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

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BACKGROUND

Neuregulin 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]

Functional NRG1 fusion ligands contain the EGF-like domain of NRG1, which binds to extracellular HER3, leading to HER2/HER3 heterodimerization. This results in increased downstream PI3K-AKT signalling and tumour growth (**Fig. 1A**).[2]

NRG1 fusions are sensitive to HER2/HER3 directed therapy *in vitro* and *in vivo*, thus emerging as clinically actionable targets.[3,4]

MCLA-128, a bispecific HER2/HER3 antibody

MCLA-128 is a humanized, full-length IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxic 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**).[5]

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

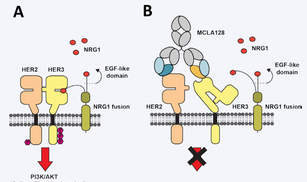
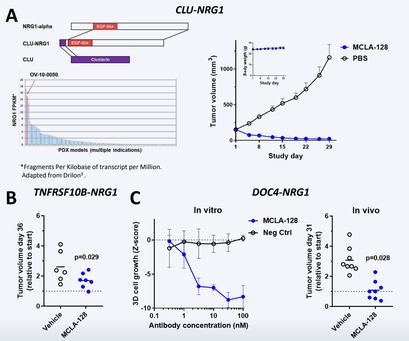


Fig. 1 DOCK & BLOCK® action of MCLA-128

A) NRG1-fusion proteins function as ligands for HER3 (similar to NRG1) and bind to HER3 with high affinity to promote HER2/HER3 dimerization and downstream signalling.
B) MCLA-128 inhibits the NRG1/HER3 interaction via its DOCK & BLOCK® mechanism, whereby one arm of the antibody binds to the HER2 receptor, optimally positioning the anti-HER3 arm to block the ligand/receptor interaction and prevent HER2/HER3 dimerization.

TUMOR INHIBITION IN *NRG1* FUSION MODELS



A) MCLA-128 was tested in OV-10-0050, an ovarian cancer model with a *CLU-NRG1* gene fusion expressing high levels of *NRG1* mRNA[3]. MCLA-128 treatment led to tumor regression *in vivo*[5].

B) MCLA-128 also reduced tumor growth in the OV5383 ovarian cancer PDX model (*TNFRSF10B-NRG1* gene fusion).

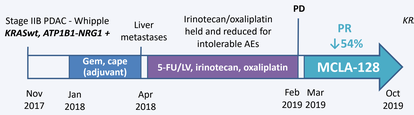
C) MCLA-128 inhibited growth of the MDA-MB-175 breast cancer cell line (*DOC4-NRG1* gene fusion), *in vitro* and *in vivo*[5].

CLINICAL PROOF-OF-CONCEPT IN NRG1-FUSION POSITIVE TUMORS

Patients harboring *NRG1* gene fusions were identified using prospective molecular profiling by DNA/RNA-based next-generation sequencing (NGS) with MSK-IMPACT[6] 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 DLBCL).

Three NRG1 fusion-positive patients with chemotherapy-resistant metastatic cancer were treated with MCLA-128 on FDA-approved single-patient protocols.

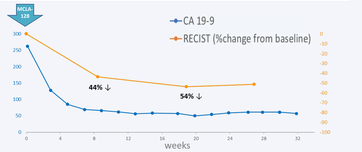
PDAC (ATP1B1-NRG1): 52-year-old male

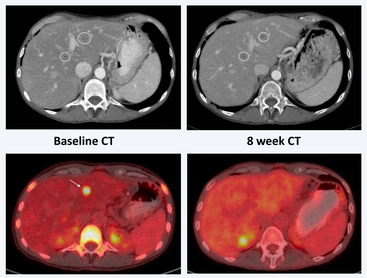


7+ months MCLA-128, 750 mg IV, q2w
Maximal related toxicity ≤ grade 2

EFFICACY OUTCOME WITH MCLA-128

CA19-9 : ↓ from 262 to 50 U/mL (81% max reduction)
RECIST (CT): 8 weeks: 44% ↓
5 months: 54% ↓ (PR)
PERCIST (PET): Complete metabolic response at 8 weeks
Clinical: Symptomatic improvement anorexia, fatigue



