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First-Line Treatment of Advanced Biliary Tract Cancers (BTCs)

Use of first-line (1L) IMFINZI® (durvalumab) in combination with gemcitabine and cisplatin (gem-cis) chemotherapy in patients with locally advanced or metastatic biliary tract cancers

FACULTY

Milind M. Javle, MD
Hurbert L. and Olive Stringer Professor
Department of Gastrointestinal Medical Oncology
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX

Dr Javle was paid for his contribution to this interview.

INTRODUCTION

Biliary tract cancers (BTCs) are comprised of a heterogeneous collection of rare, aggressive neoplasms, which are usually associated with poor prognosis. The standard of care in the first- and second-line treatments has been chemotherapy, even though responses are typically limited. Patients who receive first-line gemcitabine and cisplatin (gem-cis) experience a median overall survival of <12 months.[1] More treatments are urgently needed.

Immune checkpoint inhibitors (ICIs) work by blocking the checkpoints that cancer cells use to evade the immune system, allowing the immune system to recognize and attack the cancer cells.[2] ICIs have shown promise in the treatment of several types of cancer, including BTCs.[3,4]

TOPAZ-1 was a phase 3, randomized, double-blind, placebo-controlled, global study. Inclusion criteria included adult patients with previously untreated, histologically confirmed, unresectable, locally advanced or metastatic

(continued on next page)

IMPORTANT SAFETY INFORMATION

There are no contraindications for IMFINZI® (durvalumab).

Immune-Mediated Adverse Reactions

Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment or after discontinuation. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to

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BTCs (including intrahepatic cholangiocarcinoma [iCCA] or extrahepatic cholangiocarcinoma [eCCA] and gallbladder cancer [GBC]); Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and ≥1 measurable lesions by RECIST v1.1 criteria. Eligible patients were randomly assigned in a 1:1 ratio to receive IMFINZI® (durvalumab) in combination with gem-cis or placebo in combination with gem-cis (**Figure 1**). Randomization was stratified by disease status (initially unresectable vs recurrent) and primary tumor location (iCCA vs eCCA vs GBC).[5,6]

IMPORTANT SAFETY INFORMATION *(continued)*

Immune-Mediated Adverse Reactions *(continued)*

exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate. Withhold or permanently discontinue IMFINZI depending on severity. See USPI Dosing and Administration for specific details. 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.

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. 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

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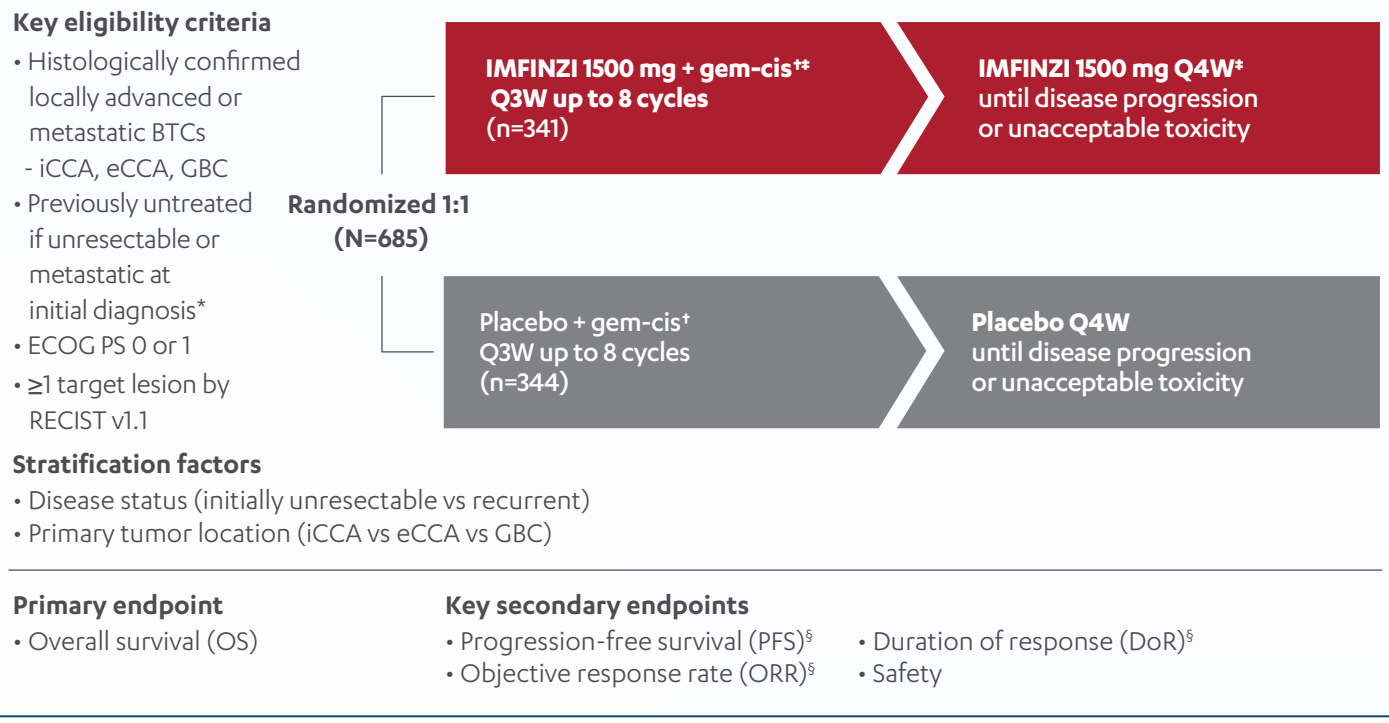
Figure 1. TOPAZ-1 Study Design[5,6]



