Welcome and Introduction

Stéphane Bancel
Chief Executive Officer
Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended including, but not limited to, statements concerning: the potential approval and commercial launch of Moderna’s development candidates, including CMV vaccine (mRNA-1647); Moderna’s belief that Phase 1 clinical data from mRNA-1944 provides support for the continued development of Moderna’s rare disease therapeutic modality; clinical program next steps; development candidate activities; future clinical study commencement, progression, enrollment, and conclusion, including the Phase 2 clinical study start and Phase 3 preparation for mRNA-1647; manufacturing capacity and scalability; regulatory submissions and approvals; risk management; estimates and forward-looking projections with respect to Moderna or its anticipated future performance or events, including the commercial opportunity and gross margins for mRNA-1647. In some cases, forward-looking statements can be identified by terminology such as “may,” “should,” “could,” “expects,” “intends,” “plans,” “aims,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties and other factors, many of which are beyond Moderna’s control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties and other factors include, among others: preclinical and clinical development is lengthy and uncertain, especially for a new category of medicines such as mRNA, and therefore Moderna’s preclinical programs or development candidates may be delayed, terminated, or may never advance to or in the clinic; no mRNA drug has been approved in this new potential class of medicines, and may never be approved; mRNA drug development has substantial clinical development and regulatory risks due to the novel and unprecedented nature of this new class of medicines; and those described in Moderna’s most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with SEC, which are available on the SEC’s website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna’s current expectations and speak only as of the date hereof.

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mRNA as a potential new class of medicines

1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology
Risk management is essential to building a new class of medicines
Risk management is essential to building a new class of medicines

Our approach is to develop technology modalities

- De-risk technology with first program in a modality
- Diversify biology risk by working on multiple programs in parallel within a modality
- Stage risk, build on learnings over time
Risk management is essential to building a new class of medicines

Our approach is to develop technology modalities

- De-risk technology with first program in a modality
- Diversify biology risk by working on multiple programs in parallel within a modality
- Stage risk, build on learnings over time

Varying technology risk

- Prophylactic vaccines
- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic secreted therapeutics
- Systemic intracellular therapeutics
Risk management is essential to building a new class of medicines.
Two important positive clinical milestones in two modalities announced today

Cytomegalovirus (CMV) vaccine (mRNA-1647)
- Positive interim phase 1 data
- Successfully immunized seronegatives and boosted seropositives
- Generally well tolerated
- Phase 2 to start in the near term
- Preparations underway for the phase 3
- Moderna owns the global commercial rights to mRNA-1647

Antibody against Chikungunya virus (mRNA-1944)
- Positive phase 1 data
- Observed dose dependent protein expression
- Achieved expected therapeutic levels at a well tolerated dose (0.3mg/kg)
- Observed expected translation from NHP to human
Body of clinical data from Moderna’s platform to date

- Moderna platform investments in research, manufacturing and clinical have enabled 16 investigational medicines to start clinical trials in the last 3.5 years.

- We have enrolled more than 1,300 subjects and patients across five modalities.

- We have administered repeat doses to patients through multiple cycles in our immuno-oncology programs (OX40L & PCV).

- Across 5 modalities we have shown that our development candidates:
  - have an acceptable safety profile and are generally well tolerated*
  - result in consistent protein expression**
  - encode functional proteins
  - translate from preclinical models to humans

*Common Adverse Events by Modality - Prophylactic Vaccines: injection site pain, myalgia, and fatigue; Cancer Vaccines: for PCV, the most common grade 2 adverse events were fatigue, soreness at the injection site, colitis, and myalgias; Intratumoral Immuno-Oncology: for OX40L, multiple grade 2 and a single grade 3 transient reversible injection related reactions; Localized Regenerative Therapeutics: for VEGF-A, mild injection-site reactions; and Systemic Secreted Therapeutics: see the section below titled Systemic Therapeutics – Secreted and Intracellular.

**Only mRNA-1325, our initial Zika vaccine did not elicit desired pharmacologic effect
Moderna’s development pipeline at IPO

- 7 Prophylactic vaccine programs
- 2 Cancer vaccine programs
- 3 Intratumoral immunology programs
- 1 Localized regenerative therapeutics program
- 3 Systemic secreted therapeutics programs
- 3 Systemic intracellular therapeutics programs

*Data in some cases are interim; positive data means the data warrant continued advancement within a trial or for further development.

Pre-Clinical Development
- VZV
- IL12
- Zika Virus Vaccine mRNA-1893
- MMA
- PKU
- PA
- Fabry
- Relaxin

Open IND
- Chikungunya antibody
- OX40L+IL23+IL36γ Triplet
- KRAS+Sting Vaccine

Phase 1
- Zika Vaccine mRNA-1325
- hMPV+PIV3 Vaccine
- OX40L for solid tumors
- PCV
- CMV Vaccine
- Chikungunya Vaccine

Phase 2 planning
- RSV (1777) Vaccine
- H7 Vaccine
- H10 Vaccine

Phase 2
- VEGF-A

Positive Phase 1 Data*

Modernatm
Moderna’s development pipeline today (9 months since IPO)

- **Positive Phase 1 Data**:
  - Chikungunya antibody
  - CMV vaccine
  - PCV
  - VEGF-A
  - OX40L
  - RSV (1777) vaccine
  - hMPV+PIV3 vaccine
  - Chikungunya vaccine
  - H7 vaccine
  - H10 vaccine

- **Pre-Clinical Development**:
  - GSD1a
  - PKU
  - PA
  - Fabry
  - Relaxin
  - MMA

- **Open IND**:
  - PCV
  - CMV vaccine
  - RSV (1777) vaccine
  - Chikungunya vaccine
  - OX40L ovarian
  - VEGF-A

- **Phase 1**:
  - KRAS Vaccine
  - IL12
  - RSV (1172) vaccine
  - Zika vaccine
  - hMPV+PIV3 vaccine
  - Chikungunya antibody
  - OX40L+IL23+IL36 γ (Triplet)
  - OX40L solid tumors
  - PCV
  - CMV vaccine
  - RSV (1172) vaccine
  - Chikungunya vaccine

- **Phase 2 planning**:
  - CMV vaccine
  - OX40L ovarian
  - PCV
  - VEGF-A

- **Phase 2**:
  - 7 Prophylactic vaccine programs
  - 2 Cancer vaccine programs
  - 3 Intratumoral immunology programs
  - 1 Localized regenerative therapeutics program
  - 3 Systemic secreted therapeutics programs
  - 4 Systemic intracellular therapeutics programs

*Data in some cases are interim; positive data means the data warrant continued advancement within a trial or for further development.
Modern in September 2019

<table>
<thead>
<tr>
<th>Pipeline</th>
<th>4</th>
<th>12</th>
<th>10</th>
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<tbody>
<tr>
<td>Programs in Development</td>
<td>4 In or preparing for Ph 2</td>
<td>5 Immuno-Oncology</td>
<td>5 Rare Disease</td>
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<td>Vaccines for major unmet needs</td>
<td>Positive Ph1 readouts: 6 vaccines, PCV, OX40L, VEGF, Chik ab</td>
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<td>• CMV preparing Phase 2</td>
<td>• PCV in Ph 2</td>
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<td>• hMPV+PIV3 – positive interim Ph 1 data</td>
<td>• OX40L preparing for Ph 2 cohort</td>
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<td>• RSV and Zika in Ph 1</td>
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<td>Rare Disease</td>
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<td>• First systemic therapeutic: Chik antibody: positive Ph 1</td>
<td>MMA – Ph 1 actively recruiting</td>
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<td>PA, PKU, Fabry &amp; GSD1a in GLP Tox</td>
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<td>Foundations</td>
<td>&gt;1,300 Healthy volunteers and patients enrolled</td>
<td>&gt;800 employees</td>
<td>A fully-integrated 200,000 sq. ft. GMP site operational in Norwood, MA</td>
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<td>Leading Biopharma Partners</td>
<td>Leading Biopharma Partners</td>
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<td>7:30–8:30 AM</td>
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<td>Introduction</td>
<td>Stéphane Bancel</td>
<td>8:30–8:40 AM</td>
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<td>CMV</td>
<td>Tal Zaks, MD, PhD&lt;br&gt;Sallie Permar, MD, PhD, Duke University School of Medicine&lt;br&gt;Tal Zaks, MD, PhD&lt;br&gt;Juan Andres&lt;br&gt;Mark Schleiss, MD, University of Minnesota&lt;br&gt;Laura Riley, MD, Weill Cornell Medical College&lt;br&gt;Stéphane Bancel</td>
<td>8:40–10:00 AM</td>
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<tr>
<td>Q&amp;A</td>
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<td>10:00–10:30 AM</td>
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<td>Break</td>
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<td>10:30–10:40 AM</td>
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<td>Immuno-oncology</td>
<td>Tal Zaks, MD, PhD&lt;br&gt;Keith Flaherty, MD, Massachusetts General Hospital</td>
<td>10:40–11:10 AM</td>
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<td>Antibody against Chikungunya virus</td>
<td>Tal Zaks, MD, PhD</td>
<td>11:10–11:50 AM</td>
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<td>Methylmalonic acidemia</td>
<td>Gregory Enns, MD, Stanford University</td>
<td>11:50–12:20 AM</td>
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<td>Stéphane Bancel</td>
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<td>Q&amp;A</td>
<td>Moderna Team</td>
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Progress by modality

- Prophylactic vaccines
- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic secreted therapeutics
- Systemic intracellular therapeutics
## Prophylactic Vaccines

<table>
<thead>
<tr>
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<th>Program</th>
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<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
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<td>mRNA-1647</td>
<td>CMV vaccine</td>
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<td>RSV vaccine</td>
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<td></td>
<td>mRNA-1653</td>
<td>hMPV+PIV3 vaccine</td>
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<td>mRNA-1893</td>
<td>Zika vaccine</td>
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<td>Worldwide BARDA funded</td>
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<td>mRNA-1851</td>
<td>Influenza H7N9 vaccine</td>
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<td>Worldwide Advancing subject to funding</td>
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<td>mRNA-1440</td>
<td>Influenza H10N8 vaccine</td>
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<td>Worldwide Advancing subject to funding</td>
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Our mRNA platform has significant advantages for the development of infectious disease vaccines

*mRNA mimics natural infection* to activate the immune system and achieve a potentially potent response

*Multiple* mRNAs in one vaccine for more compelling product profiles

*Faster discovery*, ability to respond rapidly to emerging pandemic threats

Single process and *single, multi-product facility* for all vaccines
### Progress in the prophylactic vaccines platform to date

<table>
<thead>
<tr>
<th>Category</th>
<th>H10N8 mRNA-1440</th>
<th>H7N9 mRNA-1851</th>
<th>RSV mRNA-1777</th>
<th>RSV mRNA-1172</th>
<th>Zika mRNA-1325</th>
<th>Zika mRNA-1893</th>
<th>Chik mRNA-1388</th>
<th>hMPV+PIV3 mRNA-1653</th>
<th>CMV mRNA-1647</th>
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<td><strong>Dose dependent pharmacology</strong></td>
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<td><strong>NHP protein expression</strong></td>
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### Positive readouts from six prophylactic vaccines

*Phase 1 safety and immunogenicity data (H10N8, H7N9, RSV, Chikungunya virus, hMPV+PIV3, CMV)*
# Prophylactic Vaccines

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<td><strong>Prophylactic vaccines – Commercial programs</strong></td>
<td>mRNA-1647</td>
<td>CMV vaccine</td>
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**Prophylactic vaccines – Global health programs**
Congenital CMV infection and the global need for a vaccine

SALLIE PERMAR, MD, PHD
ASSOCIATE DEAN OF PHYSICIAN SCIENTIST DEVELOPMENT
PROFESSOR, PEDIATRICS, IMMUNOLOGY, MOLECULAR GENETICS AND MICROBIOLOGY
DUKE UNIVERSITY SCHOOL OF MEDICINE
CMV: The Virus

