IMJUDO (Tremelimumab-actl) in Combination With IMFINZI (Durvalumab) Receives FDA Approval for HCC and NSCLC

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Globally, primary liver cancer is the second most common cause of cancer mortality, with an estimated mortality rate of 8.5 per 100,000 person-years, and hepatocellular carcinoma (HCC) accounts for approximately 75% of the total cases of primary liver cancer.[1] The incidence of HCC varies considerably across countries and different populations. After increasing for several decades, the HCC rates in the United States started to plateau in 2013 and began declining in 2016.[2]

In the United States, HCC is primarily caused by chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), nonalcoholic steatohepatitis, and excessive alcohol consumption.[2] For individuals with HBV, the lifetime risk of developing HCC ranges from 10% to 25%, and the risk increases 10- to 20-fold for a patient with a chronic HCV infection.[1]

Similarly, even though lung cancer is the second-most diagnosed cancer worldwide, the incidence rates in the United States have been dropping 1% to 2.6% each year since 2006. Mortality rates have also declined 4% to 5% per year from 2014 to 2020. These declines are attributed to a decrease in smoking as well as advances in diagnosis and treatment.[3]

Non–small cell lung cancer (NSCLC) accounts for 85% of lung cancer diagnoses in the United States. Even though smoking is the most common risk factor for developing NSCLC, 15% of diagnosed patients have never smoked cigarettes.[4]

For many cancers, including HCC and NSCLC, immune checkpoint inhibitors targeting receptors that restrict T-cell activity have become effective therapies.[4,5] Recent studies show that dual immunotherapy using a combination of antibodies to block multiple checkpoints, such as programmed death ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), increases the antitumor response.[6]

FDA Approval of Tremelimumab-actl Plus Durvalumab for Treatment of HCC or NSCLC

On October 21, 2022, the US Food and Drug Administration (FDA) approved the use of tremelimumab-actl (IMJUDO; AstraZeneca Pharmaceuticals), a CTLA-4–blocking antibody, in combination with durvalumab (IMFINZI; AstraZeneca Pharmaceuticals), a PD-L1–blocking antibody, for the treatment of adult patients with unresectable HCC.[7,8] The combination of tremelimumab-actl and durvalumab was reviewed using the FDA's Assessment Aid, a voluntary submission from the applicant to facilitate the assessment. Tremelimumab-actl was granted orphan drug designation by the FDA.[8,9]

Then on November 10, 2022, the FDA approved the use of tremelimumab-actl in combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic NSCLC with no sensitizing epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.[7,10] The combination therapy of tremelimumab-actl, durvalumab, and platinum-based chemotherapy was reviewed using the FDA's Assessment Aid.[7]

According to Melissa Johnson, MD, Director of Lung Cancer Research, Sarah Cannon Research Institute at Tennessee Oncology in Nashville, Tennessee, "Metastatic non–small cell lung cancer remains a significant treatment challenge because many patients' tumors do not respond well to standard therapies, including checkpoint inhibitors. The approval of this dual immunotherapy regimen with chemotherapy introduces a new, generally well-tolerated treatment option for patients with this devastating disease and gives them the chance to benefit from the long-term survival advantage seen with CTLA-4 inhibition."[11]

Mechanism of Action

Tremelimumab-actl is a monoclonal antibody that increases T-cell proliferation by blocking CD80 and CD86 from binding with CTLA-4, a negative regulator of T-cell activity.[7]

Dosing and Administration

Tremelimumab-actl is prepared as a diluted intravenous infusion and should be promptly administered after preparation. Before each infusion, patients must undergo a weight measurement for precise dosing considerations.[7]

For patients with unresectable HCC who weigh ≥30 kg, the treatment protocol involves administering a single

Table 1 Efficacy of Tremelimumab-actl Plus Durvalumab in Unresectable HCC in the HIMALAYA Study[12]

Efficacy parameter	Tremelimumab-actl plus durvalumab (n=393)	Sorafenib (n=389)
Median OS, months (95% CI)	16.43 (14.16-19.58)	13.77 (12.25-16.13)
Hazard ratio (95% CI)	0.78 (0.65-0.93)	
P value	.0035	
Median PFS, months (95% CI)	3.78 (3.68-5.32)	4.07 (3.75-5.49)
Hazard ratio (95% CI)	0.90 (0.77-1.05)	

CI indicates confidence interval; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival.

300-mg dose of tremelimumab-actl immediately on day 1 of cycle 1, followed by 1500 mg of durvalumab. Subsequently, a 1500-mg dose of durvalumab is administered every 4 weeks as a standalone treatment. In patients with unresectable HCC who weigh <30 kg, the dosage of tremelimumab-actl is adjusted to 4 mg/kg, coupled with a durvalumab dosage of 20 mg/kg on day 1 of cycle 1; durvalumab is then administered every 4 weeks. Irrespective of the patient's weight, the 4-week cycle of durvalumab as a standalone treatment continues until disease progression or if adverse events become unacceptable.[7]

