Systemic Therapy for Liver Cancer
Management of HCC

- Surgical Treatment
  - Liver transplantation
  - Resection
- Imaging guided interventions
  - Percutaneous ethanol injection (PEI)
  - Thermal ablation (RFA, MWA)
  - Chemoembolization (TACE) (Deb-TACE)
  - Yttrium (Y-90) (TARE)
  - External beam radiation (SBRT)
- Systemic therapy
  - Tyrosine kinase inhibitors
  - Immunotherapy
Transplant for HCC: BCLC Staging System

**Hepatocellular Carcinoma**

- **Very early stage (0)**
  - Single ≤ 2cm
  - Preserved liver function, ECOG PS 0
  - Potential candidate for liver transplantation

- **Early stage (A)**
  - Single or up to 3 nodules ≤ 3cm
  - Preserved liver function, ECOG PS 0
  - Solitary
  - Up to 3 nodules (≤3 cm)
  - Portal pressure
    - Normal
    - Increased
      - Associated diseases
        - No
        - Yes
          - Ablation
          - Resection
          - Transplantation

- **Intermediate stage (B)**
  - Multinodular
  - Preserved liver function, ECOG PS 0
  - Up to 3 nodules (≤3 cm)
  - Portal pressure
    - Normal
    - Increased
      - Associated diseases
        - No
        - Yes
          - Ablation
          - Chemoembolisation

- **Advanced stage (C)**
  - Portal invasion
  - Extrahepatic spread
  - Preserved liver function, ECOG PS 1-2
  - Systemic therapy†

- **Terminal stage (D)**
  - End-stage liver function*, ECOG PS 3-4
  - Best supportive care

**Survival Treatment**

- Effective treatments with impact on survival
  - Ablation: >5 years
  - Resection: >2-5 years
  - Transplantation: >1 year
  - Chemoembolisation: 3 months
  - Systemic therapy†
Treatment Recommendations According to BCLC Stage

MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy
Assessing Severity of CLD: Child-Turcotte-Pugh Score

<table>
<thead>
<tr>
<th>Clinical and Lab Criteria</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td>&lt;4</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
</tr>
</tbody>
</table>

Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)
Class A = 5 to 6 points (least severe liver disease)
Class B = 7 to 9 points (moderately severe liver disease)
Class C = 10 to 15 points (most severe liver disease)
ECOG Performance Status

- Performance status is highly correlated with survival, need for services, and may help predict ability to tolerate therapies.

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG Performance Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any selfcare; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group
Phase III SHARP Trial
Sorafenib vs Placebo in Advanced HCC

Stratification:
* Macroscopic vascular invasion (portal vein) and/or extrahepatic spread
* ECOG PS
* Geographical region

Randomization
N=602

Sorafenib (n=299)
400 mg po bid continuous dosing

Placebo (n=303)
2 tablets po bid continuous dosing

Phase III Sharp and AP Trials
Predictors of Response to Sorafenib (n=827)

<table>
<thead>
<tr>
<th>Baseline Covariate</th>
<th>Number of Patients</th>
<th>Hazard Ratio (Sorafenib/Placebo)</th>
<th>Treatment Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sorafenib</td>
<td>Placebo</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>EHS</td>
<td>No</td>
<td>187</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>261</td>
<td>201</td>
</tr>
<tr>
<td>HCV</td>
<td>No</td>
<td>303</td>
<td>265</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>111</td>
<td>88</td>
</tr>
<tr>
<td>Neutrophyl to lymphocyte ratio</td>
<td>≤median</td>
<td>238</td>
<td>192</td>
</tr>
<tr>
<td></td>
<td>&gt;median</td>
<td>207</td>
<td>184</td>
</tr>
</tbody>
</table>

HCC pool (100554 and 11849) Overall survival - Kaplan Meter-Plot by Hepatitis C (full analysis set) Hepatitis C: “Positive”

