Roche Pharma Day 2020

Infectious Diseases: A close look at our HBV pipeline

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# Late stage pipeline update

## 1. Hematology franchise
- DLBCL: Polivy, glofitamab, mosunetuzumab
- FL: mosunetuzumab, glofitamab, Polivy
- AML: Venclexta
- MM: Venclexta
- MDS: Venclexta

## 2. Breast Cancer franchise
- TNBC: Tecentriq, ipatasertib
- HR+: SERD (RG6171), PI3Kαi (RG6114)
- HER2+: Tecentriq

## 3. Lung Cancer franchise
- NSCLC: Tecentriq, tiragolumab
- SCLC: Tecentriq, tiragolumab
- ALK+: Alecensa
- ROS1+/NTRK+: Rozlytrek
- RET+: Gavreto
- KRAS G12C+: GDC-6063

## 4. Other oncology
- CRPC: ipatasertib
- Thyroid cancer: Gavreto
- Esophageal cancer: tiragolumab
- Melanoma: Tecentriq, Cotelic, Zelboraf

## 5. Non-malignant hematology
- Hemophilia A: Hemlibra
- Hemophilia A: Factor VIII Gene Therapy
- PNH: crovalimab

## 6. Neuroscience
- MS: Ocrevus; fenebrutinib
- SMA: Evrysdi
- NMOSD: Enspryng
- AD: gantenerumab, anti-Tau, brain shuttle
- Huntington’s disease: tominersen
- DMD: Micro-dystrophin Gene Therapy
- Parkinson’s disease: prasinezumab

## 7. Immunology
- IPF: rhPentraxin-2, Esbriet
- Myelofibrosis: rhPentraxin-2
- Lupus nephritis: Gazyva
- Crohn’s disease: etrolizumab

## 8. Ophthalmology
- nAMD, DME, DR: Port Delivery System
- nAMD, DME, RVO: faricimab

## 9. Infectious diseases
- HBV: TLR7 agonist, CpAM, RG6346, RG6084
- Influenza A/B: Xofluza
- SARS-CoV2: Actemra
- SARS-CoV2: REGN-COV2

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* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 20 results presentation appendix or visit the IR homepage.
Hepatitis B: High global unmet need

High burden of disease with life-threatening complications

Hepatitis B Virus (HBV)

- 257 m patients are infected with Hepatitis B
  - 86 m in China
- Low cure rates and life-long therapy with current SOC
  - (<0-3% cure rate after 1yr of therapy)
- 25% of untreated HBV patients will develop hepatocellular carcinoma
- 887 k patients die yearly from complications of HBV
  - 7th leading cause of death worldwide

Reference: WHO July 2018
Hepatitis B surface Antigen (HBsAg) loss is the most important endpoint for functional cure with finite treatment duration

HBsAg detection

1. Total HBsAg is quantitatively measured by Immunoassay (Elecsys HBsAg II quant II, Roche)

HBsAg decline associated with significantly improved patient outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver decompensation</td>
<td>0.28</td>
<td>0.13</td>
<td>0.59</td>
<td>0.001</td>
</tr>
<tr>
<td>HCC</td>
<td>0.30</td>
<td>0.20</td>
<td>0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transplant/Death</td>
<td>0.22</td>
<td>0.13</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite first clinical event</td>
<td>0.31</td>
<td>0.23</td>
<td>0.43</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Meta-analysis of 28 studies with nearly 190,000 chronic HBV patients
- Clear association between HBsAg seroclearance and improved outcome
- HBsAg seroclearance as primary endpoint in clinical trials supported

Roche HBV strategy
Combining antiviral and immunomodulatory agents

**Antiviral agents**

<table>
<thead>
<tr>
<th>HBV life cycle</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>HBV siRNA (Dicerna)</td>
<td>Nucleos(t)ide</td>
</tr>
<tr>
<td>Transcription</td>
<td></td>
<td>CpAM (Core protein Allosteric Modulator)</td>
</tr>
<tr>
<td>Secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encapsidation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg / HBeAg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Immunomodulators**

