9-ING-41, A SELECTIVE SMALL MOLECULE INHIBITOR OF GLYCOGEN SYNTHASE KINASE-3 BETA (GSK-3BETA), MAY ENHANCE NEUROBLASTOMA IMMUNOGENICITY

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Background Neuroblastoma (NBL) is an embryonic tumor originating from neural crest precursor cells. It is one of the most prevalent pediatric solid tumors, with an estimated five-year progression free survival of less than 50% in stage-4 patients. While T-cell mediated therapies, including immune checkpoint inhibition, have marked activity against many cancers in adults, NBL is relative refractory to these approaches. One reason for the limited success of the existing immune therapies is the extremely low peptide/MHC-I complex expression of NBL cells. There is an unmet need to improve immunogenicity of NBL, and thus to enhance the cytotoxic T lymphocyte (CTL)-mediated anti-tumor response. The serine/threonine kinase GSK-3beta is overexpressed by NBL and has been proposed as a therapeutic target. This kinase is broadly involved in energy metabolism pathways and thus may regulate peptide/MHC-I complex display at the tumor cell surface. 9-ING-41 has broad spectrum pre-clinical anti-cancer activity, including against NBL. It has established efficacy and a favourable safety profile in adult patients with refractory cancers – studies in children are underway. IFN-γ upregulates MHC-I expression by inducing the expression of multiple genes related to MHC-I antigen processing and presentation.

Methods We assessed the potential of 9-ING-41 to increase immunogenicity, using four distinct NBL cell lines which we cultured for 24 or 72 hours in the continuous presence of IFN-γ and/or 9-ING-41. We measured cell surface expression of MHC-I and PD-L1 using flow cytometry analyses.

Results In GIMEN, SH-SY5Y, SK-N-BE, and IMR32 NBL lines, we found that 9-ING-41 significantly increased IFN-γ-mediated MHC-I surface expression on all 4 cell lines, markedly so in the cell lines without MYCN amplification. PD-L1 expression was also upregulated in two of the cell lines, suggesting that 9-ING-41 combined with PD-1/PD-L1 immune checkpoint blockade is worthy of further investigation.

Conclusions These data indicate that 9-ING-41 may facilitate recognition and killing of NBL by CTL and support the further development of 9-ING-41 as a potential treatment for NBL.

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