- Large double-stranded DNA virus
- Herpes virus family (Zoster, HSV, EBV)
- Infection usually mild or asymptomatic
- Remains latent in host cells
- Most adults worldwide are infected with CMV
Congenital CMV Disease Burden

• 1 in 150 live births have congenital CMV, worldwide

• Most common infectious cause of birth defects
  ➢ 20% of affected infants will have long term deficits
  ➢ 25% of infant hearing loss

• Annual US burden: $4 billion

Need for a maternal vaccine against CMV

• Vaccine that can elicit protective immune responses prior to pregnancy needed to eliminate congenital CMV
• Top priority for 20 yrs
• Success of Rubella vaccine
• Eliminated congenital rubella syndrome in the Americas

“Introduction of the highly-effective rubella vaccine in 1969 led to the closure of schools for the deaf and blind due to lack of children needing these services”

- Sam Katz, MD
Unlike Rubella, natural immunity is not completely protective in congenital CMV

1000 pregnant CMV seronegative women

A
1-3% primary infection rate

10-30 maternal primary infections

30-40% cCMV transmission

3-12/1000 cCMV-infected infants

25% with deficits

1-4/1000 infants with long term deficits

1000 pregnant CMV seropositive women

B
?% reactivation rate

? maternal CMV reactivations

3-4%* cCMV transmission

7-12/1000 cCMV-infected infants

~10%* with deficits

<1-2/1000 infants with long term deficits

C
20-30%* reinfection rate (serologically defined)

200-300* Maternal CMV reinfections
Phase 2 CMV Vaccine Trial: gB/MF59 trial in postpartum women

- Most efficacious HCMV vaccine trial to-date
- Population of seronegative, postpartum US women
- Immunized with gB (Sanofi) (20μg) + MF59 squalene adjuvant (Novartis) at 0, 1, 6 months
- Primary Endpoint: Time to HCMV acquisition

→50% Efficacy in preventing maternal primary infection

Phase 2 CMV Vaccine Trial: gB/MF59 trial in adolescents girls

• Identical study design and Sanofi gB/MF59 vaccine
• Seronegative US girls age 12-17

402 CMV-naïve adolescent girls

195 administered gB/MF59 vaccine

164 Included

13 acquired HCMV

207 administered placebo (saline)

172 Included

24 acquired HCMV

→ 45% efficacy in preventing primary infection after 2 doses (p=0.08)
Why have previous vaccine efforts failed?

- Virus has coevolved with human immune system for millions of years
- Frequent exposure to high levels of virus in mucosal fluids
- Live attenuated vaccination did not impede virus acquisition, and carries risk of congenital infection
- Subunit vaccines only partially protective
Immune Correlates of Protection Against cCMV Infection

- Neutralization antibody titer, IgG avidity correlated with protection against congenital transmission

- Neutralization in epithelial cells associated with reduced congenital CMV transmission
  - Bialas *J Infect Dis* 2016; 214:1916 –1923

- gB-directed antibodies associated with prevention of infant CMV acquisition and block placental trophoblast infection
  - Saccocio *J Infect Dis* 2019

- Induction of T cell responses remains a goal for eliminating CMV-infected cells and support B cell responses
gB-transfected cell binding identified as an immune correlate of protection for the gB/MF59 vaccine

Permar et al, IHW 2019, unpublished
Why mRNA?

(1) Extremely robust, durable antibody responses

→ Antibody titers after a single immunization with modified mRNA-LNPs exceeds durability achieved by traditional subunit, vector, or DNA vaccine platforms

(1) Cell surface associated Pentamer and gB expression

(3) Limited immune exposure to cytoplasmic glycoprotein components (AD3)
Summary

- CMV vaccine is highly needed to prevent the most common infectious cause of birth defects and brain damage
- Natural immunity is only partially protective against cCMV
- Novel platforms needed to effectively induce immunity that is distinct from that of natural immunity
- mRNA will express antigens on the surface of a cell, mimicking infected cells
Cytomegalovirus (CMV) vaccine (mRNA-1647): Review of interim phase 1 data

Tal Zaks, MD, PhD
Chief Medical Officer
Congenital CMV vaccine includes 6 mRNAs
5 encode the Pentamer, 6th encodes gB antigen
CMV vaccine (mRNA-1647)

Phase 1 trial design

Key Objective:
- To assess the safety, reactogenicity, and immunogenicity of different dose levels of mRNA-1647

Primary endpoint: Safety

Secondary endpoints:
- Neutralizing antibodies against CMV infection of epithelial cells and fibroblasts
- Binding antibodies to gB and Pentamer antigens

Trial progress:
- FSFV: December 2017
- Enrollment completed June 2019 (N=169)
- Phase B – 2nd vaccination completed May 2019; interim data available
- Phase B – 3rd vaccination completed August 2019; interim data not yet available
- Phase C – 2nd vaccination completed August 2019; interim data not yet available

Dose-escalation Phase A (n=15)

Dose-escalation Phase B (n=15)
- Modified process mRNA-1647
- CMV-seronegative subjects enrolled in a 4:1 ratio of mRNA-1647:placebo
  - 30µg mRNA-1647:placebo
  - 90µg mRNA-1647:placebo
  - 180µg mRNA-1647:placebo

Dose-selection Phase B (N=104)
- Modified process mRNA-1647
- CMV-seronegative and -seropositive subjects, 1:1:1:1 parallel enrollment
  - 30µg mRNA-1647
  - 90µg mRNA-1647
  - 180µg mRNA-1647
  - placebo

Sentinel Phase C (n=5)
- Modified process mRNA-1647
- CMV-seronegative subjects enrolled in a 4:1 ratio of 300µg mRNA-1647:placebo

Expansion Phase C (n=30)
- Modified process mRNA-1647
- CMV-seronegative and -seropositive subjects enrolled in a 4:1 ratio of 300µg mRNA-1647:placebo
CMV Vaccine (mRNA-1647) Phase 1 Interim Analysis

**Immunogenicity in CMV-seronegative participants, per-protocol set**

- **Seronegative subjects successfully immunized to generate neutralizing titers against CMV**

- **Dose-related increase in neutralizing antibodies**

- **After the 2\textsuperscript{nd} vaccination, GMTs of the 90 µg and 180 µg dose levels achieved or exceeded the CMV-seropositive benchmark**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neutralizing Antibodies Against Epithelial Cell Infection</th>
<th>Placebo</th>
<th>30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline GMT</td>
<td></td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>GMT post 1\textsuperscript{st} vaccination</td>
<td></td>
<td>8</td>
<td>37</td>
<td>708</td>
<td>1,387</td>
</tr>
<tr>
<td>GMT post 2\textsuperscript{nd} vaccination</td>
<td></td>
<td>12</td>
<td>3,263</td>
<td>15,305</td>
<td>30,743</td>
</tr>
<tr>
<td>GMT/benchmark ratio</td>
<td></td>
<td>---</td>
<td>0.6</td>
<td>2.7</td>
<td>5.5</td>
</tr>
</tbody>
</table>

CMV-seropositive GMT benchmark = 5,588

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neutralizing Antibodies Against Fibroblast Infection</th>
<th>Placebo</th>
<th>30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline GMT</td>
<td></td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>GMT post 1\textsuperscript{st} vaccination</td>
<td></td>
<td>8</td>
<td>8</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>GMT post 2\textsuperscript{nd} vaccination</td>
<td></td>
<td>10</td>
<td>305</td>
<td>1,141</td>
<td>1,264</td>
</tr>
<tr>
<td>GMT/benchmark ratio</td>
<td></td>
<td>---</td>
<td>0.2</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

CMV-seropositive GMT benchmark = 1,295

GMT = geometric mean titer; CMV-seropositive benchmark values derived from baseline values of all CMV-seropositive participants

<table>
<thead>
<tr>
<th>Subject n at each timepoint</th>
<th>Placebo</th>
<th>30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Post 1\textsuperscript{st} vaccination</td>
<td>12</td>
<td>17</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Post 2\textsuperscript{nd} vaccination</td>
<td>11</td>
<td>14</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

---

Slide 36
### CMV Vaccine (mRNA-1647) Phase 1 Interim Analysis

*Immunogenicity in CMV-seropositive participants, per-protocol set*

- **Seropositive subjects** effectively boosted beyond levels seen in natural infection
- **Dose-related increase in neutralizing antibody titers**
- **mRNA-1647 boosted neutralizing antibody titers against epithelial cells to 10-fold or higher in all treatment groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Neutralizing Antibodies Against Epithelial Cell Infection</th>
<th>Neutralizing Antibodies Against Fibroblast Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo 30 µg 90 µg 180 µg</td>
<td>Placebo 30 µg 90 µg 180 µg</td>
</tr>
<tr>
<td>Baseline GMT (Benchmark = 5,588)</td>
<td>8,169 3,614 5,634 5,700</td>
<td>1,298 1,094 1,458 1,371</td>
</tr>
<tr>
<td>GMT post 1st vaccination</td>
<td>7,890 24,752 39,020 52,775</td>
<td>1,278 2,654 3,885 3,879</td>
</tr>
<tr>
<td>GMT post 2nd vaccination</td>
<td>7,490 47,435 62,400 119,829</td>
<td>1,451 2,935 3,891 5,578</td>
</tr>
<tr>
<td>GMR post 2nd vaccination</td>
<td>0.9 13.2 9.9 19.4</td>
<td>1.1 2.3 3.0 4.1</td>
</tr>
</tbody>
</table>

**GMT** = geometric mean titer; **GMR** = geometric mean ratio, defined here as the average of the ratio between Baseline/post 2nd vaccination for each participant.

<table>
<thead>
<tr>
<th>Subject n at each timepoint</th>
<th>Placebo 30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Post 1st vaccination</td>
<td>14</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Post 2nd vaccination</td>
<td>12</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>
## CMV vaccine (mRNA-1647) Phase 1 Interim Analysis

### Solicited adverse events (AE) post 2\textsuperscript{nd} vaccination, solicited safety set

<table>
<thead>
<tr>
<th>CMV Serostatus at Baseline</th>
<th>Placebo (n=13)</th>
<th>30 μg (n=15)</th>
<th>90 μg (n=16)</th>
<th>180 μg (n=15)</th>
<th>Placebo (n=13)</th>
<th>30 μg (n=12)</th>
<th>90 μg (n=11)</th>
<th>180 μg (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>-</td>
<td>11 (73%)</td>
<td>13 (81%)</td>
<td>12 (80%)</td>
<td>-</td>
<td>9 (75%)</td>
<td>8 (73%)</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
<td>-</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Redness</td>
<td>-</td>
<td>-</td>
<td>3 (21)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (18)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (13)</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
<td>-</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Swelling</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (9)</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (23)</td>
<td>5 (33)</td>
<td>10 (63)</td>
<td>9 (60)</td>
<td>2 (15)</td>
<td>4 (33)</td>
<td>4 (36)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (13)</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
<td>-</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (15)</td>
<td>5 (33)</td>
<td>8 (50)</td>
<td>11 (73)</td>
<td>1 (8)</td>
<td>7 (58)</td>
<td>7 (64)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>-</td>
<td>1 (7)</td>
<td>1 (6)</td>
<td>1 (7)</td>
<td>-</td>
<td>3 (25)</td>
<td>1 (9)</td>
<td>3 (27)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (8)</td>
<td>5 (33)</td>
<td>8 (50)</td>
<td>11 (73)</td>
<td>-</td>
<td>5 (42)</td>
<td>7 (64)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>-</td>
<td>1 (7)</td>
<td>3 (19)</td>
<td>2 (13)</td>
<td>-</td>
<td>4 (33)</td>
<td>1 (9)</td>
<td>2 (18)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Chills</td>
<td>1 (8)</td>
<td>3 (20)</td>
<td>7 (43)</td>
<td>11 (73)</td>
<td>-</td>
<td>6 (50)</td>
<td>7 (64)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>-</td>
<td>1 (7)</td>
<td>1 (6)</td>
<td>3 (20)</td>
<td>-</td>
<td>1 (8)</td>
<td>1 (9)</td>
<td>3 (27)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Fever</td>
<td>-</td>
<td>3 (20)</td>
<td>3 (19)</td>
<td>5 (33)</td>
<td>-</td>
<td>2 (17)</td>
<td>6 (55)</td>
<td>6 (55)</td>
</tr>
</tbody>
</table>