### Sorafenib Side Effects

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Sorafenib Any Grade</th>
<th>Sorafenib Grade 3/4</th>
<th>Placebo Any Grade</th>
<th>Placebo Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>46%</td>
<td>10%</td>
<td>45%</td>
<td>14%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>30%</td>
<td>2%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Hand Food Skin Rxn</td>
<td>21%</td>
<td>8%</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9%</td>
<td>4%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>14%</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55%</td>
<td>10%</td>
<td>25%</td>
<td>2%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>29%</td>
<td>3%</td>
<td>18%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**BUT:** Early onset of side effects may predict response
- Multicenter trial of 606 patients who received TACE+SOR
- Patients with grade 2 HFSR within one month of initiation had longer OS
  - 28.9 months vs 16.8 months

The Challenge: First-line Randomized Phase III Trials in HCC

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>Targets</th>
<th>Median TTP, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib vs sorafenib[1]</td>
<td>VEGFRs, PDGFRs, c-KIT, FLT3, RET[2]</td>
<td>4.1 vs 3.8</td>
<td>7.9 vs 10.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR: 1.13 (95% CI: 0.98-1.31; ( P = .8312 ))</td>
<td>HR: 1.30 (95% CI: 1.13-1.50; 2-sided ( P = .0014 ))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR: 1.01 (95% CI: 0.88-1.16; ( P = .8532 ))</td>
<td>HR: 1.07 (95% CI: 0.94-1.23; ( P = .3116 ))</td>
</tr>
<tr>
<td>Linifanib vs sorafenib[5]</td>
<td>VEGFR, PDGFR</td>
<td>5.4 vs 4.0</td>
<td>9.1 vs 9.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR: 0.759 (95% CI: 0.643-0.895; ( P = .001 ))</td>
<td>HR: 1.046 (95% CI: 0.896-1.221; ( P = \text{NS} ))</td>
</tr>
<tr>
<td>Sorafenib + erlotinib vs sorafenib + placebo[6]</td>
<td>VEGFR1/2/3, PDGFR, Ras, Raf, EGFR[6,7]</td>
<td>3.2 vs 4.0</td>
<td>9.5 vs 8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR: 1.135 (95% CI: 0.944-1.366; ( P = .18 ))</td>
<td>HR: 0.929 (95% CI: 0.781-1.106; ( P = .408 ))</td>
</tr>
<tr>
<td>Doxorubicin + sorafenib vs sorafenib (CALGB 80802)[8]</td>
<td>VEGFR1/2/3, PDGFR, Ras, Raf[7]</td>
<td>4.0 vs 3.9*</td>
<td>8.9 vs 10.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR: 0.9 (95% CI: 0.72-1.20; ( P = .98 ))</td>
<td>HR: 1.06 (95% CI: 0.8-1.4; ( P = .24 ))</td>
</tr>
</tbody>
</table>

*Median PFS.

References in slidenotes.

Slide credit: clinicaloptions.com
**Challenge: Second-line Phase III Randomized Trials in HCC**