BTC, biliary tract cancer; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; gem-cis, gemcitabine and cisplatin; iCCA, intrahepatic cholangiocarcinoma; Q3W, every 3 weeks; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
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.
*Patients who developed recurrent disease >6 months after surgery and/or completion of adjuvant therapy were eligible.
†Durvalumab 1500 mg or placebo administered on day 1 + gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by durvalumab 1500 mg or placebo every 4 weeks until disease progression or unacceptable toxicity. Treatment was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.
‡In patients weighing ≤30 kg, IMFINZI was administered using weight-based dosing at 20 mg/kg.
§Investigator assessed according to RECIST v1.1.

- TOPAZ-1 enrolled all-comers, with no biomarker requirements[5,6]
- Patient demographics and disease characteristics were well balanced between treatment arms (**Table**)[5,6]

IMPORTANT SAFETY INFORMATION

Immune-Mediated Pneumonitis *(continued)*

(475), 1.1% were fatal and 2.7% were Grade 3 adverse reactions. 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.

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Table. TOPAZ-1: Key Baseline Characteristics[5,6]

Patient characteristics	IMFINZI + gem-cis (n=341)	Placebo + gem-cis (n=344)	Total (N=685)
Median age (range), years	64 (20-84)	64 (31-85)	64 (20-85)
Female	50%	49%	50%
ECOG PS 0	51%	47%	49%
ECOG PS 1	49%	53%	51%
Race			
Asian	54%	58%	56%
White	38%	36%	37%
Black or African American	2%	2%	2%
American Indian or Alaskan Native	0%	0.3%	0.1%
Other	5%	4%	4%
Primary tumor type			
iCCA	56%	56%	56%
eCCA	19%	19%	19%
GBC	25%	25%	25%
Disease status at randomization‖			
Initially unresectable	80%	81%	81%
Recurrent	20%	19%	19%
Disease classification at diagnosis‖			
Locally advanced¶	11%	17%	14%
Metastatic	89%	83%	86%
MSI status			
High	0.9%	0.6%	0.7%
Stable	47%	49%	48%
Missing#	52%	51%	51%
Virology status			
No viral hepatitis	55%	51%	53%
Any viral hepatitis B	20%	24%	22%
Active viral hepatitis B	2%	4%	3%
Prior hepatitis C	2%	3%	3%
Missing	24%	24%	24%
PD-L1 expression			
TAP ≥1%	58%	60%	59%
TAP <1%	30%	30%	30%
Missing	12%	11%	11%

eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; gem-cis, gemcitabine and cisplatin; iCCA, intrahepatic cholangiocarcinoma; MSI, microsatellite instability; PD-L1, programmed cell death ligand 1; TAP, tumor area positivity.
‖Disease status and disease classification missing for 1 patient.
¶Patients have only locally advanced sites of disease.
#MSI status was missing for approximately 50% of patients in each treatment group due to either an insufficient tissue sample or a test result of MSI status unknown.

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At the 2022 American Society of Clinical Oncology Gastrointestinal Cancers Symposium annual meeting, researchers presented the results from the pivotal phase 3 TOPAZ-1 trial.

Q: What was your reaction to the TOPAZ-1 data given that it was the first trial to demonstrate positive findings in over 10 years versus gem-cis in first-line advanced biliary tract cancers?

A: The first reaction was a surprise because immunotherapy in general has not had a very strong signal in biliary tract cancer. A further dive into the data showed overall survival results.

Q: Could you describe the efficacy results from the trial?

A: TOPAZ-1 was a very interesting trial in that it combined an immune checkpoint inhibitor with systemic chemotherapy. In the maintenance phase, patients could get IMFINZI as a single agent, which was compared with placebo.

In the original analysis (primary endpoint), there was a 20% reduction in the risk of death with IMFINZI + gem-cis (12.8-month median overall survival [OS] [95% confidence interval [CI], 11.1-14.0]) vs gem-cis (11.5-month median OS [95% CI, 10.1-12.5]) (hazard ratio [HR]=0.80 [95% CI, 0.66-0.97]).[5,6]

This trial was powered for OS and there was a median overall survival (mOS) benefit of 1.3 months.[5,6]

- In an exploratory updated OS analysis (with 6.5 months of additional follow-up), a 24% reduction in the risk of death with IMFINZI + gem-cis was demonstrated and gem-cis (mOS: 12.9 [95% CI, 11.6-14.1] vs 11.3 [95% CI, 10.1-12.5] months; HR, 0.76 [95% CI, 0.64-0.91]) (**Figure 2**).[7]

IMPORTANT SAFETY INFORMATION

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.
- ***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.
- ***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.

