A phase 2 basket study of MCLA-128, a bispecific antibody targeting the HER3 pathway, in NRG1 fusion-favored 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 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 cytotoxicity (ADCC) activity that potently inhibits the HER3 signalling pathway.

Figure 1: DOCK & BLOCK action of MCLA-128 in HER3/2 signaling

A

B

A: NRG1-containing fusions retain 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 HER3 receptor, optimally positioning the other arm to block ligandreceptor interaction. This results in inhibition of growth and survival of fusion-positive tumors, even at the high NRG1 protein levels found in NRG1-fusion bearing tumors.

METHODOLOGY

Study Design

Conclusion: This is the first global study of MCLA-128 in patients with NRG1 fusion-positive tumors.

Figure 2: NRG1 fusion cohorts

PRIMEAKRAS & NRG1-CLC15 CLC01 NRG1 fusion tumors

Figure 3: Global distribution of recruiting centers

Treatment

Figure 4: Treatment and follow-up plan

Key Eligibility Criteria

- Locally-advanced unresectable or metastatic solid tumours 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

REFERENCES


CONTACTS

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Clinical trial enrollment: Ernesto Wasserman e.wasserman@merus.nl, Tim Ford t.ford@merus.nl

Study status: Recruitment into all three NRG2 cohorts was opened in September 2019. The study is actively accruing NRG1 fusion patients in Europe, North America & Asia.

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Key Study Objectives

- To evaluate antitumour 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 antitumour activity
- To evaluate best overall response according to PET response criteria

RESULTS

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

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