry				
Lipase increased	35	14	25	5
Hyponatremia	55	13	50	11
Hypernatremia	15	0	14	0
Amylase increased	41	9	25	6
Hypokalemia	21	7	17	2.8
Hyperglycemia	42	6	37	3.1
Increased ALT	64	6	56	4.7
Increased AST	63	5	55	2.2
Blood creatinine increased	89	4.0	83	1.9
Increased Alkaline Phosphatase	33	3.4	26	1.2
Gamma Glutamyl Transferase increased	38	2.2	35	4.7
Hyperkalemia	49	2.2	35	2.8

Table 8. Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients with NSCLC Who Received IMFINZI in the POSEIDON Study (cont'd)

Laboratory Abnormality*	IMFINZI with tremelimumab-actl and platinum-based chemotherapy†		Platinum-based chemotherapy§	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Albumin decreased	27	1.9	18	0.9
Hypocalcemia	58	0.9	49	0.9
Hypomagnesemia	12	4	23	0
Bilirubinemia	16	0.9	8	0.3
Hematology				
Neutropenia	71	37	69	32
Anemia	84	24	84	25
Leukopenia	77	21	81	18
Lymphocytopenia	67	20	60	19
Thrombocytopenia	53	11	54	12

* Graded according to NCI CTCAE version 4.03.
† The denominator used to calculate the rate varied from 45 to 326 based on the number of patients with a baseline value and at least one post-treatment value.
§ The denominator used to calculate the rate varied from 43 to 323 based on the number of patients with a baseline value and at least one post-treatment value.

Small Cell Lung Cancer

Extensive Stage Small Cell Lung Cancer – CASPIAN

The safety of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was evaluated in CASPIAN, a randomized, open-label, multicenter, active-controlled trial. A total of 265 patients received IMFINZI 1,500 mg in combination with chemotherapy every 3 weeks for 4 cycles followed by IMFINZI 1,500 mg every 4 weeks until disease progression or unacceptable toxicity. The trial excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids or immunosuppressants *[see Clinical Studies (14.2)]*. Among 265 patients receiving IMFINZI, 49% were exposed for 6 months or longer and 19% were exposed for 12 months or longer.

Among 266 patients receiving chemotherapy alone, 57% of the patients received 6 cycles of chemotherapy and 8% of the patients received prophylactic cranial irradiation (PCI) after chemotherapy.

IMFINZI was discontinued due to adverse reactions in 7% of the patients receiving IMFINZI plus chemotherapy. These include pneumonitis, hepatotoxicity, neurotoxicity, sepsis, diabetic ketoacidosis and pancytopenia (1 patient each). Serious adverse reactions occurred in 31% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%) and COPD (1.1%). Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI plus chemotherapy. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients). The most common adverse reactions (occurring in ≥ 20% of patients) were nausea, fatigue/asthenia and alopecia.

Table 9 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 9. Adverse Reactions Occurring in ≥ 10% of Patients in the CASPIAN study

	IMFINZI with etoposide and either carboplatin or cisplatin N = 265		Etoposide and either carboplatin or cisplatin N = 266	
Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Respiratory, thoracic and mediastinal disorders				
Cough/Productive Cough	15	0.8	9	0
Gastrointestinal disorders				
Nausea	34	0.4	34	1.9
Constipation	17	0.8	19	0
Vomiting	15	0	17	1.1
Diarrhea	10	1.1	11	1.1
Endocrine disorders				
Hyperthyroidism*	10	0	0.4	0
Skin and subcutaneous tissue disorders				
Alopecia	31	1.1	34	0.8
Rash†	11	0	6	0
General disorders and administration site conditions				
Fatigue/Asthenia	32	3.4	32	2.3
Metabolism and nutrition disorders				
Decreased appetite	18	0.8	17	0.8

* Includes hyperthyroidism and Basedow's disease.
† Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash and dermatitis.

Table 10 summarizes the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI plus chemotherapy.

Table 10. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20%* of Patients in the CASPIAN study

	IMFINZI with Etoposide and either Carboplatin or Cisplatin	Etoposide and either Carboplatin or Cisplatin
Laboratory Abnormality	**Grade† 3 or 4 (%)‡**	**Grade† 3 or 4 (%)‡**
Chemistry		
Hyponatremia	11	13
Hypomagnesemia	11	6
Hyperglycemia	5	5
Increased Alkaline Phosphatase	4.9	3.5
Increased ALT	4.9	2.7
Increased AST	4.6	1.2
Hypocalcemia	3.5	2.4
Blood creatinine increased	3.4	1.1
Hyperkalemia	1.5	3.1
TSH decreased < LLN§ and ≥ LLN at baseline	NA	NA
Hematology		
Neutropenia	41	48
Lymphopenia	14	13
Anemia	13	22
Thrombocytopenia	12	15

* The frequency cut off is based on any grade change from baseline.
† Graded according to NCI CTCAE version 4.03.
‡ 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: 258 to 263) and chemotherapy (range: 253 to 262) except magnesium IMFINZI + chemotherapy (18) and chemotherapy (16).
§ LLN = lower limit of normal

Biliary Tract Cancer

Locally advanced or metastatic BTC - TOPAZ-1

The safety of IMFINZI in combination with gemcitabine and cisplatin in locally advanced or metastatic BTC was evaluated in TOPAZ-1, a randomized, double-blind, placebo-controlled, multicenter trial. A total of 338 patients received IMFINZI 1,500 mg in combination with gemcitabine and cisplatin every 3 weeks up to 8 cycles followed by IMFINZI 1,500 mg every 4 weeks until disease progression or unacceptable toxicity. Patients with active or prior documented autoimmune or inflammatory disorders, HIV infection or other active infections, including tuberculosis or hepatitis C were ineligible *[see Clinical Studies (14.3)]*.

