<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>18:15–18:20</td>
<td>Welcome and introduction</td>
<td>Andrew Zhu</td>
</tr>
<tr>
<td>18:20–18:30</td>
<td>Updates in HCC pathophysiology and diagnosis</td>
<td>Peter Galle</td>
</tr>
<tr>
<td>18:30–18:40</td>
<td>Optimizing sequencing of therapies in HCC</td>
<td>Andrew Zhu</td>
</tr>
<tr>
<td>18:40–18:50</td>
<td>The evolving landscape of HCC treatment</td>
<td>Richard Finn</td>
</tr>
<tr>
<td>18:50–19:10</td>
<td>Putting evidence into practice: case studies and panel discussion</td>
<td>All</td>
</tr>
<tr>
<td>19:10–19:15</td>
<td>Summary and close</td>
<td>Andrew Zhu</td>
</tr>
</tbody>
</table>
Audience response system

Please answer the questions using your smartphone/tablet

Please login to this URL:

hcc.chime.live
First ...

Please note that the brochure is located under your seat.

Wi-Fi Network: Marriott_CONFERENCE
Passcode: ilca2019
URL for voting: hcc.chime.live
Learning objectives

• Describe advances in the pathophysiology of hepatocellular carcinoma (HCC) (including tumor microenvironment interactions) and how these may aid diagnosis and treatment

• Analyze the clinical trial data for current and emerging therapies for the first- and second-line treatment of HCC

• Debate how to integrate new HCC research and therapies into everyday clinical practice
Continuing Medical Education

• This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of Imedex® and Springer Healthcare. Imedex is accredited by the ACCME to provide continuing medical education for physicians.

• Imedex, LLC designates this live educational activity for a maximum of 1 AMA PRA Category 1 Credit™. Physicians should claim only credit commensurate with the extent of their participation in the activity.
Educational funding

This program is made possible thanks to an educational grant from Eli Lilly and Company
Before we begin...

I feel confident in selecting and sequencing the most appropriate first- and second-line treatment options for patients with HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Before we begin...

I feel confident in selecting and sequencing the most appropriate first- and second-line treatment options for patients with HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Before we begin...

I feel up to date on the emerging treatment options for the treatment of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree

URL: hcc.chime.live
Before we begin...

I feel up to date on the emerging treatment options for the treatment of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Before we begin...

I understand the role of AFP status in the diagnosis of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Before we begin...

I understand the role of AFP status in the diagnosis of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Updates in HCC pathophysiology and diagnosis

Peter Galle
University Medical Center, Mainz, Germany
Updates in HCC pathophysiology and diagnosis

Peter R. Galle
Disclosure of conflict of interest

Peter R. Galle

1. Advisory role fee: Bayer, Lilly, AstraZeneca, BMS, MSD, Merck, SIRTEX, Eisai, Ipsen, Roche

2. Stockholder: No

3. Patents and royalties: No

4. Honoraria (lecture fee): Bayer, SIRTEX, Lilly

5. Honoraria (manuscript fee): No

6. Research funding from: Bayer
## Diagnosis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of <strong>HCC in cirrhotic</strong> patients should be based on non-invasive criteria and/or pathology</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>In <strong>non-cirrhotic</strong> patients, diagnosis of HCC should be confirmed by pathology</td>
<td>Moderate</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Galle et al. *J Hepatol* 2018:69(1)182–236
Non-invasive diagnosis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Level of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive criteria(^a) can only be applied to cirrhotic patients for nodule(s) ≥1 cm, in light of the high pre-test probability and are based on imaging techniques obtained by multiphasic CT, dynamic contrast-enhanced MRI...</td>
<td>High</td>
<td>Strong</td>
</tr>
<tr>
<td>...or CEUS</td>
<td>Moderate</td>
<td>Weak</td>
</tr>
<tr>
<td>Because of their higher sensitivity and the analysis of the whole liver, CT or MRI should be used first</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>

\(^a\)Diagnosis is based on the identification of the typical hallmarks of HCC, which differ according to imaging techniques or contrast agents (APHE with washout in the portal venous or delayed phases on CT and MRI using extracellular contrast agents or gadobenate dimeglumine, APHE with washout in the portal venous phase on MRI using gadoxetic acid, APHE with late-onset (>60 s) washout of mild intensity on CEUS).

Galle et al. *J Hepatol* 2018:69(1)182–236
Hallmark pattern of HCC on radiographic imaging

Arterial Enhancement

Venous Washout
Radiological imaging

Arterial Hyperperfusion
# AFP as serological biomarker for HCC

<table>
<thead>
<tr>
<th>Pathophysiology:</th>
<th>Correlation with molecular HCC classes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Association between AFP high subclass and VEGF levels</td>
</tr>
<tr>
<td>Clinical relevance:</td>
<td>AFP for defining patients at-risk of HCC development (problem cut-off)</td>
</tr>
<tr>
<td></td>
<td>AFP for surveillance in HCC</td>
</tr>
<tr>
<td></td>
<td>AFP as a diagnostic tool in HCC</td>
</tr>
<tr>
<td></td>
<td>AFP as prognostic factor:</td>
</tr>
<tr>
<td></td>
<td>• For candidates to resection/ablation.</td>
</tr>
<tr>
<td></td>
<td>• As predictor of drop-out in waiting list</td>
</tr>
<tr>
<td></td>
<td>• As prognostic factor for HCC in LT/LDLT</td>
</tr>
<tr>
<td></td>
<td>• Prognostic factor in BCLC B treated with TACE</td>
</tr>
<tr>
<td></td>
<td>• AFP based scores (in combination with other markers)</td>
</tr>
<tr>
<td></td>
<td>Role of AFP as stratification factor in RCT</td>
</tr>
<tr>
<td></td>
<td>Role of AFP as predictor of response to treatment</td>
</tr>
</tbody>
</table>

Galle et al. *Liver Int* 2019; in press
The role of AFP in the management of HCC

Utility of AFP

Surveillance\textsuperscript{a}

Diagnosis\textsuperscript{a}

Prognosis / monitoring of treatment response

- Hepatic resection
- Liver transplantation
- LRT
- Sorafenib
- Ramucirumab
- Lenvatinib
- Other TKIs
- Checkpoint Inhibitors

\textsuperscript{a} In combination with imaging studies according to current guidelines

Galle et al. *Liver Int* 2019; in press
Insignificant wash-out in fatty liver leading to biopsy
Contra biopsy