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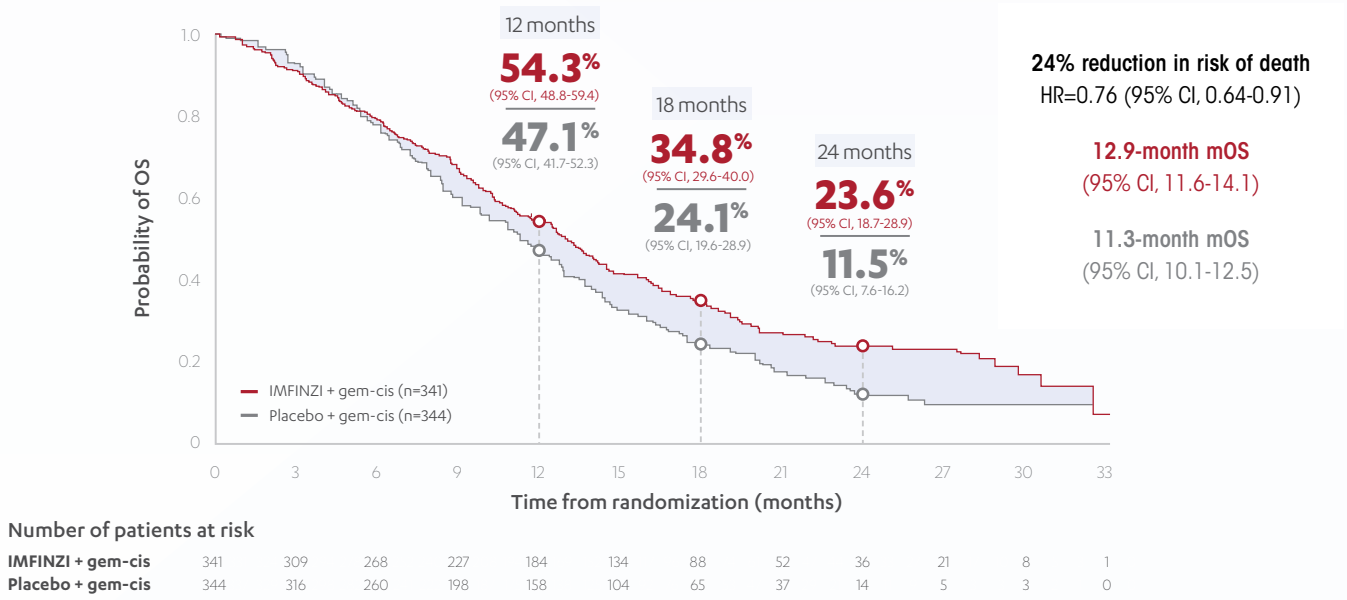
Figure 2. TOPAZ-1 Trial: Updated Overall Survival (With 6.5 Months of Additional Follow-up)[7]

The updated OS analysis was exploratory and not tested for statistical significance



CI, confidence interval; gem-cis, gemcitabine and cisplatin; mOS, median overall survival; OS, overall survival.
Median duration of follow-up: 23.4 months (95% CI, 20.6-25.2) with durvalumab + gem-cis and 22.4 months (95% CI, 21.4-23.8) with gem-cis.

- OS rates at 12, 18, and 24 months were descriptive and not tested for statistical significance[7]

IMPORTANT SAFETY INFORMATION

Immune-Mediated Endocrinopathies *(continued)*

- ***Thyroiditis***: Immune-mediated thyroiditis occurred in 0.5% (9/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
- ***Hyperthyroidism***: Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI.
- ***Hypothyroidism***: Immune-mediated hypothyroidism occurred in 8.3% (156/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
- ***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. Grade 3 immune-mediated Type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI.

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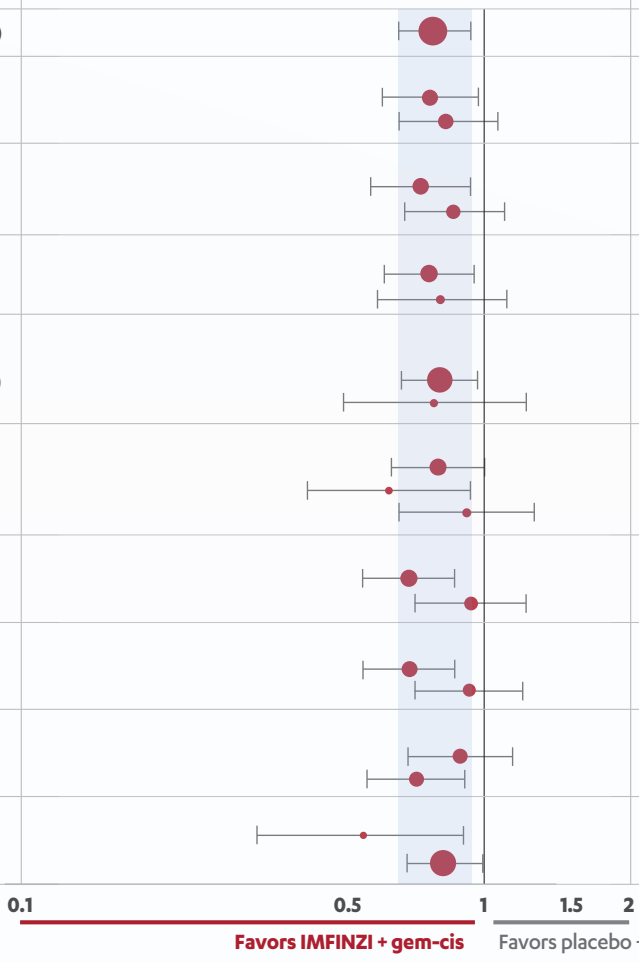
Figure 3. TOPAZ-1 Trial: Updated Overall Survival by Prespecified Subgroup[7]