<table>
<thead>
<tr>
<th>Phase III Trial</th>
<th>Target(s)</th>
<th>Median TTP, Mos</th>
<th>Median OS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab vs placebo&lt;sup&gt;[1]&lt;/sup&gt;</td>
<td>IgG1 Ab to VEGFR2</td>
<td>3.5 vs 2.6</td>
<td>9.2 vs 7.6</td>
</tr>
<tr>
<td></td>
<td>HR: 0.59 (95% CI: 0.49-0.72; P &lt; .0001)</td>
<td></td>
<td>HR 0.87 (95% CI: 0.72-1.05; P = .14)</td>
</tr>
<tr>
<td>Brivanib vs placebo&lt;sup&gt;[2]&lt;/sup&gt;</td>
<td>VEGFR2, FGFR&lt;sup&gt;[3]&lt;/sup&gt;</td>
<td>4.2 vs 2.7</td>
<td>9.4 vs 8.2</td>
</tr>
<tr>
<td></td>
<td>HR: 0.56 (95% CI: 0.42-0.76; P &lt; .001)</td>
<td></td>
<td>HR: 0.89 (95% CI: 0.69-1.15; P = .3307)</td>
</tr>
<tr>
<td>Everolimus vs placebo&lt;sup&gt;[4]&lt;/sup&gt;</td>
<td>mTOR</td>
<td>3.0 vs 2.6</td>
<td>7.6 vs 7.3</td>
</tr>
<tr>
<td></td>
<td>HR: 0.93 (95% CI: 0.75-1.15; P = NR*)</td>
<td></td>
<td>HR: 1.05 (95% CI: 0.86-1.27; P = .68)</td>
</tr>
<tr>
<td>Tivantinib vs placebo&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>cMet&lt;sup&gt;[6]&lt;/sup&gt;</td>
<td>2.4 vs 3.0</td>
<td>8.4 vs 9.1</td>
</tr>
<tr>
<td></td>
<td>HR: 0.96 (95% CI: 0.74-1.25; P = .76)</td>
<td></td>
<td>HR 0.97 (95% CI 0.75-1.25; P = .81)</td>
</tr>
</tbody>
</table>

*Difference not statistically tested per prespecified analysis plan.*

# Tyrosine Kinase Inhibitors

## TKIs / Targeted Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication/Status</th>
<th>Dosage</th>
<th>Future Directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib¹</td>
<td>First-line treatment of unresectable HCC</td>
<td>400 mg 2x/d w/o food; treatment interruption and/or dose reduction for possible AEs: 400 mg 1x/d or 400 mg every other d</td>
<td>The approval of TKI therapy in HCC has fueled additional research into the use of targeted agents in combination strategies or in settings other than advanced HCC; several examples are provided below.</td>
</tr>
</tbody>
</table>
| Lenvatinib²        | First-line treatment of unresectable HCC | 12 mg 1x/d for patients ≥60 kg or 8 mg 1x/d for patients ≤60 kg; dose modification may be needed for patients with renal or hepatic impairment | • Multiple combination strategies with locoregional therapy (Y-90, SBRT, TACE, or others)⁷  
• Combinations with immune checkpoint inhibitors⁸  
• Other next-generation TKIs are also being explored⁹ |
| Regorafenib³       | Second-line setting following treatment with sorafenib | 160 mg orally; 3 wk on, 1 wk off (4-wk cycle) |                                                                                                                                                                                                                   |
| Cabozantinib⁴ ⁵    | Second-line setting following treatment with sorafenib | 60 mg/d (dose studied in phase 2 and 3 trials) |                                                                                                                                                                                                                   |
| Ramucirumab⁶       | Evidence in second-line setting following treatment with sorafenib for advanced HCC | 8 mg/kg IV every other wk (dose studied in phase 3 trial) |                                                                                                                                                                                                                   |

1. Approved  
2. Approved  
3. Approved  
4, 5. Approved  
6. Phase 3  
7. PRACTICE AID  
8. Systemic Therapy in Advanced HCC  
Regorafenib: Dosage and Administration

• Approved by the FDA in April 2017 for pts with HCC previously treated with sorafenib[1]

• Recommended dose: 160 mg PO QD x 3 wks Q4W[1]

• 2-wk washout period recommended after discontinuing sorafenib[2]
  – Allows for elimination of sorafenib and metabolites
  – Demonstrated safety with this approach in RESORCE trial

2. Jordi Bruix, MD, personal communication.
Regorafenib for Patients with HCC who progressed on Sorafenib Treatment (RESORCE): Trial Design

Clinicaltrials.gov NCT01774344

Regorafenib 160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

Placebo
(n=194)

• HCC patients with documented radiological progression during sorafenib treatment

• Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

• 152 centers in 21 countries in North and South America, Europe, Australia, Asia
• All patients received best supportive care
• Treat until progression, unacceptable toxicity, or withdrawal

ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein
Overall Survival (OS)

