KNOCKDOWN 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 neuropi-
lin-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 neovasculariza-
tion. 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 com-
plete 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 injec-
tion 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. Fur-
thermore we observed strongly reduced tumor growth-rates in
animals treated with NRP1 ASOs as monotherapy. In combi-
nation with PD-L1 antibody we achieved a potent on-top
effect with lasting complete tumor eradication in many ani-
mals and prolonged survival (figure 1). Re-challenge experi-
ments 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. Simulta-
neous 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.