A wholly-owned subsidiary of Merck Sharp & Dohme Corp.

CM-24 / MK-6018
A novel anti CEACAM1 therapy for treating cancer

ICI meeting, March 2016, Boston

Tehila Ben Moshe
CEO, VP R&D
cCAM Biotherapeutics

- Clinical stage company. Founded in 2010 and operates from Misgav, Israel

- Innovative scientific concept → FIH phase 1 trial (under IND) in less than 4 years

- Lead agent: **CM-24 (MK60-18)** Phase 1 mAb targeting CEACAM1
  First in class immune check point blocker
  Based on the research of Prof. Markel, Ella institute, Sheba hospital, Israel

- Focus and goals:
  Development of novel therapies which specifically target immune system to eliminate tumor cells
  Dedicated to advancing new and effective candidates to the clinic

- The company was fully acquired in July 2015 and is now a wholly-owned subsidiary of Merck Sharp & Dohme Corp
CEACAM1 - a Novel Immune Check Point:

- CEACAM1- a member of the Carcino Embryonic Antigen (CEA) Family
- CEACAM1 Expression profile in Cancer and activated lymphocytes
- CEACAM1 role in regulating anti-tumor immunity
- CEACAM1 signaling in activated lymphocytes

CM-24 (MK-6018) Pre Clinical data:

- Mode of Action
- Effect on T cell signaling
- In vitro efficacy studies in lead indications
- In vivo efficacy studies
- Combination studies with immune checkpoints
CEACAM1 is a Member of the Human CEA Family
(Carcinoembryonic Antigen Cell Adhesion Molecule)

Gray-Owen and Blumberg, Nat Rev Immunol, 2006

<table>
<thead>
<tr>
<th>New name</th>
<th>Alternative names</th>
<th>Tissue expression</th>
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<tbody>
<tr>
<td>CEACAM1</td>
<td>CD66a, BGP and C-CAM</td>
<td>Epithelial cells, endothelial cells, lymphocytes and myeloid cells</td>
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<tr>
<td>CEACAM3</td>
<td>CD66d and CGM1</td>
<td>Granulocytes</td>
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<tr>
<td>CEACAM4</td>
<td>CGM7</td>
<td>Granulocytes</td>
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<td>CEACAM5</td>
<td>CD66e and CEA</td>
<td>Epithelial cells</td>
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<tr>
<td>CEACAM6</td>
<td>CD66c and NCA</td>
<td>Epithelial cells and granulocytes</td>
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<td>CEACAM7</td>
<td>CGM2</td>
<td>Epithelial cells</td>
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<td>CEACAM8</td>
<td>CD66b and CGM6</td>
<td>Granulocytes</td>
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<tr>
<td>PSG1-11</td>
<td>CD66f</td>
<td>Placenta</td>
</tr>
</tbody>
</table>

CEACAM1 is the only member that is expressed on lymphocytes.
CEACAM1
Co-inhibitory Immune Checkpoint

- Glycoprotein, belongs to IgSF
- ITIM (Immunoreceptor Tyrosine-based Inhibition Motif)
- Homophilic interaction
- Up-regulated on activated T cells and NK cells
- Over expressed in various cancers
CEACAM1 is Overexpressed in Multiple Tumors and in Intratumoral Lymphocytes

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Expression in Tumor cells</th>
<th>Expression in Intratumoral Lymphocytes</th>
<th>% Cases</th>
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<tr>
<td>Gastric</td>
<td>![Image21] ![Image22] ![Image23]</td>
<td>![Image24]</td>
<td>60</td>
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</tbody>
</table>
CEACAM1 Expression Correlates with Poor Prognosis

Thies et al. J Clin Oncol 2002

CEACAM1 Expression Increases During Tumor Progression

Staining (IHC) of tumor and normal tissue microarray using anti CEACAM1 mAb (100 cases)

Melanoma
- 90% of tumor cells are CEACAM1 positive
- Score: 3

Pancreatic cancer
- 100% of tumor cells are CEACAM1 positive
- Score: 3
Why Target CEACAM1?