Primary Endpoint

HR 0.63 (95% Cl 0.50–0.79); one-sided p<0.0001

Regorafenib
Placebo

<table>
<thead>
<tr>
<th>Events</th>
<th>232 (61%)</th>
<th>140 (72%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censored</td>
<td>147 (39%)</td>
<td>54 (28%)</td>
</tr>
<tr>
<td>Median OS (95% CI)</td>
<td>10.6 months (9.1, 12.1)</td>
<td>7.8 months (6.3, 8.8)</td>
</tr>
<tr>
<td>HR 0.62 (95% CI: 0.50, 0.78)</td>
<td></td>
<td>P&lt;0.001 (2-sided)</td>
</tr>
</tbody>
</table>

Regorafenib Conclusions

• SAEs equivalent regorafenib vs placebo
  • Bleeding events similar
  • 25% regorafenib and 19% placebo discontinued due to AEs

• Regorafenib is the first systemic therapy to show survival benefit in HCC since sorafenib in 2007

• Improvements in overall survival seen in second line treatment in patients that tolerated sorafenib for at least 28 days but progressed on treatment

• When considering time on sorafenib therapy and subsequent time on regorafenib therapy in patients with advanced HCC in RESORCE trial, overall survival was 26 months from time of start of systemic therapy

• Tolerability can be an issue and requires close monitoring and aggressive side effect management
Lenvatinib vs Sorafenib Phase III

- Lenvatinib is an:
  - Oral multiple tyrosine kinase inhibitor
  - Mainly active against VEGFR1, VEGFR2, and VEGFR3
  - Also inhibits FGFR1, 2, 3, and 4, PDGFR, KIT, RET
- Study examined lenvatinib 8 mg or 12 mg daily (based on body weight) vs sorafenib
- 954 patients enrolled globally
- BCLC B or C, Child-Pugh A, ECOG PS ≤1
- No prior systemic therapy
- Primary endpoint OS with target of non-inferiority

Cheng et al. ASCO 2017
## Lenvatinib vs Sorafenib Phase III

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>LEN</th>
<th>SOR</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>13.6 (12.1−14.9)</td>
<td>12.3 (10.4−13.9)</td>
<td>0.92 (0.79−1.06)</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)*</td>
<td>7.4 (6.9−8.8)</td>
<td>3.7 (3.6−4.6)</td>
<td>0.66 (0.57−0.77)</td>
</tr>
<tr>
<td>Median TTP, mos (95% CI)*</td>
<td>8.9 (7.4−9.2)</td>
<td>3.7 (3.6−5.4)</td>
<td>0.63 (0.53−0.73)</td>
</tr>
<tr>
<td>ORR, n (%)*</td>
<td>115 (24)</td>
<td>44 (9)</td>
<td></td>
</tr>
</tbody>
</table>

* *p<0.0001

- Similar number of patients in each arm had AEs
- 13% LEN patients and 9% SOR patients discontinued due to AEs

Cheng et al, ASCO 2017
Lenvatinib: Study 304: Efficacy

Lenvatinib (n = 478)
Sorafenib (n = 476)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lenvatinib (95% CI)</th>
<th>Sorafenib (95% CI)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, mos</td>
<td>13.6 (12.1-14.9)</td>
<td>12.3 (10.4-13.9)</td>
<td>0.92 (0.79-1.06)</td>
</tr>
<tr>
<td>mPFS, mos</td>
<td>7.4 (6.9-8.8)*</td>
<td>3.7 (3.6-4.6)</td>
<td>0.66 (0.57-0.77)</td>
</tr>
<tr>
<td>mTTP, mos</td>
<td>8.9 (7.4-9.2)*</td>
<td>3.7 (3.6-5.4)</td>
<td>0.63 (0.53-0.73)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>115 (24.1)*</td>
<td>44 (9.2)</td>
<td></td>
</tr>
</tbody>
</table>

*P < .00001 vs sorafenib.

