Final Analysis of the Phase 1a/b Study of Fibril-Reactive Monoclonal Antibody 11-1F4 (CAEL-101) in Patients with AL Amyloidosis

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Amyloidosis Mortality Remains High

Up to 80% ineligible for ASCT

Over 40% of these patients die within 1 year of diagnosis
Delayed Organ Response (OR)

Median time to OR from start of treatment 10.4 months (range, 8.7-12.8 mos)

Other variables influencing organ response
- Features of chaperone proteins (polymorphisms)
- Organ and cell specific processes in proteolysis and phagocytosis

Kauffman et al, AJH 2015
Production & Reactivity of 11-1F4 mAb (CAEL-101)

Kappa Bence Jones protein isolated and used to develop Ab

Native

Structure of soluble light chain in circulation → not reactive with 11-1F4 mAb (CAEL-101)

“Loop-Flip”

• Fibrillogenesis
• Surface adsorption

Structure of light chain in fibril → reactive with 11-1F4 mAb (CAEL-101)

Courtesy of Alan Solomon and Jonathan Wall Lab

December 10, 2017
Poly-reactivity of 11-1F4 mAb (CAEL-101) with Human AL Amyloid Deposits in Tissues

Courtesy of Jonathan Wall Lab

December 10, 2017
Immunotherapy Using the 11-1F4 mAb (CAEL-101)

The 11-1F4 mAb (CAEL-101) expedites the dissolution of human AL\(\lambda\) and \(\kappa\) amyloidomas in mice.

Specificity of Antibody Binding

Co-localization of $^{124}$I-m11-1F4 with Hepatosplenic and Bone AL Amyloid

AL11 $\lambda$

Columbia University Medical Center

December 10, 2017
Phase 1a/b Study of 11-1F4 mAb (CAEL-101) in Patients with AL Amyloidosis

- GMP-grade amyloid fibril-reactive IgG1 11-1F4 mAb (CAEL-101) was produced by NCI’s Biological Resource Branch
- open-label, dose-escalation phase 1a/b study of Ch IgG1 11-1F4 mAb (CAEL-101)
- Patients with relapsed or refractory AL Amyloidosis

Clinical trial Identifier: NCT02245867
Study Objectives

Primary Objective:
• Establish the maximum tolerated dose (up to 500 mg/m²) of chimeric 11-1F4 (CAEL-101)

Secondary Objectives:
• Demonstrate reduction in amyloid burden, as evidenced by decrease of organomegaly and/or improved organ function
• Determine the pharmacokinetics and safety of 11-1F4 (CAEL-101) when given as a single IV infusion (phase 1a) or as a series of weekly IV infusions (phase 1b)
• To determine whether there is a dose response at the highest doses 250 and 500mg/m²

https://clinicaltrials.gov/ct2/show/NCT02245867
Eligibility

**KEY INCLUSION CRITERIA**
- Confirmed diagnosis of AL amyloidosis
- Age > 21 years
- ECOG performance status ≤ 3
- Received prior systemic therapy
- Does not require plasma cell targeted therapy

**KEY EXCLUSION CRITERIA**
- EF < 40%
- Intraventricular Septum > 25mm
- Creatinine clearance < 30 cc/min
- Alkaline phosphatase > 3 times institutional upper limit of normal
- Bilirubin > 3.0 mg/dL

https://clinicaltrials.gov/ct2/show/NCT02245867
## Phase 1a Dose Escalation

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>0.125</td>
</tr>
<tr>
<td>-1</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
<td>0.5*</td>
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<tr>
<td>2</td>
<td>5</td>
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<td>3</td>
<td>10</td>
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<td>4</td>
<td>50</td>
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<tr>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>250</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
</tr>
</tbody>
</table>

- Dose escalation “up and down design”
- Once tolerated, successive patients each received progressively higher doses of 11-1F4 mAb (CAEL-101)
- Two patients enrolled at Dose Level 7
- No dose limiting toxicity observed
- MTD = 500 mg/m²