	IMFINZI + gem-cis n/N	Placebo + gem-cis n/N	HR (95% CI)
All patients	**248/341 (72.7%)**	**279/344 (81.1%)**	**0.76 (0.64-0.91)**
Sex			
Male	126/169 (74.6%)	148/176 (84.1%)	0.75 (0.59-0.95)
Female	122/172 (70.9%)	131/168 (78.0%)	0.81 (0.64-1.04)
Age at randomization			
<65 years	123/181 (68.0%)	150/184 (81.5%)	0.72 (0.56-0.91)
≥65 years	125/160 (78.1%)	129/160 (80.6%)	0.84 (0.66-1.08)
PD-L1 expression			
TAP ≥1%	149/199 (74.9%)	172/207 (83.1%)	0.75 (0.60-0.93)
TAP <1%	71/103 (68.9%)	81/103 (78.6%)	0.79 (0.58-1.09)
Disease status at randomization			
Initially unresectable	209/274 (76.3%)	240/279 (86.0%)	0.79 (0.65-0.95)
Recurrent	39/67 (58.2%)	39/64 (60.9%)	0.76 (0.49-1.20)
Primary tumor location			
iCCA	136/190 (71.6%)	153/193 (79.3%)	0.78 (0.62-0.99)
eCCA	45/66 (68.2%)	55/65 (84.6%)	0.61 (0.41-0.91)
GBC	67/85 (78.8%)	71/86 (82.6%)	0.90 (0.64-1.25)
Race			
Asian	134/185 (72.4%)	174/201 (86.6%)	0.68 (0.54-0.85)
Non-Asian	114/156 (73.1%)	105/143 (73.4%)	0.92 (0.70-1.20)
Region			
Asia	130/178 (73.0%)	170/196 (86.7%)	0.68 (0.54-0.85)
Rest of the world	118/163 (72.4%)	109/148 (73.6%)	0.91 (0.70-1.18)
ECOG PS			
0	126/173 (72.8%)	125/163 (76.7%)	0.87 (0.68-1.12)
1	122/168 (72.6%)	154/181 (85.1%)	0.70 (0.55-0.89)
Disease classification			
Locally advanced	22/38 (57.9%)	45/57 (78.9%)	0.54 (0.32-0.88)
Metastatic	226/303 (74.6%)	234/286 (81.8%)	0.80 (0.67-0.97)



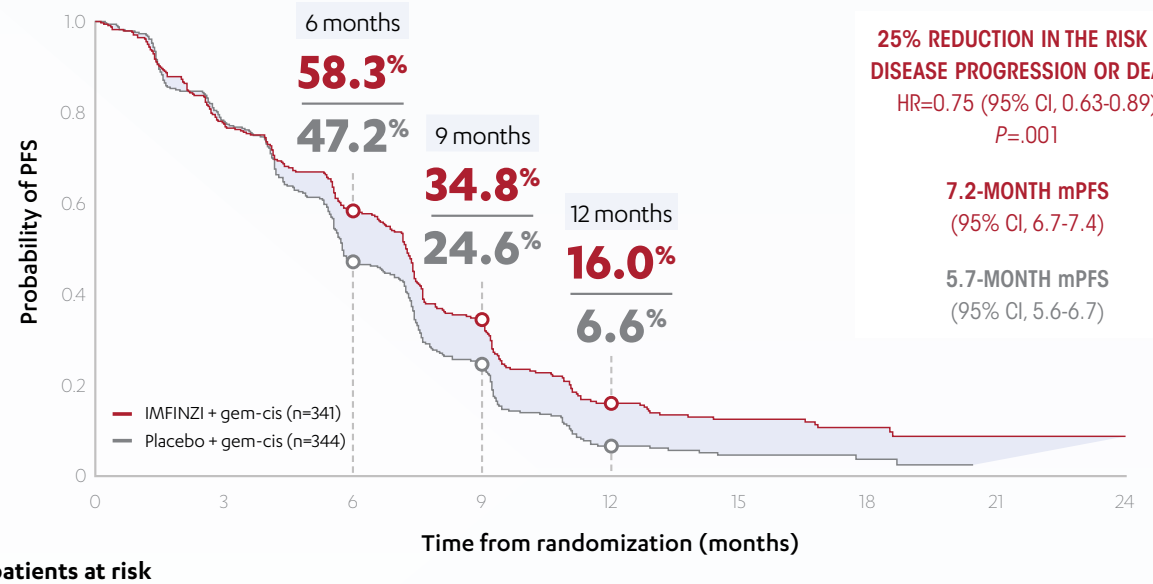
OS subgroup analysis was exploratory and not powered to show differences between or within individual subgroups, and was not formally tested for statistical significance.

CI, confidence interval; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; gem-cis, gemcitabine and cisplatin; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; PD-L1, programmed cell death ligand 1; TAP, tumor area positivity.

