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THE BYSTANDER EFFECT OF TREG DEPLETION

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Limiting bystander effects of immunosuppressive Treg-targeting therapies may be crucial for their antitumor efficacy, according to data released last week at the Society for Immunotherapy of Cancer meeting.

Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151) presented Phase I and Phase I/II data on Nov. 9 showing that while Poteligeo mogamulizumab, an anti-CC chemokine receptor 4 (CCR4; CD194) mAb, depleted Tregs in the periphery and tumor stroma, the depletion did not correlate with efficacy.

In an abstract published ahead of its oral presentation of Phase I data, Kyowa said "other important effector cell types were also depleted," and that there was no efficacy beyond what was expected from its combination partners, anti-PD-L1 mAb Imfinzi durvalumab or anti-CTLA-4 mAb tremelimumab.

FLX Bio Inc. CEO Brian Wong doesn't think Kyowa's data should discourage Treg-targeted approaches, but rather sees modality as the issue. FLX presented Phase I data at SITC for FLX475, its small molecule CCR4 antagonist.

While both companies target CCR4, which is mostly restricted to Tregs, Kyowa's antibody depletes Tregs while FLX's small molecule selectively prevents the infiltration of Tregs into the tumor by blocking the chemokine receptor's interaction with its ligands chemokine CC motif ligand 22 (CCL22; MDC) and CCL17 (see **"Flexing Against Suppression"**).

Wong thinks a key factor driving the lack of Poteligeo efficacy was its bystander effect on effector cells, some of which can express CCR4.

"Mogamulizumab can have collateral damage to beneficial cells."

Brian Wong, FLX

"Mogamulizumab can have collateral damage to beneficial cells. We think that significantly limits mogamulizumab's ability to power up an antitumor immune response," Wong said.

FLX did not see reductions in effector T cell, B cell or NK cell populations in its Phase I data in healthy volunteers for FLX475, Wong said.

Because FLX475 is designed to prevent Treg tumor infiltration, rather than deplete Tregs, it prevents off-target depletion of CCR4-expressing cells, according to Wong. He added, "These effector cells can find a way into the tumor that does not involve CCR4," so blocking CCR4 does not prevent effector cell infiltration.

In its Phase I/II trial, FLX is testing FLX475 as a monotherapy and in combination with anti-PD-1 mAb Keytruda pembrolizumab. Initial data are due in 2H19.

FLX CMO William Ho said once it shows proof of concept for FLX475 in this trial, it plans to test the therapy in combination with immunotherapy accelerators such as immune agonist antibodies, cancer vaccines or CAR T therapies. The idea is that instead of releasing one or two immunosuppressive brakes with FLX475 monotherapy and a checkpoint inhibitor, a FLX475 combination could both release a brake and step on the gas.

Kyowa was not able to comment in time for publication.