Patients with metastatic NSCLC follow a dosing schedule that involves a single combined infusion of tremelimumab-actl with durvalumab and chemotherapy every 3 weeks for 4 cycles. Following this, durvalumab is administered in combination with chemotherapy every 4 weeks. The fifth and final dose of tremelimumab-actl is administered alongside the sixth dose of durvalumab at week 16. The recommended dosage and regimen are determined based on both the patient's weight and tumor histology. For patients weighing ≥30 kg, the tremelimumab-actl dosage is 75 mg, and the durvalumab dosage is 1500 mg. For those weighing <30 kg, the tremelimumab-actl dosage is 1 mg/kg, and the durvalumab dosage is 20 mg/kg. The specific platinum-based chemotherapy recommended depends on the histology of the tumor.[7]

Pivotal Clinical Trial: HIMALAYA

The FDA approval of tremelimumab-actl plus durvalumab for the treatment of unresectable HCC was based on findings from the HIMALAYA trial (NCT03298451), a multicenter, open-label, phase 3 clinical trial of 1171 adult patients with histologically confirmed HCC.[12] Eligible participants must have had no prior systemic therapy, Barcelona Clinic Liver Cancer stage B or C, Child-Pugh class A, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Notably, individuals with HBV/HCV coinfection, ascites requiring nonpharmacologic intervention, or main portal vein thrombosis were excluded from the trial.[12]

Patients were randomly assigned to 1 of 3 arms (1:1:1): a single 300-mg dose of tremelimumab in conjunction with 1500 mg of durvalumab every 4 weeks (STRIDE), a regimen of 1500 mg of durvalumab every 4 weeks, or 400 mg of sorafenib twice daily. The primary efficacy end point was overall survival (OS), specifically comparing the STRIDE regimen to sorafenib.[12]

In terms of OS, patients on the STRIDE regimen had a median survival of 16.43 months (95% confidence interval [CI], 14.16-19.58), whereas patients receiving sorafenib exhibited a median survival of 13.77 months (95% CI, 12.25-16.13), as detailed in Table 1. Furthermore, the STRIDE cohort demonstrated an OS rate of 30.7% at the 36-month mark, compared with a 20.2% OS rate observed in the sorafenib-treated group. Progression-free survival (PFS) was not significantly different between the groups.[12]

Pivotal Clinical Trial: POSEIDON

The FDA approval of tremelimumab-actl in combination with durvalumab and platinum-based chemotherapy for treating metastatic NSCLC stemmed from the outcomes of the multicenter, open-label, phase 3 POSEIDON (NCT03164616) clinical trial. The POSEIDON study included 1013 adult patients with *EGFR/ALK* wild-type metastatic NSCLC with an ECOG performance status of 0 or 1 and measurable disease according to RECIST v1.1.[13]

Patients were uniformly and randomly allocated across 3 cohorts stratified by PD-L1 expression, disease status, and histology. The first cohort (tremelimumab plus durvalumab and chemotherapy; T+D+CT) received 75 mg of tremelimumab, 1500 mg of durvalumab, and chemotherapy for up to four 21-day cycles. Subsequently, they received a 1500-mg dose of durvalumab once every 4 weeks until disease progression. A final 75-mg dose of tremelimumab was administered at week 16 (cycle 6). The second cohort (durvalumab plus chemotherapy; D+CT) received 1500 mg of durvalumab plus chemotherapy for up to four 21-day cycles, followed by a 1500-mg dose of durvalumab once every 4 weeks until disease progression. The third cohort (chemotherapy; CT) received chemotherapy for up to six 21-day cycles. PFS and OS were determined as end points for all 3 cohorts.[13]

Comparing the T+D+CT group with the CT group, a significant improvement in PFS was observed (hazard ratio [HR], 0.72; 95% CI, 0.60-0.86; *P*=.0003). The medi-

an PFS was 6.2 months (95% CI, 5.0-6.5) for patients receiving T+D+CT versus 4.8 months (95% CI, 4.6-5.8) for patients in the CT group. Likewise, the OS was significantly higher in the T+D+CT group relative to the CT group (HR, 0.77; 95% CI, 0.65-0.92; *P*=.0030; Table 2).[13]

Table 2 Efficacy of Tremelimumab-actl Plus Durvalumab and Chemotherapy in Metastatic NSCLC in the POSEIDON Study[13]

Efficacy parameter	Tremelimumab-actl plus durvalumab and platinum-based chemotherapy (n=338)	Platinum-based chemotherapy (n=337)
Median PFS, months (95% CI)	6.2 (5.0-6.5)	4.8 (4.6-5.8)
Hazard ratio (95% CI)	0.72 (0.60-0.86)	
P value	.0003	
Median OS, months (95% CI)	14.0 (11.7-16.1)	11.7 (10.5-13.1)
Hazard ratio (95% CI)	0.77 (0.65-0.92)	
P value	.0030	

CI indicates confidence interval; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival.