Values represent \(n(\%)\) participants reporting each AE, red text=grade 3 AEs

- Solicited AEs after the second vaccination higher than after the first vaccination
- After the first vaccination, AEs higher in the seropositives relative to seronegatives
- One event triggered Study Pause: asymptomatic Grade 4 elevation in partial thromboplastin time (PTT) at 7 days post 2\textsuperscript{nd} vaccination in a subject with Grade 1 PTT elevations throughout study, PTT normal on repeat testing
- No vaccine-related serious adverse events (SAEs)
CMV vaccine (mRNA-1647) Phase 1 Interim Analysis

Durable immunogenicity demonstrated in initial cohort followed to one year

Neutralizing antibody titers against epithelial cell infection
CMV vaccine (mRNA-1647)

Phase 2 study to be initiated in the near term

**STUDY DESIGN**

A phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation trial to evaluate the safety and immunogenicity of Cytomegalovirus vaccine mRNA-1647 in healthy adults

- Evaluate intended phase 3 formulation (same LNP) at 3 dose levels (50µg, 100µg, 150µg)
- N = 252 adult females and males 18 – 40yrs of age
  - 180 CMV-seronegative
  - 72 CMV-seropositive
- Vaccination schedule: 0, 2, 6 months
- Randomization: 3:1 mRNA-1647 vs placebo
- US sites only: up to 12 clinical investigator sites
- First interim analysis: safety and immunogenicity through 1 month after 2nd vaccination

**STUDY STATUS**

- Protocol finalized and under review with FDA
- Core vendors and suppliers on-board:
  - PPD selected as clinical contract research organization (CRO)
  - Other key vendors selected, including expanded, new partnerships for critical study activities
- Investigator selection and initiation progressing well with robust interest in the program:
  - Clinical site feasibility complete
  - On-site investigator qualification visits complete
  - 12 clinical investigator sites selected, including back-up sites as risk mitigation to slow enrollment rates

= Selected investigator site location
CMV vaccine (mRNA-1647)
Phase 3 pivotal trial preparations are underway

- Solicited and received Type C meeting feedback from FDA

- Primary endpoint: prevention of primary CMV infection in a population that includes women of child bearing age (WOCBA)

- We believe we can achieve this objective with a trial with <8,000 subjects

- Country and site feasibility: outreach to 285 sites in 18 countries across North America, Europe and Asia Pac with robust positive response, feasibility assessments continue
CMV vaccine supply plans for late stage development and commercialization

Juan Andres

Chief Technical Development, Manufacturing, Quality Officer
MODERNA’S INTERNAL MANUFACTURING SITE, NORWOOD MA

- Built and operationalized in 22 months
- Pre-clinical, clinical & personalized cancer vaccine production
- 1st clinical batch manufactured in Aug ’18, 70 batches manufactured to date
**Internalizing manufacturing to enable focus on quality, speed and scale**

Norwood now provides the scalability we need for our growing pipeline.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasmid</strong></td>
<td>Sourced entirely by CMOs</td>
<td>Sourced by Moderna &amp; CMOs</td>
<td>Norwood as primary, CMOs as back-up</td>
<td></td>
</tr>
<tr>
<td><strong>mRNA</strong></td>
<td>CMO</td>
<td>CMO</td>
<td>CMO</td>
<td>Norwood</td>
</tr>
<tr>
<td><strong>Lipid Nano-particle (LNP)</strong></td>
<td>No GMP needs in this horizon</td>
<td>CMO</td>
<td>CMO</td>
<td>Norwood</td>
</tr>
<tr>
<td><strong>Form, Fill, Finish (FFF)</strong></td>
<td>CMO</td>
<td>CMO</td>
<td>Norwood + CMO</td>
<td>Norwood</td>
</tr>
<tr>
<td><strong>Quality Control</strong></td>
<td>Out-sourced</td>
<td>Out-sourced</td>
<td>Norwood</td>
<td>Norwood</td>
</tr>
</tbody>
</table>
Manufacturing in Norwood brings a competitive advantage to CMV vaccine (mRNA-1647)

mRNA technology:
- Platform allows similar manufacturing process across all products
- Process improvements implemented fast to platform processes
- Cell-free process to make mRNA
- Less future capital investment

Enables fast scale up

Cost at economical scale (anticipated 90+ % Gross Margin for mRNA-1647 in US)
CMV vials already produced for phase 2 trial

- Same lyophilized image intended for phase 3
- Norwood site can produce mRNA and LNP for phase 3
- Norwood site can support commercial launch (FFF to be done at CMO)
- Potential for >10+ million doses/year from Norwood
Cytomegalovirus (CMV) vaccines: Where do we stand?

Mark Schleiss, MD

Co-Director, Center for Infectious Diseases and Microbiology Translational Research
University of Minnesota
Cytomegalovirus Vaccines 2019: Where do we Stand? What do we Need to Learn?

Mark R. Schleiss, MD

Center for Infectious Diseases and Microbiology
Translational Research
University of Minnesota

schleiss@umn.edu

September 12, 2019
Congenital Cytomegalovirus Infection

- Most common disabling pediatric infection
- Mental retardation, developmental delay, seizures, cerebral palsy, microcephaly, neuronal migration defects
- Major infectious cause of sensorineural hearing loss
Infectious Causes of Neurologic Damage in Infancy

- *H. Influenzae* type B meningitis
- Congenital rubella
- CMV disease

Annualized Cases per Year (US) Pre-vaccine
### Annual Estimated Impact of Congenital CMV Infection and Disease in Europe and the United States

<table>
<thead>
<tr>
<th>Category of Infants</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of live births/yr</td>
<td>8,600,000</td>
</tr>
<tr>
<td>Average rate of congenital CMV infection (%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Total number of newborns with CMV infection</td>
<td>60,200</td>
</tr>
<tr>
<td>Number with symptomatic infection (12.7%)</td>
<td></td>
</tr>
<tr>
<td>Number with fatal disease (~4%)</td>
<td>306</td>
</tr>
<tr>
<td>Number of survivors with sequelae (40-58%)</td>
<td>3058-4434</td>
</tr>
<tr>
<td>Number with asymptomatic infection (87.3%)</td>
<td>52,555</td>
</tr>
<tr>
<td>Number with sequelae (13.5%)</td>
<td>7,095</td>
</tr>
<tr>
<td>Total number with sequelae or death</td>
<td><strong>10,459-11,835</strong></td>
</tr>
</tbody>
</table>

Kenneson, Rev Med Virol 2007;17:253-76
Evidence of Effectiveness of Preconception Immunity in Protection of the Fetus

- Immunity induced by prior CMV in seropositive women of childbearing age protects against secondary infection
  
  Adler, J Infect Dis, 1995; 171:26

- Preconception immunity associated with a 69% reduction in risk transmission to fetus
  
  Fowler, JAMA, 2003; 289:1008

- Risk of fetal infection during documented primary maternal infection of 30-40% compared to ~1% in seropositives
  
  Britt, J Virol 2017; 91:15

- Tremendous economic potential would be realized by CMV vaccine capable of preventing congenital infection
  
  Stratton et al, IOM Report, 1999
CMV Vaccine

If there is evidence that immunity is protective, why is a CMV vaccine such a “difficult” vaccine?

Four Unmet Challenges
Challenge 1

Uncertainty Regarding Correlate(s) of Protective Immunity at the Maternal/Fetal Interface
Viral Particle is Complex...

http://cmv.umn.edu/about-cmv
<table>
<thead>
<tr>
<th>CMV Gene Product</th>
<th>Rationale for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Envelope Glycoproteins</td>
<td></td>
</tr>
<tr>
<td>gB</td>
<td>Major target of neutralizing antibodies; target of CTLs; cornerstone of CMV vaccine development programmes; demonstrated efficacy as subunit vaccine in clinical trials</td>
</tr>
<tr>
<td>gH/gL</td>
<td>Important target of neutralizing antibodies; target of CTLs</td>
</tr>
<tr>
<td>gH, gL, UL128-131 (Pentamer)</td>
<td>Pentamer complex (p65) or gH/gL/UL128/UL130/UL131 on viral envelope; target of neutralizing antibodies; antibodies neutralize CMV infection at epithelial and endothelial cell surfaces; current focus of clinical trials (in combination with gB)</td>
</tr>
<tr>
<td>gH, gL, gO (Trimer)</td>
<td>Target of neutralizing antibody; antibodies to block cell entry/fusion?</td>
</tr>
<tr>
<td>gM/gN</td>
<td>Target of antibody neutralizing antibody responses; has not been tested as CMV subunit vaccine; hypervariability of gN in clinical isolates suggests this protein is under immune selective pressure</td>
</tr>
<tr>
<td>Structural proteins</td>
<td></td>
</tr>
<tr>
<td>pp65</td>
<td>Major target of CTLs; target of non-neutralizing antibody responses; has been evaluated (in combination with gB) in clinical trials</td>
</tr>
<tr>
<td>pp150, pp28</td>
<td>Target of CTLs and antibody responses; no data available from clinical trials</td>
</tr>
<tr>
<td>pp50</td>
<td>Target of CTLs; no data available from clinical trials</td>
</tr>
<tr>
<td>pp71, pp52</td>
<td>Targets of antibody responses; no data available from clinical trials</td>
</tr>
<tr>
<td>Nonstructural proteins</td>
<td></td>
</tr>
<tr>
<td>IE1</td>
<td>Important target of CTLs; target of non-neutralizing antibody responses; has been evaluated (alone, or in combination with gB and UL83 (pp65) in clinical trials</td>
</tr>
</tbody>
</table>
Other Preclinical CMV Vaccine Strategies

• Modified vaccinia virus Ankara (MVA)
• “Dense Body” vaccines
• Polyepitope vaccines
• Soluble pentamer vaccine (CHO)
• Messenger RNA vaccines (Moderna)
• SynCon® vaccine platform
Challenge 2

Safety and Regulatory Concerns About Live, Attenuated CMV Vaccines
**CMV Vaccines In Clinical Trials: Live Attenuated and “DISC” Vaccines**

<table>
<thead>
<tr>
<th>Live Attenuated and Disabled Virus Vaccines</th>
<th></th>
</tr>
</thead>
</table>
| **AD169 vaccine**                           | - Elicited CMV-specific antibodies in seronegative vaccine recipients  
                                           - Significant injection-site and systemic reactogenicity |
| **Towne vaccine (± rhIL12)**                | - Elicits humoral and cellular immune responses  
                                           - Favorable safety profile; no evidence for latency or viral shedding in recipients  
                                           - Reduced CMV disease but not infection in renal transplant recipients  
                                           - Augmented immunogenicity with recombinant IL-12 in Phase I studies |
| **Towne/Toledo chimera vaccines**           | - Favorable safety profile; no evidence for latency or viral shedding in CMV seropositive subjects  
                                           - Attenuated compared to Toledo strain of HCMV  
                                           - No efficacy data available; studies in seronegatives in progress |
| **V160-001 replication-defective vaccine**  | - AD169 backbone with restoration of UL128/130/131 PC components  
                                           - Rendered replication-incompetent by inclusion of ddFKBP/Shld1  
                                           - Administered with alum-based adjuvant  
                                           - Phase I studies ongoing |
Cytomegalovirus Vaccine (V160) in Healthy Adults (V160-001)

- AD169-like virus with repair of frame-shift mutation in ORF encoding UL131, restoring epithelial tropism and pentameric complex formation
- Virus rendered conditionally replication-defective (FKBP/CMV protein fusion) and propagated in presence of stabilizing protein
- Produced in retinal pigment epithelial cells
- Multiple arms, dose range, with or without with or without proprietary aluminum phosphate adjuvant (MAPA) by IM or ID
- Seropositive and seronegative

Comparison of emerging clinical data showing epithelial neutralization by replication defective and mRNA vaccine approaches

Adler et al, J Inf Dis 2019;220:411-9
Month 7 (1 month after the 3rd vaccination)

mRNA-1647
Month 3 (1 month after the 2nd vaccination)

- Both vaccines approach or exceed seropositive controls in respect study
- 3-vaccination schedule for V160 (0,1,6); 2-vaccination for mRNA1647 (0,2)
Challenge 3

Target Population for CMV Vaccine and the Issue of Transmission in the Setting of Re-Infection
Most Congenital CMV Infections Occur in the Context of Preconception Immunity and Maternal Re-Infection

### Intrauterine Transmission of Cytomegalovirus to Infants of Women with Preconceptional Immunity

Suresh B. Boppana, M.D., Lisa B. Rivera, M.P.H., M.B.A., Karen B. Fowler, Dr.P.H., Michael Mach, Ph.D., and William J. Britt, M.D.