- **Conclusion:** lenvatinib noninferior to sorafenib in OS in first-line setting for unresectable HCC
  - Statistically significant improvements in PFS, TTP, and ORR for lenvatinib vs sorafenib


Slide credit: clinicaloptions.com
HCC Systemic Therapy Updates:

• Cabozantinib is now approved for HCC, second Line. Active against VEGFR, AXL, MET
• Nivolumab and pembrolizumab are approved in the second line setting based on accelerated approval and single arm phase 2 studies.
• Phase 3: sorafenib vs nivolumab not yet presented
• Phase 3: pembrolizumab vs placebo has not been presented but press release suggests that it did not meet its statistical endpoint
Rationale for Immunotherapy in HCC

- HCC is a classical inflammation-induced tumor type
- Spontaneous immune responses are frequently observed
- Independent of liver function (no metabolism)
- Can be combined with ablative therapies
Immune-Based Approaches in HCC

Antibody

Dendritic cells

Peptides

Cytokines

CTL mediated lysis

T-cell activation

Enhanced T-cell function

Foxp3+ Treg

MDSC

IL-10, TGF-β

Oncolytic virus

Tumor ablation

Cancer vaccines

Elimination of suppressor cells

Blockade of immunosuppressive cytokines

Checkpoint blockade

Cytokines (GM-CSF, IL-2, IFN-γ, etc)

Tumor cell death


Slide credit: clinicaloptions.com
Dose Expansion (n = 214)

3 mg/kg

Without viral hepatitis

HCV infected (n = 50)

HBV infected (n = 51)

Sorafenib untreated or intolerant (n = 56)

Sorafenib progressor (n = 57)


PD-L1 < 1%

PD-L1 ≥ 1%

ORR, n/N (%) 17/99 (17.2) 8/25 (32.0)

Slide credit: clinicaloptions.com
Nivolumab: Dosage and Administration

• Received accelerated approval by the FDA on September 22, 2017, for pts with HCC previously treated with sorafenib[1]
  – Regardless of PD-L1 expression status
• Recommended dose: 240 mg Q2W IV over 60 mins
• Continued approval contingent upon validation in confirmatory trials

## Immune Checkpoint Inhibitors

### Agent Indication/Status

- **Nivolumab**
  - Second-line setting following treatment with sorafenib
  - Approved
  - Phase 3 testing (CheckMate-459; NCT02376309) as first-line treatment

- **Pembrolizumab**
  - Second-line setting following treatment with sorafenib
  - Priority review

- **Durvalumab**
  - HCC (Child-Pugh class A)
  - Phase 3

- **Atezolizumab + bevacizumab**
  - First-line treatment of advanced or metastatic HCC
  - Breakthrough therapy designation

### Dosage

- **Nivolumab**
  - 240 mg every 2 wk or 480 mg every 4 wk

- **Pembrolizumab**
  - 200 mg every 3 wk
  - (dose studied in phase 2 trial)

- **Durvalumab**
  - 10 mg/kg IV every other wk
  - (dose studied in phase 1/2 trial)

- **Atezolizumab + bevacizumab**
  - Atezo 1,200 mg IV every 3 wk or 840 mg every 2 wk and bev 15 mg/kg IV every 3 wk or 10 mg/kg every 2 wk
  - (dose studied in phase 1 trial)

### Future Directions

As in other cancer settings, multiple explorations of checkpoint inhibitors in HCC, including immune combinations or as treatments, are underway:

- Dual checkpoint blockade (anti-PD-1/L1 + anti-CTLA-4)
- Combinations with TKIs and with locoregional therapy
Adverse Event Management

Managing Adverse Events Associated With Systemic Therapies Used in Patients With Hepatocellular Carcinoma

Immune-Related Adverse Events (irAEs) Associated With Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are associated with important clinical benefits, but general immunologic enhancement can also lead to a unique spectrum of irAEs.

Why do irAEs occur?

- The precise pathophysiology is unknown, but traditional studies have shown that T-cell antibodies and cytokine responses may be involved.

What is the spectrum of potential irAEs?