- CEACAM1 is overexpressed in many tumors and correlates with poor prognosis
- CEACAM1 is expressed on TIL in which are in close proximity to the tumor cells
- CEACAM1 can bind in homophilic interactions and inhibit T cell cytotoxicity

Are Tumor cells using CEACAM1 to suppress the immune system?
In-Vitro System to Test the effect of CEACAM1-mediated Interactions in T Cells

- Beads are loaded with anti CD3 and either IgG as control or with rhCEACAM1-Ig (anti CD3/rhCEACAM1-Ig)
- Upon incubation of the anti CD3/rhCEACAM1-Ig beads with T cells (either TILs or T cell line) a CEACAM1-CEACAM1 inhibitory signal is propagated
CEACAM1-CEACAM1 interactions Inhibit the immunological activity of TIL

* P<0.001 T-test
Peripheral blood lymphocyte were activated by PHA for 72 hr

CEACAM1 and PD1 Expression in activated PBMC
CEACAM1 and PD1 Inhibitory Effect in T cells

**Tumor infiltrate lymphocyte**

protein bound on plate

**Peripheral blood lymphocyte**

* P<0.05
** P<0.0001
Proximity of CEACAM-1 and TCR Effect on Cytokine Secretion

**Separated presentation**
- Bead bound with αCD3
- Bead bound with IgG
- T cell
- Cytokine secretion

**Coupled presentation**
- Bead bound with αCD3
- T cell
- Cytokine secretion
The inhibitory Effect of CEACAM1 is Dependent on Spatial Proximity to the TCR

TIL were incubated overnight in the presence of magnetic beads covered with αCD3 and CEACAM1 in conjunction or on separate beads * P≤0.001 paired T-test compared to no CEACAM1-Ig presented on beads (αCD3/IgG beads).
CEACAM1 Reduces αCD3 Dependent ZAP70 Phosphorylation

Similar results obtained with HuT78 cells (T-cell cell line)

Gray-Owen and Blumberg, Nat Rev Immunol, 2006
CEACAM1 Reduces αCD3 dependent Immunoreceptor Activation

TIL were incubated with αCD3/IgG or αCD3/CEACAM1-Ig covered magnetic beads for 5hr followed by cells lysis. The tyrosine phosphorylation signals of 59 human immunoreceptors were analyzed using a human proteome profiler array membranes (ARY004B; R&D Systems). Phosphorylation levels of individual analyte were determined by average pixel density of duplicate spots. Values were obtained after subtracting background signals and dividing by the value obtained in resting TIL.
It was shown that CEACAM1 homophilic interactions:

- Reduce the phosphorylation level of ZAP70 in T cells
- Inhibit the immune activity of TIL as demonstrated by the decrease of IFNY secretion
- Diminish TCR activation directly which results in low phosphorylation of immuno-receptors

CEACAM1-CEACAM1 Interactions inhibit TCR mediated T-cell activation
Human CEACAM1 is a Modulator of T cell Function

- CEACAM1 expression up-regulated on
  - activated T and NK cells
  - various cancer cells
- CEACAM1 (tumor) and CEACAM1 (T-cell) interaction prevents killing of tumor cell
- Conceptually, analogous to PD-1/PDL-1
  - Predominantly modulation of T cell activity at tumor site
- Different MOA than CTLA-4
  - Predominantly modulation of APC-based T cell activation in lymph nodes

Adapted and modified from Freeman G J PNAS 2008
CM-24 is a Blocking mAb that Prevents CEACAM1-Mediated Interactions Enhancing the Cytotoxic Activity of Lymphocytes
CM-24/MK-6018 Counteracts the Inhibitory Activity of CEACAM1 in T Cells
CM-24/MK-6018 Restores αCD3 Dependent ZAP70 Phosphorylation Upon CEACAM1 Stimulation in TIL

Adapted from Gray-Owen and Blumberg, Nat Rev Immunol, 2006
CM-24/MK-6018 Enhances the Cytotoxic Activity of TIL and NK Cells Against CEACAM1-Positive Melanoma Cell Lines

Cytotoxicity was quantified by LDH release
CM-24/MK-6018 Enhances the Cytotoxic Activity of Effector Lymphocytes Against Various Tumor Cells

Cytotoxicity

Granzyme B

IFN-γ
CM-24/MK-6018 Enhances the Cytotoxic Activity of TIL and NK Cells Against CEACAM1-Positive Cancer Cell Lines

