New Targets and New Agents in Hepatocellular Carcinoma

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Disclosures

• Consulting role:
  – Pfizer
  – Novartis
  – Eli Lilly
  – Ipsen
Normalization of Tumor Microenvironment in Hepatocellular Carcinoma

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Cellular & Molecular Components of the Hepatocellular Carcinoma Microenvironment

- **Endothelial cells**
  - Pericytes
  - VEGFR-PDGFR

- **T cells (CD4-Treg)**
  - CD4:PD1-CTLA4-CD28
  - Treg: CD73-CD39

- **Tumor cells**
  - TGFβR-MET-PDL1

- **Tumor associated macrophages**
  - CXCR4-TGFβR

- **Dendritic cells**
  - PDL1-PD1-MSH II-CD80/86

- **Fibroblasts**
  - FGFR

- **SDF1/CXCL12**
  - TGFβ HGF
  - FGF19 IL8 IL10
Characteristics of Hepatocellular Carcinoma Microenvironment

• Likely to vary according to the type of tumor carcinogenesis
  – Alcohol
  – Viral hepatitis B/C induced inflammation
  – NASH
  – Others

• Likely to be influenced by focal hypoxia
  – Tumor angiogenesis being genuine or induced by sorafenib
  – Induction of mesenchymal differentiation
  – Induction of lactic acid metabolism
  – Facilitate the occurrences of specific oncogenic mutations

• Associated with local immunosuppression
  – Inhibition of T-cell functions (PD1/PDL1, CTLA4)

‘Epigenetic’ changes may be focal accounting for tumor heterogeneity and drift occurring over time facilitating resistance to single agent therapy, pledging for combinations
New Targets and New Agents in Hepatocellular Carcinoma

VEGFR & PDGFR as Anti-angiogenic Targets for Hepatocellular Carcinoma
Learning from 7 Years of Experience with Sorafenib in Advanced hepatocellular carcinoma

*Sorafenib Better than Sorafenib*

So far no drug has been able to compete with sorafenib as first line therapy in HCC

Faivre S, de Gramont A, Raymond E. Target Oncol. 2016
Regorafenib a Mutikinase Inhibitor

phase III RESORCE trial
WHIPPANY, N.J., May 4, 2016 /PRNewswire/ -- Bayer today announced that a Phase III trial evaluating its oncology compound Stivarga® (regorafenib) tablets for the treatment of patients with unresectable hepatocellular carcinoma (HCC) has met its primary endpoint of a statistically significant improvement in overall survival. The study, called RESORCE, evaluated the efficacy and safety of regorafenib in patients with HCC whose disease has progressed after treatment with sorafenib. The safety and tolerability were generally consistent with the known profile of regorafenib. Detailed efficacy and safety analyses from this study are expected to be presented at an upcoming scientific congress.

"Effective treatment options are urgently needed for patients with unresectable liver cancer," said Dr. Joerg Moeller, member of the Executive Committee of Bayer AG’s Pharmaceutical Division and Head of Development. "With sorafenib having been the only systemic option for the treatment of unresectable HCC since 2007, regorafenib could now become the second proven systemic option. We would like to thank the patients and the study investigators for their contributions and participation in this study."

Bayer plans to submit data from the RESORCE study as the basis for marketing authorization of regorafenib in the treatment of unresectable HCC in 2016.
Regorafenib was announced to provide overall survival benefit over placebo in second line in patients who have failed sorafenib first line (Data presented at this WORLD GI 2016)

Bayer plans to submit data from the RESORCE study as the basis for marketing authorization of regorafenib in the treatment of unresectable HCC in 2016.
New Targets and New Agents in Hepatocellular Carcinoma

PD1 & PDL1 as Targets for Hepatocellular Carcinoma
Immune Checkpoint Inhibition by Nivolumab

- Nivolumab is a fully human IgG4 anti-PD-1 monoclonal antibody that selectively blocks the interaction between PD-1 and PD-L1/PD-L2,\(^1\) restoring T-cell immune activity directed against the tumor cell

