ASP2616
Non-Confidential Summary

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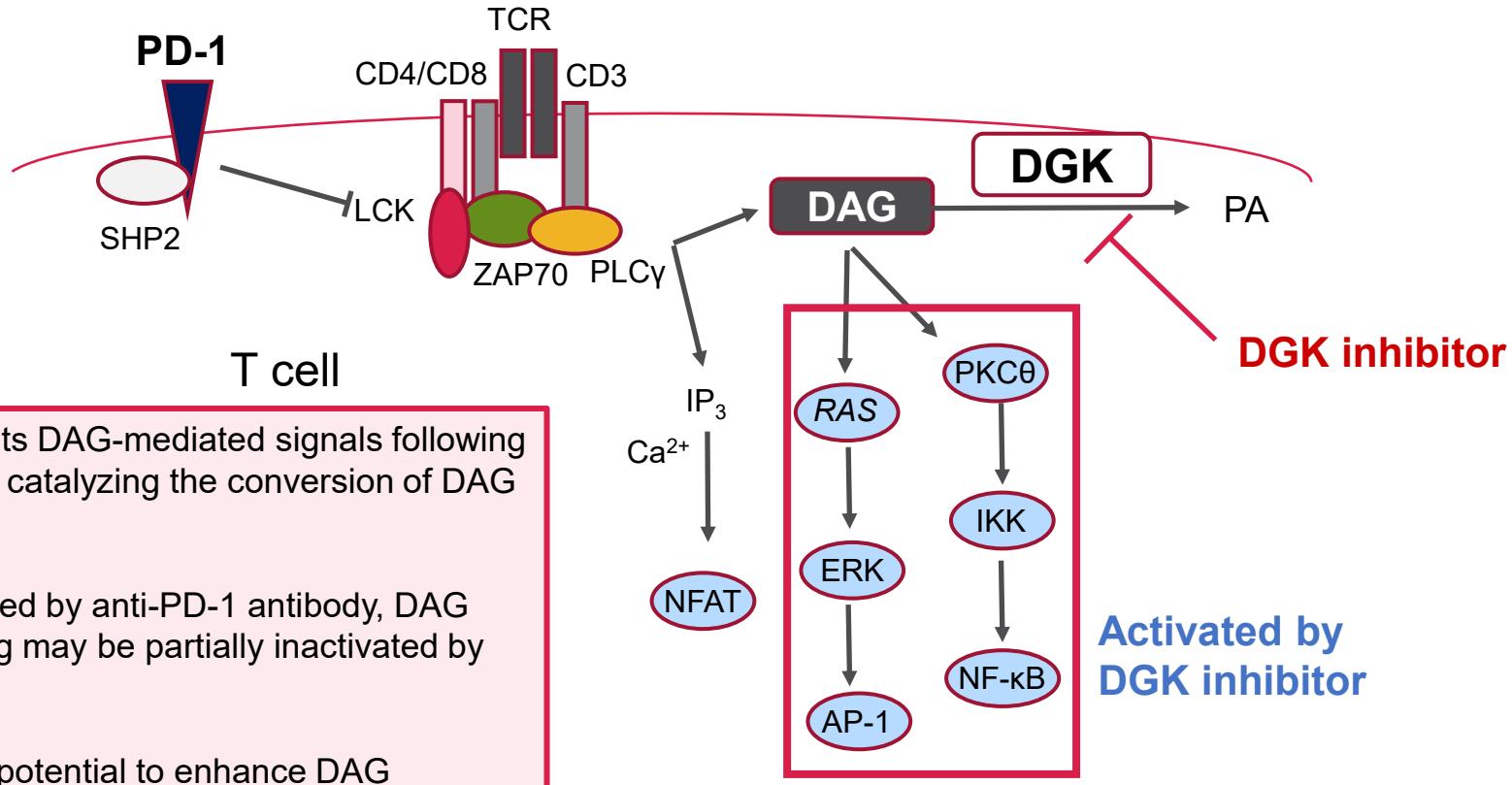
ASP2616 SUMMARY

Items	Note
Product name	ASP2616
Mechanism of Action	Inhibitor against diacylglycerol kinase (DGK)ζ. DGKζ is known to be a negative regulator of T cell receptor signaling
Formulation	Oral 10 mg and 50 mg tablets
Target Indication at Astellas	Advanced solid Tumors
Latest development phase	Pre-clinical

Mechanism of Action



- In T cells, DGK inhibits DAG-mediated signals following TCR engagement by catalyzing the conversion of DAG to PA
- Even if PD-1 is blocked by anti-PD-1 antibody, DAG downstream signaling may be partially inactivated by DGK
- DGK inhibitors have potential to enhance DAG downstream signaling, leading to T cell activation regardless of PD-1 signal

Figure adapted from: Krishna and Zhong, Crit Rev Immunol. 2013; 33(2): 97–118

AP-1, Activator protein-1; CD, cluster of differentiation; DAG, Diacylglycerol; DGK, diacylglycerol kinase; ERK, extracellular signal-related kinases; IC50, half maximal inhibitory concentration; IKK, IκB kinase; IP3, inositol trisphosphate; LCK, lymphocyte-specific protein tyrosine kinase; NFAT, nuclear factor of activated T cells; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; PA, Phosphatidic acid; PD-1, Programmed cell death protein 1; PKCθ, Protein Kinase C theta; PLCγ, Phosphatidylinositol-specific phospholipase Cγ; SHP2, cytoplasmic protein tyrosine phosphatase non-receptor type 11; TCR, T-cell receptor; ZAP70, Zeta-chain-associated protein kinase-70.

Preclinical Summary

Pharmacology

- ASP2616 potently inhibited DGKζ activity compared to other DGK subtypes.
- ASP2616 upregulated DAG downstream signals, enhanced TCR-stimulated T cell activation, and released T cells from the T cell exhaustion state
- ASP2616 significantly inhibited tumor growth in TIL-poor and inflamed syngeneic mouse tumor models

ADME

- Oral bioavailability was generally moderate to high, with some species-dependent variability. Systemic exposure increased with dose in rats and cynomolgus monkeys, and it was unchanged or increased after repeated dosing.
- ASP2616 showed high plasma protein binding across species, with no marked concentration dependency.
- The major metabolic pathways of ASP2616 involved oxidation and hydrolysis in human hepatocytes, with no human-specific metabolites identified. CYP2D6 and CYP3A4 were involved in the metabolism of ASP2616. CYP inhibition was generally limited, with time-dependent inhibition of CYP2D6 observed.

Toxicology

- ASP2616 showed no potential to induce gene mutation in bacteria. ASP2616 has no genotoxic potential in vivo
- In a preliminary study in rats, ASP2616 had no adverse effects on embryo-fetal development
- Toxicological targets or effects identified from the pivotal 4-week repeated oral dose toxicity studies in rats and cynomolgus monkeys recovered or tended to recover by the end of a 4-week recovery period.

Clinical Summary

- Initial IND submitted to FDA 31May 2022
- Study may proceed letter received 30June 2022
- Asset was deprioritized; site initiation visits and subject screening activities were not initiated
- IND inactivated 08May 2026

Intellectual Property

Patent covering ASP2616

- WO-2022114164 (filed on 29 November 2021)
- WO-2023248109 (filed on 19 June 2023)