- Durvalumab + gem-cis demonstrated consistent OS results across patient subgroups (**Figure 3**)[7]

- **Durvalumab + gem-cis resulted in a 25% reduction in the risk of disease progression or death versus gem-cis (median progression-free survival: 7.2 [95% CI, 6.7-7.4] vs 5.7 [95% CI, 5.6-6.7] months; HR, 0.75 [95% CI, 0.63-0.89]; *P*=.001) (Figure 4)[5,8]**

Figure 4. Progression-Free Survival (Secondary Endpoint)[5,8]



Number of patients at risk

IMFINZI + gem-cis	341	258	189	100	38	25	15	5	0
Placebo + gem-cis	344	255	149	71	17	7	4	0	0

PFS rates at 6, 9, and 12 months were descriptive endpoints and not tested for statistical significance

CI, confidence interval; gem-cis, gemcitabine and cisplatin; HR, hazard ratio; mPFS, median progression-free survival; PFS, progression-free survival.
Median duration of follow-up: 16.8 months (95% CI, 14.8-17.7) with durvalumab + gem-cis and 15.9 months (95% CI, 14.9-16.9) with gem-cis.
Hazard ratio 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 0.048.[1]

- PFS at 6, 9, and 12 months were descriptive endpoints and were not formally tested for statistical significance.[5,8] Because superior OS was demonstrated at the prespecified interim analysis, PFS was formally evaluated at this time. At data cutoff (August 11, 2021), 573 events (276 in the IMFINZI group and 297 in the placebo group) had occurred[5]

Q: What is the impact of the FDA approval of durvalumab plus gem-cis in the community as a standard of care for locally advanced and metastatic biliary tract cancers?

A: In the past decade, the field has been relatively static in the first-line setting, with no third agent after gemcitabine (gem) and gem-cis. So, this first positive trial has completely changed the field.

> Over the past decade, TOPAZ-1 is the first global phase 3 study that demonstrated **positive results** versus gem-cis for advanced BTCs[1,5,10,11]

IMPORTANT SAFETY INFORMATION

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.

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Q: What other additional analyses from TOPAZ-1 have been conducted, and what is your opinion of the impact of those additional analyses?

A: Some analyses of the TOPAZ-1 trial have not only taught us about the impact of IMFINZI, but also have taught us about the disease. This was the first large, prospective, genetic genomic profiling study done in the first-line setting; most of the previous studies had been done in second or subsequent lines.

- An exploratory analysis (with 6.5 months of additional follow-up) of TOPAZ-1 assessed the prevalence of genomic alterations and the biomarker-evaluable patient population (IMFINZI: 214/341 [63%]; placebo: 227/344 [66%]) (**Figure 5**)[9]

IMPORTANT SAFETY INFORMATION

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.

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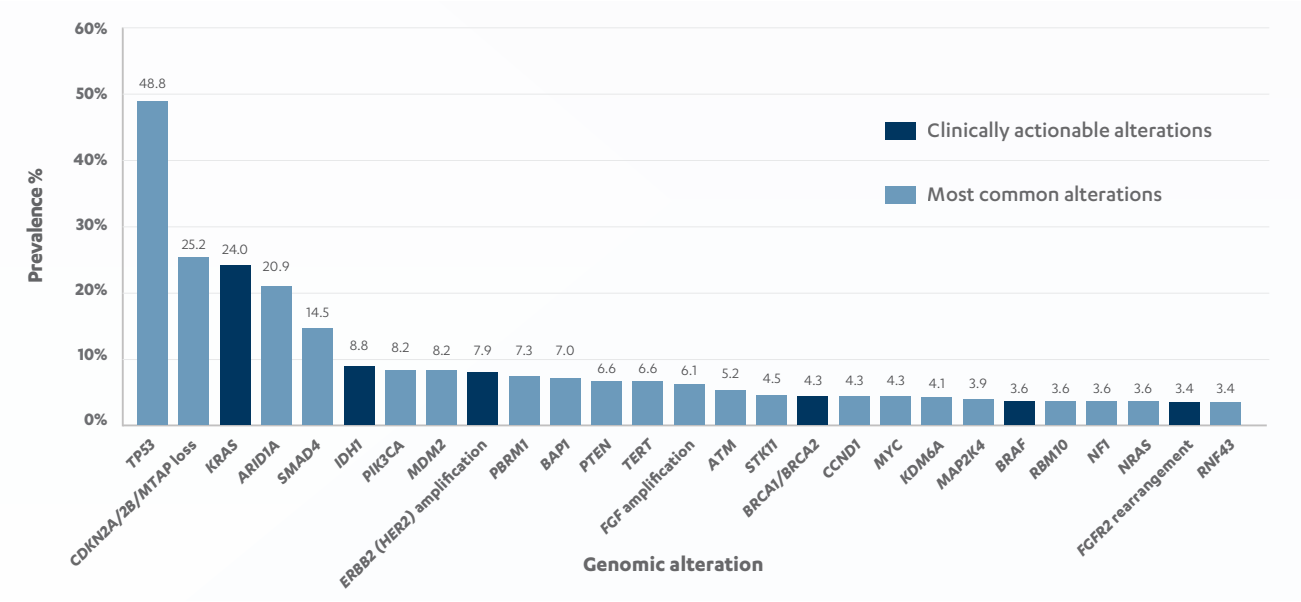
Figure 5. TOPAZ-1 Trial: Prevalence of Genomic Alterations (≥3%)[9]

This exploratory analysis was conducted and descriptively assessed with 6.5 months of additional follow-up (data cutoff: February 25, 2022)



Genomic profiling of formalin-fixed paraffin-embedded tumor tissues was done using the FoundationOne® panel (Foundation Medicine, Cambridge, MA).

