BAY 2965501: A HIGHLY SELECTIVE DGK ZETA INHIBITOR FOR CANCER IMMUNOTHERAPY

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Background The second messenger diacylglycerol plays a key role in T-cell receptor (TCR) downstream signaling and T-cell activation. Diacylglycerol kinase zeta (DGKζ) is a lipid kinase that regulates T-cell activation by phosphorylating diacylglycerol to produce phosphatidic acid, thereby acting as a ligand-independent, intracellular immune checkpoint. The inhibition of DGKζ offers the potential to enhance T-cell priming against suboptimal tumor antigens and to overcome multiple immunosuppressive mechanisms in the tumor microenvironment in a TCR engagement-dependent manner. We evaluated the specificity, efficacy, and safety of the DGKζ inhibitor BAY 2965501 in various preclinical in vitro and in vivo studies.

Methods and Results BAY 2965501 is a highly selective, potent human/mouse cross-reactive DGKζ inhibitor. In vitro, BAY 2965501 increased natural killer cell- and T-cell-mediated tumor cell killing and enhanced interleukin 2-induced natural killer cell activation. Importantly, the inhibition of DGKζ by BAY 2965501 was able to overcome inhibitory signals conferred by transforming growth factor beta, prostaglandin E2, and adenosine signaling in T cells. However, BAY 2965501 showed no direct anti-proliferative effects on human tumor cell lines in vitro. Single-cell sequencing of human tumor-infiltrating lymphocytes isolated from primary human tumors revealed high expression of DGKζ specifically in exhausted CD8+ TCR clonotypes, suggesting a potential immunosuppressive role in this T-cell subpopulation. Furthermore, BAY 2965501 effectively enhanced the in vitro anti-tumor reactivity of human T cells expressing tumor-reactive TCRs. In vivo, BAY 2965501 reduced T-cell exhaustion markers, such as programmed cell death receptor 1 and T-cell immunoglobulin mucin 3, and enhanced antiviral T-cell responses in mice chronically infected with lymphocytic choriomeningitis virus. In MB49, F9, and Hepa129 syngeneic mouse tumor models, BAY 2965501 as monotherapy reduced tumor growth when compared with vehicle treatment. Combining BAY 2965501 with an anti-programmed cell death ligand-1 (anti-PDL-1) antibody reduced tumor growth vs anti-PDL-1 monotherapy. Preclinical toxicology studies showed only low-grade gastrointestinal effects, suggesting a tolerable clinical profile.

Conclusions In summary, BAY 2965501 is a highly potent and selective, orally available DGKζ inhibitor. A first-in-human clinical trial of BAY 2965501 in solid tumors is currently enrolling patients (NCT05614102). This study will evaluate the safety, tolerability, maximum tolerated or administered dose, pharmacokinetics, pharmacodynamics, and tumor response profile of BAY 2965501.

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Ethics Approval All animal experiments were conducted in accordance with the German Animal Welfare Law and approved by Berlin authorities (Landesamt für Arbeitsschutz, Gesundheitschutz und technische Sicherheit Berlin, LAGetSi; code number A0378/12).