1393 DISCOVERY OF PLX-4107, A SELECTIVE IKZF2 MOLECULAR GLUE DEGRADER, THAT MODULATES SUPPRESSIVE REGULATORY T CELLS AND DEMONSTRATES ANTI-TUMOR ACTIVITY

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Background Immune checkpoint inhibitors (CPI) have significantly advanced cancer treatment; nevertheless, responses are limited to patient subsets, thereby necessitating additional treatment strategies. Regulatory T-cells (Tregs) are a specialized population of CD4+ T-cells that maintain normal immune tolerance and homeostasis; however, in the tumor microenvironment (TME), Tregs are potent immunosuppressive cells that promote tumor immune evasion and reduced clinical response to CPI. The transcription factor IKZF2 is a marker of highly suppressive Tregs and is required to maintain a stable, suppressive Treg cell phenotype in the inflammatory TME. Depletion of IKZF2 reprograms suppressive Tregs into effector-like T-cells leading to anti-tumor immunity, but targeting transcription factors has been challenging due to the lack of defined structures and binding pockets. Protein degradation using the endogenous Ubiquitin Proteasome System (UPS) has enabled accessing undruggable proteins, such as IKZF2, through chemically induced proximity that promotes degradation.

Methods Through computational modeling, compound screening and optimizing for enhanced reprogramming of Treg function, highly selective IKZF2 degraders were identified.

Results PLX-4107 is a molecular glue that was designed to promote a novel interaction between IKZF2 and the E3 ubiquitin ligase substrate receptor, Cereblon, leading to potent and selective degradation of IKZF2. Degradation of IKZF2 by PLX-4107 is blocked by co-treating with proteasome and neddylation inhibitors or a Cereblon knock-out cell line, confirming that degradation is UPS mediated and dependent on Cereblon. Global cellular proteomics demonstrated that PLX-4107 selectively depleted IKZF2 protein levels without degrading other Cereblon neo-substrates. *In vitro*, PLX-4107 mediated degradation of IKZF2 caused human Tregs to lose their suppressive function and produce effector cytokines (IL2, IFNγ) resulting in increased proliferation of effector T-cells and tumor cell killing. Oral administration of PLX-4107 to primates or humanized mice demonstrated sustained depletion of IKZF2 and reprogramming of Tregs. *In vivo* xenograft efficacy studies showed that administration of PLX-4107 resulted in dose dependent single agent anti-tumor activity. PLX-4107 treatment resulted in destabilization of Tregs by decreasing CD25 expression and increasing Treg expression of effector-like cytokines leading to increased infiltration of activated CD4/8+ effector T-cells into tumor tissue. Co-administration of PLX-4107 and pembrolizumab in xenograft studies resulted in tumor growth inhibition and significant combination benefit.

Conclusions PLX-4107 is a novel molecular glue that selectively degrades IKZF2, a transcription factor of suppressive Tregs. PLX-4107 mediated IKZF2 degradation reverses tumor immune evasion by converting Tregs to an effector-like T-cell phenotype, resulting in single agent antitumor activity and the ability to enhance CPI efficacy.

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