IMFINZI was discontinued due to adverse reactions in 6% of the patients receiving IMFINZI plus chemotherapy. The most frequently reported events resulting in discontinuation were sepsis (3 patients) and ischemic stroke (2 patients). The remaining events were dispersed across system organ classes and reported in 1 patient each. Serious adverse reactions occurred in 47% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 2% of patients were cholangitis (7%), pyrexia (3.8%), anemia (3.6%), sepsis (3.3%) and acute kidney injury (2.4%). Fatal adverse reactions occurred in 3.6% of patients receiving IMFINZI plus chemotherapy. These include ischemic or hemorrhagic stroke (4 patients), sepsis (2 patients) and upper gastrointestinal hemorrhage (2 patients). The most common adverse reactions (occurring in ≥ 20% of patients) were fatigue, nausea, constipation, decreased appetite, abdominal pain, rash and pyrexia. Table 11 summarizes the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 11. Adverse Reactions Occurring in ≥ 10% of Patients in the TOPAZ-1 Study

	IMFINZI with Gemcitabine and Cisplatin N = 338		Placebo with Gemcitabine and Cisplatin N = 342	
Adverse Reaction	**All Grades* (%)**	**Grade* 3-4 (%)**	**All Grades* (%)**	**Grade* 3-4 (%)**
General disorders and administration site conditions				
Fatigue†	42	6	43	6
Pyrexia	20	1.5	16	0.6
Gastrointestinal disorders				
Nausea	40	1.5	34	1.8
Constipation	32	0.6	29	0.3
Abdominal pain‡	24	0.6	23	2.9
Vomiting	18	1.5	18	2.0
Diarrhea	17	1.2	15	1.8
Metabolism and nutrition disorders				
Decreased appetite	26	2.1	23	0.9
Skin and subcutaneous tissue disorders				
Rash§	23	0.9	14	0
Pruritus	11	0	8	0
Psychiatric disorders				
Insomnia	10	0	11	0

* Graded according to NCI CTCAE version 5.0.
† Includes fatigue, malaise, cancer fatigue and asthenia.
‡ Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.
§ Includes rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash erythematous, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, erythema, dermatitis and rash.

Table 12 summarizes the laboratory abnormalities in patients treated with IMFINZI plus chemotherapy.

Table 12. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20%* of Patients in the TOPAZ-1 study

	IMFINZI with Gemcitabine and Cisplatin	Placebo with Gemcitabine and Cisplatin
Laboratory Abnormality	**Grade† 3 or 4 (%)**	**Grade† 3 or 4 (%)**
Chemistry		
Hyponatremia	18	13
Gamma-glutamyltransferase increased	12	13
Increased bilirubin	10	14
Hypokalemia	8	4.4
Increased AST	8	8
Increased ALT	7	6
Blood creatinine increased	5	2.1
Hypomagnesemia	4.5	2.2
Hypoalbuminemia	3.6	2.9
Hyperkalemia	2.1	2.1
Increased Alkaline Phosphatase	1.8	3.8
Hypocalcemia	1.8	2.4
Hematology		
Neutropenia	48	49
Anemia	31	28
Leukopenia	28	28
Lymphopenia	23	15
Thrombocytopenia	18	18

* The frequency cut off is based on any grade change from baseline.
† Graded according to NCI CTCAE version 5.0. Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI + Gem/Cis (range: 312 to 335) and Placebo + Gem/Cis (range: 319 to 341).

Hepatocellular Carcinoma

Unresectable HCC - HIMALAYA

The safety of IMFINZI in combination with tremelimumab-actl was evaluated in a total of 388 patients with uHCC in HIMALAYA, a randomized, open-label, multicenter study *[see Clinical Studies (14.1)]*. Patients received IMFINZI 1,500 mg administered as a single intravenous infusion in combination with tremelimumab-actl 300 mg on the same day, followed by IMFINZI every 4 weeks or sorafenib 400 mg given orally twice daily.

Serious adverse reactions occurred in 41% of patients who received IMFINZI in combination with tremelimumab-actl. 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 in combination with tremelimumab-actl, including death (1%), hemorrhage intracranial (0.5%), cardiac arrest (0.5%), pneumonitis (0.5%), hepatic failure (0.5%), and immune-mediated hepatitis (0.5%). The most common adverse reactions (occurring in ≥ 20% of patients) were rash, diarrhea, fatigue, pruritis, musculoskeletal pain, and abdominal pain.

Permanent discontinuation of treatment regimen due to an adverse reaction occurred in 14% of patients; the most common adverse reactions leading to treatment discontinuation (≥ 1%) were hemorrhage (1.8%), diarrhea (1.5%), AST increased (1%), and hepatitis (1%).

Dosage interruptions or delay of the treatment regimen due to an adverse reaction occurred in 35% of patients. Adverse reactions which required dosage interruption or delay in ≥ 1% of patients included ALT increased (3.6%), diarrhea (3.6%), rash (3.6%), amylase increased (3.4%), AST increased (3.1%), lipase increased (2.8%), pneumonia (1.5%), hepatitis (1.5%), pyrexia (1.5%), anemia (1.3%), thrombocytopenia (1%), hyperthyroidism (1%), pneumonitis (1%), and blood creatinine increased (1%).

Table 13 summarizes the adverse reactions that occurred in patients treated with IMFINZI in combination with tremelimumab-actl in the HIMALAYA study.

Table 13. Adverse Reactions Occurring in ≥ 10% of Patients in the HIMALAYA study

	IMFINZI and Tremelimumab-actl (N = 388)		Sorafenib (N = 374)	
Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Gastrointestinal disorders				
Diarrhea*	27	6	45	4.3
Abdominal pain*	20	1.8	24	4
Nausea	12	0	14	0
Skin and subcutaneous tissue disorders				
Rash*	32	2.8	57	12
Pruritus	23	0	6	0.3
Metabolism and nutrition disorders				
Decreased appetite	17	1.3	18	0.8
General disorders and administration site conditions				
Fatigue*	26	3.9	30	6
Pyrexia*	13	0.3	9	0.3
Psychiatric disorders				
Insomnia	10	0.3	4.3	0
Endocrine disorders				
Hypothyroidism*	14	0	6	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain*	22	2.6	17	0.8

* Represents a composite of multiple related terms.

