Tremelimumab-actl (IMJUDO) in Hepatocellular Carcinoma
National Drug Mini-Monograph
March 2024

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Tremelimumab-actl (treme) is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)
Indication Under Review[1]	In combination with durvalumab for the treatment of unresectable hepatocellular carcinoma (uHCC)
Dosage Regimen	≥ 30kg: Cycle 1, day 1: treme 300 mg x 1 with durvalumab 1500 mg, then durvalumab as single agent every 4 weeks < 30kg: Cycle 1, day 1: treme 4mg/kg x 1 with durvalumab 20mg/kg, then durvalumab as single agent every 4 weeks
Dosage Forms Under Review	Injection 20mg/ml solution in SDV as 25mg/1.25ml and 300mg/15ml

EFFICACY CONSIDERATIONS

Trial	**HIMALAYA**
Design	Randomized 1:1:1, OL, MC Arms: treme + durvalumab (STRIDE): durvalumab: sorafenib
Population	Confirmed uHCC, no prior systemic treatment STRIDE n = 393; durvalumab n = 389; sorafenib n = 389
Intervention	STRIDE / durvalumab / sorafenib 400mg PO BID until toxicity or PD
Results	**Primary endpoint: STRIDE vs. sorafenib, superiority** mOS 16.43 (95% CI, 14.16 to 19.58) vs. 13.77 months (95% CI, 12.25 to 16.13) [HR 0.78 (96.02% CI, 0.65-0.93; p=0.0035)]
	Secondary: Durvalumab vs. sorafenib, non-inferiority mOS 16.56 (14.06 – 19.12) vs. 13.77 months (95% CI, 12.25 to 16.13) [HR 0.86 (95.67% CI 0.73-1.03; noninferiority margin 1.08)] Durvalumab vs. sorafenib, superiority; p=0.0674; durvalumab did not demonstrate superiority
	PFS: STRIDE 3.78 months (95% CI, 3.68-5.32) vs. sorafenib 4.07 (95% CI 3.75-5.49); [HR 0.90 (95% CI 0.77-1.05)] Durvalumab 3.65 months (95% CI 3.19-3.75) vs. sorafenib 4.07 (95% CI 3.75-5.49); [HR 1.02 (95% CI 0.88-1.19)]
	ORR: STRIDE 20.1%; durvalumab 17%; sorafenib 5.1%
	TTP: STRIDE 5.4 months; durvalumab 3.8 months; sorafenib 5.6 months
	mTTD: STRIDE 7.5 months; durvalumab 7.4 months; sorafenib 5.7 months
Summary	• mOS STRIDE is superior to sorafenib • mOS durvalumab monotherapy is noninferior to sorafenib • It's unclear if STRIDE is better than durvalumab monotherapy, as this was not studied • Based on delayed separation of K-M curves and exploratory assessment of smoothed hazard ratios it is speculated that treme added to OS benefit of durvalumab
Additional Info	**CheckMate 459.** A randomized, multicenter, open-label, phase 3 trial **Patient population:** advanced HCC, Child-Pugh class A, ECOG PS 0-1 and no previous systemic therapy N = 743 patients [n=371 nivolumab, n=372 sorafenib] from 22 countries **Intervention:** nivolumab 240mg IV q 2 weeks vs. sorafenib 400mg PO BID until toxicity or PD **Primary endpoint**: mOS @ 22.8 months was 16.4 vs. 14.7 months (nivolumab vs. sorafenib) [HR 0.85 (0.72-1.02); p=0.075] which did not meet protocol-defined p-value boundary for significance, p= 0.0419 **Secondary:** ORR 15 (12-19) vs. 7% (5-10); mPFS 3.7 vs. 3.8 months [HR 0.93 (95% CI 0.79-1.10)] **AEs:** Grade 3 AEs: 18 vs. 47%: AST increase 6 vs. 4%; diarrhea 5 vs. < 1%; PPE <1% vs. 14%; HTN 0 vs. 7%
Key	mOS median overall survival; PFS progression-free survival; ORR Overall response rate; TTP time to progression; mTTD median time to deterioration or patient-reported quality of life

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None
Other Warnings	**Immune-mediated adverse reactions** can impact any organ or tissue (i.e. immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic reactions and immune-mediated pancreatitis) Monitor for early identification and management. Evaluate appropriate labs. Withhold or discontinue based on severity and type of reaction. **Infusion-related reactions**. Interrupt, reduce rate or permanently discontinue based upon the severity. **Embryo-fetal toxicity**. Can cause fetal harm.
Top 5 AEs (≥ 20 %)	Rash, diarrhea, fatigue, pruritus, musculoskeletal pain and abdominal pain
Drug Interactions	In combination with durvalumab (PD-L1 inhibitor), can increase immune-related AEs and infusion-related reactions; Corticosteroids at therapy initiation may lessen therapeutic effect of treme-durvalumab; although treatment of treme-durvalumab immune-mediated AEs may require use of corticosteroids

