546 THE FSTL1-DIP2A AXIS AS A PROMISING TARGET IN THE ANTI-PD1 THERAPY OF ADVANCED GASTRIC CANCER

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Background We previously demonstrated that FSTL1 is a key driver of cancer stemness and metastasis accompanied by immune exhaustion and dysfunction leading to anti-PD1 resistance in a variety of cancers, including gastrointestinal cancer. However, the clinical relevancy of targeting FSTL1 and its receptor DIP2A remains to be determined in the clinical settings.

Methods We collected peripheral blood from 91 patients with advanced gastric cancer (AGC) before and after nivolumab monotherapy in the WJOG10417GTR study according to the protocol (No. 2017–473) approved by the IRB, and analyzed sera for FSTL1 by ELISA, and peripheral blood cells for $DIP2A^+$ cells by flow cytometry. Progression-free survival (PFS) and overall survival (OS) were compared between high/low groups divided by the cutoff value determined by visually assessing the continuous trend and change point of log hazard ratios obtained by applying penalized splines to each molecular marker. This study was supported by ONO PHARMACEUTICAL CO. and Bristol Myers Squibb.

Results The baseline FSTL1-high group showed significantly shorter PFS/OS as compared to the lower group (median PFS [mPFS] 52 vs 61 days, HR = 1.85, P = 0.015; median OS [mOS] 153 vs 274 days, HR = 2.32, P = 0.002), while the post-treatment level showed no significant differences. The higher level of $DIP2A^+$ peripheral blood cells before treatment was also associated with worse prognosis as compared to the lower level: a $CD11b^+DIP2A^+$ myeloid subset, mPFS 25.5 vs 57 days (HR = 2.40, P = 0.007) and mOS 64 vs 206 days (HR = 2.21, P = 0.024); a $CD3^+DIP2A^+$ T-cell subset, mPFS 51 vs 69 days (HR = 2.04, P = 0.005) and mOS 175 vs 219 days (HR = 1.32, P = 0.294); and a $CD56^+DIP2A^+$ NK subset, mPFS 48 vs 72 days (HR = 1.87, P = 0.024) and mOS 166 vs 302 days (HR = 1.77, P = 0.080). The post-treatment high levels of these subsets, particularly of the $DIP2A^+$ T-cell subset, showed clearer association with worse prognosis than pretreatment levels: mPFS 57 vs 130 days (HR = 2.87, P = 0.001) and mOS 228 vs 716 days (HR = 2.15, P = 0.033).

Conclusions The high levels of FSTL1 and $DIP2A^+$ cells in peripheral blood, particularly after the treatment, are critical risk factors for poor prognosis in the nivolumab therapy for AGC. Targeting the FSTL1-DIP2A axis may be a promising strategy to improve the clinical outcome in the treatment of AGC.

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