Adverse Reactions

For patients with unresected HCC, the most common adverse reactions (≥20%, any grade) were rash (32%), diarrhea (27%), fatigue (26%), pruritus (23%), musculoskeletal pain (22%), and abdominal pain (20%). Also, the most common laboratory abnormalities (≥40%, any grade) included elevated serum levels of aspartate aminotransferase (63%), alanine aminotransferase (56%), bilirubin (41%), and alkaline phosphatase (41%) as well as decreased serum levels of hemoglobin (52%), sodium (46%), and lymphocytes (41%).[7]

For patients with metastatic NSCLC, the most common adverse reactions (≥20%, all grades) were nausea (42%), fatigue (36%), musculoskeletal pain (29%), decreased appetite (28%), rash (27%), and diarrhea (22%).[7]

Tremelimumab-actl has no contraindications.[7]

Use in Specific Populations

Administering tremelimumab-actl to pregnant women poses a risk of fetal harm, as supported by animal studies and the established ability of human immunoglobulin G2 to traverse the placental barrier. The background risk of miscarriage in recognized pregnancies stands at 15% to 20% within the United States general population. Pregnant individuals should be advised of these potential risks. Moreover, those of reproductive potential should practice effective contraception throughout the treatment period and continue for 3 months after receiving the final dose.[7]

Data are not available on the presence of tremelimumab-actl in human milk, the effect on milk production, or the effect on a breast-fed child. Patients should not breastfeed during treatment and for 3 months after the final dose.[7]

Tremelimumab-actl is not approved for use in pediatric patients. Safety and efficacy have not been established in children.[7]

No overall differences in safety or effectiveness were reported between patients aged ≥65 years and adult patients <65 years.[7]

Warnings and Precautions

Immune-mediated adverse reactions, which may be severe or fatal, should be monitored for early detection and management by evaluating liver enzymes, creatinine, adrenocorticotropic hormone level, and thyroid function at baseline and before each dose. Depending on the severity of adverse reactions, tremelimumab-actl may be withheld or permanently discontinued.[7]

It is also necessary to monitor for possible infusion-related reactions. Infusion interruption, rate decrease, or permanent discontinuation may be necessary depending on the severity of the reaction.[7]

Because tremelimumab-actl may cause fetal harm, advise patients who are of reproductive potential of the possible fetal risk and to use effective contraception.[7]

Conclusion

Patients diagnosed with advanced HCC or metastatic NSCLC often face a challenging prognosis, but advances in dual immunotherapy offer patients significant benefits by complementing antitumor immune responses. The HIMALAYA study demonstrated that a priming dose of tremelimumab-actl serves as a catalyst for initiating HCC treatment with substantial impact. In addition, the findings from the POSEIDON clinical trial underscore the potency of the tremelimumab-actl and durvalumab combination, coupled with chemotherapy in a cyclic regimen, yielding enhanced PFS and OS rates among patients with metastatic NSCLC. Combining distinct checkpoint inhibitors—an anti–PD-L1 and an anti–CTLA-4—helps activate T-cell responsiveness to increase OS.

References

1. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology*. 2021;73(suppl 1):4-13.
2. Shiels MS, O'Brien TR. Recent decline in hepatocellular carcinoma rates in

the United States. *Gastroenterology*. 2020;158(5):1503-1505.e2.
3. American Society of Clinical Oncology. Lung cancer - non-small cell: statistics. Cancer.Net. Published March 2023. https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics. Accessed August 17, 2023.
4. Arbour KC, Riely GJ. Systemic therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA*. 2019;322(8):764-774.
5. Sangro B, Yau T, El-Khoueiry AB, et al. Exposure-response analysis for nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma (CheckMate 040). *Clin Transl Sci*. 2023;16(8):1445-1457.
6. Alifu M, Tao M, Chen X, Chen J, Tang K, Tang Y. Checkpoint inhibitors as dual immunotherapy in advanced non-small cell lung cancer: a meta-analysis. *Front Oncol*. 2023;13:1146905.
7. IMJUDO (Tremelimumab-Actl) Injection, for Intravenous Use [Prescribing Information]. AstraZeneca Pharmaceuticals LP; November 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761270s000lbl.pdf. Accessed August 16, 2023.
8. US Food & Drug Administration. FDA approves tremelimumab in combination with durvalumab for unresectable hepatocellular carcinoma. Published October 24, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-unresectable-hepatocellular-carcinoma. Accessed August 16, 2023.
9. US Food & Drug Administration. Tremelimumab-actl. Search orphan drug designations and approvals. Published January 15, 2020. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=721419. Accessed August 16, 2023.
10. US Food & Drug Administration. FDA approves tremelimumab in combination with durvalumab and platinum-based chemotherapy for metastatic non-small cell lung cancer. Published November 18, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-and-platinum-based-chemotherapy-metastatic-non. Accessed August 16, 2023.
11. Kemp A. Imfinzi and Imjudo with chemotherapy approved in the US for patients with metastatic non-small cell lung cancer. AstraZeneca. Published November 11, 2022. https://www.astrazeneca.com/media-centre/press-releases/2022/imfinzi-and-imjudo-approved-in-us-for-lung-cancer.html. Accessed August 13, 2023.
12. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1(8):EVIDoa2100070.
13. Johnson ML, Cho BC, Luft A, et al. Durvalumab with or without tremelimumab in combination with chemotherapy as first-line therapy for metastatic non–small-cell lung cancer: the phase III POSEIDON study. *J Clin Oncol*. 2023;41(6):1213-1227.