CA209-040: Study Design

- Patients received nivolumab Q2W for up to 2 years (maximum of 48 doses), depending on response
  - Imaging for disease assessment performed every 6 weeks
- A 3+3 design was used in the phase 1 dose escalation phase
- Here, we report interim results from the ongoing dose escalation phase and part of the expansion phase
CA209-040: Durable Partial Response to Nivolumab

- 58-year-old white male with HCV-infected HCC, ECOG 0, Child-Pugh A5
- Progressed on sorafenib

Anthony B. El-Khoueiry et al. ASCO 2015
CA209-040: Response Kinetics

ORR: around 15% - Median Duration response 17 months

<table>
<thead>
<tr>
<th>Months, range</th>
<th>Uninfected (n=21)</th>
<th>HCV (n=11)</th>
<th>HBV (n=10)</th>
<th>Total Evaluable (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR</td>
<td>7.2* – 12.5*</td>
<td>1.4* – 8.3*</td>
<td>11.9</td>
<td>1.4* – 12.5*</td>
</tr>
<tr>
<td>Duration of SD</td>
<td>1.1* – 17.3*</td>
<td>2.9† – 14.0</td>
<td>2.7* – 6.9*</td>
<td>1.1* – 17.3*</td>
</tr>
</tbody>
</table>

* Censored
† Patient with resolved HCV infection
+ First occurrence of new lesion
### CA209-040: Preliminary Overall Survival

<table>
<thead>
<tr>
<th>Overall Survival Rate, % (95% CI)*</th>
<th>Total (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 9 months</td>
<td>70 (52–82)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>62 (42–76)</td>
</tr>
</tbody>
</table>

*Overall survival estimated using Kaplan-Meier method

**Update ASCO 2016**

Median OS: 14 months irrespective of prior sorafenib treatment

AE≥ grade 3: 1% - Well tolerated

Anthony B. El-Khoueiry et al. ASCO 2015
HGF & c-MET Inhibition in Hepatocellular Carcinoma

New Targets and New Agents in Hepatocellular Carcinoma
Chronic liver inflammation (viral – others)

Fibroblasts and fibrosis

Local immunosupression

Genuine Hypoxia

Treatment induced hypoxia (embolization, anti-angiogenic)

HGF stimulation of hepatocytes and hepatocarcinoma cells harboring c-MET

Epigenetic changes associated with HGF/c-MET activation
c-MET inhibitors in late stage drug development

METIV-HCC – Tivantinib – phase 3 trial

CELESTIAL – Cabozantinib – phase 3 trial

• First generation
• Specificity?
• Results pending
Inhibition of c-MET With Tepotinib
Tolerability and Activity of Second-Line Tepotinib, a Potent and Highly Selective c-Met Inhibitor, in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib

Abstract No. 238

faivre et al. world GI 2016

Dose level

- Tepotinib 300 mg
- Tepotinib 500 mg

Best relative change in sum of longest diameter (%)

CT after 2 cycles showed objective response by RECIST (-48%)

PET scan after 2 cycles showed significant decrease of size and metabolic activity

Faivre et al. World GI 2016
New Targets and New Agents in Hepatocellular Carcinoma

FGF19 & FGFR4 as Targets in Hepatocellular Carcinoma
Inhibition of FGF19/FGFR4 Activation With BLU-554

Paralog Selectivity

<table>
<thead>
<tr>
<th>FGFR4 Paralog</th>
<th>BLU-554</th>
<th>BGJ-398</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR4 IC_{50} (nM)</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>FGFR1 IC_{50} (nM)</td>
<td>624</td>
<td>&lt;1</td>
</tr>
<tr>
<td>FGFR2 IC_{50} (nM)</td>
<td>1,202</td>
<td>&lt;1</td>
</tr>
<tr>
<td>FGFR3 IC_{50} (nM)</td>
<td>2,203</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Hep3B - FGF19 amplification

LIX-066 - FGF19 overexpression (no amplification)

HCC Dose Escalation → HCC Expansion

- Assess FGF19 expression and amplification status
- HCC with FGFR4 pathway activation