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**A**

---

**B**

<table>
<thead>
<tr>
<th>Maternal Serologic Reactivity</th>
<th>Acquisition of New Antibody Specificity</th>
<th>Sequence Homology</th>
<th>Predicted Amino Acid Sequences of the Amino-Terminal Region of Glycoprotein H from CMV Isolates from Seven Infected Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEFORE PREGNANCY</td>
<td>AT DELIVERY</td>
<td>Sequence Homology</td>
<td>Predicted Amino Acid Sequences of the Amino-Terminal Region of Glycoprotein H from CMV Isolates from Seven Infected Infants</td>
</tr>
<tr>
<td>AP86</td>
<td>TO86</td>
<td>AP86 TO86</td>
<td>YLLSHLPSQRYGADAEEALDPHAFHLLLNTYGRPIRFLRENTT</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Positive Positive</td>
<td>AP86 TO86</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive Positive</td>
<td>YLLSHLPSQRYGADAEEALDPHAFHLLLNTYGRPIRFLRENTT</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Negative Negative</td>
<td>YLLSHLPSQRYGADAEEALDPHAFHLLLNTYGRPIRFLRENTT</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive Positive</td>
<td>YLLSHLPSQRYGADAEEALDPHAFHLLLNTYGRPIRFLRENTT</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Negative Negative</td>
<td>YLLSHLPSQRYGADAEEALDPHAFHLLLNTYGRPIRFLRENTT</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Positive Positive</td>
<td>YLLSHLPSQRYGADAEEALDPHAFHLLLNTYGRPIRFLRENTT</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Negative Negative</td>
<td>YLLSHLPSQRYGADAEEALDPHAFHLLLNTYGRPIRFLRENTT</td>
</tr>
</tbody>
</table>
Table 2. Power analysis for Phase III efficacy trials for the prevention of congenital CMV disease by immunizing seronegative women by study endpoint.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine efficacy = 80%</th>
<th></th>
<th>Vaccine efficacy = 50%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate for placebo arm (%)</td>
<td>Rate for vaccine arm (%)</td>
<td>Total no. of subjects needed</td>
<td>Rate for placebo arm (%)</td>
</tr>
<tr>
<td>Maternal infection</td>
<td>50*</td>
<td>10</td>
<td>48</td>
<td>50*</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>2.4</td>
<td>264</td>
<td>12</td>
</tr>
<tr>
<td>Transmission to the fetus</td>
<td>4</td>
<td>1</td>
<td>976</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.075</td>
<td>1310</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.5</td>
<td>1976</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.25</td>
<td>3404</td>
<td>1</td>
</tr>
<tr>
<td>Disease in the newborn</td>
<td>0.4</td>
<td>0.08</td>
<td>8542</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.04</td>
<td>17 154</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Assumes an equal number of vaccine and placebo subjects with an alpha of 0.05 and a beta of 0.8. Calculated by the method of Fleiss.47
### Proposed endpoints for CMV vaccine clinical trials in different target populations

<table>
<thead>
<tr>
<th>Target Population</th>
<th>Objectives</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &lt;2 yrs of age</td>
<td>Prevent maternal and congenital CMV infection by removing an important source of maternal infections. Prevent primary CMV infection which may have long-term deleterious consequences to the host</td>
<td>Rate of CMV infection in vaccinees.</td>
</tr>
<tr>
<td>Adolescent girls</td>
<td>Prevent infection in future mothers and their children (preventing congenital infection) Prevent primary CMV infection which may have long-term deleterious consequences to the host</td>
<td>Rate of CMV infection in vaccinees.</td>
</tr>
<tr>
<td>Women of childbearing age (women likely to become pregnant)</td>
<td>Prevent maternal and congenital CMV infection</td>
<td>Rate of CMV infection in vaccinees.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rate of cCMV infection in their children.</td>
</tr>
<tr>
<td>Hematopoietic stem cell transplant recipients</td>
<td>Prevent CMV disease by reducing the rate of occurrence of surrogate markers</td>
<td>Prevention of CMV viremia (and associated antiviral use) Composite endpoints including CMV disease</td>
</tr>
<tr>
<td>Solid organ transplant recipients</td>
<td>Prevent CMV disease</td>
<td>Prevention of CMV-associated disease (including CMV syndrome) Prevention of CMV viremia (and associated antiviral use)</td>
</tr>
</tbody>
</table>
Employing a Cytomegalovirus Vaccine

- All seronegative adolescents age 12
- Girls 11-13 years of age (MCV4/TdAcP/HPV)
- Seronegative women (seropositives?)
- SOT recipients
- HSCT donors/recipient
- All infants (universal)
- Will transplacental immunity ameliorate CMV disease in infants even if transmission occurs?

Stratton et al, 1999, IOM Report
Griffiths, Vaccine. 2001;19(11-12):1356-62
Challenge 4

Increase Knowledge and Awareness of the Problem of Congenital CMV and Enlist Parents in Advocacy for CMV Research
Conclusions

• There is a major public health need for a vaccine against cytomegalovirus infection, particularly congenital CMV

• A variety of protein and DNA subunit, vectored vaccines, and live attenuated vaccines are in clinical trials

• A better understanding of: 1) the correlates of protection of the fetus; 2) the problems of re-infection and viral immune evasion; 3) the issue of safety of live, attenuated vaccines is needed; 4) increased knowledge and awareness of CMV
Acknowledgements

CIDMTR/University of Minnesota
◆ Craig Bierle
◆ Beth Swanson
◆ Claudia Fernandez
◆ Nelmary Hernandez-Alvarado
◆ Jason Zabeli
◆ Kaitlyn Anderholm

FHCRC
◆ Adam Geballe

VCU
◆ Michael McVoy
◆ Jian Ben Wang
◆ Zainab Almahdi

COH
◆ Don Diamond
◆ Heidi Contreras
◆ Felix Wussow

Hookipa
◆ Anders Lilja
◆ Klaus Orlinger

Leah Henriksen
Kelly Fenton

NICHD
NIAID
March of Dimes
Cytomegalovirus (CMV): An Obstetrician’s Perspective on CMV vaccine

Laura Riley, MD
Obstetrician and Gynecologist-in-Chief
New York-Presbyterian Hospital

Chair of the Department of Obstetrics and Gynecology; Professor of Clinical Obstetrics and Gynecology
Weill Cornell Medical Colle
An Ob’s Perspective on the CMV Vaccine

Laura E. Riley, M.D
Given Foundation Professor and Chair
Obstetrician and Gynecologist-in-Chief
New York Presbyterian Hospital
Epidemiologic factors related to CMV:

• Seropositivity: 40-90% of women ages 15 – 44 years

• Seropositivity increases with demographic factors: lower SES, contact with children <3 yrs, black or Mexican ethnicity, age >25-30 yrs, higher parity, residence in developing country

• Multiple routes of transmission (nonsexual contact, sexual exposure, transfusion, organ transplant, multiple bodily fluids)
Annual Seroconversion Rates

- Pregnant Women: 2.3% (95% CI 2.1-2.4%)
- Healthcare Workers: 2.3% (95% CI 1.9-2.9%)
- Daycare Providers: 8.5% (95% CI 6.1-11.6%)
- Parents of a Child:
  - Non-shedding: 2.1% (95% CI 0.3-6.8%)
  - Shedding: 24% (95% CI 18-30%)

Hyde et al Rev Med Virol 2010; 20; 311
Maternal CMV disease

- Primary CMV - may be symptomatic
- Reactivation of latent CMV – no symptoms
- Reinfection with different strain - may or may not have symptoms

- Current recommendations to test for maternal CMV:
  - Mothers with mono-like illness
  - Fetuses with anomalies or findings c/w congenital CMV
## M-F Transmission Rate (Primary maternal disease)

<table>
<thead>
<tr>
<th>Period</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preconception period (2 months – 3 weeks prior to conception)</td>
<td>5.2%</td>
</tr>
<tr>
<td>Periconception period (3 weeks – 3 weeks after conception)</td>
<td>16.4%</td>
</tr>
<tr>
<td>First Trimester (4 weeks – 12 weeks)</td>
<td>36.5%</td>
</tr>
<tr>
<td>Second Trimester</td>
<td>40.1%</td>
</tr>
<tr>
<td>Third Trimester</td>
<td>65.0%</td>
</tr>
</tbody>
</table>

Picone et al. Prenat Diagn 2013; 33: 751
Timing of maternal infection is important!

Study of 248 Primary Maternal Infection Newborn symptoms

- preconception (1-10 weeks before LMP) 0/24
- periconception (1 week prior to LMP – 4 to 6 weeks) 1/29
- 1st trimester (5-13 and 6 weeks) 7/83
- 2nd trimester 4/76
- 3rd trimester 0/36

Enders et al. J Clin Virol 2011; 52:244
M-F Transmission Rate

If mother has reactivated or infection with a new strain:

0.15-2%

Severity of disease: unchanged

Mussi-Pinhata et al. JID 2018; 218:1200
Fowler et al. NEJM 1992; 326:663
**M-F transmission w/ reactivated or reinfection of CMV**

- “The true impact of recurrent maternal infection on both the incidence of congenital CMV infection and the long-term neurologic deficits in children .is not known.”

- Diagnosis of non-primary disease is difficult using CMV-IgG, CMV-IgM, CMV IgG avidity and maternal viremia yields variability despite known fetal infection.

Current Prevention Strategies

• No routine screening

• Education about personal hygiene, avoid kissing less than 6 years old, sharing food etc., clean surfaces

• Breastfeeding benefits “outweigh” risks

• If recent infection, wait 6 months

Public awareness:

CMV is short for cyto-megalovirus

CMV is preventable

Pregnant women who already have young children, or who work with young children, are at highest risk of catching CMV

Avoid contact with saliva - Kiss kids under the age of 6 on the forehead instead of lips or cheek

Wash your hands after contact with bodily fluids of kids under the age of 6

75% of toddlers have CMV in their urine or saliva in studies at child-care settings

Don't share utensils, drinks, or toothbrushes with kids under the age of 6

Risk of catching CMV can be reduced by simple hygiene precautions

DON'T SHARE

Don't share dummies, cutlery, drinks or food with anyone
Don't share wet kisses with small children

WASH WITH CARE

Wash hands and any items that have come into contact with bodily fluids with soap and water

DO WEAR

Use condoms during sex after conception

Avoid kissing on the mouth. Kiss on the cheek or give them a hug

The CMV virus is destroyed by soap and water

It's very difficult to tell if others are infected so follow hygiene precautions around everyone
Current Treatment Strategies

• CMV IVIG - doesn’t work!

