KNOWLDOWN OF NEUROPILIN-1 BY THIRD GENERATION ANTISENSE Oligonucleotides Has STRONG ANTITUMOR ACTIVITY THAT CAN BE FURTHER INCREASED BY COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

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Background Immune checkpoint inhibitors (ICI) are considered as a breakthrough in cancer therapy, however only a subset of patients actually responds to current treatments, indicating a strong remaining medical need. Locked nucleic acid (LNA) modified antisense oligonucleotides (ASOs) allow for a specific target knockdown after systemic injection without delivery agents. The membrane bound multi domain protein neuropilin-1 (NRP1) is a promising therapeutic target, since it has been implicated in various pro-tumorigenic processes, including stability of regulatory T-cells, exhaustion of CD8+ T-cells, macrophage migration and polarization, and neovascularization. Since these effects are mediated by different domains, blocking antibodies that only bind to a single domain might only have limited effects. Thus, the knockdown of the complete protein is conceptually advantageous.

Methods Using our in-house Oligofyer™ bioinformatics system, we designed LNA-modified NRP1 specific ASOs and were able to identify potent candidates in cellular screens. The most promising candidates were tested by intraperitoneal injection in two syngeneic tumor models, either as a monotherapy, or in combination with an anti-PD-L1 antibody.

Results In syngeneic mouse models, systemically administered NRP1-specific ASOs achieved a potent target knockdown in several relevant cell types within the tumor microenvironment and a strong reduction in plasma levels of soluble NRP1. Furthermore we observed strongly reduced tumor growth-rates in animals treated with NRP1 ASOs as monotherapy. In combination with PD-L1 antibody we achieved a potent on-top effect with lasting complete tumor eradication in many animals and prolonged survival (figure 1). Re-challenge experiments with mice that were tumor-free after the treatment indicated establishment of anti-tumor immunity in treated mice.

Conclusions NRP1 is a promising new target with multiple pro-tumorigenic roles mediated by different domains. Simultaneous inhibition of all of these functions via knockdown of its expression by ASOs appears to be a favorable treatment modality in this regard, which could overcome limitations faced by alternative approaches. Systemically administered LNA-modified ASOs targeting NRP1 have the potential to become a new treatment option - both as a monotherapy and in combination with other ICIs - in various cancer indications that do not respond to current treatments. Further mechanistic research will be instrumental to translate these findings to the clinics.