Neurulin 1 (NRG1) gene fusions

NRG1 gene fusions, which encode NRG1 fusion proteins, are oncogenic drivers found in <1% of solid tumors. NRG1 fusions occur across various tumor types and are enriched in KRAS wild-type pancreatic ductal adenocarcinomas (PDAC) and invasive mucinous lung adenocarcinomas.1,2

Functional NRG1 fusion ligands contain the EGF-like domain of NRG1, which binds to HER3 from binding to HER3, inhibiting downstream signaling, even in the emerging as clinically actionable targets.3,4

Clinical proof-of-concept for MCLA-128, a bispecific HER2/3 antibody therapy, in NRG1 fusion-positive cancers

Patients harboring NRG1 gene fusions were identified using prospective molecular profiling by DNA/RNA-based next-generation sequencing (NGS) with MSK-IMPACT6 and/or MSK-Fusion.7 NGS identified 29 patients with NRG1 fusions across 8 tumor types (pancreas, lung, breast, sarcoma, prostate, gallbladder, unknown primary, and DLBC). Three NRG1 fusion-positive patients with chemotherapy-resistant metastatic cancer were treated with MCLA-128 on FDA-approved single-patient protocols.

We provide a clinical proof-of-concept of MCLA-128 in NRG1 fusion-positive pancreatic and lung cancers with demonstrated sustained improvement in all clinical parameters (radiologic, biomarker, and symptomatic).

MCLA-128 has a very well tolerated safety profile.

Three NRG1 fusion-positive cohorts (pancreas, lung, and other tumors) have been opened in the ongoing phase 2 basket trial with MCLA-128.

**BACKGROUND**

MCLA-128, a bispecific HER2/HER3 antibody

MCLA-128 is a humanized, single-domain antibody with enhanced antibody-dependent cell-mediated cytotoxicity activity. This bispecific antibody docks on HER2 and blocks NRG1 from binding to HER3, inhibiting downstream signaling, even in the presence of very high ligand expression (Fig. 1B).3

MCLA-128 thus carries a novel therapeutic paradigm for NRG1 fusion-positive cancers.

**TUMOR INHIBITION IN NRG1 FUSION MODELS**

A) MCLA-128 was tested in OV-10-0050, an ovarian cancer model with a CCD0-NRG1 gene fusion expressing high levels of NRG1 (HER2). MCLA-128 treatment led to tumor regression in vivo2.

B) MCLA-128 also reduced tumor growth in the OV138 ovarian cancer PDX model (75% reduction of tumor growth vs. control)2.

C) MCLA-128 inhibited growth in a human PDAC cell line (SW1990-NRG1 gene fusion), in vitro and in vivo.2

**REFERENCES**


**WELL TOLERATED SAFETY PROFILE**

AEs with single-agent MCLA-128 (N=117)

- Dose-limiting toxicity (DLT): No DLTs were evaluated in the ongoing phase 2 expansion (750 mg q3w; 800-400 mg weekly).
- The majority of suspected related AEs were grade 1-2, with <5% of patients having grade 3 events and no grade 5 related events.
- No severe related skin or GI toxicity was reported, and there was an absence of clinically significant UVE decreases and cardiac AEs.

**CONCLUSIONS**

- MCLA-128 potently inhibits NRG1-driven tumor growth in vitro and in vivo, including at high NRG2 levels present in NRG1 fusion-positive cancers.
- We provide a clinical proof-of-concept of MCLA-128 in NRG1 fusion-positive pancreatic and lung cancers with demonstrated sustained improvement in all clinical parameters (radiologic, biomarker, and symptomatic).
- MCLA-128 has a very well tolerated safety profile.
- Three NRG1 fusion-positive cohorts (pancreas, lung, and other tumors) have been opened in the ongoing phase 2 basket trial with MCLA-128.