• Antiviral medications – focused on ameliorating symptoms of congenital CMV rather than prevention of congenital disease
This Ob’s Perspective on a CMV Vaccine:

• Safety

• Efficacy

• Durability

• Much needed intervention for the most common congenital viral infection affecting 20,000-40,000 newborns/yr in U.S.
Selected references:


CMV commercial opportunity

Stéphane Bancel
Chief Executive Officer
Our development plan for our CMV vaccine mRNA-1647

- Preparing for the pivotal phase 3 trial

- Near-term initiation of the dose-confirmation phase 2 (supply and clinical operations preparation is already advanced)

- Rapid phase 2 with 252 healthy subjects and a three-month interim analysis (IA) endpoint

- Phase 3 to demonstrate prevention of CMV infection in a sub-8,000 participant study in healthy women
CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity

Women of child bearing age (WOCBA)
~ 8 million (USA+EU only)

Adolescents
HPV vaccine precedent

Infants
Early vaccination
Rubella precedent (ubiquitous MMR vaccine)
CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity
- Total addressable market could be as high as 40-70 million vaccinations per year
CMV vaccine infant cohort opportunity size

<table>
<thead>
<tr>
<th>2030 Birth Cohort Opportunity Size</th>
<th>2040 Birth Cohort Opportunity Size</th>
<th>2050 Birth Cohort Opportunity Size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td><strong>Births</strong></td>
<td><strong>Region</strong></td>
</tr>
<tr>
<td>U.S.</td>
<td>~3.6 M</td>
<td>U.S.</td>
</tr>
<tr>
<td>Europe</td>
<td>~5.4 M</td>
<td>Europe</td>
</tr>
<tr>
<td>Japan</td>
<td>~0.9 M</td>
<td>Japan</td>
</tr>
<tr>
<td>10% of China</td>
<td>~1.4 M</td>
<td>25% of China</td>
</tr>
<tr>
<td>10% of India</td>
<td>~2.5 M</td>
<td>25% of India</td>
</tr>
<tr>
<td>10% of ROW</td>
<td>~8.8 M</td>
<td>25% of ROW</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>~22.6 M</td>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

Accessible male & female birth cohort exceeding 20 million around the anticipated time of potential launch.

10 years later, improved market access expands the cohort to over 40 million.

Further market maturation grows the addressable cohort to more than 70 million by 2050.

Source: UN Population Division; INED; UNICEF.
CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity
- Total addressable market could be as high as 70 million vaccinations per year
- Focused sales effort: OBGYN and Pediatricians
CMV is a blockbuster commercial opportunity

• Large unmet medical need with no approved vaccine
• Indication expansion opportunity
• Total addressable market could be as high as 70 million vaccinations per year
• Focused sales effort: OBGYN and Pediatricians
• Opportunity to leverage social media during Phase 3 for pre-launch activities to educate a motivated initial target population, women of childbearing age (WOCBA)
We aim to raise CMV awareness in the medical community and the public to accelerate trial recruitment and launch uptake

<table>
<thead>
<tr>
<th>Strategic Initiatives</th>
<th>Description</th>
<th>Beneficial to Trial Recruitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 <strong>Partner with national and regional CMV advocacy groups</strong></td>
<td>• Establishing early relationships with advocacy groups to influence policy and guidelines</td>
<td>✔️</td>
</tr>
<tr>
<td>2 <strong>Educate OB/GYNs, pediatricians, and PCPs about congenital CMV infection</strong></td>
<td>• Educating physicians in the near term, particularly with PCPs who have limited awareness</td>
<td>✔️</td>
</tr>
<tr>
<td>3 <strong>Distribute educational materials to key populations through physicians</strong></td>
<td>• Informational pamphlets on risks of congenital CMV infection and current prevention tactics can be distributed through OB/GYN, pediatrician, and PCP offices to engage key populations</td>
<td>✔️</td>
</tr>
<tr>
<td>4 <strong>Leverage online platforms to raise CMV awareness in key populations</strong></td>
<td>• Additional raising of awareness of CMV and its consequences in key populations</td>
<td>✔️</td>
</tr>
<tr>
<td>5 <strong>Promote awareness of mRNA-1647</strong></td>
<td>• Emphasizing antibody titer profile of mRNA-1647</td>
<td>◼️</td>
</tr>
</tbody>
</table>

Source: ClearView
CMV is a blockbuster commercial opportunity

- Large unmet medical need with no approved vaccine
- Indication expansion opportunity
- Total addressable market could be as high as 70 million vaccinations per year
- Focused sales effort: OBGYN and Pediatricians
- Opportunity to leverage social media during Phase 3 for pre-launch activities to educate a motivated initial target population, women of childbearing age (WOCBA)
- Pricing power for innovative vaccines due to value proposition (GARDASIL® US pricing=$450)

*GARDASIL® is a registered trademark of Merck & Co., Inc.*
CMV is a blockbuster commercial opportunity

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- Vaccine sales are annuity-like, scaling with population growth
- Innovative vaccines have EBIT margins of approximately 50%

*GARDASIL ® is a registered trademark of Merck & Co., Inc.
## R&D Day 2019 agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda Item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30–8:30 AM</td>
<td>Sign-in, Coffee, Breakfast</td>
<td>60 min</td>
</tr>
<tr>
<td>8:30–8:40 AM</td>
<td>Introduction</td>
<td>Stéphane Bancel</td>
</tr>
<tr>
<td>8:40–10:00 AM</td>
<td>CMV</td>
<td>Tal Zaks, MD, PhD&lt;br&gt;Sallie Permar, MD, PhD, Duke University School of Medicine&lt;br&gt;Tal Zaks, MD, PhD&lt;br&gt;Juan Andres&lt;br&gt;Mark Schleiss, MD, University of Minnesota&lt;br&gt;Laura Riley, MD, Weill Cornell Medical College&lt;br&gt;Stéphane Bancel</td>
</tr>
<tr>
<td>10:00–10:30 AM</td>
<td>Q&amp;A</td>
<td></td>
</tr>
<tr>
<td>10:30–10:40 AM</td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>10:40–11:10 AM</td>
<td>Immuno-oncology</td>
<td>Tal Zaks, MD, PhD&lt;br&gt;Keith Flaherty, MD, Massachusetts General Hospital</td>
</tr>
<tr>
<td>11:10–11:50 AM</td>
<td>Antibody against Chikungunya virus</td>
<td>Tal Zaks, MD, PhD</td>
</tr>
<tr>
<td>11:50–12:20 AM</td>
<td>Methylmalonic acidemia</td>
<td>Gregory Enns, MD, Stanford University</td>
</tr>
<tr>
<td>12:20–12:30 PM</td>
<td>Conclusion</td>
<td>Stéphane Bancel</td>
</tr>
<tr>
<td>12:30–1:00 PM</td>
<td>Q&amp;A</td>
<td>Moderna Team</td>
</tr>
<tr>
<td></td>
<td>Lunch</td>
<td></td>
</tr>
</tbody>
</table>

**September 12, 2019**
Cancer vaccines and Intratumoral immuno-oncology

Tal Zaks, MD, PhD
Chief Medical Officer
Modalities

- Prophylactic vaccines
- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic secreted therapeutics
- Systemic intracellular therapeutics
### Cancer Vaccines

<table>
<thead>
<tr>
<th>Modality</th>
<th>Program #</th>
<th>Program Indication</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-4157</td>
<td>Personalized cancer vaccine (PCV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-50 global profit sharing with Merck</td>
</tr>
<tr>
<td>NCI-4650</td>
<td>Personalized cancer vaccine (PCV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-50 global profit sharing with Merck</td>
</tr>
<tr>
<td>mRNA-5671 V941</td>
<td>KRAS vaccine CRC, NSCLC, pancreatic cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: NCI-4650 differs from mRNA-4157 in its neoantigen selection process.
mRNA advantages in immuno-oncology

- **Natural cellular processing** *(antigen presentation, membrane proteins)*

- **Combinations** *(neoantigens, immuno-stimulatory agents)*

- **Single process** and single, multi-product facility enables **rapid production** and economies of scale

- **Transient, localized** immuno-stimulatory effect at the tumor site

- mRNA sequences can be engineered to **reduce off-target effects**
mRNA opportunity in immuno-oncology
Combining with PD1/PDL1 inhibitors to improve the benefit to patients

**Immuno-oncology today**

- Powerful antitumor responses can be achieved by activating antigen specific T cells
- Checkpoint inhibitors available to unleash tumor-reactive T cells and provide significant benefit to a subset of patients
- However, majority of patients with epithelial cancers do not respond fully or at all to checkpoint inhibitors

**Cancer vaccines**

- Our vaccines focused on expressing neoantigens found in a particular cancer
- Potential to improve efficacy of checkpoint inhibitors by increasing number and antitumor activity of T cells that recognize neoantigens

**Intratumoral immuno-oncology**

- Focused on activating T cells and transforming the tumor micro-environment to drive anti-cancer response
- In combination with checkpoint inhibitors
Moderna’s mRNA vaccines elicit T cell activation for curative intent cancer therapy
Personalized cancer vaccine (mRNA-4157)
Designed to target an individual patient’s unique tumor mutations

- Partnered with Merck (Keytruda combo)
- Interim Phase 1 data presented at ASCO 2019
- Dosed for up to 9 cycles
- Randomized Phase 2 trial in adjuvant melanoma started

**Tissue Samples**
Tumor (biopsy) and Normal (blood)

**Next Generation Sequencing (NGS)**
Mutations identified in protein neoantigen and major histocompatibility complex

**Vaccine Design**
Up to 34 neoantigens
Automated algorithm integrated with workflow

**mRNA encoding up to 34 neoantigens**
Personalized Cancer Vaccines

**mRNA-4157: Phase 1 data**

**Clinical & regulatory update**

- Continuing to enroll patients in phase 1 safety, tolerability and immunogenicity trial monotherapy and in combination with pembrolizumab
- Part C&D: Continuing to enroll patients
- Interim safety, tolerability immunogenicity data presented at ASCO 2019
- First patients consented for phase 2 Randomized Controlled Trial

**Select clinical data**

- **Safety**: mRNA-4157 is well tolerated at all dose levels studied with no DLTs reported. No mRNA-4157 related grade 3/4 AE or SAE was reported. The most common grade 2 adverse events were fatigue, soreness at the injection site, colitis and myalgias.

- **Activity**: Neoantigen specific CD8 T-cell responses were detected in 10 out of 18 class I neoantigens in patient 40033, the first patient dosed at 1 mg who underwent apheresis. 100% of positive CD8 T-cell responses post vaccination were to neoantigens with a high predicted binding affinity of <500 nm

- **Early clinical**: Clinical responses have been seen in 6 out of 20 patients treated with mRNA-4157/pembrolizumab combination. Of these 6 patients, 2 responses have been seen in patients previously treated with PD-(L)1 inhibitor and 1 patient achieved CR prior to vaccination

---

1 Data cutoff as of May 10, 2019
KRAS opportunity: mutation is present in >20% of human cancers

- KRAS is a key regulator of cell proliferation and survival; mutations cause dysregulated cell proliferation
- One of the most frequently mutated oncogenes in human cancers
- Mutations found principally in pancreatic cancer, lung cancer, and colorectal cancer
- Most prevalent KRAS mutations G12D, G12V, G13D, and G12C 80-90% of KRAS mutations

![KRAS Mutation Prevalence (% with KRAS mutation)](image)

**Percentage of KRAS mutation type by histology**

<table>
<thead>
<tr>
<th>Histology</th>
<th>G12C</th>
<th>G12D</th>
<th>G13D</th>
<th>G12V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>3%</td>
<td>13%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Lung Adenocarcinoma</td>
<td>13%</td>
<td>4%</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>1%</td>
<td>34%</td>
<td>&lt;1%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Patients whose tumors harbor KRAS mutations have worse outcomes
KRAS Vaccine

mRNA-5671/Merck V941:

KRAS Overview:

• KRAS is a key regulator of cell proliferation and survival; mutations cause dysregulated cell proliferation
• One of the most frequently mutated oncogenes in human cancers; mutation is present in >20% of human cancers
• Mutations found principally in pancreatic, lung and colorectal cancers
• Recognition of mutated KRAS epitopes by T-cells can lead to cancer cell regression as proven by adoptive T-cell transfer

mRNA-5671/Merck V941:

• Codes for the four most prevalent KRAS mutations G12D, G12V, G13D, and G12C covering 80-90% of KRAS mutations

---

1 T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer, NEJM, Eric Tran, Ph.D., et al.
KRAS vaccine (mRNA-5671)/Merck V941
Patients dosed in Phase 1 trial

Phase 1 study overview

— A Phase 1, Open-Label, Multicenter Study to Assess the Safety and Tolerability of mRNA-5671/Merck V941 as a Monotherapy and in Combination With Pembrolizumab in Participants With KRAS Mutant Advanced or Metastatic Non-Small Cell Lung Cancer, Colorectal Cancer or Pancreatic Adenocarcinoma