IMPORTANT SAFETY INFORMATION

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-

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Q: What were the adverse events in the trial?

A: In the TOPAZ-1 trial, there were grade 3 and 4 toxicities between the treatment and study arms (75.7% vs 77.8%) (**Figure 6**).[5] However, it must be noted that, since the TOPAZ-1 trial was conducted at cancer centers and tertiary centers, patients were carefully followed for these toxicities.

- Safety data are available for the 680 patients who received at least 1 dose of IMFINZI + gem-cis (n=338) or placebo + gem-cis (n=342)[5,6]
- Serious adverse reactions occurred in 47% of patients receiving IMFINZI + gem-cis. 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%)[6]
- Fatal adverse reactions occurred in 3.6% of patients receiving IMFINZI + gem-cis, and included ischemic or hemorrhagic stroke (reported in 4 patients), sepsis (2 patients), and upper gastrointestinal hemorrhage (reported in 2 patients)[6]
- The most common adverse reactions (occurring in ≥20% of patients) with IMFINZI + gem-cis were fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia[6]

IMPORTANT SAFETY INFORMATION

Complications of Allogeneic HSCT after IMFINZI *(continued)*

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.

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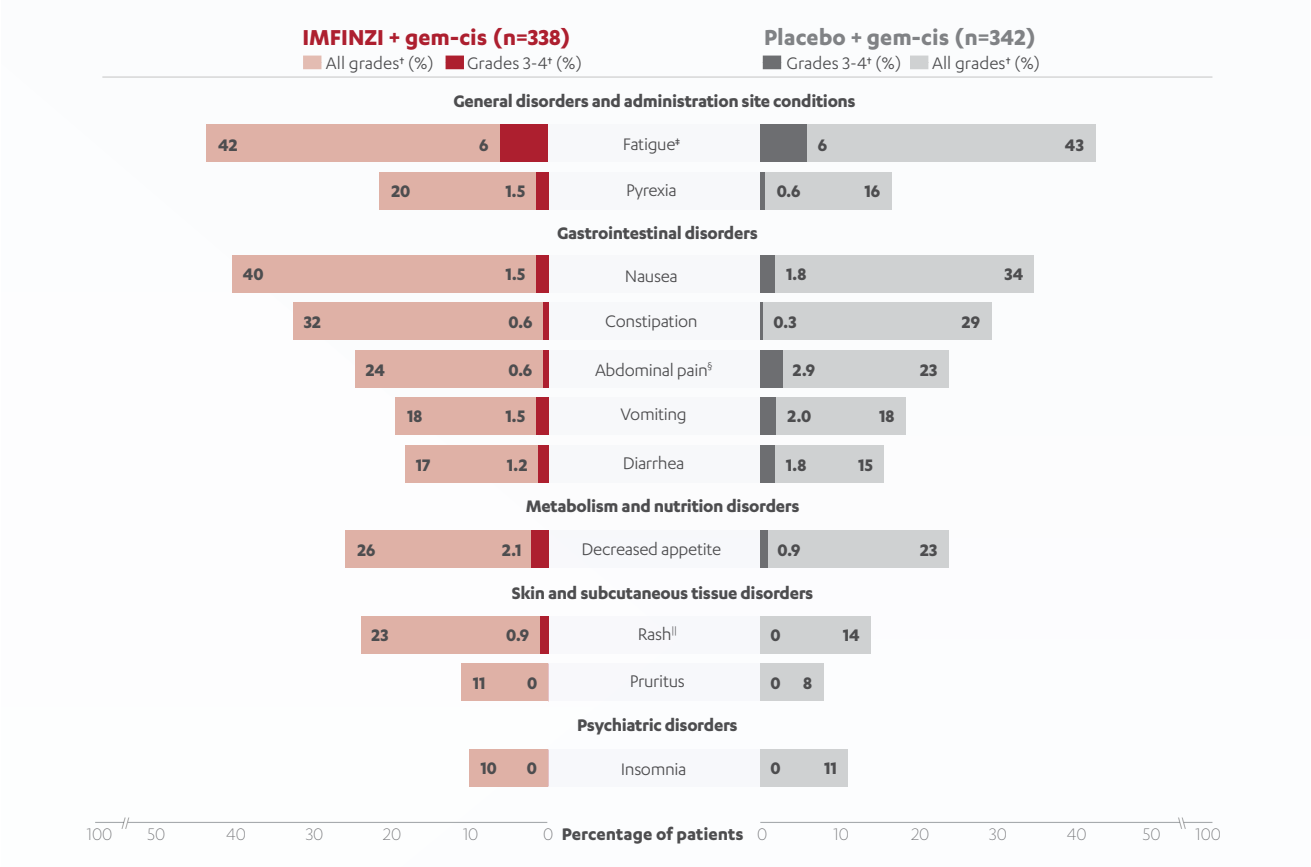
Figure 6. TOPAZ-1 Trial: Adverse Events Occurring in ≥10% of Patients*[6]



ARS, adverse reactions; gem-cis, gemcitabine and cisplatin; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
*Table summarizes the ARs that occurred in ≥10% of patients treated with IMFINZI + gem-cis.
†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.