Ch 11-1F4 mAb (CAEL-101) infusion

Clinical Evaluation

https://clinicaltrials.gov/ct2/show/NCT02245867
Phase 1b Dose Escalation

<table>
<thead>
<tr>
<th>Level</th>
<th>Dose (mg/m(^2))</th>
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<tbody>
<tr>
<td>-2</td>
<td>0.125</td>
</tr>
<tr>
<td>-1</td>
<td>0.25</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>5</td>
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<td>3</td>
<td>10</td>
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<td>4</td>
<td>50</td>
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<td>5</td>
<td>100</td>
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<tr>
<td>6</td>
<td>250</td>
</tr>
<tr>
<td>7</td>
<td>500</td>
</tr>
</tbody>
</table>

- Ch 11-1F4 mAb (CAEL-101) infusion
- Clinical Evaluation

- 11-1F4 mAb (CAEL-101) infusion once per week for 4 weeks
- Starting again at Dose Level 1
- Once tolerated, successive patients each received progressively higher doses of 11-1F4 mAb (CAEL-101)
- 6 additional patients enrolled at Dose level 6
- 6 additional patients enrolled at Dose level 7

https://clinicaltrials.gov/ct2/show/NCT02245867
Patient Disposition

27 patients completed treatment

Phase 1a
8 patients completed treatment

Original Cohort
7 patients completed treatment
(1 patient was taken off study for AE)

Phase 1b

Expansion cohort
DOSE LEVEL 6
6 patients completed treatment

Expansion cohort
DOSE LEVEL 7
6 patients completed treatment
# Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (N=27 patients)</strong></td>
<td>66 yrs (Range: 34 – 79)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>N=19 (70%)</td>
</tr>
<tr>
<td>Female</td>
<td>N=8 (30%)</td>
</tr>
<tr>
<td><strong>Light Chain type</strong></td>
<td></td>
</tr>
<tr>
<td>$\lambda$</td>
<td>N=15 (56%)</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>N=12 (44%)</td>
</tr>
<tr>
<td><strong>Revised Mayo Stage</strong></td>
<td>II (Range: I to IV)</td>
</tr>
<tr>
<td><strong>Organ Involvement (No.)</strong></td>
<td>2 (Range: 1 – 4)</td>
</tr>
<tr>
<td>Heart</td>
<td>N=16 (59%)</td>
</tr>
<tr>
<td>Kidney</td>
<td>N=13 (48%)</td>
</tr>
<tr>
<td>Skin/Soft tissue</td>
<td>N=12 (44%)</td>
</tr>
<tr>
<td>GI</td>
<td>N=8 (30%)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>N=3 (11%)</td>
</tr>
<tr>
<td>Liver</td>
<td>N=3 (11%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>N=3 (11%)</td>
</tr>
<tr>
<td>Lung</td>
<td>N=1 (4%)</td>
</tr>
<tr>
<td><strong>Best Hematologic Response to Plasma Cell Directed Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>N=4 (15%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>N=19 (70%)</td>
</tr>
<tr>
<td>PR</td>
<td>N=2 (7%)</td>
</tr>
<tr>
<td>NR</td>
<td>N=2 (7%)</td>
</tr>
<tr>
<td><strong>Previous Plasma cell Directed Therapy (No.)</strong></td>
<td>2 (Range: 1 – 9)</td>
</tr>
<tr>
<td>1 Regimen 30% (N=8), 2 Regimen 30% (N=8), ≥3 Regimen 40% (N=11)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline NT-proBNP (ng/L)</strong></td>
<td>1915 (Range: 815.5 – 8274)</td>
</tr>
<tr>
<td><strong>Baseline 24 hr Urine Protein (mg/24hr)</strong></td>
<td>4796 (Range: 1078 – 10,260)</td>
</tr>
<tr>
<td><strong>Time Since last Exposure to Chemotherapy (mos)</strong></td>
<td>6 (Range 1 – 51)</td>
</tr>
</tbody>
</table>

^a Baseline NT-proBNP in patients with cardiac involvement who were evaluable for response (Baseline NT-proBNP ≥ 650pg/mL)

^b Baseline 24 hour urine protein in patients evaluable for renal response
## Safety Summary