Real time cell analysis

Cytotoxicity was quantified by a system (iCELLigence) which measures electrical impedance induced by the cells allowing the monitoring of physiological changes such as cell death.
CM-24/MK-6018 Exhibits Anti Tumor Immunological Activity In-Vivo

<table>
<thead>
<tr>
<th>Mouse #</th>
<th>1</th>
<th>2</th>
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<td>IgG</td>
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<td>TIL + IgG</td>
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Lung lesion melanoma xenograft model

% CD107α positive cells from human infiltrating T cells

Average tumor weight (mg)

CM-24
CEACAM1 and PDL1 Synergize to inhibit T cell activity which is countereact by specific immune checkpoint blockers

* P<0.001
T-test between with and without antibodies

αCD3 (5 µg/ml) + αCD28 (1 µg/ml) + recombinant protein (4 µg/ml)
CEACAM1/PDL1 bound on plate
CM-24/MK-6018 displays similar activity to PD1/PDL1 blockers and synergize with them to enhance T cell cytotoxicity.
Combination Studies in Immunocompetent Mouse Tumor Model

- Groups distribution
  (Ave tumors volume of 45mm^3)

- A20, 5x10^6, SC abdomen
- Abs(6mg/kg)- IV

- N=11-12 Balb/C mice /group

- Groups distribution
  (Ave tumors volume of 45mm^3)

- A20, 5x10^6, SC abdomen
- Anti mCEACAM1
- Anti mPD-1 (clone RPM-14)
- Anti mCEACAM1+ anti mPD-1

- N=11-12 Balb/C mice /group
Anti PD1+Anti CEACAM1 combination study in Immunocompetent mice
IND clearance – Dec, 2014

FIH study initiation in metastatic cancer patients – started in March, 2015

**US sites:** Yale (Mario Sznol), UCLA (Deborah Jean Lee Wong in connection with Antoni Ribas)

**Israel sites:** Tel Hashomer (Ronnie Shapira-Frommer), Ichilov (Ravit Geva)

**Phase 1 study in metastatic cancer**

**Dose escalation cohort** - Selected solid tumors.

- Melanoma (all subtypes)
- NSCLC (adenocarcinoma)
- Bladder
- GI (gastric, CRC)
- Ovarian

3+3 standard design for dose escalation

Repeated dosing cycle of 4 treatments (q2W). Patients with clinical benefit may be retreated
Primary Objectives
- Assess the safety and tolerability of escalating multiple doses of MK-6018 (IV)
- Determine a recommended phase 2 dose (RP2D) of MK-6018

Secondary Objectives
- Characterize the pharmacokinetic profile of MK-6018
- Characterize the immunogenicity of MK-6018
- Evaluate preliminary efficacy based on objective and duration of response in subjects treated with MK-6018

Exploratory
- Explore potential predictive markers
- Investigate the immunomodulatory activity of MK-6018 on selected immune cell populations and soluble factors
- Assess the overall survival in subjects treated with MK-6018
CEACAM1 is a novel immune checkpoint expressed on T and NK cells upon activation

CEACAM1 is expressed across multiple tumor types and its presence correlates with poor prognosis

CEACAM1 induces a co-inhibitory signal to T and NK cells through homophilic CEACAM1 interactions

CM-24/ MK-6018 is a first in class humanized anti-CEACAM1 antibody with proven in vitro and in vivo PoC

CM-24/ MK-6018 inhibits the immunosuppressive effect of CEACAM1, leading to enhanced cancer cell killing by T and NK cells

CM-24/ MK-6018 synergizes with various immune checkpoint modulators, including ones that target the PD-1 pathway and therefore may be suitable for combination therapy

FIH clinical study under IND in various cancer indications is ongoing
Tehila Ben Moshe, PhD – CEO, VP R&D
Gal Markel, MD, PhD – CSO, Scientific Founder
Sharon Hashmueli, PhD - VP Regulatory & Clinical Operations
Raanan Cohen, MD, MBA - VP Clinical Development & Strategy
Yair Sapir, PhD - Director of Product Development
Ilana Mandel, PhD - Director of Research and Discovery
Motti Hakim, PhD - Senior scientist and Project Manager
Edna Mielin, PhD – Scientist
Rony Shaked, MSc – Scientist

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