Table 14 summarizes the laboratory abnormalities that occurred in patients treated with IMFINZI in combination with tremelimumab-actl in the HIMALAYA study.

Table 14. Laboratory Abnormalities Worsening from Baseline Occurring in ≥ 20% of Patients in the HIMALAYA study

	IMFINZI and Tremelimumab-actl		Sorafenib	
Laboratory Abnormality	**Any grade† (%)‡**	**Grade 3† or 4 (%)‡**	**Any grade† (%)‡**	**Grade 3† or 4 (%)‡**
Chemistry				
Aspartate Aminotransferase increased	63	27	55	21
Alanine Aminotransferase increased	56	18	53	12
Sodium decreased	46	15	40	11
Bilirubin increased	41	8	47	11
Alkaline Phosphatase increased	41	8	44	5
Glucose increased	39	14	29	4
Calcium decreased	34	0	43	0.3
Albumin decreased	31	0.5	37	1.7
Potassium increased	28	3.8	21	2.6
Creatinine increased	21	1.3	15	0.9
Hematology				
Hemoglobin decreased	52	4.8	40	6
Lymphocytes decreased	41	11	39	10
Platelets decreased	29	1.6	35	3.1
Leukocytes decreased	20	0.8	30	1.1

† Graded according to NCI CTCAE version 4.03.
‡ Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI with tremelimumab-actl (range: 367-378) and sorafenib (range:344-352).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, IMFINZI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available 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 at exposure levels approximately 6 to 20 times higher than those observed at the clinical dose of 10 mg/kg based on area under the curve (AUC), 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 to 4% and 15 to 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 prenatal 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 a 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 are no data on the presence of durvalumab in human milk, its effects on the breastfed child, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to IMFINZI are unknown. 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 a breastfed child, advise women not to breastfeed during treatment with IMFINZI and for 3 months after the last dose. Refer to the Prescribing Information for the agents administered in combination with IMFINZI for recommended duration to not breastfeed, as appropriate.

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.

8.3 Females and Males of Reproductive Potential

Pregnancy testing

Verify pregnancy status of females of reproductive potential prior to initiating treatment with IMFINZI.

Contraception

Females

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 3 months following the last dose of IMFINZI. Refer to the Prescribing Information for the agents administered in combination with IMFINZI for recommended contraception duration, as appropriate.

8.4 Pediatric Use

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

8.5 Geriatric Use

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.

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy 101 (38%) patients were 65 years or older and 19 (7.2%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

Of the 330 patients with metastatic NSCLC treated with IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy, 143 (43%) patients were 65 years or older and 35 (11%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

Of the 338 patients with BTC treated with IMFINZI in combination with chemotherapy in the TOPAZ-1 study, 158 (47%) patients were 65 years or older and 38 (11%) patients were 75 years or older. No overall differences in safety or effectiveness of IMFINZI have been observed between patients 65 years of age and older and younger adult patients.

Of the 393 patients with uHCC treated with IMFINZI in combination with tremelimumab-actl, 50% of patients were 65 years of age or older and 13% of patients were 75 years of age or older. No overall differences in safety or effectiveness of IMFINZI have been observed between patients 65 years of age and older and younger adult patients.

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.

12.2 Pharmacodynamics

The steady state AUC, Ctrough, and Cmax in patients administered with 1,500 mg every 4 weeks are 6% higher, 19% lower, and 55% higher than those administered with 10 mg/kg every 2 weeks, respectively. Based on the modeling of pharmacokinetic data and exposure relationships for safety, there are no anticipated clinically meaningful differences in efficacy and safety for the doses of 1,500 mg every 4 weeks compared to 10 mg/kg every 2 weeks in patients weighing > 30 kg with NSCLC.

12.3 Pharmacokinetics

The pharmacokinetics of durvalumab as a single agent was studied in 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.

The pharmacokinetics of durvalumab is similar when assessed as a single agent, when in combination with chemotherapy, when in combination with tremelimumab-actl and when in combination with tremelimumab-actl and platinum-based chemotherapy.

Distribution

The geometric mean (% coefficient of variation [CV%]) steady state volume of distribution (Vss) was 5.4 (13.1%) 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 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 21 (26%) days.

Specific Populations

There were no clinically significant differences in the pharmacokinetics of durvalumab based on body weight (31 to 175 kg), age (18 to 96 years), sex, race (White, Black, Asian, Native Hawaiian, Pacific Islander, or Native American), albumin levels (4 to 57 g/L), lactate dehydrogenase levels (18 to 15,800 U/L), soluble PD-L1 (67 to 3,470 pg/mL), tumor type (NSCLC, SCLC, BTC and HCC), mild or moderate renal impairment (CLcr 30 to 89 mL/min), and mild or moderate hepatic impairment (bilirubin ≤ 3x ULN and any AST). The effect of severe renal impairment (CLcr 15 to 29 mL/min) or severe hepatic impairment (bilirubin > 3x ULN and any AST) on the pharmacokinetics of durvalumab is unknown.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparison of the incidence of ADAs in the studies described below with the incidence of ADAs in other studies including those of IMFINZI.

Of the 2,280 patients who received IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as a single-agent, 69 patients (3%) tested positive for ADAs and 12 (0.5%) tested positive for neutralizing antibodies. The development of ADAs against durvalumab appears to have no clinically relevant effect on its pharmacokinetics or safety.

Of the 201 patients in the CASPIAN study who received IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy for four doses followed by IMFINZI 1,500 mg every 4 weeks, no patients tested positive for ADAs.

Of the 240 patients in the TOPAZ-1 study who received IMFINZI 1,500 mg every 3 weeks in combination with chemotherapy up to 8 cycles followed by IMFINZI 1,500 mg every 4 weeks, 2 (0.8%) patients tested positive for treatment-emergent ADAs and neutralizing antibodies, respectively. There were insufficient numbers of patients with ADAs or neutralizing antibodies (2 patients each) to determine whether ADAs have an impact on pharmacokinetics, pharmacodynamics, safety and/or effectiveness of IMFINZI.

