S-531011, A NOVEL ANTI-HUMAN CCR8 ANTIBODY: ANTI-TUMOR RESPONSES THROUGH DEPLETION OF TUMOR-INFILTRATING CCR8-POSITIVE TREGS

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Background Regulatory T cells (Tregs) are suppressive immune cells required for the maintenance of immune homeostasis, but tumor-infiltrating Tregs are known to suppress the antitumor immune system and promote tumor progression. Therefore, selective reduction of tumor-infiltrating Tregs is anticipated to reinvigorate antitumor immunity without inducing autoimmunity. S-531011 is a novel anti-human IgG1 antibody targeting human CCR8 (C-C motif chemokine receptor 8) which is selectively expressed in tumor-infiltrating Tregs, with both in vitro antibody dependent cellular cytotoxicity (ADCC) against CCR8-expressing cells and neutralizing activity against CCL1-CCR8 signaling. Here, to evaluate antitumor activities and safety aspects of S-531011, we conducted non-clinical pharmacology studies of S-531011 using human CCR8 knock-in (KI) mice and human tissues.

Methods S-531011 was administrated to CT26WT tumor-bearing hCCR8-KI mice, and the effect on the presence of tumor-infiltrating CCR8+ Treg and tumor growth were evaluated. We also investigated the antitumor efficacy of S-531011 in combination with anti-mouse PD-1 antibody. Next, human lung cancer tissues and human NK-cells were co-cultured, and the ex vivo ADCC against tumor-infiltrating Tregs by S-531011 was verified. We also incubated human peripheral blood-derived mononuclear cells (PBMC) from healthy individuals with S-531011 to investigate the effects on the proportion of Tregs in human PBMC.

Results Intravenous administration of S-531011 to CT26WT tumor-bearing hCCR8-KI mice significantly reduced tumor-infiltrating CCR8+ Tregs and markedly suppressed tumor growth. Furthermore, the combined therapy of S-531011 with anti-mouse PD-1 antibody showed greater anti-tumor effect than monotherapy without any apparent side effects. Ex vivo ADCC studies using human lung cancer tissues and FCM analysis of CCR8 expression in tumor-infiltrating Tregs suggested that most of the tumor-infiltrating CCR8+ Tregs were depleted by S-531011. On the other hand, S-531011 didn’t reduce Tregs in human PBMC.

Conclusions S-531011 is a promising drug which has a strong antitumor effect by depleting tumor-infiltrating CCR8+ Tregs, as a not only monotherapy but also combination therapy with other immune checkpoint inhibitors.

Ethics Approval The present study was approved by the Institutional Ethics Committee of Osaka University Hospital (approved number: 13266-15) and Shionogi Co., Ltd. (approved number: 021-003). Animal studies were approved by the Institutional Animal Care and Use Committee (approved number: S20093D, S20197D and S20198D).

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