89

THE IMMUNE MARKER LAG-3 INCREASES THE PREDICTIVE VALUE OF CD38$^+$ IMMUNE CELLS FOR SURVIVAL OUTCOME IN IMMUNOTHERAPY-TREATED HEPATOCELLULAR CARCINOMA

[1]Chun Chau Lawrence Cheung*, [2]Yong Hock Justin Seah, [2]Juntao Fang, [3]Nicole Orpilla, [4]Justina Nadia Li Wen Lee, [5]Han Chong Toh, [5]Su Pin Choo, [1]Kiat Hon Lim, [5]Wai Meng David Tai, [4]Joe Yeong. *[1]Singapore General Hospital, Singapore, Singapore; [2]National University of Singapore, Singapore, Singapore; [3]Temasek Polytechnic, Singapore, Singapore; [4]Institute of Molecular and Cell Biology, Singapore, Singapore; [5]National Cancer Centre Singapore, Singapore, Singapore*

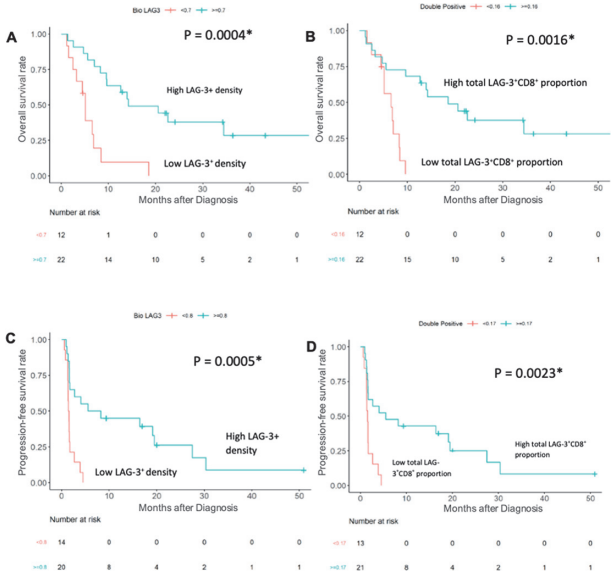
Background Immune check-point blockade (ICB) is one of the emerging therapeutic options for advanced hepatocellular carcinoma (HCC). However, low response rates amongst patients necessitates the development of robust predictive biomarkers that identify patients who likely benefit from ICB. Previously our group found that immunohistochemical scoring of CD38 in the tumour microenvironment predicts responsiveness to anti-PD-1/anti-PD-L1 immunotherapy in HCC.[1] Recently BMS 4-gene inflammatory signature, comprising the 4 genes CD8, PD-L1, LAG-3 and STAT1, has been shown to be associated with better overall response to immunotherapy in various cancer types.[2–4] In the present study, we examined the relationship between tissue expression of BMS 4-gene inflammatory signature and the responsiveness of HCC to immunotherapy, and whether BMS 4-gene inflammatory signature increases the predictive power of CD38.

Methods HCC tissue samples from 124 Asian patients that underwent conventional treatment and from 49 Asian patients that underwent ICB were analysed for CD8, PD-L1, LAG-3, STAT1, CD38 and CD68 tissue expression using immunohistochemistry and multiplex immunohistochemistry, followed by survival and statistical analysis.

Results Survival analysis of the 124 samples showed that high LAG-3 tissue expression was associated with shorter progression-free survival (PFS). On the other hand, immunohistochemical analyses on the 49 patient samples treated with ICB revealed that high LAG-3 density and high total LAG-3$^+$CD8$^+$ T cell proportion were associated with improved response to ICB (figure 1). However, CD8, PD-L1 and STAT1 levels did not significantly correlate with improved survival. The addition of total LAG-3$^+$ cell proportion to total CD38$^+$ cell proportion significantly increased the predictive value for both PFS (DeltaLRChi^2=9.97; P=0.0016; table 1) and overall survival (OS) (DeltaLRChi^2=8.84; P=0.0021; table 1), compared with total CD38$^+$ cell proportion alone. Similarly findings were obtained after adding total LAG-3$^+$CD8$^+$ cell proportion to total CD38$^+$ cell proportion (PFS: DeltaLRChi^2=7.21; P=0.0072; OS: DeltaLRChi^2=8.06; P=0.0045; table 1), compared with total CD38+ cell proportion alone. Lastly, when the total LAG-3$^+$CD8$^+$ cell proportion was added to total CD38$^+$ and CD38$^+$CD68$^+$ cell proportion, the predictive value of the biomarker was significantly increased (PFS: DeltaLRChi^2=6.10; P=0.0136; OS: DeltaLRChi^2=6.18; P=0.0129; table 1). Ongoing works include further validation of the findings in various cohorts, and correlating with clinical outcome of the patients.