- Reliable diagnosis of HCC possible through non-invasive radiological imaging (excepting cases of uncertainty)
- Misleading results in biopsy of small lesions with a diameter of 1-2cm
- Risks of biopsy:
  - Bleeding (especially in cirrhosis patients)
  - Injury of other organs (e.g. pneumothorax)
  - Needle track seeding

Severe bleeding in approximately 0.5%
Incidence 2.7%

Rokey DC et al. *Hepatology* 2009;49(3):1017–1044
Silva et al. *Gut* 2008;57:1592–1596
Pro biopsy

- Possibility to establish biomarkers
- Knowledge of tumor grading and additional information through histology
- Optimizing data interpretation in clinical trials for the sake of future patients
- (Retrospective) definition of subgroups for targeted treatments
  - Well known from other tumors
  - Potentially undeserved failure of new drugs without subgroup analysis
  - Decision against biopsy from time before systemic therapies
Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer

Global gene expression analysis of human HCC

Lee and Thorgeirsson SS. Gastroenterology 2004;127:S51–S55
Unsupervised transcriptome based classification of HCC

16 gene signature predicts the 6-group classification

Classification of HCC

Main molecular subgroups
- Proliferative subgroup
  - Stem cell (G1, stem cell like, hepatoblast like and S2 subtype)
  - Other proliferative HCC (G2-G3, late TGFβ and S1 subgroup)
  - Chromosomal instability
- Non proliferative subgroup
  - Hepatocyte like (G4, interferon and S3 subgroup)
  - Wnt/β-catenin (G5-G8, CTNNB1 and S3 subgroup)
  - Chromosomal stability

Gene mutation
- TP53 and AXIN1 mutations
- FGF19 amplification

Clinical and histological features
- CK19 and EPCAM et IHC
- HBV infection
- Macrotrabecular massive HCC
- Poor prognosis

# Accepted signaling pathways in HCC

<table>
<thead>
<tr>
<th>Pathway/Signaling</th>
<th>Process</th>
<th>Phenotypic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53</td>
<td>Cell cycle, DNA damage, telomere stability</td>
<td>Loss during tumor progression, driver mutation (Codon 249) in Aflatoxin B1 induced tumors</td>
</tr>
<tr>
<td>Wnt/β-Catenin</td>
<td>Target gene activation (Myc, Cyclin D1, E-Cadherin, etc.)</td>
<td>Early and late stage HCC, genomic stability, cancer stem cells</td>
</tr>
<tr>
<td>EGFR</td>
<td>Proliferation, survival (via AKT, STATs, RAS/RAF)</td>
<td>Aggressive phenotype, dedifferentiation</td>
</tr>
<tr>
<td>IGF</td>
<td>Proliferation, development</td>
<td>Pre-neoplastic lesions, early stage HCC</td>
</tr>
<tr>
<td>HGF/c-MET</td>
<td>Proliferation, migration, morphogenesis</td>
<td>Metastatic potential, invasion</td>
</tr>
<tr>
<td>TGF-B</td>
<td>Development, differentiation, migration</td>
<td>Bad prognosis, metastasis, cancer stem cells</td>
</tr>
<tr>
<td>Nf-κB</td>
<td>Inflammation, proliferation, survival</td>
<td>Chronic inflammation, tumor progression</td>
</tr>
<tr>
<td>VEGF</td>
<td>Neo-angiogenesis</td>
<td>Aggressive phenotype, poor prognosis</td>
</tr>
<tr>
<td>Hippo</td>
<td>Growth control, cell-contact, polarity, proliferation</td>
<td>Oval cell expansion</td>
</tr>
</tbody>
</table>

Precision medicine approaches in HCC

- Prevention
- Tumor development
- Molecular analysis
- Classification
- Prediction
- Individualized therapy

Therapy A
Therapy B

Poor Prognosis
Good Prognosis

p=0.007

Days of Survival
Percent survival
Landscape of mutations in HCC

No oncogene addiction: individualized approaches!
Importance of the microenvironment for the outcome of liver cancer patients

The role of the microenvironment in HCC

The tumor microenvironment of HCC inhibits immunogenic functions

Immunotherapy

‘Hot’ Tumors – the immune class in HCC

Sia et al. Gastroenterology 2017;153(3):812–826

TCGA Network et al. Cell 2017;169:1327–1341
## Precision medicine approaches in HCC

<table>
<thead>
<tr>
<th>HCC immune classes</th>
<th>Inflamed <em>hot</em> tumors</th>
<th>Noninflamed tumors</th>
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</thead>
<tbody>
<tr>
<td>Immune classes</td>
<td>Immune class -30%</td>
<td>Immune intermediate class</td>
</tr>
<tr>
<td></td>
<td>Active immune -20%</td>
<td>Immune exclusion class -30%</td>
</tr>
<tr>
<td></td>
<td>Exhausted immune -10%</td>
<td></td>
</tr>
</tbody>
</table>

### Immune subtypes

- **Active immune -20%**
  - T cells, cytotoxic cells, TIL structures, macrophages, PD-1 signaling

- **Exhausted immune -10%**
  - T cells, B cells, cytotoxic cells

### Molecular pathways and gene signatures

- **IFNγ, GZMB, PRF1**
  - Activated stroma
- **TGFβ**
  - T-cell exhaustion
- **Signatures of response to immunotherapy**

### Chromosomal aberrations and mutations

- **Chromosomal aberrations**
  - WNT/CTNNB1 mutations
  - PD-1/PD-L1 positive TIL structures
  - PD-1/PD-L1 negative TIL structures

### Immunohistology

- **Immune cell infiltration**
  - PD-1/PD-L1 positive TIL structures
  - PD-1/PD-L1 negative TIL structures

### Response to immunotherapy

- **Responders to immune checkpoint inhibitors**
  - Primary resistance to immune checkpoint inhibitors
The immune contexture of HCC correlates with survival

Foerster et al. 2018;8(5351)
The novel immune cell based gene signature predicts survival in HCC

- Signature comprising 64 genes associated with
  - T cells
  - Cytotoxic cells
  - Th2 cells
  - Macrophages
- Stratification of samples using a scoring algorithm

\[ p = 0.00015 \]

Strata

<table>
<thead>
<tr>
<th>Number at risk by time</th>
<th>good survival</th>
<th>poor survival</th>
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<tbody>
<tr>
<td>0</td>
<td>154</td>
<td>170</td>
</tr>
<tr>
<td>1</td>
<td>87</td>
<td>85</td>
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<td>5</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>3</td>
</tr>
</tbody>
</table>

Foerster et al. 2018;8(5351)
Summary

- Diagnosis of HCC mostly relies on **radiographic imaging**

- **Biopsies** may provide important histological and (epi-)genetic information on the tumor and its microenvironment

- HCC are characterized by **molecular heterogeneity** and activation of prognostic adverse signaling pathways

- Molecular diversity in advanced stages requires **individual treatment strategies**

- Therapeutic targets are **tumor cells and immune cells** (microenvironment)
Q1: The role of Biopsy in HCC

Which answer is not correct?

