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

#685TiP

AM Schram[1], A Drilon[1], T Macarulla Mercade[2], EM O'Reilly[1], J Rodon[3], B Wolpin[4], S-HI Ou[5], D-W Kim[6], JCH Yang[7], YC Lam[8], A Varga[9], AJ de Langen[10], P Witteveen[11], V Boni[12], G Cerea[13], M Duruisseaux[14], SV Liu[15], E Wasserman[16], DM Hyman[1], J Tabernero[2]

1) Memorial Sloan Kettering/Weill Cornell Medical College, NY, USA; 2) Vall d'Hebron University Hospital/VHIO, Barcelona, Spain; 3) MD Anderson Cancer Center, TX, USA; 4) Dana-Farber Cancer Institute, MA, USA; 5) University of California Irvine, CA, USA; 6) Seoul National University Hospital, Seoul, Republic of Korea ; 7) National Taiwan University Cancer Center/Hospital, Taipei, Taiwan; 8) National Cancer Centre Singapore, Singapore; 9) Gustave Roussy, Villejuif, France; 10) Netherlands Cancer Institute, Netherlands, 11) UMC Utrecht Cancer Center, Netherlands; 12) START Madrid-CIOCC/University Hospital Sanchinarro, Madrid, Spain; 13) Niguarda Cancer Center, Ospedale Niguarda/Università degli Studi di Milano, Italy; 14) Hôpital Louis Pradel-Hospices Civils de Lyon, France; 15) Lombardi Cancer Center Georgetown University, Washington, USA; 16) Merus N.V., Utrecht, Netherlands

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.

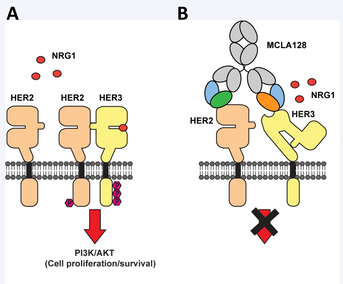
Functional NRG1 fusions result in expression of the EGF-like domain of NRG1, which binds to extracellular HER3, leading to HER2/HER3 heterodimerization. This in turn causes increased downstream PI3K/AKT/mTOR signalling and tumour growth.

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 signalling pathway.

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



A: NRG1-fusion proteins retaining the EGF-like domain, function as ligands for HER3 (similar to NRG1); they bind with high affinity to promote receptor dimerization and downstream signalling. **B:** MCLA-128 inhibits this high affinity interaction via the DOCK & BLOCK® mechanism whereby one arm of the antibody binds to the HER2 receptor, optimally positioning the other arm to block ligand/receptor interaction. This results in inhibition of growth and survival, activated via the HER3 pathway, even at the high NRG1 protein levels found in NRG1-fusion bearing tumors.

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])[Geuijen et al, 2018].

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 [Alsina, 2017] and gastric cancer [Alsina, 2018] 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.

METHODOLOGY

Study Design

Figure 2: *NRG1* fusion cohorts

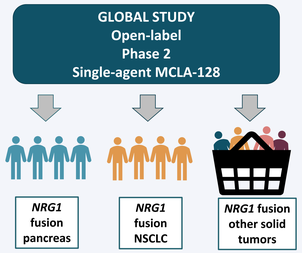


Figure 3: Global distribution of recruiting centers

Key Eligibility Criteria

- Locally-advanced unresectable or metastatic solid tumour 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 tumour biopsy sample

Phase 2 Study Objectives

Primary objectives:
- ✓ To explore anti-tumour 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

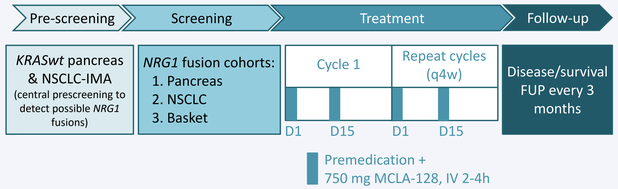
Secondary objectives:
- ✓ To evaluate progression-free and overall survival
- ✓ To characterise the pharmacokinetic profile and immunogenicity

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

Treatment

- Patients with *NRG1*-fusion positive tumours 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 & Asia.

Country	City	Site	Investigators
Canada	Toronto	Princess Margaret Hospital	J. Knox
France	Paris	Gustave Roussy Cancer Center Grand Paris	A. Varga / A. Hollebecque
France	Lyon	Hôpital Louis Pradel-Hospices Civils de Lyon	M. Duruisseaux / T. Walter
Italy	Milan	Niguarda Cancer Centre	S. Siena / A. Amatu
Israel	Tel Aviv	Sheba Medical Centre	T. Golan
Netherlands	Utrecht	University Medical Center Utrecht	E. Witteveen / E. Gort
Netherlands	Amsterdam	Netherlands Cancer Institute (NKI)	F. Opdam / A.J. de Langen
Netherlands	Amsterdam	Amsterdam Medical Center (AMC)	H. Wilmink
Netherlands	Nijmegen	Radboud University Medical Centre	H. Verheul
Singapore	Singapore	National Cancer Centre	J. Lam Yick Ching / D.S.W. Tan
South Korea	Seoul	Seoul National University Hospital	D.-W. Kim / D.Y. Oh
Spain	Madrid	Hospital Fundación Jimenez Díaz	V. Moreno
Spain	Madrid	University Hospital Madrid Sanchinarro	V. Boni
Spain	Barcelona	Vall d'Hebron University Hospital	T. Macarulla / E. Felip
Spain	Madrid	Hospital 12 October	R. Carbonero / S. Ponce
Taiwan	Taipei	National Taiwan Cancer Centre	J. Chih-Hsin Yang
USA	New York, NY	Memorial Sloan Kettering Cancer Center	A. Schram / A. Drilon
USA	Houston, TX	U.T.M.D. Anderson Cancer Center	J. Rodon
USA	Boston, MA	Dana Farber Cancer Institute	J. Cleary / G. Shapiro
USA	Washington, DC	Georgetown University Hospital	S.V. Liu
USA	Irvine, CA	University of California Irvine	I. Ou
USA	Palo Alto, CA	Stanford University	S. Kummar
USA	Phoenix, AZ Rochester, MN Jacksonville, FL	Mayo Clinic	T. Bekaii-Saab
USA	Detroit, MI	Karmanos Cancer Institute	M. Nagasaka / P. Philip

Contacts

Corresponding author:
PI: Alison Schram schrama@mskcc.org

Clinical trial enrollment:
Ernesto Wasserman e.wasserman@merus.nl; Jim Ford j.ford@merus.nl

Sponsor / funding: Merus N.V. enquiries@merus.nl
ESMO Annual Meeting 2019, 27 Sep-1 Oct, Barcelona, Spain

References

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

Conflicts of Interest

Honoraria/consultancy/advisory board fees: AD, TM, EMO, JD, BW, SHIO, JCHY, AJL, VB, MD, SL, DMH, JT. Institutional research funding: AD, TM, EMO, JD, BW, SHIO, JCHY, AV, AJL, VB, MD, SL, DMH. Travel/accommodation expenses: TM, JD, VB, DMH. Company stock: SHIO, EW, DMH. Company employee: EW. Other support: AD, AJL. None: AMS, DWK, JL, PW, GC.