During the 12 week treatment period in the HIMALAYA study, of the 294 patients who received IMFINZI once every 4 weeks in combination with a single dose of tremelimumab-actl and who were evaluated for the presence of ADAs against IMFINZI at predose week 0, week 4 and week 12, 3.1% (9/294) of patients tested positive for anti-durvalumab-antibodies. Among the 9 patients who tested positive for ADA, 55.6% (5/9) tested positive for neutralizing antibodies against durvalumab. There was no identified clinically significant effect of anti-durvalumab antibodies on the safety of durvalumab; however, the effect of ADAs on the pharmacokinetics and effectiveness of durvalumab is unknown.

During 16 weeks of treatment during the POSEIDON study, among 286 patients who received IMFINZI 1,500 mg in combination with tremelimumab-actl 75 mg every 3 weeks for five doses and chemotherapy for four cycles followed by IMFINZI 1,500 mg every 4 weeks 10% (29/286) of patients tested positive for anti-durvalumab antibodies with predose sampling at week 0, week 3 and week 12. Among the 29 patients who tested positive for ADAs, 10% (3/29) tested positive for neutralizing antibodies against durvalumab. The geometric mean of durvalumab concentration in patients with ADA positive was 46 mcg/mL compared to 89 mcg/mL in patients with ADA negative. There was no clinically significant effect of anti-durvalumab antibodies on the safety of durvalumab; however, there is insufficient data to assess whether the observed ADA associated pharmacokinetic changes reduce effectiveness of durvalumab.

13 NONCLINICAL TOXICOLOGY

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 toxicology 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. *Mycobacterium 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-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-L1 and PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC)

Unresectable Stage III NSCLC - PACIFIC

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 v1.1-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 v1.1, and overall survival (OS). Additional efficacy outcome measures included ORR and DoR 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).

At a pre-specified interim analysis for OS based on 299 events (61% of total planned events), the study demonstrated a statistically significant improvement in OS in patients randomized to IMFINZI compared to placebo. The pre-specified interim analysis of PFS based on 371 events (81% of total planned events) demonstrated a statistically significant improvement in PFS in patients randomized to IMFINZI compared to placebo. Table 15 and Figure 1 summarizes the efficacy results for PACIFIC.

Table 15. Efficacy Results for the PACIFIC Study

Endpoint	IMFINZI (N = 476)*	Placebo (N = 237)*
Overall Survival (OS)†		
Number of deaths	183 (38%)	116 (49%)
Median in months (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)
Hazard Ratio (95% CI)‡	0.68 (0.53, 0.87)	
p-value‡,§	0.0025	
Progression-Free Survival (PFS)¶,#		
Number (%) of patients with event	214 (45%)	157 (66%)
Median in months (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)
Hazard Ratio (95% CI)‡,Þ	0.52 (0.42, 0.65)	
p-value‡,ß	< 0.0001	

* 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

† OS results are based on the interim OS analysis conducted at 299 OS events which occurred 46 months after study initiation.

‡ Two-sided p-value based on a log-rank test stratified by sex, age, and smoking history

§ Compared with allocated α of 0.00274 (Lan-DeMets spending function approximating O'Brien Fleming boundary) for interim analysis

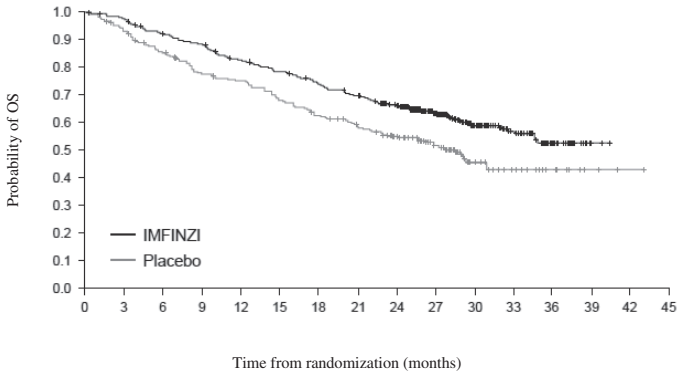
¶ As assessed by BICR RECIST v1.1

PFS results are based on the interim PFS analysis conducted at 371 PFS events which occurred 33 months after study initiation.

Þ Pike estimator

ß Compared with allocated α of 0.011035 (Lan-DeMets spending function approximating O'Brien Fleming boundary) for interim analysis

Figure 1. Kaplan-Meier Curves of Overall Survival in the PACIFIC Study



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Metastatic NSCLC - POSEIDON

The efficacy of IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy in previously untreated metastatic NSCLC patients with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations was investigated in POSEIDON, a randomized, multicenter, active-controlled, open-label trial (NCT03164616). Eligible patients had Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 and must have had no prior chemotherapy or any other systemic therapy for metastatic NSCLC. Choice of platinum-based chemotherapy was at the investigator's discretion, taking into consideration the calculated creatinine clearance. Patients with active and/or untreated brain metastases; a history of active primary immunodeficiency; autoimmune disorders including active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except physiological dose of systemic corticosteroids were ineligible.

Randomization was stratified by tumor cells (TC) PD-L1 expression (TC ≥ 50% vs. TC < 50%), disease stage (Stage IVA vs. Stage IVB), and histology (non-squamous vs. squamous).

Patients were randomized 1:1:1 to receive IMFINZI in combination with tremelimumab-actl and platinum-based chemotherapy according to the regimens listed below, IMFINZI and platinum-based chemotherapy (an unapproved regimen for metastatic NSCLC), or platinum-based chemotherapy. The evaluation of efficacy for metastatic NSCLC relied on comparison between:

- IMFINZI 1,500 mg with tremelimumab-actl 75 mg (or 1 mg/kg for patients < 30 kg) and platinum-based chemotherapy every 3 weeks for 4 cycles, followed by IMFINZI 1,500 mg every 4 weeks as a single agent. A fifth dose of tremelimumab-actl 75 mg (or 1 mg/kg for patients < 30 kg) was given at Week 16 in combination with IMFINZI dose 6.
- Platinum-based chemotherapy every 3 weeks as monotherapy for 4 cycles. Patients could receive an additional 2 cycles (a total of 6 cycles post-randomization), as clinically indicated, at investigator's discretion.