A. Biopsy allows grading and prognosis prediction
B. Biopsy is mandatory for diagnosis of HCC
C. Biopsy may help in patient stratification
D. The risk for tumor cell dissemination is < 5%.
E. The risk for significant bleeding is < 1%
Q1: The role of Biopsy in HCC

Which answer is **not** correct?

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E. The risk for significant bleeding is < 1%
Optimizing sequencing of therapies of hepatocellular carcinoma

Andrew X. Zhu, MD, PhD
Professor of Medicine, Harvard Medical School
Director, Liver Cancer Research, MGH Cancer Center
Andrew Zhu – disclosures

Honoraria and consultancy fees from:

- AstraZeneca
- Bayer
- Bristol Myers Squibb
- Eisai
- Incyte
- Lilly
- Merck
- Roche
Approved Options

- Sorafenib
- Lenvatinib
- Regorafenib
- Nivolumab
- Pembrolizumab
- Cabozantinib
- Ramucirumab

First Line

Second/Third Line

Chemotherapy

Targeted therapy

Immunotherapy

Combination therapy

Evolving systemic treatment landscape for HCC 2019
Sorafenib in advanced HCC

SHARP vs Asia-Pacific study: Overall Survival

**SHARP Trial**

10.7 vs 7.9 mo
HR: 0.69 (0.55-0.87)

**Asia-Pacific Trial**

6.5 vs 4.2 mo
HR: 0.68 (0.50-0.93)

REFLECT: lenvatinib vs sorafenib as first-line treatment in patients with unresectable HCC

Global, randomized, open-label, phase 3 non-inferiority study

Patients with unresectable HCC (N=954)
- No prior systemic therapy for unresectable HCC
- ≥1 measurable target lesion based on mRECIST
- BCLC stage B or C
- Child-Pugh A
- ECOG PS ≤1
- Adequate organ function
- Patients with ≥50% liver occupation, clear bile duct invasion, or portal vein invasion at the main portal vein were excluded

Stratification
- Region: (Asia-Pacific or Western)
- MVI and/or EHS: (yes or no)
- ECOG PS: (0 or 1)
- Body weight: (< 60 kg ≥60 kg)

Primary endpoint:
- OS

Secondary endpoints:
- PFS
- TTP
- ORR
- Quality of Life
- PK lenvatinib exposure parameters

Tumor assessments were performed according to mRECIST by the investigator

Lenvatinib (n=478)
8 mg (BW <60 kg) or 12 mg (BW ≥60 kg) once daily

Sorafenib (n=476)
400 mg twice daily

REFLECT: primary endpoint: Kaplan-Meier estimate of OS

PFS: LEN 7.4 vs SOR 3.7 mo., HR 0.66
ORR: LEN 24.1% vs SOR 9.2% (p<0.001)

Regorafenib vs placebo in the second-line (RESORCE)

HCC patients with documented radiologic progression during sorafenib treatment

- Stratified by:
  - Geographic region (Asia vs rest of the world)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (< or ≥ 400 ng/mL)

N = 573

Regorafenib
160 mg orally; 3 wk on, 1 wk off (4 wk cycle)

n = 379

Placebo
n = 194

- All patients received best supportive care
- Patients were treated until disease progression, death, or unacceptable toxicity
- Primary endpoint: OS in ITT population
- Secondary endpoints: PFS, TTP, RR, DCR

RESORCE trial: Overall Survival

**Probability of Overall Survival, %**

**Events**
- Regorafenib (n = 379): 232 (61%)
- Placebo (n = 194): 140 (72%)

**Censored**
- Regorafenib (n = 379): 147 (39%)
- Placebo (n = 194): 54 (28%)

**Median OS, mo (95% CI)**
- Regorafenib: 10.6 (9.1-12.1)
- Placebo: 7.8 (6.3-8.8)

**HR (95% CI)**
- 0.63 (0.50-0.79); P < .0001 (2-sided)

---

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>379</td>
<td>194</td>
</tr>
<tr>
<td>316</td>
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<td>149</td>
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<tr>
<td>224</td>
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<td>1</td>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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*a Based on mRECIST.
CELESTIAL: A phase III study of cabozantinib vs placebo in patients with HCC who have received prior sorafenib

Advanced HCC (N=760)
- Unresectable HCC
- Received prior sorafenib
- <2 prior systemic therapies
- Child-Pugh A
- ECOG PS 0 or 1

Primary endpoint
- OS

Secondary endpoints
- PFS, ORR

R 2:1

Cabozantinib 60 mg qd orally

Placebo qd orally

Other endpoints
Safety/tolerability, PK, biomarkers, HRQOL

Overall Survival cabozantinib

- **Cabozantinib** (N=470)
  - Median OS: 10.2 (9.1-12.0) months
  - No. of Deaths: 317

- **Placebo** (N=237)
  - Median OS: 8.0 (6.8-9.4) months
  - No. of Deaths: 167

Hazard ratio 0.76 (95% CI 0.63-0.92), P=0.0049*

*Critical p-value ≤ 0.021 for second interim analysis

REACH-2: study design

**Stratification factors**
- Baseline AFP ≥ 400 ng/mL
- BCLC stage B/C
- Child Pugh A
- ECOG PS 0/1
- Prior sorafenib

**Primary endpoint:**
- Overall survival

**Secondary endpoints:**
- PFS, TTP, ORR
- Time to deterioration in FACT Hepatobiliary Symptom Index-8 (FHSI-8)
- Time to deterioration in ECOG PS
- Safety, PK, Immunogenicity

**Statistical assumptions and analysis**
- 80% power, alpha 0.05
- HR 0.67
- mOS 6.7 months ramucirumab vs 4.5 months placebo
- N = 278 (2:1 randomization, ramucirumab vs placebo)
- 221 event

**Placebo + BSC Q2W**

**Ramucirumab + BSC 8 mg/kg IV Q2W**

Ramucirumab improves OS in HCC with elevated AFP and prior sorafenib

Pooled Overall Survival: REACH-2/REACH (AFP ≥400 ng/mL)

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab (n = 316)</th>
<th>Placebo (n = 226)</th>
<th>Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>246 (77.8)</td>
<td>190 (84.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>8.1</td>
<td>5.0</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.694 (0.571, 0.842)</td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
</tbody>
</table>

No heterogeneity in treatment effect observed across both studies.