Abstract 89 Table 1 Log-likelihood of models with added predictive terms

Variables	Progression-free Survival		Overall Survival	
	ΔLRχ2	P-value	ΔLRχ2	P-value
CD38$^+$ + CD38$^+$ CD68$^+$ proportion vs CD38$^+$ proportion	3.78	0.0519	4.55	0.0329
CD38$^+$ + PD-L1 proportion vs CD38$^+$ proportion	0.77	0.3813	0.15	0.7010
CD38$^+$ + CD8$^+$ proportion vs CD38$^+$ proportion	1.30	0.2541	2.89	0.0890
CD38$^+$ + STAT-1 proportion vs CD38$^+$ proportion	2.58	0.1083	2.48	0.1153
CD38$^+$ + LAG-3 proportion vs CD38$^+$ proportion	9.97	0.0016	8.84	0.0029
CD38$^+$ + LAG-3$^+$CD8$^+$ proportion vs CD38$^+$ proportion	7.21	0.0072	8.06	0.0045
CD38$^+$ cells + CD38$^+$CD68$^+$ + LAG-3$^+$CD8$^+$ proportion vs CD38$^+$ + CD38$^+$CD68$^+$ proportion	6.10	0.0136	6.18	0.0129



Abstract 89 Figure 1 HCC patients' response to ICB in relation to LAG-3 density. (A) Kaplan-Meier curve showing the association between a high LAG-3 density and improved overall survival after treatment with ICB. (B) Kaplan-Meier curve showing the association between a high total LAG-3$^+$CD8$^+$ T cell proportion and improved overall survival after treatment with ICB. (C) Kaplan-Meier curve showing the association between a high LAG-3 density and improved progression-free survival after treatment with ICB. (D) Kaplan-Meier curve showing the association between a high total LAG-3$^+$CD8$^+$ T cell proportion and improved progression-free survival after treatment with ICB.

Conclusions High LAG-3 expression on tissue-infiltrating immune cells predicted greater response to ICB. LAG-3$^+$ and LAG3$^+$CD8$^+$ cell proportion added predictive value to CD38$^+$ cells for predicting survival outcome in immunotherapy-treated HCC. LAG-3 may be used in conjunction with CD38 to predict responsiveness to ICB in HCC.

J Immunother Cancer: first published as 10.1136/jitc-2021-SITC2021.089 on 10 November 2021. Downloaded from http://jitc.bmj.com/ on April 28, 2024 by guest. Protected by copyright.

REFERENCES

1. Ng HHM, Lee RY, Goh S, et al. Immunohistochemical scoring of CD38 in the tumor microenvironment predicts responsiveness to anti-PD-1/PD-L1 immunotherapy in hepatocellular carcinoma. *J Immunother Cancer* 2020;**8**.
2. Hodi FS, Wolchok JD, Schadendorf D, et al. Abstract CT037: Genomic analyses and immunotherapy in advanced melanoma. *AACR* 2019.
3. Lei M, Siemers NO, Pandya D, et al. Analyses of PD-L1 and Inflammatory Gene Expression Association with Efficacy of Nivolumab ± Ipilimumab in Gastric Cancer/Gastroesophageal Junction Cancer. *Clinical Cancer Research* 2021;**27**:3926–35.
4. Sangro B, Melero I, Wadhawan S, et al. Association of inflammatory biomarkers with clinical outcomes in nivolumab-treated patients with advanced hepatocellular carcinoma. *J Hepatol* 2020.

Ethics Approval This study was approved by the Centralised Institutional Review Board of SingHealth (CIRB ref: 2009/907/B).

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.089

J Immunother Cancer: first published as 10.1136/jitc-2021-SITC2021.089 on 10 November 2021. Downloaded from http://jitc.bmj.com/ on April 28, 2024 by guest. Protected by copyright.