A phase 2 basket study of MCLA-128, a bispecific antibody targeting the HER3 pathway, in *NRG1* fusion-positive advanced solid tumors

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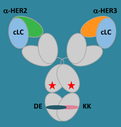


BACKGROUND & RATIONALE

Neuregulin 1 (NRG1)

NRG1 gene fusions, which encode chimeric NRG1 fusion proteins, are oncogenic drivers found in various cancers including pancreatic and lung adenocarcinomas.

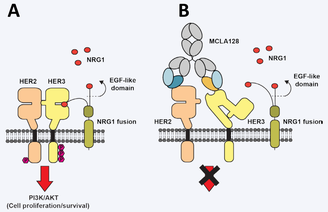
Functional NRG1 fusions result in expression of the EGF-like domain of NRG1, which binds to extracellular HER3, leading to HER2/HER3 heterodimerization. This in turn causes increased downstream PI3K/AKT/mTOR signaling and tumor growth.

NRG1 gene fusions are emerging as clinically actionable genomic targets.

MCLA-128

MCLA-128 is a bispecific, humanized, full-length IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxic (ADCC) activity that potently inhibits the HER3 signaling pathway.

Figure 1: DOCK & BLOCK® action of MCLA-128 in HER2/3 signaling



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 signaling.
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.

Potent in vitro/vivo activity was observed with MCLA-128 in *NRG1*-fusion positive models (MDA-MB-175 [breast], OV5383 [ovarian], OV-10-0050 [ovarian])[1].

In the clinic, MCLA-128 has shown promising single-agent activity in the first-in-human study across several tumor types. Clinical proof-of-concept has been achieved in metastatic breast cancer[2] and gastric cancer[3] in heavily pretreated patients progressing on multiple anti-HER2 therapies. MCLA-128 has a very well tolerated safety profile with grade 3-4 events reported in <5% of patients, and an absence of clinical cardiotoxicity and severe gastrointestinal events.

MCLA-128 is now being investigated in patients with *NRG1* fusion-positive tumors in the ongoing Phase 2 part of the study.

References

1. Geuijen et al. *Cancer Cell.* 2018;33(5):922-36.
2. Alsina et al. *J Clin Onc.* ASCO 2017; 35 (15 Suppl): #2522.
3. Alsina et al. *Ann Onc.* ESMO 2018; 29 (8Suppl); #664P.

METHODOLOGY

Study Design

Figure 2: *NRG1* fusion cohorts

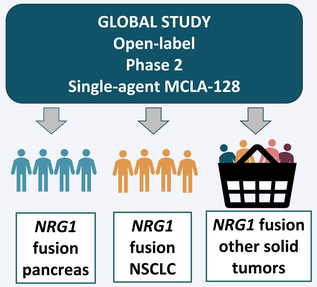


Figure 3: Global distribution of recruiting centers

Key Eligibility Criteria

- Locally-advanced unresectable or metastatic solid tumor with documented *NRG1* gene fusion, identified by a molecular assay such as PCR, NGS (RNA or DNA) or FISH
- At least 18 years-old
- At least one measurable lesion by RECIST v1.1 (evaluable non-measurable is permitted for up to 10 patients)
- Failure or non-suitability of standard therapy
- Availability of a fresh or archived FFPE tumor biopsy sample

Phase 2 Study Objectives

Primary objectives:
- ✓ To explore antitumor activity of MCLA-128 according to RECIST v1.1, per local investigator assessment, in terms of overall response rate and duration of response
- ✓ To characterize safety/tolerability of MCLA-128

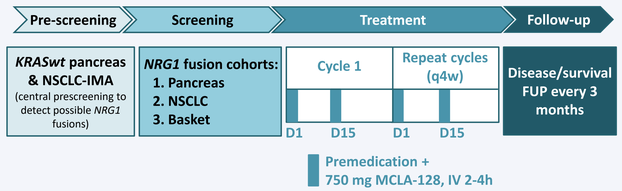
Secondary objectives:
- ✓ To evaluate progression-free and overall survival
- ✓ To characterize the pharmacokinetic profile and immunogenicity

Exploratory objectives:
- ✓ To identify potential biomarkers and their relationship with anti-tumor activity
- ✓ To evaluate best overall response according to PET response criteria

Treatment

- Patients with *NRG1*-fusion positive tumors receive a regimen of 750 mg MCLA-128, IV over 2 hours, every other week, in 4-week cycles.
- After treatment discontinuation, patients are followed-up every 3 months, for up to 2 years.