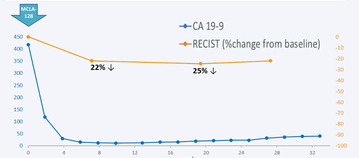


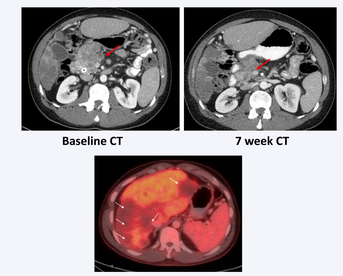
PDAC (ATP1B1-NRG1): 34-year-old male

7+ months MCLA-128, 750 mg IV, q2w
Maximal related toxicity ≤ grade 1

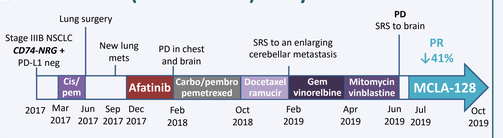
EFFICACY OUTCOME WITH MCLA-128

CA19-9 : ↓ from 418 to 11 U/mL (97% max reduction)
Normalization <4 weeks
RECIST (CT) : 7 weeks: 22% ↓, incl. massive liver involvement
5 months: 25% ↓ (SD)
PET: Non-avid FDG liver metastases at 10 weeks
Endoscopy: Tumor shrinkage
Clinical: Symptomatic improvement of pain resolution





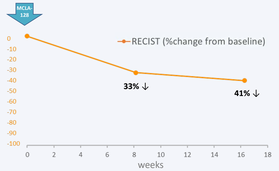
NSCLC (CD74-NRG1): 54-year-old male

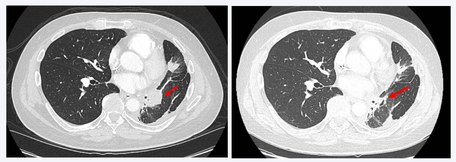


4.5+ months MCLA-128, 750 mg IV, q2w
Maximal related toxicity ≤ grade 1

EFFICACY OUTCOME WITH MCLA-128

RECIST (CT): 8 weeks: 33% ↓
16 weeks: 41% ↓ (PR)





WELL TOLERATED SAFETY PROFILE

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

	AEs irrespective (>7.5% patients)		AEs related (>2% + >G3)	
	All grades	G3*	All grades	G3*
≥1 adverse event	109 (93%)	43 (37%)	67 (57%)	5 (4.3%)
Diarrhea	35 (30%)	1 (0.9%)	22 (19%)	0
Asthenia	27 (23%)	3 (2.6%)	10 (8.5%)	1 (0.9%)
Anemia	22 (19%)	4 (3.4%)	1 (0.9%)	0
Nausea	20 (17%)	0	10 (8.5%)	0
Fatigue	18 (15%)	2 (1.7%)	8 (6.8%)	0
Vomiting	17 (15%)	0	3 (2.6%)	0
Decreased appetite	15 (13%)	1 (0.9%)	6 (5.1%)	0
Dyspnea	15 (13%)	7 (6.0%)	2 (1.7%)	1 (0.9%)
Hypomagnesaemia	14 (12%)	1 (0.9%)	0	0
Constipation	12 (10%)	0	1 (0.9%)	0
Cough	12 (10%)	1 (0.9%)	2 (1.7%)	1 (0.9%)
Abdominal pain	11 (9.4%)	0	2 (1.7%)	0
ALT increased	10 (8.5%)	4 (3.4%)	0	0
AST increased	10 (8.5%)	4 (3.4%)	0	0
Abdominal pain upper	9 (7.7%)	0	0	0
IRR	9 (7.7%)	2 (1.7%)	9 (7.7%)	2 (1.7%)
Pyrexia	6 (5.1%)	0	3 (2.6%)	0
Myalgia	5 (4.3%)	1 (0.9%)	3 (2.6%)	1 (0.9%)
Mucosal inflammation	5 (4.3%)	0	4 (3.4%)	0
Chills	4 (3.4%)	0	4 (3.4%)	0
Hypersensitivity**	4 (3.4%)	0	4 (3.4%)	0
Stomatitis	3 (2.6%)	0	3 (2.6%)	0

Data cut off: 12-Jan-2019.
* 3 patients (2.6%) each had 1 grade 4 unrelated AE; no patients had grade 4 related AEs.
** A 71-year-old patient had a grade 5 hypersensitivity reaction followed by cardiorespiratory arrest (previously reported [8]). The patient's baseline cardiac condition (severe aortic stenosis) contributed to the fatal outcome.

Of 145 solid tumor patients treated with single agent MCLA-128 in the phase 1/2 trial, 117 received the RP2Ds 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 4 related events.

No severe related skin or GI toxicity was reported, and there was an absence of clinically significant LVEF decreases and cardiac AEs.

KEY FINDINGS & FUTURE DIRECTIONS

- ✓ MCLA-128 potently inhibits NRG1-driven tumor growth *in vitro* and *in vivo*, including at high *NRG1* 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, & other tumors) have been opened in the ongoing phase 2 basket trial with MCLA-128.

Open-label worldwide phase 2 study with single-agent MCLA-128 in *NRG1* fusion-positive cancers

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