<table>
<thead>
<tr>
<th>Virus mediated suppression</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR7 Agonist</td>
<td>Peg-IFNα</td>
</tr>
</tbody>
</table>

**Standard of Care**

Functional cure
**HBV siRNA (RG6346)**

*Inhibiting HBV gene expression by targeting the viral genome*

- Proprietary liver-targeted RNAi technology (GalXC™) with unique ‘tetraloop’ folded design
- Designed to inhibit HBV gene expression through targeting of S open reading frame of the HBV genome

**siRNA simultaneously inhibiting multiple HBV genes**

**Ph I (dose finding) interim results**

- Durable HBsAg decline up to day 336
- 6 out of 10 patients, who completed day 112, had HBsAg < 100 IU/mL
- Safe and well tolerated

*Interim analysis from 25 June 2020 data cutoff; https://investors.dicerna.com/static-files/0507fc43-4023-4a40-92fb-0c06b9c4a4b7; In collaboration with Dicerna*
CpAM (RG7907)

Leads to incorrect assembly of HBV core protein followed by degradation

**Core protein allosteric modulator (CpAM)**
- Effective against all major HBV genotypes
- Showing successful HBsAg reduction in preclinical mouse model

**Ph I (dose finding)**
- Strong HBV DNA decline in all patients within first week of treatment
- 81% (13/16) HBeAg-negative patients achieved HBV DNA levels below LLOQ (20 IU/ml)

EASL 2019 poster FRI-219; HBeAg=Hepatitis B e-antigen; LLOQ=lower limit of quantification
TLR7 agonist (RG7854)
Stimulating innate and adaptive antiviral response via TLR7 pathway

**TLR7 agonist (RG7854)**

**Stimulating innate and adaptive antiviral response via TLR7 pathway**

**Ph I (dose finding) results**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>ISG15</th>
<th>OAS1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fraction responding</td>
<td>Geometric mean fold change (range)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0/16</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1/8</td>
<td>2.4 (2.4–2.6)</td>
</tr>
<tr>
<td>10</td>
<td>0/8</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>1/8</td>
<td>2.6 (2.6–2.8)</td>
</tr>
<tr>
<td>40</td>
<td>1/8</td>
<td>2.9 (2.9–3.0)</td>
</tr>
<tr>
<td>60</td>
<td>1/8</td>
<td>2.6 (2.6–2.8)</td>
</tr>
<tr>
<td>100</td>
<td>5/8</td>
<td>5.9 (2.3–9.3)</td>
</tr>
<tr>
<td>140</td>
<td>8/8</td>
<td>11.0 (2.3–48.0)</td>
</tr>
<tr>
<td>170</td>
<td>8/8</td>
<td>11.2 (2.5–132.2)</td>
</tr>
</tbody>
</table>

- TLR7 detects single-stranded viral RNA and mediates anti-viral cytokine production and dendritic cell activation
- Unique double pro-drug selectively activated in the liver
- Dose dependent immunomodulatory activity established
- TLR7 activation induces mRNA expression of interferon-inducible genes (e.g. ISG15, OAS1) first observed at 100 mg dose and plateaued at 170 mg dose

Modified from Ma Z et al. Cell Mol Immunol 2015, 12(3):273-82; Gane E et al. EASL 2018; ISG15=Interferon-stimulated gene 15; OAS1=2’-5’-oligoadenylate synthetase 1
Highly adaptive HBV combination platform
Screening novel drug combinations efficiently

• Nimble and adaptive platform for Ph II screening with shared control arm
• First interim analysis after 12 weeks; second interim analysis after 24 weeks; interim analysis helps inform combos B, C and D
• Opportunity to seamlessly add and terminate different drug combinations
CpAM + TLR7 agonist in HBV
First combination to move into Ph II testing

- Ph II combination trial (n=60) started in Q3 2020
- First 12-week interim analysis planned for Q2 2021
- A 4th HBV program molecule (undisclosed novel immunomodulator) moved into Ph I testing
Doing now what patients need next