A random effect frailty model after adjusting for study (as random effect) produced a similar treatment result (HR=0.689; p=0.0002)

Zhu AX, et al. Lancet Oncology 2019
CheckMate 040 Study Design

**Study Endpoints**

**Primary**
- Safety and tolerability (escalation)
- Objective response rate\(^a\) (expansion)

**Secondary**
- Objective response rate\(^a\) (escalation)
- Disease control rate
- Time to response
- Duration of response
- Overall survival

**Other**
- Biomarker assessments
- Patient-reported outcomes\(^b\)

- Disease assessment imaging (CT or MRI) every 6 weeks
- Interim analysis data cutoff date: August 8, 2016
  - Median follow-up was 13.3 months in the dose-escalation phase and 10.5 months in the dose-expansion phase

**RECIST v1.1; \(^b\) Baseline and every 6 weeks through week 25 using the EQ-5D utility index and visual analog scale (VAS).**

Melero I, et al. *GI Symposium* 2017
Nivolumab (Anti–PD-1) in HCC

El-Khoueiry AB et al. Lancet 2017; S0140-6736(17)31046-2
KEYNOTE-224: pembrolizumab in patients with advanced HCC previously treated with sorafenib

Based on RESIST v1.1 by central radiology review in patients who had both pre- and post-treatment image measurements. Dotted line is threshold for response. Data cutoff date: Aug 24, 2017.

Zhu AX, et al. Lancet Oncol 2018
How to select and sequence each agent in clinical decision

• No level 1 evidence
• Mechanism of action of drugs and predictive biomarkers:
  • Checkpoint inhibitors: PD-L1 status, MSI status, tumor mutation burden and immune signature
  • TKIs: angiogenesis signatures
• Survival benefits with sorafenib-regorafenib sequencing
• Safety profiles of each agent
• Tumor burden and aggressiveness
• Subgroup analyses from phase III trials
**Multikinase inhibitors and antiangiogenic agents**

<table>
<thead>
<tr>
<th>Positive Phase 3 Trials in HCC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Oral TKI targeting RAF-1 and BRAF, VEGFR1–3, PDGFRβ</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Oral TKI targeting VEGFR1–3, FGFR1–4, RET, KIT, PDGFRα</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>Oral TKI targeting VEGFR1–3, TIE2, PDGFRβ, KIT, RET, RAF</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Oral TKI targeting MET, AXL, and VEGFR</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>Human IgG1 monoclonal antibody against VEGFR2</td>
</tr>
</tbody>
</table>

Predictive marker of response to sorafenib

Bruix J et al, J Hepatology 2017
<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Lenvatinib (n = 476)</th>
<th>Sorafenib (n = 475)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>201 (42)</td>
<td>111 (23)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>184 (39)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>162 (34)</td>
<td>22 (5)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>147 (31)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>141 (30)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>128 (27)</td>
<td>14 (3)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>117 (25)</td>
<td>27 (6)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>113 (24)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>93 (20)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>87 (18)</td>
<td>26 (6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>81 (17)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>78 (16)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>77 (16)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>76 (16)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase</td>
<td>65 (14)</td>
<td>24 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>46 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14 (3)</td>
<td>0 (N/A)</td>
</tr>
</tbody>
</table>
### Lenvatinib in first-line treatment

<table>
<thead>
<tr>
<th>A</th>
<th>Events/patients</th>
<th>HR (95% CI)</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lenvatinib</td>
<td>Sorafenib</td>
<td>Lenvatinib vs sorafenib</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>273/270</td>
<td>204/283</td>
<td>0.94 (0.77-1.15)</td>
</tr>
<tr>
<td>≥65</td>
<td>148/208</td>
<td>146/193</td>
<td>0.84 (0.66-1.07)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>293/405</td>
<td>293/401</td>
<td>0.91 (0.77-1.07)</td>
</tr>
<tr>
<td>Female</td>
<td>58/13</td>
<td>57/16</td>
<td>0.84 (0.66-1.06)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia Pacific</td>
<td>243/321</td>
<td>248/319</td>
<td>0.86 (0.72-1.01)</td>
</tr>
<tr>
<td>Western</td>
<td>98/145</td>
<td>98/147</td>
<td>1.10 (0.83-1.46)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS=0</td>
<td>221/304</td>
<td>223/261</td>
<td>0.88 (0.73-1.06)</td>
</tr>
<tr>
<td>PS=1</td>
<td>123/374</td>
<td>127/325</td>
<td>0.97 (0.84-1.15)</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>210/353</td>
<td>213/314</td>
<td>0.95 (0.87-1.02)</td>
</tr>
<tr>
<td>≥60</td>
<td>241/325</td>
<td>237/330</td>
<td>1.02 (0.90-1.15)</td>
</tr>
<tr>
<td>Macroscopic portal vein invasion, extrahepatic spread, or both</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>250/229</td>
<td>259/326</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>No</td>
<td>331/149</td>
<td>311/140</td>
<td>1.05 (0.87-1.27)</td>
</tr>
<tr>
<td>AFP at baseline (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>167/225</td>
<td>193/350</td>
<td>0.91 (0.77-1.11)</td>
</tr>
<tr>
<td>≥200</td>
<td>181/222</td>
<td>213/387</td>
<td>0.99 (0.74-1.38)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>196/259</td>
<td>186/244</td>
<td>0.83 (0.68-1.02)</td>
</tr>
<tr>
<td>HCV</td>
<td>75/103</td>
<td>97/135</td>
<td>0.51 (0.39-0.66)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>22/33</td>
<td>23/23</td>
<td>0.61 (0.41-0.93)</td>
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<tr>
<td>BCLC staging</td>
<td></td>
<td></td>
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<tr>
<td>Stage A</td>
<td>71/104</td>
<td>65/92</td>
<td>0.91 (0.65-1.28)</td>
</tr>
<tr>
<td>Stage C</td>
<td>208/247</td>
<td>213/264</td>
<td>0.92 (0.77-1.09)</td>
</tr>
<tr>
<td>Post-treatment anticancer therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>143/206</td>
<td>173/243</td>
<td>0.84 (0.67-1.06)</td>
</tr>
<tr>
<td>No</td>
<td>208/272</td>
<td>176/233</td>
<td>0.51 (0.74-1.31)</td>
</tr>
<tr>
<td>Post-treatment anticancer procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63/90</td>
<td>83/112</td>
<td>0.71 (0.53-1.01)</td>
</tr>
<tr>
<td>No</td>
<td>288/379</td>
<td>268/364</td>
<td>0.94 (0.79-1.11)</td>
</tr>
<tr>
<td>Post-treatment anticancer medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>110/136</td>
<td>133/184</td>
<td>0.87 (0.67-1.14)</td>
</tr>
<tr>
<td>No</td>
<td>214/222</td>
<td>218/202</td>
<td>0.90 (0.73-1.10)</td>
</tr>
<tr>
<td>Overall</td>
<td>351/478</td>
<td>350/476</td>
<td>0.92 (0.79-1.06)</td>
</tr>
</tbody>
</table>