— Selecting for HLA subtypes (HLA-A*1101 and/or HLA-C*0802) most likely to respond
## Intratumoral Immuno-Oncology

<table>
<thead>
<tr>
<th>Modality</th>
<th>Program #</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Intratumoral immuno-oncology</td>
<td>mRNA-2416</td>
<td>OX40L Solid tumors/lymphoma Advanced ovarian Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-2752</td>
<td>OX40L+IL23+IL36γ (Triplet) Solid tumors/lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>MEDI1191</td>
<td>IL12 Solid tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50-50 U.S. profit sharing; AZ to pay royalties on ex-U.S. sales</td>
</tr>
</tbody>
</table>
OX40L (mRNA-2416)

**OX40L Overview:**
- OX40L is a potent co-stimulator, which promotes T-cell proliferation and enhanced survival in the presence of antigen

**mRNA-2416:**
- mRNA-2416 encodes for OX40L, which is a membrane protein that we believe cannot be manufactured by recombinant technologies
OX40L (mRNA-2416)

**OX40L expression demonstrated: progressing to phase 2 cohort**

**Clinical:**

- Interim analysis SITC 2018: mRNA-2416 is tolerable at all dose levels studied with no DLTs reported and the majority of AE’s being grade 1 or 2
- A clear increase in OX40L protein expression from mRNA-2416 was observed in both tumor and stromal regions in three out of the five post-treatment biopsies collected from injected tumors
- Repeat dosing through 12 doses (6 cycles) continues at highest levels (8mg) in phase 1
- Phase 2 cohort in patients with ovarian cancer, including in combination with durvalumab is being prepared

OX40L protein production in tumor cells of an injected lesion of a patient with ovarian cancer
OX40L+IL23+IL36γ (Triplet) (mRNA-2752)

**OX40L+IL23+IL36γ (Triplet) Overview:**
- OX40L powerful co-stimulatory protein that enhances T-cell expansion, function and memory formation
- IL23 and IL36γ have established roles in mediating immune responses

**mRNA-2752:**
- mRNA-2752 encodes for OX40L which is a membrane protein and secreted pro-inflammatory cytokines IL-23 and IL-36γ
OX40L+IL23+IL36γ (Triplet) (mRNA-2752)

Phase 1 ongoing; First patient dosed in combination durvalumab

Key Objectives

• Evaluate safety and tolerability of mRNA-2752 administered alone and in combination with checkpoint inhibitors

• Define MTD and recommended dose for expansion for mRNA-2752 alone and in combination with durvalumab

• Intended to assess:
  • Anti-tumor activity
  • Protein expression in tumors
  • Pharmacokinetics

Patients dosed in combination arm
**IL12 (MEDI1191)**

**IL12 Overview:**
- IL12 is a potent immune modulator associated with type 1 immune response and production of interferon gamma

**MEDI1191:**
- Encodes for IL12, a secreted cytokine that acts locally in the tumor microenvironment (TME)
IL12 (MEDI1191)
First patient dosed in phase 1

**Preclinical:**
Approximately 30% complete responders with highest dose tested for mL12 mRNA in MC38 mouse model study

- Vehicle Control
- mL12 mRNA at 0.05 µg
- mL12 mRNA at 0.5 µg
- mL12 mRNA at 5 µg

70% complete responders at highest tested dose for mouse IL12 mRNA with PD-L1 antibody in MC38 mouse model study

**Clinical:**
- Phase 1, open-label, multicenter, dose escalation and expansion study of MEDI1191 administered intratumorally as monotherapy and in combination with durvalumab in subjects with advanced solid tumors
- Key objectives to evaluate safety and tolerability in monotherapy and combination arms and objective response rate in patients within expansion arms
- First patient dosed with IL12 monotherapy in phase 1 trial
Immunoncology

Keith T. Flaherty, MD

Director of Henri and Belinda Termeer Center for Targeted Therapy, Cancer Center;
Director of Clinical Research, Cancer Center
Massachusetts General Hospital
The remaining unmet need: the aftermath of the PD-1/PD-L1 revolution

Keith T. Flaherty, M.D.
Massachusetts General Hospital Cancer Center
Kaplan-Meier Estimates of Progression-free Survival: Pembrolizumab

Hamid O et al. ASCO 2018
Complete Responders Who Stopped Pembrolizumab for Observation (N = 61)

- 59 (97%) of responses were maintained

Robert et al. ASCO 2016

Time on therapy
- Complete response
- Time to last scan
- Partial response
- Last dose

Time, months

Robert et al. ASCO 2016
“Inflamed” tumors are more likely to respond to PD-1 antibody therapy

Tumor gene expression, but not immune checkpoints sorts response/non-response

Hugo et al. Cell 2016
Interrogating mechanism of action & resistance
MGH Termeer Center checkpoint antibody serial biopsy cohort
Two CD8+ T cell states associate with CPB response

Sade-Feldman et al. Cell 2018
Mutational burden tightly correlates with T cell inflammation across cancer types

...and mutation burden correlates with response rates & approvals

Adapted from Alexandrov et al. Nature 2013
Immunizing against mutated neoantigens

Ott et al. Nature 2018
Anti-KRAS T cell transfer shows human efficacy (Rosenberg, NIH)
Tissue Specific
eg. CD19, BCMA, Mesothelin

Tumor Specific
eg. Neoantigen. NY-ESO, CTA\(g\)

Patient Specific
eg. Neoantigen. HLA-Allele

Bispecific
CAR-T, ADC

ImmTAC

CPI, IDO Vaccination

Self
Surface
Replace Immunity

Non-Self
Intracellular
Harness Immunity

Tolerance

Personalization

HLA-restriction
Patient Specific
<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Combination</th>
<th>Tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAMPs</td>
<td>CpG (CMP-001)</td>
<td>Pembrolizumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>CpG (SD-101)</td>
<td>Pembrolizumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>CpG (IMO-2125)</td>
<td>Ipilimumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>STING agonists (ADU)</td>
<td>Ipilimumab</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Oncolytic viruses</td>
<td>T-VEC (HSV-1)</td>
<td>None</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>T-VEC (HSV-1)</td>
<td>Ipilimumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>T-VEC (HSV-1)</td>
<td>Pembrolizumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>HF10 (HSV-1)</td>
<td>Ipilimumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>Coxsackievirus A21</td>
<td>Ipilimumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Vector encoded IL-12</td>
<td>None</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Monoclonal AB</td>
<td>Ipilimumab</td>
<td>Nivolumab</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>INTUVAX (allo DC)</td>
<td>None</td>
<td>GISTS</td>
</tr>
</tbody>
</table>
Summary of lesion-level and patient-level responses to T-VEC (ITT population)


*Exclusion criteria of OPTiM limited the number and size of visceral metastases – please see slide notes for details. Vertical axis depicts maximal change in individual tumour lesion size (products of the 2 largest perpendicular diameters) from baseline. Lesions with ≥ 2 measurements recorded at 2 separate time points. Patients with ≥ 1 lesion(s) with ≥ 2 measurements recorded at 2 separate time points. Assessed by the investigators with modified WHO criteria.

<table>
<thead>
<tr>
<th></th>
<th>Lesion, % n = 2116</th>
<th>Patient, % n = 277</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% decrease</td>
<td>64 OR 32</td>
<td></td>
</tr>
<tr>
<td>100% decrease</td>
<td>47 CR 15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Lesion, % n = 981</th>
<th>Patient, % n = 177</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% decrease</td>
<td>34 OR 18</td>
<td></td>
</tr>
<tr>
<td>100% decrease</td>
<td>22 CR 6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Lesion, % n = 177</th>
<th>Patient, % n = 79</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50% decrease</td>
<td>15 OR 14</td>
<td></td>
</tr>
<tr>
<td>100% decrease</td>
<td>9 CR 3</td>
<td></td>
</tr>
</tbody>
</table>
OS data analysis (ITT population and subgroups)\(^1\)

Patients at risk:

<table>
<thead>
<tr>
<th>Patients at risk:</th>
<th>T-VEC</th>
<th>GM-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>269</td>
<td>141</td>
<td></td>
</tr>
<tr>
<td>230</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>187</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>159</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>145</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>125</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>46</td>
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</tr>
<tr>
<td>66</td>
<td>36</td>
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</tr>
<tr>
<td>36</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Events/n (%) |

<table>
<thead>
<tr>
<th>Events/n (%)</th>
<th>T-VEC</th>
<th>GM-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>189/295 (64)</td>
<td>101/141 (72)</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI), months |

<table>
<thead>
<tr>
<th>Median (95% CI), months</th>
<th>T-VEC</th>
<th>GM-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>23.3 (19.5–29.6)</td>
<td>18.9 (16.0–23.7)</td>
<td></td>
</tr>
</tbody>
</table>

HR, 0.79 (95% CI, 0.62–1.00)  
Log-rank P = 0.051  
Median follow-up = 44.4 months (range 32.4–58.7)


\(^1\)Andtbacka, JCO 2015
MASTERKEY-265 Phase 1b T-VEC/pembrolizumab – responses

**Injected lesions**

Change in tumour area from baseline | n (%)  
--- | ---  
≥ 25% | 4 (8)  
< 25% to ≥ -50% | 5 (10)  
< -50% to ≥ -100% | 3 (6)  
< -100% | 38 (76)

**Non-injected, non-visceral lesions**

Change in tumour area from baseline | n (%)  
--- | ---  
≥ 25% | 8 (34.8)  
< 25% to ≥ -50% | 5 (21.7)  
< -50% to ≥ -100% | 0  
< -100% | 10 (43.5)

**Non-injected, visceral lesions**

Change in tumour area from baseline | n (%)  
--- | ---  
≥ 25% | 9 (37.5)  
< 25% to ≥ -50% | 7 (29.2)  
< -50% to ≥ -100% | 4 (16.7)  
< -100% | 4 (16.7)

*Patients with Stage IIIb/C, IV M1a (n = 9) and with Stage IV M1b/c (n = 12)
Epacadostat + pembrolizumab
ECHO-202 phase 1 preliminary efficacy in melanoma (N=19)

ORR = 58%, DCR = 74% by RECIST v1.1

Gangadhar TC, et al. ESMO 2016; poster #1110PD.
T-VEC: Converting an immune desert into a T cell inflamed?

Data from MASTERKEY-265 phase Ib trial:¹
- T cell infiltrate observed following T-VEC
- Injected and non injected lesions showed marked increase in CD8+ T cells
- Baseline biomarker
  - Baseline CD8+ T cells nor INF-γ signature were associated with response
- On treatment biomarker:
  - Responders had increased CD8+ T cells, elevated PD-L1 and IFN-γ signature after T-VEC
  - This suggests T-VEC + PD-1 MoA involves reprogramming of the tumor µ-environment

¹ Ribas, *Cell* 2017
Phase 2 T-VEC combination study with ipilimumab – best change in overall tumour area from baseline

**T-VEC + ipilimumab (n = 89)**

- Change tumour area from baseline
  - Any: 53 (60)
  - ≤ -50%: 45 (51)
  - -100%: 22 (25)

**Ipilimumab (n = 86)**

- Change tumour area from baseline
  - Any: 46 (54)
  - ≤ -50%: 30 (35)
  - -100%: 17 (20)

---

1 Chesney, JCO 2018

ORR 39% vs. 18%

P = 0.002
Phase 1b, CVA21 + ipilimumab MITCI study in Stage IIIC/IV unresectable melanoma: preliminary analysis of safety

- No DLTs have been reported in 18 patients who received treatment
- One Grade 3 or higher treatment-related AE was reported (ipilimumab-related fatigue)

**Best overall response**

<table>
<thead>
<tr>
<th>Response rate (irRC), n (%)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3 (17.6)</td>
<td>6 (35.3)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>BORR (CR + PR)</td>
<td>9 (52.9)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCR (CR + PR + SD)</td>
<td>14 (82.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Intent-to-treat population: 17 patients evaluable for tumour assessment; †BORR in ipilimumab-naïve patients: 57.1%. BORR, best overall response rate.
TLR 9 agonist: CMP-001

• CMP-001 is a virus-like particle-packaged TLR-9 agonist
• Activity seen in melanoma patients having failed PD-1 mono or combo in the CMP-001-001 study\(^1\)
• 69 subjects enrolled
  – ORR 22.5% for q1w (n=40) cohort
  – ORR 7.7% for q3w (n=13) cohort
  – ORR 33.3% for q1w (3 and 5 mg, n=18) cohort
  – Responses seen in non injected lesions
• TR part showed increase CD8+ infiltrate and PD-L1 expression

\(^1\) Milhem, AACR 2018
Intratumor CTLA-4 combined with PD-1 combos

**Intratumor CTLA-4 blockade**

- NCT02857569: 65 melanoma Patients (IGR)
  - Ipi 3 (IV) + nivo 1 x 4, followed by nivo 3 mg/kg q2w till PD
  - Ipi 0.3 (IT) + nivo 1 x 4, followed by nivo 3 mg/kg q2w till PD

**Systemic PD-1 blockade**

ESMO 2018 | Munich | September 22nd 2018
Injecting visceral disease?