Patients received IMFINZI in combination with tremelimumab-actl with one of the following platinum-based chemotherapy regimens:

- Non-squamous NSCLC
  - Pemetrexed 500 mg/m^2 with carboplatin AUC 5-6 or cisplatin 75 mg/m^2 every 3 weeks for 4 cycles.
- Squamous NSCLC
  - Gemcitabine 1,000 or 1,250 mg/m^2 on Days 1 and 8 with cisplatin 75 mg/m^2 or carboplatin AUC 5-6 on Day 1 every 3 weeks for 4 cycles.
- Non-squamous and Squamous NSCLC
  - Nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 with carboplatin AUC 5-6 on Day 1 every 3 weeks for 4 cycles.

Tremelimumab-actl was given up to a maximum of 5 doses. IMFINZI and histology-based pemetrexed continued every 4 weeks until disease progression or unacceptable toxicity. Administration of IMFINZI monotherapy was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients with disease progression during IMFINZI monotherapy were given the option to be retreated with 4 additional cycles of tremelimumab-actl in combination with IMFINZI. Tumor assessments were performed at Week 6, Week 12, and then every 8 weeks thereafter.

The major efficacy outcome measures were progression free survival (PFS) and overall survival (OS) of IMFINZI and tremelimumab-actl in combination with platinum-based chemotherapy compared to platinum-based chemotherapy alone. Additional efficacy outcome measures were overall response rate (ORR) and duration of response (DoR). PFS, ORR, and DoR were assessed using Blinded Independent Central Review (BICR) according to RECIST v1.1.

A total of 675 patients were randomized to receive either IMFINZI with tremelimumab-actl and platinum-based chemotherapy (n = 338) or platinum-based chemotherapy (n = 337). The median age was 63 years (range: 27 to 87), 46% of patients age ≥ 65 years, 77% male, 57% White, 34% Asian, 0.3% Native Hawaiian or Other Pacific Islander, 3% American Indian or Alaska Native, 2% Black or African American, 4% Other Race, 79% former or current smoker, 34% ECOG PS 0, and 66% ECOG PS 1. Thirty-six percent had squamous histology, 63% non-squamous histology, 29% PD-L1 expression TC ≥ 50%, 71% PD-L1 expression TC < 50%.

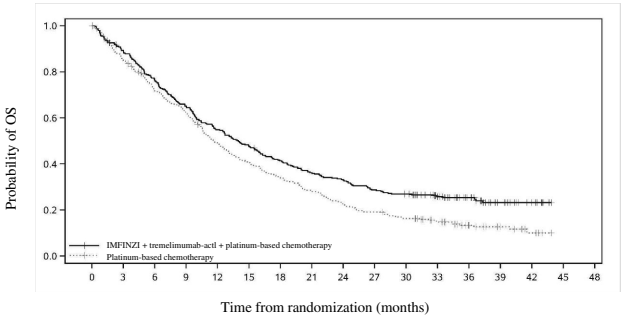
Efficacy results are summarized in Table 16 and Figure 2.

Table 16. Efficacy Results for POSEIDON

	IMFINZI with tremelimumab-actl and platinum-based chemotherapy (n = 338)	**Platinum-based chemotherapy (n = 337)**
OS[1]		
Number of deaths (%)	251 (74)	285 (85)
Median OS (months) (95% CI)	14.0 (11.7, 16.1)	11.7 (10.5, 13.1)
HR (95% CI)	0.77 (0.65, 0.92)	
p-value[2]	0.00304	
PFS[2]		
Number of events (%)	238 (70)	258 (77)
Median PFS (months) (95% CI)	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)
HR (95% CI)	0.72 (0.60, 0.86)	
p-value[2]	0.00031	
ORR % (95% CI) [3]	39 (34, 44)	24 (20, 29)
Median DoR (months) (95% CI)	9.5 (7.2, NR)	5.1 (4.4, 6.0)

[1] PFS/OS results are based on planned analyses which occurred 25/45 months respectively after study initiation.
[2] 2-sided p-values based on log-rank tests stratified by PD-L1, histology and disease stage and compared to a boundary value of 0.00735 for PFS and 0.00797 for OS.
[3] Confirmed responses with 95% Clopper-Pearson confidence interval.
NR=Not Reached, CI=Confidence Interval

Figure 2. Kaplan-Meier curves of OS in POSEIDON



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
IMFINZI + tremelimumab-actl + platinum-based chemotherapy	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0
Platinum-based chemotherapy	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0

14.2 Small Cell Lung Cancer (SCLC)

Extensive-stage SCLC – CASPIAN

The efficacy of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was investigated in CASPIAN, a randomized, multicenter, active-controlled, open-label trial (NCT03043872). Eligible patients had WHO Performance Status of 0 or 1 and were suitable to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC. Patients with asymptomatic or treated brain metastases were eligible. Choice of platinum agent was at the investigator's discretion, taking into consideration the calculated creatinine clearance. Patients with history of chest radiation therapy; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome; active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except physiological dose of systemic corticosteroids were ineligible.

Randomization was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin).

The evaluation of efficacy for ES-SCLC relied on comparison between:

IMFINZI 1,500 mg, and investigator's choice of carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m^2) on Day 1 and etoposide (80-100 mg/m^2) intravenously on Days 1, 2, and 3 of each 21-day cycle for 4 cycles, followed by IMFINZI 1,500 mg every 4 weeks until disease progression or unacceptable toxicity, or

Investigator's choice of carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m^2) on Day 1 and etoposide (80-100 mg/m^2) intravenously on Days 1, 2, and 3 of each 21-day cycle, up to 6 cycles. After completion of chemotherapy, PCI as administered per investigator discretion.