First-line: sorafenib vs lenvatinib vs clinical trials

• Sorafenib: extensive clinical experience with AE management and dosing adjustment; HCV subgroup

• Lenvatinib: higher RR and longer PFS
Selection of second-line treatment for HCC

- Regorafenib: patients who have tolerated prior sorafenib
- Cabozantinib: more than one line of prior treatment
- Ramucirumab: baseline AFP $\geq 400$ ng/mL
- Nivolumab and pembrolizumab: high tumor burden
Cabozantinib vs placebo in second-line advanced HCC

Overall Survival and PFS in Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Overall Survival</th>
<th>Progression-free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>707</td>
<td>0.76</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>175</td>
<td>1.01</td>
</tr>
<tr>
<td>Other Regions</td>
<td>532</td>
<td>0.71</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>241</td>
<td>0.86</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>423</td>
<td>0.75</td>
</tr>
<tr>
<td>EHS and/or MVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>598</td>
<td>0.73</td>
</tr>
<tr>
<td>no</td>
<td>109</td>
<td>0.99</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>267</td>
<td>0.69</td>
</tr>
<tr>
<td>HCV</td>
<td>156</td>
<td>1.11</td>
</tr>
<tr>
<td>Other</td>
<td>284</td>
<td>0.72</td>
</tr>
<tr>
<td>Prior lines of therapy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One prior regimen</td>
<td>509</td>
<td>0.74</td>
</tr>
<tr>
<td>Two prior regimens</td>
<td>192</td>
<td>0.90</td>
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</table>

Median OS of 26 months from first sorafenib dose to death on regorafenib

Exploratory analysis of time from start to prior sorafenib treatment to death on RESORCE study drug

<table>
<thead>
<tr>
<th></th>
<th>(CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n 120</td>
<td>(17.5 - 25.9)</td>
</tr>
<tr>
<td>n 231</td>
<td>(23.3 - 28.9)</td>
</tr>
<tr>
<td>n 73</td>
<td>(12.2 - 24.9)</td>
</tr>
<tr>
<td>n 143</td>
<td>(19.6 - 27.8)</td>
</tr>
<tr>
<td>n 193</td>
<td>(16.3 - 22.8)</td>
</tr>
<tr>
<td>n 374</td>
<td>(22.6 - 28.1)</td>
</tr>
</tbody>
</table>

Finn RS, et al. J Hepatol 2018
Conclusions

• Targeted therapy and checkpoint inhibitors (US) have become the standard treatment for advanced HCC

• Assessing the molecular biomarkers capable of predicting treatment response remains an unmet medical need

• Level one evidence is lacking to guide clinical decision regarding sequencing of treatment

• Clinicians should make clinical decision based on the safety profiles, tumor aggressiveness including AFP level, tumor burden, and specific population
All of the following drugs were approved by FDA for the treatment of advanced HCC based on positive phase III trials except:

A. Regorafenib
B. Nivolumab
C. Cabozantinib
D. Lenvatinib
E. Ramucirumab
Q2

All of the following drugs were approved by FDA for the treatment of advanced HCC based on positive phase III trials except:

A. Regorafenib
B. Nivolumab
C. Cabozantinib
D. Lenvatinib
E. Ramucirumab
The evolving landscape of HCC treatment

Richard Finn
Geffen School of Medicine, University of California, USA
The Evolving Landscape for HCC Treatment

Richard S. Finn, MD
Professor of Clinical Medicine
Division of Hematology/ Oncology
Director, Signal Transduction and Therapeutics Program
Jonsson Comprehensive Cancer Center at UCLA
Geffen School of Medicine at UCLA
Disclosures

- Consultant: Astra Zeneca, Bayer, Bristol Myers Squibb, Eisai, Eli-Lilly, Exilixis, Merck, Novartis, Pfizer, Roche/Genentech
Will increasing exposure to systemic treatments improve OS?

Front-line

Sorafenib

Lenvatinib

Radiographic Progression

Second-line

Regorafenib
Cabozantinib
Ramucirumab (>AFP)
Nivolumab/ Pembrolizumab

Regorafenib
Cabozantinib*
Ramucirumab*
Nivolumab/ Pembrolizumab
Sorafenib

Radiographic Progression

Beyond

One of the agents the patient has not yet received

One of the agents the patient has not yet received

Bejjani and Finn. Clin Liver Dis 2019; in press
Challenges to clinical development

- Where do we place new treatments?
  - Third-line?
  - Second-line: control arm “dealers” choice?
  - Front-line: single agents vs combinations?
    - Biomarker driven single agents
    - Combinations based on strong rational
KEYNOTE 240: Time-to-Progression

Data Cutoff: Jan 2, 2019.
Finn RS et al. ESMO GI 2019
Progression-Free Survival

**Primary Analysis**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>203</td>
<td>0.775 (0.609-0.987)</td>
</tr>
<tr>
<td>Placebo</td>
<td>105</td>
<td></td>
</tr>
</tbody>
</table>

Pre-specified p=0.002 required for statistical significance

**Final Analysis**

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>214</td>
<td>0.718 (0.570-0.904)</td>
</tr>
<tr>
<td>Placebo</td>
<td>118</td>
<td></td>
</tr>
</tbody>
</table>