Key Endpoints

Primary
- Safety
- Tolerability
- MTD

Secondary
- Response rate (RECIST)
- Biomarkers

Follow-on Studies to Include
- Cholangiocarcinoma, front line HCC
New Targets and New Agents in Hepatocellular Carcinoma

**TGFβ & TGFβ-R as Targets in Hepatocellular Carcinoma**

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- VEGFR-PDGFR

**Tumor cells**
- TGFβR-MET-PDL1

**Tumor associated macrophages**
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Canonical and Non-Canonical TGFβ Pathway

- >30 TGFβ members (TGFβ1-3, activins, NODAL, BMP, GDF, AMH)

Galunisertib: TGF-βRI Inhibitor in Hepatocellular Carcinoma
Evaluation of Drugs in *Ex Vivo* Organotypic Culture Assays From Surgical Specimens of Human Hepatocellular Carcinoma: Studying the Tumor Cells in Their Genuine Stroma

By Serova et al, Oncotarget 2015
TGFβRI Inhibition Induced by Galunisertib in Human Hepatocellular Carcinoma Explants

Ex vivo

Proliferation

Apoptosis

P-STAT3 (PD biomarker)

By Serova et al, Oncotarget 2015
A Phase 2 Study of a Second Line Galunisertib in Patients With Advanced Hepatocellular Carcinoma

Study Design for Part A and Part B

Screening Patients with Child Pugh A or B7 Hepatocarcinoma who progress Under sorafenib

Part A
AFP ≥1.5 ULN

Randomize

Galunisertib 160 mg/day

Galunisertib 300 mg/day

Part B
AFP <1.5 ULN

Galunisertib 300 mg/day

Abbreviation: ULN, upper limit of normal.

Galunisertib (TGFβRI Inhibitor) in Patients With Hepatocellular Carcinoma

Part A
AFP ≥1.5 ULN

Part B
AFP <1.5 ULN

Overall survival

AFP responders

AFP non responders

AFP responders = patients who decreased circulating AFP levels by >20%

<table>
<thead>
<tr>
<th>n/N (%)</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP responders</td>
<td>25/103 (24%)</td>
</tr>
<tr>
<td>AFP non-responders</td>
<td>78/103 (76%)</td>
</tr>
</tbody>
</table>

Courtesy of Faivre S. et al.
Pres. ASCO GI 2014 and ASCO 2016
PD-L1 Expression in Hepatocellular Carcinoma

In vivo transgenic C57B16/ASB-B mice model

Tumor boundary

Combination with PD-L1 inhibitors

T-cells
CD3
PD-L1

Cancer cells

AdG unpublished
Galunisertib in Combination With Sorafenib

In vivo transgenic C57B16/ASB-B mice model

Randomization
N = 32

Transgenic C57Bl6/ASV-B Mice; age 8 weeks

Placebo
N = 8

Sorafenib (30 mg.kg⁻¹)
N = 8

Sorafenib (100 mg.kg⁻¹)
N = 8

Galunisertib
100mg/kg
N = 8

Sorafenib + galunisertib
N = 8

At 12 weeks

Rijeras-Raballan et al. Unpublished data
New Targets and New Agents in Hepatocellular Carcinoma

Tumor angiogenesis
- Sorafenib (1st line)
- Regorafenib (2nd line)

Microenvironment signaling
- Gelunisertib (TGFβ-RI)
- Tepotinib (c-MET)
- BLU-554 (FGF19/FGFR4)

Immune stroma
- Nivolumab
- Pembrolizumab (PD-L1)
- Ipilimumab
- Tremelimumab (CTLA4)

Combinations
Conclusions

• Various components of tumor microenvironment could be used as targets to control tumor growth in hepatocellular carcinoma

• Inhibition of tumor angiogenesis, microenvironment signaling and local immunosuppression appear as promising options for tumor growth control

• Combination therapies normalizing the microenvironment offer promise for optimal control of hepatocellular carcinogenesis
Thanks for your attention

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