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

Alison M Schram¹, Eileen M O'Reilly¹, Romel Somwar¹, Ryma Benayed¹, Sara Shameem¹, Thrusha Chauhan¹, Jean Torrisi¹, Jim Ford², David Maussang², Ernesto Wasserman², Marc Ladanyi¹, David M Hyman¹, L Andres Sirulnik², Alexander E Drilon¹

¹ Memorial Sloan Kettering
² Merus N.V., Utrecht, Netherlands
I have no financial relationships to disclose

I will discuss the following investigational agent in my presentation: MCLA-128
NRG1 fusions: clinically actionable targets

- Neuregulin 1 (NRG1) is a ligand that binds HER3, promoting HER2/HER3 heterodimerization and activation of PI3K/AKT/mTOR signalling\(^1\)

- NRG1 fusions are oncogenic drivers found across numerous solid tumor types\(^2,3\)
  - Low overall incidence <1%
  - Enriched in RASwt pancreas and lung invasive mucinous adenocarcinoma (IMA)

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3. Schram et al. ASCO Annual Meeting. 2019
NRG1 fusions: clinically actionable targets

• Numerous fusion partners have been identified\(^1,2\)
  - Some recurrent, others unique
  - Detected by DNA/RNA-based NGS or FISH
• Functional fusions include the EGF-like domain
• *NRG1* fusion-positive models are sensitive to HER2/HER3 directed therapy *in vitro/in vivo*, and are emerging as clinically actionable targets\(^3,4\)

2. Schram et al. ASCO Annual Meeting. 2019
MCLA 128: a HER2/HER3 bispecific antibody

- MCLA-128 is a bispecific antibody with enhanced ADCC activity

- One arm binds the HER2 receptor, optimally positioning the anti-HER3 arm to block the HER3/ligand interaction

- MCLA-128 blocks NRG1 from binding to HER3, even in the presence of very high ligand expression

- This prevents HER2/HER3 dimerization and downstream PI3K/AKT/mTOR signaling

→ MCLA-128 offers a novel therapeutic paradigm for NRG1 fusion-positive cancers

MCLA-128 inhibits tumor growth in NRG1 fusion-positive models

52-year-old male with *ATP1B1-NRG1* pancreatic CA

Stage IIB PDAC - Whipple

**KRASwt, ATP1B1-NRG1 +**

Liver metastases

Irinotecan/oxaliplatin held and reduced for intolerable AEs

PD

**PR ↓54%**

Gem, cape (adjuvant)

5-FU/IV, irinotecan, oxaliplatin

**MCLA-128**

Nov 2017

Jan 2018

Apr 2018

Feb 2019

Mar 2019

Oct 2019

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

Baseline CT

8 week CT

Baseline PET

8 week PET
34-year-old male with *ATP1B1-NRG1* pancreatic CA

**KRASwt PDAC liver metastases**

- Oxali discontinued at C11 for neuropathy
- Liver biopsy & biliary stent
- *KRASwt, ATP1B1-NRG1* +

5-FU/LV, irinotecan, oxaliplatin

**MCLA-128**

- SD
- 25% ↓

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

**Baseline CT**

**7 week CT**

**10 week PET**
54-year-old male with **CD74-NRG1 NSCLC**

- **Lung surgery**
- **Stage IIIB NSCLC**
  - **CD74-NRG + PD-L1 neg**
- **New lung mets**
- **PD in chest and brain**
- **SRS to an enlarging cerebellar metastasis**
- **PD**
  - SRS to brain
  - **MCLA-128**

**Treatment Timeline**:
- **Cis/pem**
- **Afatinib**
- **Carbo/pembro pemetrexed**
- **Docetaxel ramucir**
- **Gem vinorelbine**
- **Mitomycin vinblastine**

**4.5+ months MCLA-128, 750 mg IV, q2w**

**Maximal related toxicity ≤ grade 1**

** Baseline  
Week 16**

**Graph**:
- **RECIST (% change from baseline)**
  - **-33% ↓**
  - **-41% ↓**

**Graph Data**:
- **Weeks 0-18**
- **Week 16**
MCLA-128: well tolerated safety profile

**AEs at RP2D (N=117)**

<table>
<thead>
<tr>
<th></th>
<th>AEs irrespective (&gt;7.5% patients)</th>
<th>AEs related (&gt;2% + &gt;G3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>G3*</td>
</tr>
<tr>
<td>≥1 adverse event</td>
<td>109 (93.2)</td>
<td>43 (36.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35 (29.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Astenia</td>
<td>27 (23.1)</td>
<td>3 (2.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>22 (18.8)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (17.1)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (15.4)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (14.5)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15 (12.8)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>15 (12.8)</td>
<td>7 (6.0)</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>14 (12.0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>12 (10.3)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (10.3)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (9.4)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>10 (8.5)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>AST increased</td>
<td>10 (8.5)</td>
<td>4 (3.4)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>9 (7.7)</td>
<td>0</td>
</tr>
<tr>
<td>IRR</td>
<td>9 (7.7)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (5.1)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (4.3)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>5 (4.3)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>4 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Hypersensitivity**</td>
<td>4 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>3 (2.6)</td>
<td>0</td>
</tr>
</tbody>
</table>

- 117 patients treated with single-agent MCLA-128 at the RP2Ds in the ongoing phase 2 study (750 mg q3w; 800+400 mg weekly)
- Most suspected related AEs were grade 1-2, with grade 3 in <5% of patients and no grade 4 related events
- No severe related gastrointestinal or skin toxicity, nor clinically significant LVEF decreases or cardiac AEs

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 (Alsina et al. ESMO. 2018 #664P). The patient’s baseline cardiac condition (severe aortic stenosis) contributed to the fatal outcome.
Conclusions

✓ MCLA-128 potently inhibits NRG1 fusion-positive tumors *in vitro* and *in vivo*

✓ We provide a clinical proof-of-concept of MCLA-128 in *NRG1* fusion-positive pancreatic and lung cancers

✓ Very well tolerated safety profile, with a notable lack of cardiotoxicity and severe gastrointestinal or skin toxicity

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