Administration of IMFINZI as a single agent was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

The major efficacy outcome measure was overall survival (OS) of IMFINZI plus chemotherapy vs. chemotherapy alone. Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS) and objective response rate (ORR), per RECIST v1.1.

The study population characteristics were: median age of 63 years (range: 28 to 82); 40% age 65 or older; 70% male; 84% White, 15% Asian, and 0.9% Black; 65% WHO/ECOG PS of 1; and 93% were former/current smokers. Ninety percent of patients had Stage IV disease and 10% had brain metastasis at baseline. A total of 25% of the patients received cisplatin and 74% of the patients received carboplatin. In the chemotherapy alone arm, 57% of the patients received 6 cycles of chemotherapy, and 8% of the patients received PCI.

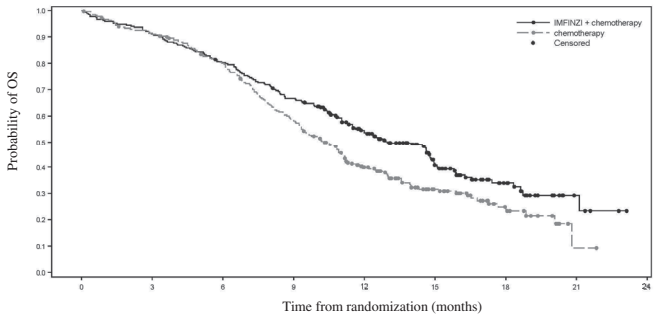
The OS results are summarized in Table 17 and Figure 3.

Table 17. OS Result for the CASPIAN Study

Endpoint	**IMFINZI with Etoposide and either Carboplatin or Cisplatin (n = 268)**	**Etoposide and either Carboplatin or Cisplatin (n = 269)**
Overall Survival (OS)		
Number of deaths (%)*	155 (58)	181 (67)
Median OS (months) (95% CI)	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)
Hazard Ratio (95% CI)†	0.73 (0.59, 0.91)	
p-value[1]	0.0047	

* At a pre-specified interim analysis, 336 OS events (79% of total planned events) were observed, and the boundary for declaring efficacy (0.0178) was determined by a Lan-Demets alpha spending function with O'Brien Fleming type boundary.
† The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin) and using the rank tests of association approach.

Figure 3. Kaplan-Meier Curves of Overall Survival in the CASPIAN Study



Number of patients at risk	0	3	6	9	12	15	18	21	24
IMFINZI + chemotherapy	268	244	214	177	116	57	25	5	0
chemotherapy	269	242	209	153	82	44	17	1	0

Investigator-assessed PFS (96% of total planned events) showed a HR of 0.78 (95% CI: 0.65, 0.94), with median PFS of 5.1 months (95% CI: 4.7, 6.2) in the IMFINZI plus chemotherapy arm and 5.4 months (95% CI: 4.8, 6.2) in the chemotherapy alone arm. The investigator-assessed confirmed ORR was 68% (95% CI: 62%, 73%) in the IMFINZI plus chemotherapy arm and 58% (95% CI: 52%, 63%) in the chemotherapy alone arm.

In the exploratory subgroup analyses of OS based on the planned platinum chemotherapy received at cycle 1, the HR was 0.70 (95% CI 0.55, 0.89) in patients who received carboplatin, and the HR was 0.88 (95% CI 0.55, 1.41) in patients who received cisplatin.

14.3 Biliary Tract Cancer (BTC)

Locally advanced or metastatic BTC - TOPAZ-1

The efficacy of IMFINZI in combination with gemcitabine and cisplatin in patients with locally advanced or metastatic BTC was investigated in TOPAZ-1 (NCT03875235), a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 685 patients with histologically confirmed locally advanced unresectable or metastatic BTC who have not previously received systemic therapy. Patients with recurrent disease > 6 months after surgery and/or completion of adjuvant therapy were eligible. Patients had an ECOG Performance status of 0 and 1 and at least one target lesion by RECIST 1.1. Patients with ampullary carcinoma; active or prior documented autoimmune or inflammatory disorders; HIV infection or active infections, including tuberculosis or hepatitis C; current or prior use of immunosuppressive medication within 14 days before the first dose of IMFINZI were ineligible.

Randomization was stratified by disease status (recurrent vs. initially unresectable) and primary tumor location (intrahepatic cholangiocarcinoma [ICCA] vs. extrahepatic cholangiocarcinoma [ECCA] vs. gallbladder cancer [GBC]). Patients were randomized 1:1 to receive:

- IMFINZI 1,500 mg on Day 1+ gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 on Days 1 and 8 of each 21-day cycle up to 8 cycles, followed by IMFINZI 1,500 mg every 4 weeks, or
- Placebo on Day 1+ gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 on Days 1 and 8 of each 21-day cycle up to 8 cycles, followed by placebo every 4 weeks.

Treatment with IMFINZI or placebo continued until disease progression, or unacceptable toxicity. Treatment beyond disease progression was permitted if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures were investigator-assessed progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR). Tumor assessments were conducted every 6 weeks for the first 24 weeks after the date of randomization, and then every 8 weeks until confirmed objective disease progression.

The study population characteristics were: 50% male, median age of 64 years (range 20-85), 47% age 65 or older; 56% Asian, 37% White, 2% Black or African American, 0.1% American Indian or Alaskan Native, and 4% other; 51% had an ECOG PS of 1; primary tumor location was ICCA 56%, ECCA 18% and GBC 25%; 20% of patients had recurrent disease; 86% of patients had metastatic and 14% had locally advanced disease.

At a pre-specified interim analysis, the trial demonstrated a statistically significant improvement in OS and PFS in patients randomized to IMFINZI in combination with chemotherapy compared to placebo in combination with chemotherapy. Table 18 summarizes the efficacy results for TOPAZ-1.