### Adverse events for Phase 1a/b study independent of relation to 11-1F4 mAb (CAEL-101)

- No dose limiting toxicity
- No drug-related deaths

<table>
<thead>
<tr>
<th>Adverse Event (n=27)</th>
<th>Any (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory symptoms</td>
<td>3 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Flatulence/ Bloating</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Parasthesia/ Tremors</td>
<td>2 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus/ Dry Skin</td>
<td>2 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Flushing/ Vasovagal reaction</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Depression/ Anxiety</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Pleural/ Pericardial effusion</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Skin infection/ Other infection</td>
<td>4 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased WBC count</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>2 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Elevation of transaminases</td>
<td>4 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkalemia/ Hypokalemia</td>
<td>4 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Increase Cardiac Troponin</td>
<td>2 (7)</td>
<td>0</td>
</tr>
</tbody>
</table>
Results

• 27 Patients were accrued and evaluable for toxicity
  • N=3 had no measurable disease
• 24 Patients evaluable for response
• 12 out of 18 patients (67%) with cardiac and/or renal involvement showed a response in Phase 1a/b
  • 67% Cardiac (8 of 12 evaluable for response)
  • 50% Renal (5 of 10 evaluable for response)
• 3 Patients responded with other organ system involvement
  • 1 GI response (n = 4)
  • 1 Liver response (n = 2)
  • 1 soft tissue response with improvement of arthritis Grade 3→1 (n = 4)
• 15 out of 24 patients (63%) showed organ response in Phase 1a/b
• No patients showed organ progression
• Overall Median Time to response was 3 weeks after the first dose of 11-1F4 mAb (CAEL-101)
Best Cardiac Response After Treatment with 11-1F4 mAb (CAEL-101)

Cardiac Response Criteria  
[Pallidini et al, JCO 2012]

- **PROGRESSION**
  - >30% and >300 pg/ml increase in NT-proBNP

- **STABLE**
  - Baseline NT-proBNP ≥650 pg/ml

- **RESPONSE**
  - >30% and >300 pg/ml decrease in NT-proBNP

12 patients evaluable for response

8 responders – 67%
4 stable

Median time to cardiac response - 3 weeks

December 10, 2017
**11-1F4 mAb (CAEL-101) Improves Left Ventricular Global Longitudinal Strain (GLS)**

**Patient 1-21B, 250mg/m², Dose Level 6**

**Week 0**

**Pre-11-1F4 mAb (CAEL-101)**

GLS: -9.58

NTproBNP 2549pg/mL

**Week 12**

**Post-11-1F4 mAb (CAEL-101)**

GLS: -13.39

NTproBNP 1485 pg/mL
Best Renal Response After Treatment with 11-1F4 mAb (CAEL-101)

10 patients evaluable for response
5 responders – 50%
5 stable

Median time to renal response – 4 weeks*

*24 hour urine protein measured at screening and Week 8 in Phase 1a and at screening and Weeks 5, 8 and 12 in Phase 1b

Renal Response Criteria
[Pallidini et al., Blood 2014]
Patient with Liver AL Amyloidosis (Kappa) had organ response 8 months before FLC - VGPR

US-Liver Pre-treatment

06-02-16: “The liver is **enlarged** with normal echogenicity. **The liver measures 19.4 cm** in length. Liver surface is smooth.”

US-Liver Post-treatment

08-02-16: “The liver is **normal in size** and echogenicity. The surface is smooth. **Right lobe measures 17.3 cm** in length at the midclavicular”
Organ Response Occurs Independent of Depth of Response to Chemotherapy

- Patient with cardiac Lambda AL Amyloidosis
- 6 prior treatments with best Hematologic Response PR
- Prior to 11-1F4 mAb (CAEL-101) NO Organ response
Overall Survival

- Median follow up 1.6 yrs (18.6 months), range 0.34 to 2.79 yrs
- OS at 18.6 mos: 93%

Time to death from any cause as of 11/15/2017
Summary and Future Outlook

- Treatment with 11-1F4 mAb (CAEL-101) is well tolerated and safe
  - No dose limiting toxicity up to an MTD of 500mg/m$^2$
  - Potential to extend organ responses with doses above 500 mg/m$^2$.
- 11-1F4 mAb (CAEL-101) is clinically efficacious
  - early organ response when the mAb is administered as a single infusion or as a weekly infusion for 4 weeks
  - Cardiac, Renal, GI, Liver, Skin and Soft tissue responses observed
- 11-1F4 mAb (CAEL-101) represents a novel and promising treatment for AL Amyloidosis
  - safely promotes amyloid resolution
  - leads to improvement in organ function
- Multicenter Phase 2 SWOG trial and Phase 3 trial conducted by Caelum Biosciences
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