IMPORTANT SAFETY INFORMATION

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.

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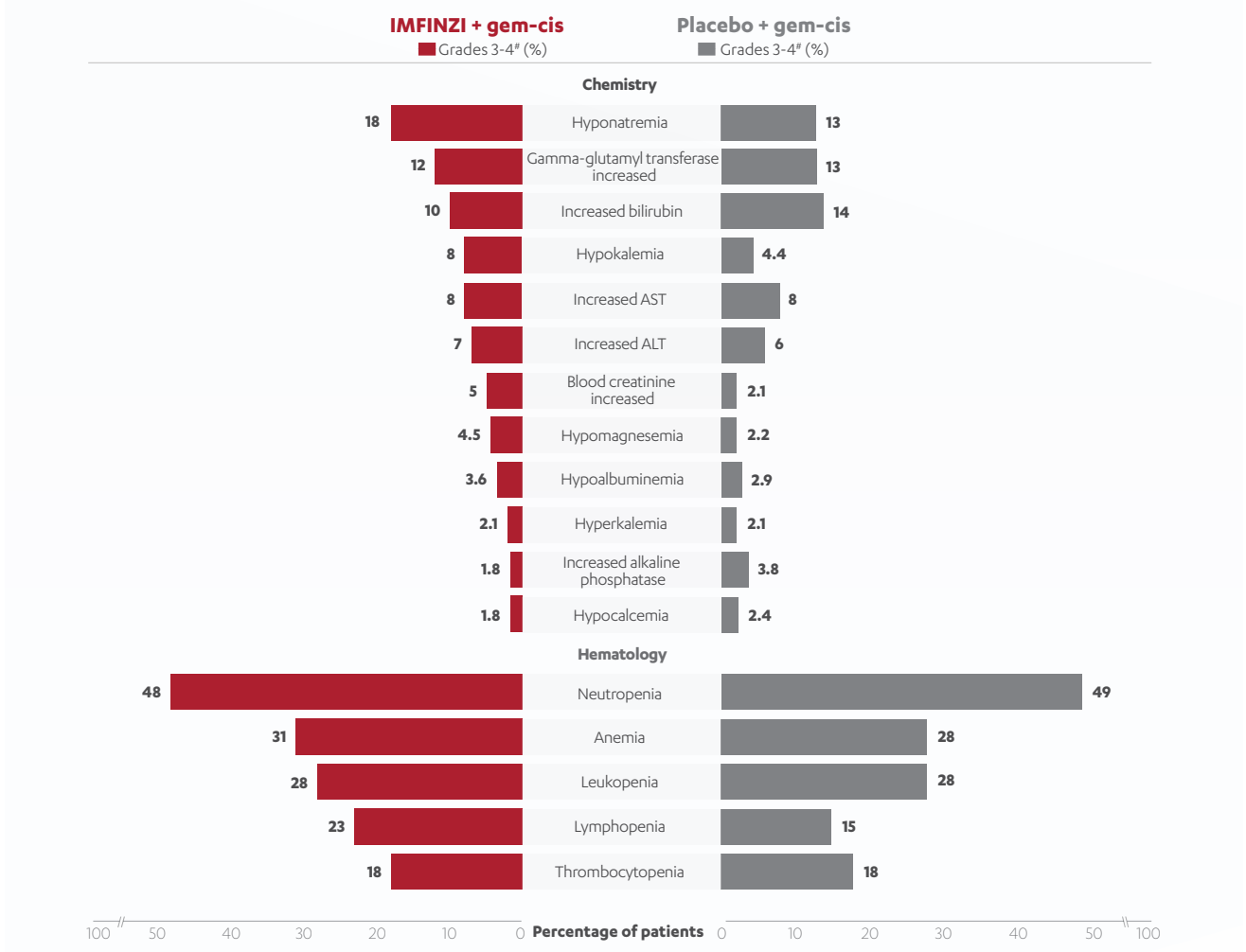
Figure 7. Grades 3-4 Laboratory Abnormalities Worsening From Baseline in ≥20% of Patients[6]



ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Table summarizes the laboratory abnormalities that occurred in ≥20% of patients treated with IMFINZI + gem-cis. The frequency cutoff 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 1 on-study laboratory measurement available: IMFINZI + gem-cis (range: 312 to 335) and placebo + gem-cis (range: 319 to 341).

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Sponsored by AstraZeneca

Q: We know that community healthcare providers (HCPs) are always looking for guidance in managing the difficult-to-treat patient. What would be your advice for the community HCPs on using IMFINZI with chemotherapy as first-line therapy for their patients with locally advanced or metastatic biliary tract cancers? Is there a pearl or two that you would have for these folks?

A: We must remember that it is an immune therapy, so it may be potentially hazardous for patients, for instance, those who have autoimmune diseases like Crohn's disease, ulcerative colitis, or autoimmune primary sclerosing cholangitis. In such cases, you certainly have to work with a tertiary center, and follow these patients carefully.

The toxicities associated with IMFINZI are immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic reactions, immune-mediated pancreatitis, and solid organ transplant rejection. IMFINZI can cause severe or life-threatening infusion-related reactions. So, like any immune therapy, we do need to monitor them carefully for immune toxicities. We have closely monitored and treated hundreds of patients in my group.