Finn RS et al. ASCO 2019
KEYNOTE 240: Overall Survival

Data Cutoff: Jan 2, 2019.
Finn RS et al. ASCO 2019

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>183</td>
<td>0.781 (0.611-0.998)</td>
<td>0.0238</td>
</tr>
<tr>
<td>Placebo</td>
<td>101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pre-specified p=0.0174 required for statistical significance
Checkmate-459: 1L nivolumab vs sorafenib
Phase 3 study design

Phase III, multi-center, randomized clinical trial (N=726)
Nivolumab vs Sorafenib as 1L treatment in patients with advanced HCC

Advanced HCC
Systemic therapy naïve

R 1:1

Nivolumab 240 mg (30 minutes IV Q2W)

Sorafenib 400 mg po BID

Unacceptable toxicity
Or
disease progression*

*Patients may be treated beyond progression under protocol-defined circumstances

Follow-up
and
Survival follow-up

Primary Endpoint: OS

Countries
US, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hong Kong, Japan, Korea, Poland, Singapore, Spain, Taiwan, UK

Status
Recruiting

Clinicaltrials.gov. NCT02576509. Accessed May 21, 2018
Checkmate-459: 1L nivolumab vs sorafenib
Phase 3 study design

Phase III, multi-center, randomized clinical trial
Nivolumab vs Sorafenib as 1L treatment in patients with advanced HCC

**Countries**
US, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hong Kong, Japan, Korea, Poland, Singapore, Spain, Taiwan, UK

**Status**
Recruiting

Clinicaltrials.gov. NCT02576509. Accessed May 21, 2018
Lenvatinib is a receptor tyrosine kinase inhibitor that inhibits the activities of the following receptors:\(^1,^2\)

- **RET, KIT, PDGFR**
  - Tumor growth control

- **VEGFR1-3**
  - Inhibition of neoangiogenesis and lymphangiogenesis

- **FGFR, PDGFR**
  - Inhibition of tumor microenvironment

- **FGFR1-4**
  - Reverse resistance to antiangiogenic drugs

FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; VEGF, vascular endothelial growth factor receptor

1. LENVIMA. Prescribing Information. Eisai Inc, Woodcliff Lake, NJ; May 2016
Lenvatinib + Pembrolizumab: tumor response

Figure 2. Waterfall Plots of Maximum Tumor Shrinkage by mRECIST per Independent Imaging Review (Efficacy Analysis Set)

Ikeda et al. AACR 2019
Lenvatinib + pembrolizumab: summary of tumor response (investigator assessment by mRECIST; efficacy analysis set\textsuperscript{a})

<table>
<thead>
<tr>
<th>Parameter, n (%)</th>
<th>LEN + PEM</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Part 1 (n = 6)</td>
<td>Part 2 (n = 20)</td>
<td>Overall (n = 26)</td>
</tr>
<tr>
<td>BOR, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR\textsuperscript{b}</td>
<td>0</td>
<td>1 (5.0)</td>
<td>1 (3.8)</td>
</tr>
<tr>
<td>PR\textsuperscript{c}</td>
<td>4 (66.7)</td>
<td>6 (30.0)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (33.3)</td>
<td>13 (65.0)</td>
<td>15 (57.7)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ORR (including unconfirmed response), n (%)</td>
<td>4 (66.7)</td>
<td>7 (35.0)</td>
<td>11 (42.3)</td>
</tr>
<tr>
<td>95% CI</td>
<td>22.3, 95.7</td>
<td>15.4, 59.2</td>
<td>23.4, 63.1</td>
</tr>
<tr>
<td>ORR (excluding unconfirmed responses), n (%)</td>
<td>3 (50.0)</td>
<td>4 (20.0)</td>
<td>7 (26.9)</td>
</tr>
<tr>
<td>95% CI</td>
<td>11.8, 88.2</td>
<td>5.7, 43.7</td>
<td>11.6, 47.8</td>
</tr>
</tbody>
</table>

Median time to response was 1.41 months (95% CI 1.35, 2.83)

\textsuperscript{a}Patients with post-evaluable tumor assessment; \textsuperscript{b}0 CR confirmed; \textsuperscript{c}7 PR confirmed.

BOR, best overall response; CI, confidence interval; CR, complete response; LEN, lenvatinib; mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate; PEM, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.
Regorafenib plus nivolumab in patients with advanced gastric (GC) or colorectal cancer (CRC): an open-label, dose-finding, and dose-expansion phase 1b trial (REGONIVO, EPOC1603)

Clinical Activity

- Forty patients were evaluable for response at ≥16 weeks follow-up. Confirmed ORR was 17.5% (7/40 patients with a partial response (PR)).

- ORR on the basis of confirmed + unconfirmed responses was 25.0% (10/40).

- Median time to response was 8.0 (range 7.6–24.0) weeks.

- Confirmed responses were robust and durable; all but 1 patient with a confirmed response were still responding to treatment by the snapshot date; 1 HBV+ patient had an unconfirmed PR.

- 1 HCV+ patient had a confined PR; 6 confirmed PRs were in uninfected patients, and tumor change from baseline appeared to be most pronounced in this population.

- Decrease from baseline in AFP over time was observed in several patients with PRs.

Overall Response Rates in HBV+, HCV+ and Uninfected Patients

<table>
<thead>
<tr>
<th>Investigator-assessed response</th>
<th>HBV+ n=11</th>
<th>HCV+ n=9</th>
<th>Uninfected n=20</th>
<th>Total N=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (all PR), % (95% CI)</td>
<td>0 (0.0–28.5)</td>
<td>11.1 (0.3–48.2)</td>
<td>30.0 (11.9–54.3)</td>
<td>17.5 (7.3–32.8)</td>
</tr>
<tr>
<td>CR + PR (confirmed + unconfirmed), % (95% CI)</td>
<td>9.1 (0.2–41.3)</td>
<td>11.1 (0.3–48.2)</td>
<td>40.0 (19.1–63.9)</td>
<td>25.0 (12.7–41.2)</td>
</tr>
<tr>
<td>CR + PR + SD ≥16 weeks (DCR 16), % (95% CI)</td>
<td>45.5 (16.7–76.6)</td>
<td>44.4 (13.7–78.8)</td>
<td>70.0 (45.7–88.1)</td>
<td>57.5 (40.9–73.0)</td>
</tr>
</tbody>
</table>

CE, complete response; DCR, disease control rate; ORR, objective response rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease
Nivolumab plus ipilimumab combination therapy in patients with advanced HCC: results from CheckMate 040.