Any organ system can be affected; commonly occurring are pulmonary (pneumonitis), dermatologic (psoriasis, pruritus, rashes), gastrointestinal (diabetes, enteritis, colitis, cholecystitis), and endocrine (thyroiditis, hyperthyroidism, adrenal insufficiency). NA.

How should irAEs be diagnosed and managed?

- Advice after diagnosis by an expert in the field.
- Grade 1 & 2 irAEs may be managed with dose reduction, with consideration of T-cell/monoclonal antibody and corticosteroids.
- Grades 3 & 4 irAEs may be managed with dose reduction, with consideration of T-cell/monoclonal antibody and corticosteroids.

General recommendations and management principles include the following:

- Depending on severity of irAEs, management may require discontinuation and re-introduction of immunotherapy.
- Use of immunosuppression therapy to manage irAEs may require re-escalation or immunotherapy.
- For organ-specific assessment and management of irAEs, please see the ASCO guidelines.

For more information, please refer to the ASCO guidelines.
### Guidelines for Hepatic irAE Management by Grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>ICPi Therapy</th>
<th>Monitor</th>
<th>Corticosteroid</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Asymptomatic (AST or ALT &gt; ULN to 3.0 × ULN and/or total bilirubin &gt; ULN to 1.5 × ULN)</td>
<td>Continue</td>
<td>Weekly or more</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>2 Asymptomatic (AST or ALT &gt;3 to ≤5 × ULN and/or total bilirubin &gt;1.5 to ≤3 × ULN)</td>
<td>Hold</td>
<td>Every 3 d</td>
<td>0.5-1 mg/kg/d</td>
<td>Consider resuming ICPI when grade 1 or lower</td>
</tr>
<tr>
<td>Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN)</td>
<td>Discontinue permanently</td>
<td>Every 1-2 d</td>
<td>1-2 mg/kg/d Taper at 4-6 wk</td>
<td>If no improvement in 3 d, consider mycophenolate mofetil (infliximab not recommended)</td>
</tr>
<tr>
<td>4 Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT &gt;20 × ULN and/or total bilirubin &gt;10 × ULN)</td>
<td>Discontinue permanently</td>
<td>Daily; consider impatient</td>
<td>2 mg/kg/d Taper at 4-6 wk</td>
<td></td>
</tr>
</tbody>
</table>
Management of AEs Associated With TKIs

### Hand-Foot-Skin Reaction

#### Symptoms
- Erythema with or without blisters
- Hyperkeratotic lesions on palms and soles
- Commonly accompanied by dysesthesia (burning, pain, tingling)

#### Onset
- Typically within 45 d of therapy initiation

#### Prophylaxis
- Perform full-body skin examination, focusing on deformities and hyperkeratotic areas on palms and soles, before treatment initiation
- Have patients remove their shoes and examine their feet during each visit
- Recommend podiatric evaluation (can help with removal of calluses and hyperkeratotic regions) and orthotic evaluation and use of orthotic devices in patients with abnormal weight bearing
- During early therapy (2-4 wk), encourage rest and avoidance of vigorous exercise and traumatic activity

#### RAAR
- Calluses and hyperkeratotic regions
- Hot water, direct sunlight, constriction footwear, excessive friction, vigorous activity, and contact with cleaning products with strong chemicals

#### Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristic</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tingling, numbness, accompanied by minimal skin changes or dermatitis, such as erythema, edema, or hyperkeratosis of the hands and/or feet without pain; does not disrupt ADLs</td>
<td>Avoid hot water, wear thick socks, wear cotton gloves/socks at night, use moisturizing creams and keratolytics (urea 20% to 40%; salicylic acid 5% to 10%); no dose reduction needed; follow up within 2 wk</td>
</tr>
<tr>
<td>2</td>
<td>Skin changes of the hands and/or feet, may include peeling, blisters, bleeding, edema, or hyperkeratosis of the hands and/or feet discomfort affecting ADLs</td>
<td>Employ grade 1 strategies, consider clobetasol 0.05% ointment 2x/d for erythematous areas, use topical and systemic analgesics (if no contraindications [eg, bleeding, kidney dysfunction]); consider 50% dose reduction for 7-28 d until HFSR is grade 0/0 → full dose</td>
</tr>
<tr>
<td>3</td>
<td>Severe skin changes of the hands and/or feet; may include peeling, blisters, bleeding, edema, or hyperkeratosis with pain and/or severe discomfort causing inability to work or perform ADLs</td>
<td>Employ grade 1/2 strategies; treatment interruption for ≥7 d until HFSR is grade 1/0 → 50% of full dose → escalation, if possible; resume treatment at lower dose as recommended in package insert; dose may be escalated if reaction does not recur</td>
</tr>
</tbody>
</table>
AE Management 4