- With advances in interventional radiology, most lesions become injectable
- Clinical trials looking at feasibility have started and results are eagerly awaited
- Examples:
  - Talimogene Laherparepvec for the Treatment of Peritoneal Surface Malignancies (NCT03663712)
  - Trial to Evaluate the Safety of Talimogene Laherparepvec Injected Into Liver Tumors Alone and in Combination With Systemic Pembrolizumab (MASTERKEY-318)
  - ...
Take-home messages

• Immunotherapy advances have been almost entirely on the basis of disrupting PD-1/PD-L1 interactions
• As predictive markers are elaborated for PD-1 antibody response prediction, it is increasingly clear what is lacking in non-responders
• Vaccines are receiving renewed interest as a means of reshaping T cell repertoire
• Intratumoral therapy has proven capable of influencing distant disease outcomes
• More so than systemic therapies, intratumor therapy platforms appear capable of remodeling the tumor-immune microenvironment with multiple interventions at once
• Intermediate markers of mechanistic effect (in tumors) are needed for both vaccines and intratumoral therapy
Acknowledgements

**MGH Melanoma group**
Ryan Sullivan
Genevieve Boland
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Moshe Sade-Feldman
Arnav Mehta
Dennie T Frederick
David Lieb
Benchun Miao
Gyulnara Kasumova
Michelle Kim
Xue Bai
Patrick Kurpaska
Systemic Therapeutics - Secreted and Intracellular

Tal Zaks, MD, PhD
Chief Medical Officer
Progress by modality

- Prophylactic vaccines
- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic secreted therapeutics
- Systemic intracellular therapeutics
## Systemic secreted therapeutics

<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program</th>
<th>Indication</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1944</td>
<td></td>
<td></td>
<td>Antibody against Chikungunya virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td>AZD7970</td>
<td></td>
<td>Relaxin</td>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DARPA funded</td>
</tr>
<tr>
<td>mRNA-3630</td>
<td></td>
<td>α-GAL</td>
<td>Fabry disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

- **mRNA-1944**: Antibody against Chikungunya virus
- **AZD7970**: Relaxin
- **mRNA-3630**: α-GAL
## Systemic secreted therapeutics

<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program Indication</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
</tbody>
</table>
Antibody against Chikungunya virus (mRNA-1944)
mRNA-1944 contains two mRNAs that encode for the heavy and light chains of CHKV-24 antibody, which may confer passive immunity.
Antibody against Chikungunya virus (mRNA-1944)

Preclinical evidence that mRNA-1944 encodes for functional antibody against Chikungunya virus

Species: Mouse

Expression of antibody against Chikungunya virus

Survival after prophylactic vaccination with mRNA-1944

mRNA-1944 produces an antibody against Chikungunya virus that is

- Functional
- Protective
- Translates between pre-clinical species

Species: NHP

Expression of antibody against Chikungunya virus with repeat dosing of mRNA-1944 in non-human primate study

Therapeutic level for autoimmune and oncology drugs

Expected protective level

C_max 16.2 µg/mL

C_max 28.8 µg/mL

Human IgG [mg/mL]

PBS

mRNA-1944 [0.3 mg/kg]

mRNA-1944 [1 mg/kg]

mRNA-1944 [3 mg/kg]

Dose 1

Dose 2

Time [hrs]

Human IgG [mg/mL]

LLOQ
Antibody against Chikungunya virus (mRNA-1944)

**Trial design**

- Randomized, placebo-controlled, single ascending dose study in healthy adults
- All subjects received premedication with antihistamines
- No subjects received corticosteroids (permitted by protocol)

**Key Objectives**

- **Safety**: Evaluate safety and tolerability of escalating doses of mRNA-1944 administered via intravenous infusion
- **Translation of protein**: Evaluate pharmacology of mRNA-1944
- **Activity**: Determine ability of antibody to neutralize viral infection
Antibody against Chikungunya virus (mRNA-1944)

Protective antibody levels of >1 µg/mL expected to endure at least 16 weeks at the middle dose of 0.3 mg/kg

Pharmacology

- Administration of mRNA-1944 resulted in dose-related increase in levels of CHKV-24
- Half life ($t_{1/2}$) of antibody was 62 days
- Middle and high dose (0.3 and 0.6 mg/kg) projected to exceed 1 µg/mL target for at least 16 weeks

<table>
<thead>
<tr>
<th>Cohort</th>
<th>0.1 mg/kg (N=6)</th>
<th>0.3 mg/kg (N=6)</th>
<th>0.6 mg/kg (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (µg/mL)</td>
<td>2.0</td>
<td>7.9</td>
<td>10.2</td>
</tr>
<tr>
<td>$C_{max}$ range (µg/mL)</td>
<td>1.1-3.1</td>
<td>6.3-10.0</td>
<td>7.0-14.2</td>
</tr>
<tr>
<td>$C_{max}$ % CV</td>
<td>40.6%</td>
<td>18.2%</td>
<td>29.7%</td>
</tr>
</tbody>
</table>
Antibody against Chikungunya virus (mRNA-1944)
mRNA-1944 driven protein expression results in functional antibody (CHKV-24)

Serum neutralization activity 48 hr after mRNA-1944 administration

- Neutralizing antibody titers observed at all dose levels, indicating functional antibody production by mRNA-1944
- All placebo subjects below the lower limit of detection
- 100% of subjects administered 0.3 and 0.6 mg/kg had titers >100
Antibody against Chikungunya virus (mRNA-1944)

**Summary of related adverse events**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=6)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>mRNA-1944 0.1 mg/kg (N=6)</td>
<td>Feeling of warmth, transient (1)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>mRNA-1944 0.3 mg/kg (N=6)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>mRNA-1944 0.6 mg/kg (N=4)</td>
<td>Sinus tachycardia, fever, infusion associated shivering, lightheadedness, hypotension</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Subject 1</td>
<td>None</td>
<td>Nausea, emesis</td>
<td>None</td>
</tr>
<tr>
<td>Subject 2</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Subject 3</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Subject 4</td>
<td>Chills, headache, lightheadedness, gaseousness</td>
<td>EKG abnormal (T wave inversion), emesis, nausea, fever</td>
<td>Sinus tachycardia, elevated WBC</td>
</tr>
</tbody>
</table>

- All AEs were transient and resolved spontaneously without treatment
- No serious AEs in the study
- No meaningful changes in liver or kidney laboratory results
Antibody against Chikungunya virus (mRNA-1944)

Translation from preclinical species to humans

- Solid line = Median predicted
- Shaded area = 90% prediction interval
- Symbols = Individual participant observations
Conclusions: mRNA-1944 achieved the target level of functional protein translation at a well tolerated dose

- Administration of mRNA-1944 resulted in dose-dependent increases in levels of antibody against Chikungunya (CHKV-24)
- Neutralizing antibodies were observed at all dose levels, indicating functional antibody production by mRNA-1944
- None of the participants treated with mRNA-1944 at the low (0.1 mg/kg) or middle (0.3 mg/kg) doses experienced significant adverse events (AEs). Three of the four participants at the high (0.6 mg/kg) dose had infusion related AEs, with the highest grade by subject being Grade 1 (n=1), Grade 2 (n=1) and Grade 3 (n=1)
- mRNA-1944 at 0.3 mg/kg and 0.6 mg/kg provides antibody levels that are expected to be protective against Chikungunya infection (>1 µg/mL) for at least 16 weeks, supporting further development.
- mRNA to protein translation in human was predicted by preclinical data
MRNA-1944 enables Moderna's systemic therapeutics

- For the first time, the systemic administration of an mRNA containing LNP has been demonstrated to produce a fully functional complex protein in humans
- Dose dependent pharmacology has been fully predicted from preclinical species with no loss of potency
- Target therapeutic concentrations have been achieved at a well tolerated dose in a healthy volunteer population
- We believe these data strongly support the continued development of our systemic rare disease therapeutic modality that targets both secreted and intracellular proteins
Progress in the systemic intracellular therapeutics modality to date

<table>
<thead>
<tr>
<th>Clinical</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Phase 1/2</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Recruiting patients</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>IND Open</td>
<td></td>
<td></td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Natural history study</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>N/A</td>
</tr>
<tr>
<td>initiated</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>N/A</td>
</tr>
<tr>
<td>Successful INN-enabling</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GLP toxicology studies</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Pre-clinical activity</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>and dose dependent</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>pharmacology in animal</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>models</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Systemic intracellular therapeutics

- **MMA** mRNA-3704
- **PA** mRNA-3927
- **PKU** mRNA-3283
- **GSD1a** mRNA-3745

Sites open for MMA phase 1/2 trial and actively recruiting patients

**MMA (mRNA-3704)** utilizes the same LNP formulation as antibody against Chikungunya virus (mRNA-1944)
Methylmalonic acidemia overview

Gregory Enns, MD

Professor of Pediatrics (Genetics) at the Lucile Salter Packard Children’s Hospital

Stanford University
Methylmalonic Acidemia
Overview

Gregory Enns, MD
Professor of Pediatrics
Director, Biochemical Genetics Program
Lucile Packard Children’s Hospital
Stanford University
Disclosures

• Consultant – Moderna Therapeutics, Horizon Pharma
• Clinical trials – Aeglea Biotherapeutics, BioElectron, Moderna, Inc., Stealth Therapeutics
• DSMB – Biomarin, Audentes Therapeutics, Amicus, RegenxBio, Neurovia
• Co-Founder – Evvia Therapeutics
Methylmalonic Acidemia (MMA)

- Autosomal recessive
- Complete \((mut^0)\) or partial \((mut^-)\) decreased activity of methylmalonyl-CoA mutase
- Prevalence in North America ~1/50,000
Methylmalonyl-CoA mutase

- Nuclear encoded
- Mitochondrial localized
- Homodimer
- Requires 5’-deoxyadenosylcobalamin (Adocbl)
### Table 3 Acute and chronic presentations of MMA/PA