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	SUMMARY ENDPOINTS/AE PROFILE & GUIDELINES
Tremelimumab + durvalumab[2]	TBD	TBD	Combination for uHCC	• **mOS 16.4 (14.2-19.6) months** • **mOS 16.6 (14.1-19.1) months – durvalumab** • **mOS 13.8 (12.3-16.1) months – sorafenib** • **AE: diarrhea 27/pruritis 23/rash 22/↓appetite 19%** • AASLD CPG 2023 on HCC, as 1L option in non-VEGF candidates (i.e. bevacizumab) • National VA Clinical Gastrointestinal Pathway 2023, as 1L option in HCC, in candidates for ICI, but not candidates for bevacizumab • NCCN v2.2023 Hepatocellular Carcinoma as a preferred 1L systemic therapy (category 1)
Atezolizumab + bevacizumab-bvzr[3]	PA-F PA-F	CFU H/O	Combination for uHCC or mHCC	• **mOS 19.2 (17.0-23.7) months** • **mOS 13.4 (11.4-16.9) months – sorafenib** • **AE: HTN 30/fatigue 20/ proteinuria 20/ AST ↑20/pruritis 20%** • AASLD CPG 2023 on HCC, as 1L option • National VA Clinical Gastrointestinal Pathway 2023, as 1L option in HCC, in candidates for ICI, and bevacizumab • NCCN v2.2023 Hepatocellular Carcinoma as a preferred 1L systemic therapy; Child-Pugh Class A only (cat 1)
Durvalumab monotherapy[2]	PA-F	CFU	Approved in combination with tremelimumab for uHCC	• **mOS 16.6 (14.1-19.1) months** • **AE: diarrhea 15/ pruritis 14/ constipation 11/ AST ↑14%** • AASLD CPG 2023 as 1L option if patient is not a candidate for combination therapy • NCCN v2.2023 Hepatocellular Carcinoma as Other Recommended Regimen as 1L systemic therapy (category 1)
Nivolumab Monotherapy[7]	PA-F	CFU	Approved in combination with ipilimumab; monotherapy indication removed	• **mOS @ 22.8 months was 16.4 vs. 14.7 months (nivolumab vs. sorafenib)** • [HR 0.85 (0.72-1.02); p=0.075] which did not meet protocol-defined p-value boundary for significance, p= 0.0419
Sorafenib[2, 3, 4]	PA-F	CFU	HCC	• **mOS 13.8 (12.3-16.1) months** • **AE: diarrhea 45/ PPE 49/ HTN 24/ fatigue 21/ ↓appetite 24%** • NCCN v2.2023 Hepatocellular Carcinoma as Other Recommended Regimen as 1L systemic therapy (category 1) • AASLD CPG 2023 as 1L option if patient is not a candidate for combination therapy
Lenvatinib[4]	PA-F	CFU	uHCC	• **mOS 13.6 (12.1-14.9) months** • **AE: HTN 42/ diarrhea 39/ ↓appetite 34/ fatigue 30/ PPE 27%** • NCCN v2.2023 Hepatocellular Carcinoma as Other Recommended Regimen as 1L systemic therapy (category 1) • AASLD CPG 2023 as 1L option if patient is not a candidate for combination therapy

VHA PLACE IN THERAPY		
	Potential Use in VHA	• Consistent with the VA Clinical Pathway for HCC, in the 1L setting, the combination of tremelimumab and durvalumab is an appropriate option in patients who are not candidates for the regimen of atezolizumab and bevacizumab. • Results from HIMALAYA indicate that durvalumab monotherapy was noninferior to sorafenib; durvalumab monotherapy was not formally compared to STRIDE, PFS and K-M curves may lead reviewers to question if activity may be sufficient to serve as a therapeutic option in those who are unable to tolerate the combination regimen. • Evidence for immune checkpoint inhibitor monotherapy (i.e. nivolumab) in advanced HCC has not been shown to improve OS compared to sorafenib, but may serve to benefit patients who would be unable to tolerate an ICI combination regimen

Prepared November 2023.
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References

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5 Singal AG, Llovet JM, Yarchoan M, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023; Dec 1;78(6):1922-1965. doi: 10.1097/HEP.0000000000000466.
6 NCCN Guidelines Version 2.2023. Hepatocellular Carcinoma https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf Accessed November 2023
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