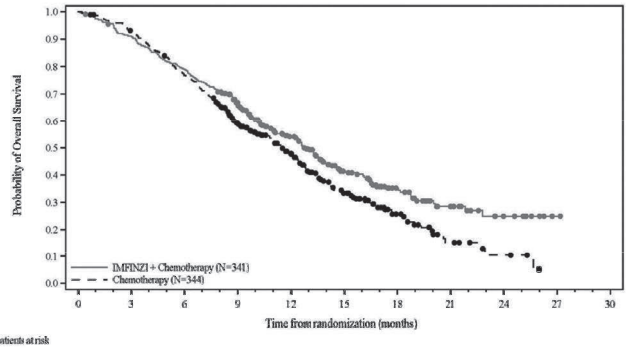
Table 18. Efficacy Results for the TOPAZ-1 Study

Endpoint	IMFINZI with Gemcitabine and Cisplatin (n = 341)	Placebo with Gemcitabine and Cisplatin (n = 344)
Overall Survival (OS)		
Number of deaths (%)	198 (58)	226 (66)
Median OS (months) (95% CI)*	12.8 (11.1, 14)	11.5 (10.1, 12.5)
Hazard Ratio (95% CI)†	0.80 (0.66, 0.97)	
p-value‡	0.021	
Progression-Free Survival (PFS)		
Number of patients with event (%)	276 (81)	297 (86)
Median in months (95% CI)*	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)
Hazard Ratio (95% CI)†	0.75 (0.63, 0.89)	
p-value§	0.001	

* Kaplan-Meier estimated median with 95% CI derived using Brookmeyer-Crowley method
† Based on Cox proportional hazards model stratified by disease status and primary tumor location
‡ 2-sided p-value based on a stratified log-rank test compared with alpha boundary of 0.030
§ 2-sided p-value based on a stratified log-rank test compared with alpha boundary of 0.048

The investigator-assessed ORR was 27% (95% CI: 22% - 32%) in the IMFINZI plus chemotherapy arm and 19% (95% CI: 15%-23%) in the chemotherapy alone arm.

Figure 4: Kaplan-Meier Curve of OS in TOPAZ-1 Study



Number of patients at risk																									
IMFINZI + Chemotherapy	341	331	324	309	294	278	268	252	238	208	174	151	135	118	93	79	74	57	49	39	29	24	15	12	9	8	4	1	0
Chemotherapy	344	337	329	317	299	283	265	242	220	183	159	143	125	97	78	65	52	40	29	21	15	10	8	4	4	3	0	0	0

14.4 Hepatocellular Carcinoma (HCC)

The efficacy of IMFINZI in combination with tremelimumab-actl was evaluated in the HIMALAYA study (NCT03298451), a randomized (1:1:1), open-label, multicenter study in patients with confirmed uHCC who had not received prior systemic treatment for HCC. Patients were randomized to one of two investigational arms (IMFINZI plus trememlimumab-actl or IMFINZI) or sorafenib. Study treatment consisted of IMFINZI 1,500 mg in combination with tremelimumab-actl as a one-time single intravenous infusion of 300 mg on the same day, followed by IMFINZI every 4 weeks; IMFINZI 1,500 mg every 4 weeks; or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. The efficacy assessment of IMFINZI is based on patients randomized to the IMFINZI plus tremelimumab-actl arm versus the sorafenib arm. Randomization was stratified by macrovascular invasion (MVI) (yes or no), etiology of liver disease (hepatitis B virus vs. hepatitis C virus vs. others) and ECOG performance status (0 vs. 1).

The study enrolled patients with BCLC Stage C or B (not eligible for locoregional therapy). The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented gastrointestinal (GI) bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders. Esophagogastroduodenoscopy was not mandated prior to enrollment but adequate endoscopic therapy, according to institutional standards, was required for patients with history of esophageal variceal bleeding or those assessed as high risk for esophageal variceal bleeding by the treating physician.

Study treatment was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

The major efficacy outcome measure was overall survival (OS) between the IMFINZI plus tremelimumab-actl arm versus the sorafenib arm. Additional efficacy outcomes were investigator-assessed progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) according to RECIST v1.1. Tumor assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

The baseline demographics of the IMFINZI plus tremelimumab-actl and sorafenib arms were as follows: male (85%), age < 65 years (50%), median age of 65 years (range: 18 to 88 years), White (46%), Asian (49%), Black or African American (2%), Native Hawaiian or other Pacific Islander (0.1%), race Unknown (2%), Hispanic or Latino (5%), Not Hispanic or Latino (94%), ethnicity Unknown (1%), ECOG PS 0 (62%); Child-Pugh Class score A (99%), macrovascular invasion (26%), extrahepatic spread (53%), viral etiology; hepatitis B (31%), hepatitis C (27%), and uninfected (42%).

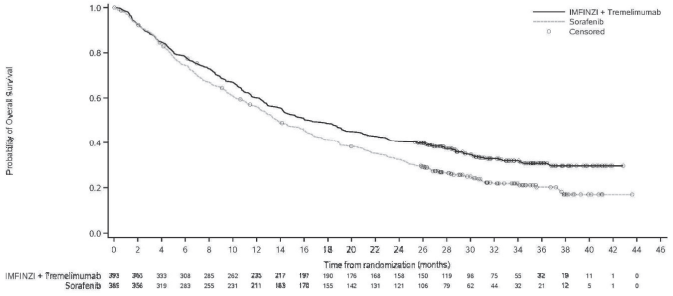
Efficacy results are presented in Table 19 and Figure 5.

