RxAdvance

NEW DRUG APPROVAL

Brand Name	Imjudo®
Generic Name	tremelimumab-actl
Drug Manufacturer	AstraZeneca AB

New Drug Approval

FDA Approval Date: October 21, 2022

Review designation: N/A; Orphan

Type of review: Biologic License Application (BLA): 761289

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. In the United States, HCC is the ninth leading cause of cancer deaths. Despite advances in prevention techniques, screening, and new technologies in both diagnosis and treatment, incidence and mortality continue to rise. Cirrhosis remains the most important risk factor for the development of HCC.

Epidemiology

In the United States, HCC is the ninth leading cause of cancer deaths.1 A total of 30,640 new liver and intrahepatic bile duct cancers were estimated to occur in 2013 in addition to 21,670 deaths.2 HCC occurred more often in males than females (2.4:1), with a higher incidence in Eastern and Southern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia. The age-adjusted incidence of liver cancer has risen from 1.6 per 100,000 individuals to 4.6 per 100,000 individuals among American Indians and Alaskan Natives followed by blacks, Whites, and Hispanics.4 There are pockets in the United States where certain ethnic groups have significantly increased incidence of HCC. Importantly, the incidence of HCC will continue to escalate as hepatitis C reaches its maturity and as nonalcoholic steatohepatitis (NASH) and obesity become more prevalent in the United States.

Efficacy

Hepatocellular Carcinoma (HCC)

The efficacy of Imjudo® in combination with durvalumab 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 (Imjudo®plus durvalumab or durvalumab) or sorafenib. Study treatment consisted of Imjudo® as a one-time single intravenous infusion of 300 mg in combination with durvalumab 1,500 mg on the same day, followed by durvalumab every 4 weeks; durvalumab 1,500 mg every 4 weeks (an unapproved regimen for uHCC); or sorafenib 400 mg given orally twice daily, until disease progression or unacceptable toxicity. The efficacy assessment of Imjudo® is based on patients randomized to the Imjudo® plus durvalumab 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 a 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 was deriving clinical benefit as determined by the investigator.

The major efficacy outcome measure was overall survival (OS) between the Imjudo® plus durvalumab 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 Imjudo® plus durvalumab 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%), uninfected (42%).

Efficacy results are presented in Table 1 and Figure 1.

Endpoint	Imjudo® and Durvalumab (N=393)	Sorafenib (N=389)
OS		
Number of deaths (%)	262 (66.7)	293 (75.3)
Median OS (months) (95% CI)	16.4 (14.2, 19.6)	13.8 (12.3, 16.1)
HR (95% CI) [1]	0.78 (0.66, 0.92)	
p-value[2,3]	0.0035	
PFS		
Number of events (%)	335 (85.2)	327 (84.1)
Median PFS (months) (95% CI)	3.8 (3.7, 5.3)	4.1 (3.7, 5.5)
HR (95% CI)[1]	0.90 (0.77, 1.05)	
ORR		
ORR % (95% CI)[4,5]	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

1 HR (Imjudo® and durvalumab vs. sorafenib) based on the stratified Cox proportional hazard model.

2 Based on a stratified log-rank test.

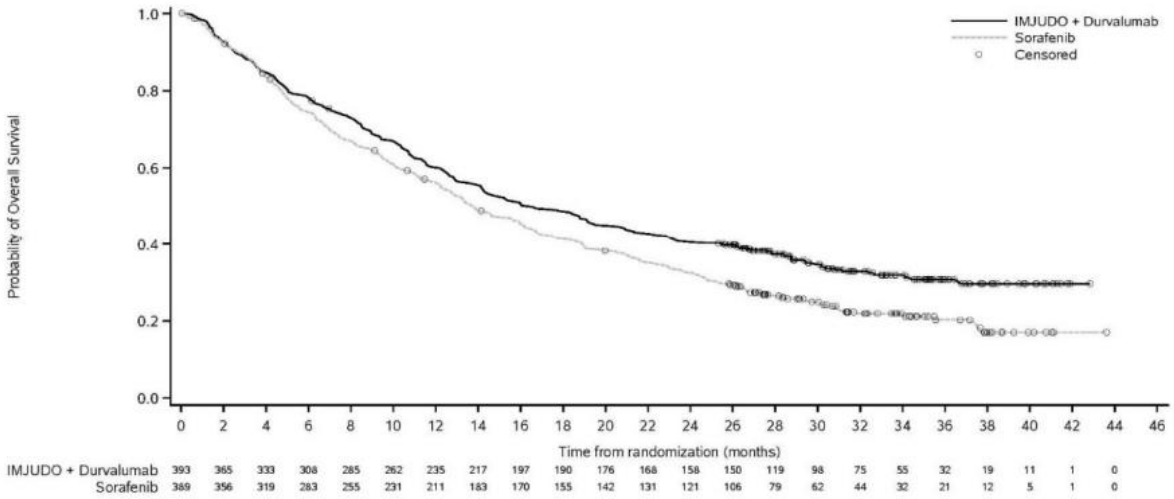
[3] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for Imjudo® and durvalumab vs. sorafenib was 0.0398.

[4] Confirmed complete response or partial response.

[5] Based on Clopper-Pearson method.

CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached

Figure 1. Kaplan-Meier curve of OS



Safety

ADVERSE EVENTS

Most common adverse reactions (≥ 20%) of patients with uHCC are rash, diarrhea, fatigue, pruritus, musculoskeletal pain, and abdominal pain. Most common laboratory abnormalities (≥ 40%) of patients with uHCC are AST increased, ALT increased, hemoglobin decreased, sodium decreased, bilirubin increased, alkaline phosphatase increased, and lymphocytes decreased.

WARNINGS & PRECAUTIONS

Immune-Mediated Adverse Reactions

- 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 with renal dysfunction and immune-mediated pancreatitis.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose.
  - Withhold or permanently discontinue based on severity and type of reaction.
- Infusion-Related Reactions: Interrupt, slow the rate of infusion, or permanently discontinue treatment based on the severity of the reaction.

- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception.

CONTRAINDICATIONS

None reported

Clinical Pharmacology

MECHANISMS OF ACTION

CTLA-4 is a negative regulator of T-cell activity. Tremelimumab-actl is a monoclonal antibody that binds to CTLA-4 and blocks the interaction with its ligands CD80 and CD86, releasing CTLA-4-mediated inhibition of T-cell activation. In synergistic mouse tumor models, blocking CTLA-4 activity resulted in decreased tumor growth and increased proliferation of T cells in tumors.

Dose & Administration

ADULTS

The recommended dosage of Imjudo® is presented in Table 2

Indication	**Recommended Imjudo® Dosage**	**Duration of Therapy**
uHCC	Patients with a body weight of 30 kg and more: • A single dose of Imjudo® 300 mg followed by durvalumab 1,500 mg at Day 1 of Cycle 1; • Continue durvalumab 1,500 mg as a single agent every 4 weeks Patients with a body weight of less than 30 kg: • A single dose of Imjudo® 4 mg/kg followed by durvalumab2 20 mg/kg at Day 1 of Cycle 1. • Continue durvalumab 20 mg/kg as a single agent every 4 weeks	After Cycle 1 of combination therapy, administer durvalumab as a single agent every 4 weeks until disease progression or unacceptable toxicity

PEDIATRICS

The safety and effectiveness of tremelimumab- actl have not been established in pediatric patients.

GERIATRICS

Refer to adult dosing

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

- Injection: 25 mg/1.25 mL (20 mg/mL) solution in a single-dose vial.
- Injection: 300 mg/15 mL (20 mg/mL) solution in a single-dose vial.