Managing Adverse Events Associated With Systemic Therapies Used in Patients With Hepatocellular Carcinoma

Management of AEs Associated With TKIs

Diarrhea

Frequent, watery, bloody, or nocturnal stools

General Management
- Monitor bowel habits, and report any increase in activity above normal
- Avoid spicy or fatty foods; plain, simple foods are best
- Avoid fruit and caffeine
- Maintain adequate fluid intake to avoid dehydration
- Monitor/manage electrolytes

Medical Intervention
- Loperamide is usually effective
- If loperamide is ineffective, consider diphenoxylate/atropine

Patient should notify medical team of diarrhea or abdominal distress!

Fatigue

Educating your patients on managing fatigue is essential!

Patient Education
- Staying as active as possible helps regulate sleep
- Maintain a normal work and social schedule
- Take breaks as needed
- Tell your medical team if activity is intolerable or fatigue worsens
New Directions in HCC Treatment: Clinical Trials

- New targeted therapies
- Newer locoregional therapies
  - Stereotactic radiation therapy
  - Radioembolization
  - Proton therapy
- Combinations of targeted therapies with
  - Traditional chemotherapies
  - Locoregional therapies (TACE, RFA)
- Molecular markers to predict Rx response
Conclusions

• Early-stage HCC may be cured with
  – Ablation
  – Resection
  – Liver transplantation
• BCLC B, intermediate disease may be managed by TACE or TARE
• Data for TACE and TARE in advanced HCC is lacking: there have been 3 NEGATIVE studies of TARE in advanced HCC (SARAH, SirVENIB, and SORAMIC studies were all negative vs sorafenib)

• Local measures often fail in tumors with aggressive biology
• Application of therapies may be limited by severity of cirrhosis
• Clinical trials should be considered for selected patients
• Choosing the optimal treatment requires collaboration of multiple specialties
Cholangiocarcinoma
Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study

John Primrose, Richard Fox, Juan Valle, Daniel Palmer, Raj Prasad, Darius Mirza, Alan Anthoney, Philippa Corrie, Stephen Falk, Harpreet Wasan, Paul Ross, Lucy Wall, Jonathan Wadsley, Jeffry Evans, Deborah Stocken, Raaj Praseedom, David Cunningham, James Garden, Clive Stubbs and John Bridgewater on behalf of the BILCAP investigators
Adjuvant Therapy CholangioCA

Patients with macroscopically resected biliary tract cancer
ECOG Performance Status ≤ 2
Liver and pancreatic resection

Control Arm
Observation
205 Patients

Treatment Arm
Capecitabine: 8 cycles 1250mg/m²
bd D1-14 of 21
205 Patients

Primary endpoint: Overall Survival
Secondary endpoints: Relapse free survival, toxicity, QoL and health economics
Statistics: To detect a 31% reduction in risk (HR 0.69) with 2-sided significance level of 5% and 80% power, required 410 patients (234 events)
Adjuvant Therapy CholangioCA

>80% of patients followed up for 36 months

Median OS months (95%CI)
- Capecitabine: 51.1 (34.6, 59.1)
- Observation: 36.4 (29.7, 44.5)

HR (95%CI)
- Capecitabine: 0.81 (0.63, 1.04)
- Observation: p=0.097

Sensitivity analyses adjusting prognosticators:
- HR: 0.70 95%CI (0.55, 0.91) p=0.007