Table 19. Efficacy Results for the HIMALAYA Study

Endpoint	IMFINZI and Tremelimumab-actl (N = 393)	Sorafenib (N = 389)
OS		
Number of deaths (%)	262 (66.7)	293 (75.3)
Median OS (months)	16.4	13.8
(95% CI)	(14.2, 19.6)	(12.3, 16.1)
HR (95% CI) *	0.78 (0.66, 0.92)	
p-value†, ‡	0.0035	
PFS		
Number of events (%)	335 (85.2)	327 (84.1)
Median PFS (months)	3.8	4.1
(95% CI)	(3.7, 5.3)	(3.7, 5.5)
HR (95% CI)*	0.90 (0.77, 1.05)	
ORR		
ORR % (95% CI)§, ¶	20.1 (16.3, 24.4)	5.1 (3.2, 7.8)
Complete Response n (%)	12 (3.1)	0
Partial Response n (%)	67 (17.0)	20 (5.1)
DoR		
Median DoR (months) (95% CI)	22.3 (13.7, NR)	18.4 (6.5, 26.0)
% with duration ≥ 6 months	82.3	78.9
% with duration ≥ 12 months	65.8	63.2

* HR (IMFINZI and tremelimumab-actl vs. sorafenib) based on the stratified Cox proportional hazard model.
† Based on a stratified log-rank test.
‡ Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMFINZI and tremelimumab-actl vs. sorafenib was 0.0398 (Lan and DeMets 1983).
§ Confirmed complete response or partial response.
¶ Based on Clopper-Pearson method.
CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached

Figure 5. Kaplan-Meier curve of OS



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 (50 mg/mL) (NDC 0310-4611-50)
- 120 mg/2.4 mL (50 mg/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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of IMFINZI *[see Warnings and Precautions (5.1)]*, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath.
- 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.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea, blood or mucus in stools, or severe abdominal pain.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, adrenal insufficiency, type 1 diabetes mellitus, or hypophysitis.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis.
- Dermatological Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of severe dermatological reactions.
- Pancreatitis: Advise patients to contact their healthcare provider immediately for signs or symptoms of pancreatitis.
- Other Immune-Mediated Adverse Reactions: Advise patients to contact their healthcare provider immediately for signs or symptoms of pancreatitis, aseptic meningitis, encephalitis, immune thrombocytopenia, myocarditis, hemolytic anemia, myositis, uveitis, keratitis, and myasthenia gravis.

Infusion-Related Reactions:

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT:

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.3)]*.

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 (5.4) and Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of IMFINZI *[see Use in Specific Populations (8.3)]*.

Lactation:

- Advise female patients not to breastfeed while taking IMFINZI and for 3 months after the last dose *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.2)]*.

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

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Cambridge, England CB2 0AA
US License No. 2043

6/23 US-77358 6/23

MEDICATION GUIDE

IMFINZI® (im-FIN-zee)
(durvalumab)
injection

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

IMFINZI is a medicine that may treat certain cancers by working with your immune system.

IMFINZI can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worsening signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

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

Liver problems.

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

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increase 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
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

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

Skin problems.

- 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

Pancreas problems

- pain in your upper stomach area (abdomen)
- severe nausea or vomiting
- loss of appetite

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with IMFINZI. Call or see your healthcare provider right away for any new or worsening signs or symptoms, which may include:

- 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 eye-sight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Infusion reactions that can sometimes be severe or life-threatening. Signs and symptoms of infusion reactions may include:

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

Complications, including graft-versus-host disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).
These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with IMFINZI. Your healthcare provider will monitor you for these complications.

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 also need to delay or completely stop treatment with IMFINZI, if you have severe side effects.

What is IMFINZI?

IMFINZI is a prescription medicine used to treat adults with:

- **a type of lung cancer called non-small cell lung cancer (NSCLC)**.
  - IMFINZI may be used alone 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.
  - IMFINZI may be used in combination with tremelimumab-actl and chemotherapy that contains platinum when your NSCLC:
    - has spread to other parts of your body (metastatic), **and**
    - your tumor does not have an abnormal “EGFR” or “ALK” gene.
- **a type of lung cancer called small cell lung cancer (SCLC)**. IMFINZI may be used with the chemotherapy medicines etoposide and carboplatin or cisplatin as your first treatment when your SCLC:
  - has spread within your lungs or to other parts of the body, (extensive-stage small cell lung cancer, or ES-SCLC).
- **a type of cancer called biliary tract cancer (BTC),** including cancer of the bile ducts (cholangiocarcinoma) and gallbladder cancer. IMFINZI may be used in combination with chemotherapy medicines gemcitabine and cisplatin when your BTC:
  - has spread to nearby tissues (locally advanced), **or**
  - has spread to other parts of the body (metastatic).
- **a type of liver cancer that cannot be removed by surgery (unresectable hepatocellular carcinoma or uHCC).** IMFINZI is used in combination with tremelimumab-actl to treat uHCC.

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 received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have received radiation treatment to your chest area
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. IMFINZI can harm your unborn baby
- are breastfeeding or plan to breastfeed. It is not known if IMFINZI passes into your breast milk. Do not breastfeed during treatment and for 3 months after the last dose of IMFINZI

Females who are able to become pregnant:

- Your healthcare provider will give you a pregnancy test before you start treatment with IMFINZI.
- You should use an effective method of birth control during your treatment and for 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 or think you may be pregnant during treatment with 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, 3 or 4 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 adults with NSCLC include:

- cough
- feeling tired
- inflammation in the lungs
- upper respiratory tract infections
- shortness of breath
- rash

The most common side effects of IMFINZI when used with tremelimumab-actl and platinum-containing chemotherapy in adults with metastatic NSCLC include:

- nausea
- feeling tired or weak
- muscle or bone pain
- decreased appetite
- rash
- diarrhea

The most common side effects of IMFINZI when used with other anticancer medicines in adults with ES-SCLC include:

- nausea
- hair loss
- feeling tired or weak

The most common side effects of IMFINZI when used with other anticancer medicines in adults with BTC include:

- feeling tired
- nausea
- constipation
- decreased appetite
- stomach (abdominal) pain
- rash
- fever

The most common side effects of IMFINZI when used with tremelimumab-actl in adults with uHCC include:

- rash
- diarrhea
- feeling tired
- itchiness
- muscle or bone pain
- stomach (abdominal) pain

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 doctor 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

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US License No. 2043

For more information, call 1-800-236-9933 or go to www.IMFINZI.com