Response, disease control and durability

<table>
<thead>
<tr>
<th>ORR by BICR using RECIST v1.1, n (%)</th>
<th>Arm A NIVO1/IP13 Q3W(^b) n = 50</th>
<th>Arm B NIVO3/IP11 Q3W(^b) n = 49</th>
<th>Arm C NIVO3 Q2W/IP11 Q6W n = 49</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR by BICR using RECIST v1.1, n (%)</td>
<td>16 (32)</td>
<td>15 (31)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>CR</td>
<td>4 (8)</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>12 (24)</td>
<td>12 (24)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>9 (18)</td>
<td>5 (10)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>20 (40)</td>
<td>24 (49)</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Unable to determine, n (%)</td>
<td>3 (6)</td>
<td>4 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>DCR, n (%)</td>
<td>27 (54)</td>
<td>21 (43)</td>
<td>24 (49)</td>
</tr>
<tr>
<td>Median TTR (range), months</td>
<td>2.0 (1.1–12.8)</td>
<td>2.6 (1.2–5.5)</td>
<td>2.7 (1.2–8.7)</td>
</tr>
<tr>
<td>Median DOR (range), months</td>
<td>17.5 (4.6 to 30.5+)</td>
<td>22.2 (4.2 to 29.9+)</td>
<td>16.6 (4.1+ to 32.0+)</td>
</tr>
<tr>
<td>ORR by investigator assessment using RECIST v1.1, n (%)</td>
<td>16 (32)</td>
<td>13 (27)</td>
<td>14 (29)</td>
</tr>
</tbody>
</table>

\(^b\)NIVO1/IP13 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; \(^b\)NIVO3/IP11 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; \(^c\)Defined as CR + PR; \(^d\)SD was reported as non-CR/non-PR in 2 patients in Arm A and 1 patient in Arm B who only had non-target lesions at baseline and so did not meet the definition of SD by BICR; \(^e\)Defined as CR + PR + SD + non-CR/non-PR.

NE, not evaluable; PR, partial response; SD, stable disease.

Yau T, et al. ASCO 2019
Bevacizumab + Atezolizumab

Phase Ib GO30140 Study (NCT02715531)

Eligibility Criteria:
- Measurable disease per RECIST 1.1
- ECOG PS 0/1
- Adequate hematologic and organ function
- No prior systemic therapy
  - No prior treatment with anti-CTLA-4, anti-PD-1 or anti-PD-L1 therapeutic antibodies

Arm A: unresectable HCC (n = 104)
- Up to Child-Pugh score B7
- Atezolizumab 1200 mg IV q3w + bevacizumab 15 mg/kg IV q3w

Arm B: Gastric cancer
Arm C: Pancreatic cancer
Arm E: Oesophageal cancer
Arm F: Randomized first-line HCC (atezolizumab + bevacizumab vs atezolizumab)

Until disease progression, unacceptable toxicity or loss of clinical benefit

Primary endpoints (Arm A)
- IRF-assessed ORR per RECIST 1.1, safety

Key secondary endpoints (Arm A)
- DOR and PFS per IRF RECIST 1.1
- ORR, DOR and PFS per IRF HCC mRECIST
- ORR, DOR and PFS per INV-assessed RECIST 1.1
- OS

At clinical data cutoff (14 June 2019), 104 patients with HCC treated with atezolizumab + bevacizumab were evaluable for safety and efficacy with a median follow-up of 12.4 months

Lee et al. APPLE 2019
Proposed Mechanism of Action: Bevacizumab + Atezolizumab

- Bevacizumab (anti-VEGF) is an antiangiogenic agent with additional immuno-modulatory effects
- In combination, bevacizumab may further enhance atezolizumab’s efficacy by reversing VEGF-mediated immuno-suppression to promote T-cell infiltration into the tumor

DC, dendritic cell; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

## Objective Response and Durability of Response

**Arm A: Atezolizumab + Bevacizumab**  
**N = 104**

<table>
<thead>
<tr>
<th></th>
<th>IRF RECIST 1.1</th>
<th>IRF HCC mRECIST</th>
<th>INV RECIST 1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI), %</td>
<td>37 (36)</td>
<td>41 (39)</td>
<td>34 (33)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>12 (12)</td>
<td>16 (15)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>25 (24)</td>
<td>25 (24)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>DCR, n (%)</td>
<td>74 (71)</td>
<td>74 (71)</td>
<td>78 (75)</td>
</tr>
<tr>
<td>On-going response, n (%)</td>
<td>28 (76)</td>
<td>28 (68)</td>
<td>24 (71)</td>
</tr>
</tbody>
</table>

| **Median DOR (mo)**      | NE (11.8 – NE) | NE (11.8 – NE) | NE (11.7 – NE) |
| (95% CI)                 |               |                 |               |
| DOR range (mo)           | 1.6+ – 31.0+   | 1.6+ – 31.0+    | 3.5+ – 31.0+   |
| ≥ 9 mo, n (%)            | 20 (54)        | 25 (61)         | 21 (62)        |
| ≥ 12 mo, n (%)           | 11 (30)        | 11 (27)         | 12 (35)        |
Bevacizumab + Atezolizumab

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Any Grade N = 104</th>
<th>Grade 3-4 N = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>38 (37)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>36 (35)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29 (28)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>24 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24 (23)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (22)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (21)</td>
<td>15 (14)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21 (20)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>21 (20)</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AESIs by Medical Concepta (≥ 5% of pts), n (%)</th>
<th>Any Grade N = 104</th>
<th>Grade 3-4 N = 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>39 (38)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Laboratory abnormalities</td>
<td>35 (34)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Rash</td>
<td>30 (29)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>38 (37)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Bleeding/Hemorrhage</td>
<td>30 (29)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Upper gastrointestinal bleedingb</td>
<td>6 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (21)</td>
<td>15 (14)</td>
</tr>
</tbody>
</table>

a Hepatitis, rash and hypothyroidism are atezolizumab AESIs; proteinuria, bleeding and hypertension are bevacizumab AESIs.
b Includes reports of esophageal varices hemorrhage, gastrointestinal hemorrhage, and upper gastrointestinal hemorrhage.