Figure 4: Treatment and follow-up plan



STUDY STATUS / CURRENT SITES

Recruitment into all three *NRG1* cohorts was opened in September 2019.
The study is actively accruing *NRG1* fusion patients in Europe, North America, and Asia. There are currently 23 sites open, and another 12 are planned to be opened by Q4 2020 (listed below).

EUROPE			
France	Lyon	Hôpital Louis Pradel-Hospices Civils de Lyon	M. Duruisseaux / T. Walter
France	Paris	Gustave Roussy Cancer Center Grand Paris	C. Massard / A. Hollebecque
France	Paris	Hôpital Cochin	M. Wislez / R. Coriat
France	Paris	Hôpital Curie	C. Neuzillet
Germany	Heidelberg	National Center for Tumor Disease	C. Springfeld
Italy	Milan	Niguarda Cancer Centre	S. Siena / A. Amatu
Netherlands	Amsterdam	Netherlands Cancer Institute (NKI)	F. Opdam / AJ. de Langen
Netherlands	Amsterdam	Amsterdam Medical Center (AMC)	H. Wilmink
Netherlands	Nijmegen	Radboud University Medical Centre	H. Verheul
Netherlands	Rotterdam	Erasmus Medical Center	C. Van Eijck
Netherlands	Utrecht	University Medical Center Utrecht	E. Witteveen / E. Gort
Norway	Oslo	Oslo University Hospital	TK. Guren
Spain	Barcelona	Vall d'Hebron University Hospital	H. Verdaguer/ T. Macarulla
Spain	Madrid	Hospital Fundación Jimenez Diaz	V. Moreno
Spain	Madrid	University Hospital Madrid Sanchinarro	V. Boni
Spain	Madrid	Hospital 12 October	R. Carbonero / S. Ponce
Spain	Valencia	Instituto Valenciano Oncologia	Dr. Roda
NORTH AMERICA			
Canada	Toronto	University Health Network	G. O'Kane
USA	Boston, MA	Dana Farber Cancer Institute	J. Cleary / G. Shapiro
USA	Detroit, MI	Karmanos Cancer Institute	M. Nagasaka / P. Philip
USA	Houston, TX	U.T.M.D. Anderson Cancer Center	J. Rodon
USA	Irvine, CA	University of California Irvine	I. Ou
USA	New York, NY	Memorial Sloan Kettering Cancer Center	A. Schram / A. Drilon
USA	Palo Alto, CA Phoenix, AZ	Stanford University	SK. Padda
USA	Rochester, MN Jacksonville, FL	Mayo Clinic	T. Bekaii-Saab
USA	Washington, DC	Georgetown University Hospital	S. Liu / B Weinberg
ASIA & ISRAEL			
Israel	Tel Aviv	Sheba Medical Centre	T. Golan
Japan	Tokyo	National Cancer Hospital	K. Goto / M. Ikeda
Japan	Tokyo	St. Marianna Medical University Hospital	K. Umemoto
Singapore	Singapore	National Cancer Centre	J. Lam Yick Ching / DSW. Tan
South Korea	Seoul	Samsung Medical Center	J. Oh Park
South Korea	Seoul	Seoul National University Hospital	D-W. Kim / DY. Oh
Taiwan	Taipei	National Taiwan Cancer Centre	J. Chih-Hsin Yang

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ASCO Annual Meeting 2020, May 29 to June 3 (virtual meeting)
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