Q: Can you tell me what are some of the questions that you and your colleagues in the biliary tract space are getting from the community since the TOPAZ-1 data were originally presented?

A: Some of the questions that I am getting are:

- What is the median overall survival improvement?
- If you use the TOPAZ-1 regimen, does that preclude the patient from getting surgery later on or radiotherapy or some sort of other multidisciplinary care?

Q: How would you incorporate IMFINZI plus gem-cis in your practice for patients with locally advanced or metastatic biliary tract cancers?

A: At this point, for all patients who have locally advanced or unresectable biliary tract cancers, which includes advanced or metastatic patients, IMFINZI plus gem-cis is a regimen to consider.

- **What would be the exceptions?** Those patients who present with an ECOG performance status of 2 or higher, biliary tract obstruction and jaundice that cannot be controlled with stenting, or renal impairment are not candidates to consider for this regimen

However, I am glad to say that, for the vast majority (at least 85% or 90%) of patients in my practice who have a good performance status, this would be a regimen to consider. In my practice, we use this regimen in the first-line setting.

Q: In your opinion, what resources would you find the most useful that others may benefit from, resources for physicians as well as for patients? Are there resources that you and your colleagues commonly use to help community physicians and patients understand and manage the very complex world of biliary tract cancers?

A: Biliary tract cancer is a complicated area, and I would not trivialize some of the challenges that community oncologists and academic oncologists face.

I use several resources. The manufacturer has very nice online resources. There are many tertiary cancer centers where patients can be referred to. There are specialists such as hepatologists, gastroenterologists, and others who have more experience treating immunotherapy; for instance, patients with melanoma and lung cancer. You have to identify a team of people within your practice and in tertiary centers who can assist you.

Q: If you have any closing comments or remarks about TOPAZ-1 and where these great results are headed, we greatly appreciate that.

A: I think the TOPAZ-1 study has truly been quite a remarkable study in advanced biliary tract cancer. The survival results have been satisfactory. Now that we know that we are going to use this platform to build on, we can hopefully add other treatments to this regimen and get an incremental result. This is an exciting time in immuno-oncology and biliary tract cancer, and this study has contributed to it.

Q: Are there advocacy organizations that you recommend to the patients?

A: Cholangiocarcinoma Foundation has a strong advocacy group that has played a wonderful role. They have a CholangioConnect program where they often connect you to other patients in the space.

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IMPORTANT SAFETY INFORMATION
There are no contraindications for IMFINZI® (durvalumab).

Immune-Mediated Adverse Reactions
Important immune-mediated adverse reactions listed under Warnings and Precautions may not include all possible severe and fatal immune-mediated reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting treatment or after discontinuation. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate 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 USPI Dosing and Administration for specific details. 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.

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. 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. 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.

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.

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.

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

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.
- ***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.
- ***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.
- ***Hyperthyroidism***: Immune-mediated hyperthyroidism occurred in 2.1% (39/1889) of patients receiving IMFINZI.
- ***Hypothyroidism***: Immune-mediated hypothyroidism occurred in 8.3% (156/1889) of patients receiving IMFINZI, including Grade 3 (<0.1%) adverse reactions.
- ***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. Grade 3 immune-mediated Type 1 diabetes mellitus occurred in <0.1% (1/1889) of patients receiving IMFINZI.

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.

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

IMPORTANT SAFETY INFORMATION *(continued)*

Other Immune-Mediated Adverse Reactions *(continued)*

- ***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.

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

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.

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).

IMPORTANT PRODUCT INFORMATION

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

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. IMFINZI 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 PD-1/PD-L1 blocking antibody.

Advise women not to become pregnant or breastfeed during treatment with IMFINZI and for 3 months after the last dose.

The most frequent serious adverse reactions reported in at least 2% of patients with locally advanced or metastatic BTC were cholangitis (7%), pyrexia (3.8%), anemia (3.6%), sepsis (3.3%) and acute kidney injury (2.4%).

The most common adverse reactions (≥20% of adult patients with locally advanced or metastatic biliary tract cancer) were fatigue, nausea, constipation, decreased appetite, abdominal pain, rash, and pyrexia.

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

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

About the Expert

Milind M. Javle, MD
Hurbert L. and Olive Stringer Professor
Department of Gastrointestinal Medical Oncology
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, TX

Dr Milind Javle is a Professor of Gastrointestinal (GI) Medical Oncology at MD Anderson Cancer Center, Houston, TX, where he leads the Biliary Cancer Program. He graduated from Grant Medical College in India and did his residency at SUNY Buffalo and Oncology Fellowship at Roswell Park Cancer Center, where he specialized in GI cancers. He has been at MD Anderson since 2007 and has built a reputation as a leader in GI oncology, particularly biliary and pancreatic cancers. He has over 200 publications in the field, and has extensive research support from NIH, foundations, industry, and philanthropy. In addition to his leadership roles at MD Anderson Cancer Center, Dr Javle is the current Chair of the NCI Task Force in Hepatobiliary Cancers, the former Chair of the International Cholangiocarcinoma Research Network, Vice President of the Cholangiocarcinoma Foundation, and Co-Chair of the SWOG Hepatobiliary Committee.

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