Data cutoff: 14 June 2019
Ongoing Phase 3 Studies: Front-line

- **RATIONALE**  Tislelizumab vs sorafenib (non-inferiority)
- **ImBRAVE 150**  Bevacizumab/Atezolizumab vs sorafenib
- **LEAP 002**  Lenvatinib/ Pembrolizumab vs lenvatinib
- **HIMALAYA**  Durvalumab/ Tremelimumab vs sorafenib
- **COSMIC**  Cabozantinib/ Atezolizumab vs sorafenib
Conclusions

• After nearly a decade, we have had 4 positive phase 3 studies of new drugs in HCC that improve survival
  – Lenvatinib- non-inferior to sorafenib, HR 0.92
  – Regorafenib vs placebo, 2\textsuperscript{nd} line, HR 0.62
  – Cabozantinib vs placebo, 2\textsuperscript{nd} and 3\textsuperscript{rd} line (HR 0.70 prior sor)
  – Ramucirumab vs placebo, 2\textsuperscript{nd} line, high AFP

• Level 1 Evidence for Checkpoint inhibitors still needed
  – Nivolumab vs sorafenib front-line
  – Pembrolizumab vs placebo second line

• Ongoing studies looking at novel combinations
  – Checkpoint inhibitors and TKIs
  – PD-1+CTLA4
  – PD-L-1 +Bev
All of the following combinations are being studied in phase 3 trials in advanced HCC except?

A. lenvatinib and pembrolizumab
B. bevacizumab and atezolizumab
C. durvalumab and tremelumab
D. cabozantinib and atezolizumab
E. sorafenib and nivolumab
Q3

All of the following combinations are being studied in phase 3 trials in advanced HCC except?

A. lenvatinib and pembrolizumab
B. bevacizumab and atezolizumab
C. durvalumab and tremelulmab
D. cabozantinib and atezolizumab
E. sorafenib and nivolumab
Putting evidence into practice: case studies and panel discussion

Andrew Zhu, Peter Galle and Richard Finn
Case Report 1

Peter Galle
Case 1

46 years old male patient with elevated liver enzymes

- Elevated liver enzymes
- Fatigue
- Pruritus
- Metabolic syndrome
  - Insulin-dependent type 2 diabetes for 20 years
  - Arterial hypertension
  - Hyperlipidemia
  - Obesity (107 kg, 185 cm (BMI 31 kg/m²))
Diagnosis – NASH Cirrhosis
Surveillance – 18 months later
Diagnosis - HCC

MDT recommended:

1. Bridging with TACE
2. LTx (Liver transplantation)
Case Report 2

Richard Finn
Case study

- 64 y/o male history of cirrhosis from HCV and alcohol
- Initially presented in with abdominal pain and syncope
- Found to have hemoperitoneum from a peripheral 5 cm tumor that ruptured and also with multi-focal HCC
- Underwent urgent embolization and presented for management
- Eventually recovers, CP A and undergoes repeat TACE but develops multiple new lesions after procedure. No EHS or MVI
- Labs 5.1>10.8<125 Alb 3.0, T bili 1.4 AFP 1500

Options?
Case continues

- Pt is started on sorafenib 200 mg BID in June 2016
- Titrated to 400 mg BID without significant toxicity
- Continues on 400 mg BID with rising AFP on drug: 3300 to 4500 to 5800 ng/mL
- Early September, reimaged, consistent with PD
- Options?
Case continues

- Pt started on ramucirumab 8 mg IV q 2 weeks
- Has a rapid fall in AFP
- Imaging consistent with response
AFP Response

- AFP Concentration (µg/L)
- Baseline, Cycle 3, Cycle 6, Cycle 8, Cycle 9, Cycle 12, Cycle 15, Cycle 18, Cycle 21, Cycle 24, Cycle 27, Long-term follow-up
Imaging response

October 2016 (baseline), AFP 6425 ng/mL

June 2017 (-19%), AFP 36 ng/mL
Case continues

• Continues on ramucirumab for 13 months when develops a rising bilirubin (3.0) and has to come off study, scans without clear PD

• Options?
Case continues

• Gets started on regorafenib 80 mg a day

• Attempt to titrate to 120 mg but not tolerated, fatigue, asthenia

• T bili falls a bit, AFP slowly rising

• Stays on regorafenib until for 4 months when has radiographic PD, rising AFP
  • Also has developed ascites, edema, CP B

• Options?
Case continues

- Starts nivolumab
- Remains on nivolumab for 3 months with no clear benefit
- Worsening liver dysfunction
- Referred to hospice
Case Report 3

Andrew X. Zhu
Case 3

- 49 year old male with history of HBV and alcohol related compensated Child-Pugh A cirrhosis and biopsy proven multifocal HCC. S/p bland embolization times two (6/17 and 10/17). Recent evidence of rapid disease progression with markedly elevated AFP

- His performance status is excellent

- WBC 9.4, HCT 37.4, Platelet 233K, Creatinine 0.73, albumin 3.9, total bilirubin 0.3, ALT 21, AST 45, AFP 28422

- Liver MRI showed multifocal HCC, predominantly in the right hepatic lobe. Enlarged upper abdominal lymph nodes
Discussion: What would we recommend for treatment now?

- Nivolumab
- Sorafenib
- Regorafenib
- Cabozantinib
- Lenvatinib
- Pembrolizumab
- Ramucirumab
Summary from the Chair

Andrew Zhu
Before we finish...

I feel confident in selecting and sequencing the most appropriate first- and second-line treatment options for patients with HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Before we finish...

I feel confident in selecting and sequencing the most appropriate first- and second-line treatment options for patients with HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Before we finish...

I feel up to date on the emerging treatment options for the treatment of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree

URL: hcc.chime.live
Before we finish...

I feel up to date on the emerging treatment options for the treatment of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree
Before we finish...

I understand the role of AFP status in the diagnosis of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree

URL: hcc.chime.live
Before we finish...

I understand the role of AFP status in the diagnosis of HCC

A. Strongly disagree
B. Disagree
C. Neither agree nor disagree
D. Agree
E. Strongly agree

URL: hcc.chime.live
Your opinion matters

• Please remember to fill out your evaluation form on your smartphone/tablet or use the printed form with your brochure
• This program was approved by the International Liver Cancer Association as an independent activity held in conjunction with the ILCA 13th annual congress. This program is not sponsored or endorsed by ILCA

Thank you for attending