<table>
<thead>
<tr>
<th>Acute presentation</th>
<th>Chronic presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal sepsis-like picture, temperature instability, respiratory distress, hyperventilation</td>
<td>Often episodic characteristic signs and symptoms</td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
</tr>
<tr>
<td>• Altered level of consciousness (from lethargy and somnolence to coma) mimicking encephalitis or drug intoxication</td>
<td><strong>Nervous system</strong></td>
</tr>
<tr>
<td>• Acute encephalopathy</td>
<td>• Hypotonia</td>
</tr>
<tr>
<td>• Seizures (in general not isolated but in the context of altered level of consciousness)</td>
<td>• Developmental delay (learning disabilities, intellectual disability)</td>
</tr>
<tr>
<td>• Movement disorders (more frequent in PA)</td>
<td>• Movement disorders/dystonia</td>
</tr>
<tr>
<td>• Stroke-like episodes (more frequent in MMA)</td>
<td>• Seizures</td>
</tr>
<tr>
<td><strong>Gastrointestinal system</strong></td>
<td></td>
</tr>
<tr>
<td>• Vomiting and feeding difficulties</td>
<td><strong>Gastrointestinal system</strong></td>
</tr>
<tr>
<td></td>
<td>• Optic atrophy</td>
</tr>
<tr>
<td></td>
<td>• Psychiatric symptoms (hallucinations, psychotic attacks)</td>
</tr>
<tr>
<td><strong>Hematologic findings</strong></td>
<td><strong>Hematologic findings</strong></td>
</tr>
<tr>
<td>• Neutropenia, pancytopenia</td>
<td>• Neutropenia, pancytopenia</td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>• Secondary hemophagocytosis (rare)</td>
</tr>
<tr>
<td>• Acute cardiac failure (mostly on basis of cardiomyopathy)</td>
<td><strong>Heart (more frequent in PA)</strong></td>
</tr>
<tr>
<td>• Arrhythmias</td>
<td>• Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td>• Prolonged QTc interval in ECG</td>
</tr>
<tr>
<td></td>
<td><strong>Kidney (more frequent in MMA)</strong></td>
</tr>
<tr>
<td></td>
<td>• Chronic renal failure in MMA</td>
</tr>
<tr>
<td></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td></td>
<td>• Dermatitis</td>
</tr>
<tr>
<td></td>
<td>• Hearing loss</td>
</tr>
</tbody>
</table>
BRAIN INJURY IN ORGANIC ACIDEMIAS

caudate and putamen hyperintensity

delayed myelination
MMA Therapy

- Special low-protein diet
- Emergency/sick-day protocols
- Carnitine supplementation
- Vitamin $\text{B}_{12}$ in some cases
- Dialysis – $\uparrow\text{NH}_3$, metabolic acidosis, renal failure
- Liver or combined liver/kidney transplantation
- Kidney transplantation
Gene Therapy with a Scalpel

- Liver transplantation
- Kidney transplantation
- Combined liver/kidney transplantation
Combined liver-kidney transplantation in methylmalonic acidemia

W. G. van’t Hoff, BSc, MD, MRCP, M. Dixon, BSc, SRD, J. Taylor, BM, MRCP, P. Mistry, PhD, MRCP, K. Rolles, MS, FRCS, L. Rees, MD, FRCP, and J. V. Leonard, PhD, FRCP

A 13-year-old boy with non-B12-responsive methylmalonic acidemia (MMA) had chronic renal failure. Hemodialysis led to symptomatic and biochemical improvement. He subsequently received a combined liver-kidney transplant. After 16 months of follow-up he has a normal lifestyle and a marked reduction in plasma and urine methylmalonate. (J Pediatr 1998;132:1043-4.)
Combined Liver-Kidney Transplantation in MMA

(A) Serum/Urinary MMA levels over time post-transplant

(B) Serum and Urine MMA levels over time post-transplant

\[ \text{BMI}^{\star} \]
\[ \text{Alb}^{\star} \]
\[ \text{Protein}^{\star} \]
\[ \text{GFR}^{\star} \]

Time in weeks post transplant

5 yr follow up

1.5

107.56

102

18 month follow up

1

101.2

88.7

Pre Transplant

Post Transplant

JIMD 28:517-524, 2005
LT or LKT for MMA

Treatment of Methylmalonic Acidemia by Liver or Combined Liver-Kidney Transplantation

Anna-Kaisa Niemi, MD, PhD\(^1\), Irene K. Kim, MD\(^2\), Casey E. Krueger, PhD\(^3\), Tina M. Cowan, PhD\(^4\), Nancy Baugh, MS, RD\(^5\), Rachel Farrell, MS\(^1,6\), Clark A. Bonham, MD\(^2\), Waldo Concepcion, MD\(^2\), Carlos O. Esquivel, MD, PhD\(^2\), and Gregory M. Enns, MB, ChB\(^1\)

- Mean age for transplantation 8.75 ± 7 years (0.8-20.7 y)
- LKT 13.3 ± 4.9 years (5.9-20.7 y)
  - 88% underwent pre-operative hemodialysis
- LT 1.5 ± 0.9 years (0.8-3.3 y)

J Pediatr 166:1455-61, 2015
Postoperative period

- Mean follow-up 3.3y

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient survival</td>
<td>100%</td>
</tr>
<tr>
<td>Liver allograft survival</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>(hepatic artery thrombosis, n=1)</td>
</tr>
<tr>
<td>Kidney allograft survival</td>
<td>100%</td>
</tr>
</tbody>
</table>

Other clinical outcomes
- No hyperammonemia or metabolic acidosis
- Renal function normal on those with LT only
  - mean follow-up 1.1 years

J Pediatr 166:1455-61, 2015
Mean serum MMA before and after transplantation

- **ALL**
- **NBS/LT**
- **Non NBS/LKT**

<table>
<thead>
<tr>
<th>Time</th>
<th>Serum MMA (umol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td></td>
</tr>
<tr>
<td>3 days</td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td>4 mo</td>
<td></td>
</tr>
</tbody>
</table>
Other clinical outcomes

- No hyperammonemia or metabolic acidosis

- Renal function normal on those with LT only
  - mean follow-up 1.1 years
Neurological outcomes

Pretransplant:
- 1/6 global developmental delay
- 3/6 mild developmental delay
- 2/6 mild motor delay, otherwise age appropriate

Post:
- 3/5 gained motor skills
- No neurological deterioration

Pretransplant:
- 4/8 global developmental delay
- 2/8 mild developmental delay

Post:
- Maintained previous level
- No neurological deterioration

LT 6

14

LKT 8
Liver Transplantation Complications

- Mortality
- Lactic acidemia
- Metabolic decompensation
- ‘Metabolic stroke’
- Graft rejection
- Post-op pancreatitis

- Immunosuppression complications
  - Diabetes
  - Hypertension
  - Seizures
  - Infections
  - Nephrotoxicity

- Surgical complications
  - Hepatic artery thrombosis
  - Subphrenic abscess
  - Splenic rupture

J Pediatr 140:261-3, 2002
Ther Apher Dial 15:488-92, 2011
J Pediatr 166:1455-61, 2015
Persisting morbidity

- Biochemical abnormalities persist
- Renal insufficiency after LT
- Risk of metabolic strokes remains

Pediatr Transpl 20:1081-6, 2016
MMA Gene Therapies in Development

- Gene therapy
  - Transgenic model
  - Hepatic targeting > phenotypic correction

- AAV
  - Hepatic genotoxicity
  - Immune responses
    - Neutralizing antibodies
Gene Therapy (Pre-Clinical)

- Adenovirus, AAV, Lentivirus

Hum Gene Ther 19:53-60, 2008
Mol Ther 18:11-16, 2010
Hum Gene Ther 25:529-38, 2014
mRNA Therapy

- No insertional mutagenesis
- Dose dependent pharmacology avoids constitutive gene activation
- No conventional ERT
- Lipid nanoparticles
  - Encapsulation
  - Biodegradable
  - Systemic delivery, liver targeting
Improved Metabolism in \textit{mut} and \textit{mut}^0 MMA Mice after i.v. \textit{hMUT} mRNA

\textbf{hMUT Protein Levels in Liver (tg/mg protein)}

\textbf{Plasma Methylmalonic Acid (mM)}

\textbf{Body Weight (g)}

\textbf{Days}

\textbf{Weeks}
Summary

- MMA $mut^0$ associated with high morbidity/mortality
- Liver or combined liver/kidney transplantation
  - Decreased frequency of metabolic crises and hospitalizations
  - Stabilization of neurological function
  - Liberalization of diet
  - Weight gain
  - Improved quality of life
- mRNA and gene therapies in development
Acknowledgements

- Anna-Kaisa Niemi, M.D., Ph.D
- Tina Cowan, Ph.D.
- Tereza Moore, Ph.D.
- Nancy Baugh, M.S., R.D.
- Carlos Esquivel, M.D., Ph.D.
- Irene Kim, M.D.
- Waldo Concepcion M.D., Ph.D.
- Maria T. Millan, M.D.
- Clark A. Bonham, M.D.
- Marcia Castillo, R.N., B.S.N.
- Casey E. Krueger, Ph.D.
- Karen Wayman, Ph.D.
- Rachel Farrell
- Stanford Medical Genetics Residents, Genetic Counselors, RNs, RDs
Conclusion

Stéphane Bancel
Chief Executive Officer
Two important positive clinical milestones in two modalities announced today

Cytomegalovirus (CMV) vaccine (mRNA-1647)
- Positive interim phase 1 data
- Successfully immunized seronegatives and boosted seropositives
- Generally well tolerated
- Phase 2 to start in the near term
- Preparations underway for the phase 3
- Moderna owns the global commercial rights to mRNA-1647

Antibody against Chikungunya virus (mRNA-1944)
- Positive phase 1 data
- Observed dose dependent protein expression
- Achieved expected therapeutic levels at a well tolerated dose (0.3mg/kg)
- Observed expected translation from NHP to human
Moderna continues to mature and clinical data are validating the quality and relevance of our science

- 4 programs in or preparing for phase 2
- 10 positive phase 1 studies (6 vaccines, PCV, OX40, VEGF and Chikungunya antibody)
- 12 programs in phase 1

Vaccine modality:
- Six vaccines with positive phase 1 data, including CMV
- CMV, RSV, hMPV+PIV3 in clinical trials, each as a potential blockbuster opportunity

5 I/O programs dosing patients in Phase 2 or Phase 1:
- PCV and KRAS with Merck (50/50 global profit share)
- IL12 with AstraZeneca (50/50 US profit share)
- OX40L and Triplet wholly owned by Moderna

Antibody against Chikungunya virus (mRNA-1944) phase 1 data validates:
- mRNA approach for making a functional IgG antibody
- LNP delivery technology shared by rare disease pipeline candidates
We believe innovative vaccines are a great business

<table>
<thead>
<tr>
<th>Me too vaccines (i.e., Tetanus, …)</th>
<th>Innovative vaccines (i.e., Prevnar, HPV…)</th>
<th>Public health vaccines (i.e., Yellow Fever…)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pricing: $</td>
<td>$$$$</td>
<td>$</td>
</tr>
<tr>
<td>%EBIT: 10-25%</td>
<td>~50%</td>
<td>0-25%</td>
</tr>
</tbody>
</table>

Moderna will not fund, but might partner. Moderna will fund or partner. Moderna will partner with governments and foundations to pursue social and public health goals.
Several vaccines have realized this value-add with strong, recurring revenues

### Top selling vaccines, by 2024 projected sales

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indication</th>
<th>Company</th>
<th>Launch Year</th>
<th>2018 WW Sales</th>
<th>2024E WW Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevnar 13*</td>
<td>Pneumococcus</td>
<td>Pfizer</td>
<td>2000 (PCV7)</td>
<td>$5.8 bn</td>
<td>$6.7 bn</td>
</tr>
<tr>
<td>GARDASIL**</td>
<td>HPV</td>
<td>Merck</td>
<td>2006</td>
<td>$3.2 bn</td>
<td>$5.9 bn</td>
</tr>
<tr>
<td>SHINGRIX***</td>
<td>Herpes zoster</td>
<td>GSK</td>
<td>2017</td>
<td>$1.0 bn</td>
<td>$3.5 bn</td>
</tr>
</tbody>
</table>

Source: EvaluatePharma

*Prevnar 13 ® is a registered trademark of Wyeth LLC.

**GARDASIL ® is a registered trademark of Merck & Co., Inc.

***Shingrix is a registered trademark of GSK
Our strategy for the mid-term

1. Build a strong vaccine business based on innovative vaccines like CMV, RSV, hMPV+PIV3, Zika…

2. Execute the clinical research plans on 5 I/O programs to potentially improve on PD1/PDL1 mono therapy

3. Build a rare disease business, with an initial focus on metabolic diseases

4. Expand into new therapeutic areas
Moderna’s vision is intact: more than ever, we believe mRNA could be a potential new class of medicines

1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology
Our Mission
To deliver on the promise of mRNA science to create a new generation of transformative medicines for patients.
Thank you