*Nodal status, Disease Grade, Gender*
Adjuvant Therapy CholangioCA

The safety population was conditional on receiving capecitabine (n=213)

There were no deaths related to chemotherapy

<table>
<thead>
<tr>
<th>Toxicity type</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16 (7.5%)</td>
</tr>
<tr>
<td>Plantar palmar erythema</td>
<td>44 (20.7%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (7.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
</tr>
</tbody>
</table>
• Capecitabine compared to surveillance improves median overall survival in resected biliary tract cancer from 36 to 53 months
• The toxicities were modest
• Capecitabine should become the standard of care for patients following curative resection of biliary tract cancer
Systemic Therapy
Advanced Cholangiocarcinoma

<p>| Table 1. Selected Phase II Clinical Trials of single agent chemotherapy in CCA |
|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>N</th>
<th>ORR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil/Folinic Acid</td>
<td>28</td>
<td>32%</td>
<td>Not Reported</td>
<td>6</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>23</td>
<td>30%</td>
<td>Not Reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>23</td>
<td>26.1%</td>
<td>8.1</td>
<td>13.1</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>24</td>
<td>20%</td>
<td>6.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>25</td>
<td>8%</td>
<td>Not Reported</td>
<td>10</td>
</tr>
</tbody>
</table>

<p>| Table 2. Selected Phase II Clinical Trials of combination chemotherapy in CCA |
|---|---|---|---|---|
| Gemcitabine Based Regimens |</p>
<table>
<thead>
<tr>
<th>N</th>
<th>ORR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine &amp; Capecitabine</td>
<td>23</td>
<td>34%</td>
<td>9.0</td>
<td>19</td>
</tr>
<tr>
<td>Gemcitabine &amp; Oxaliplatin</td>
<td>33</td>
<td>36%</td>
<td>5.7</td>
<td>15.4</td>
</tr>
<tr>
<td>Gemcitabine &amp; Irinotecan</td>
<td>39</td>
<td>20.5%</td>
<td>4.3</td>
<td>7.6</td>
</tr>
</tbody>
</table>

| Oxaliplatin Based Regimens |
| Oxaliplatin & Irinotecan | 28 | 17.9% | 2.7 | 9.2 | (9) |
| Oxaliplatin & Capecitabine | 56 | 27% | 6.5 (median TTP) dCCA | 12.8 dCCA | (15) |

Only Randomized Phase III ABC Trial established Cisplatin + Gemcitabine as SOC in 1st Line Metastatic Disease
OS 11.7 mo vs 8.1 mo HR 0.64; p<0.001
East vs West: Molecular Differences

- **Asian CCA**
  - Liver fluke – p53, KRAS, MLL3, ROBO2, RNF43, PEG3 and GNAS genes
  - Non-liver fluke – higher rate of IDH1/2 and BAP1 mutations, higher TMB

- **Western CCA**
  - Chromatin modulating gene mutation: ARID1A, BAP1, and PBRM1. Low TMB

- FGFR mutations, gene fusions/translocations in 10% of IHCCA in Western population but only 3-5% of Asian patients.
Cholangiocarcinoma
Targeting Molecular Pathways

Geynisman Discovery Medicine Vol 18 (101), Dec 2014
Table 3. Selected Clinical Trials with Molecular Targeted Agents in CCA

<table>
<thead>
<tr>
<th></th>
<th>Line</th>
<th>Phase</th>
<th>N</th>
<th>ORR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GemOx-/Erlotinib</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>III</td>
<td>268</td>
<td>16% vs 30%</td>
<td>4.2 vs 5.8</td>
<td>9.5 versus 9.5</td>
<td>(13)</td>
</tr>
<tr>
<td>GemOx/Cetuximab</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>II</td>
<td>30</td>
<td>63%</td>
<td>8.8</td>
<td>15.2</td>
<td>(7)</td>
</tr>
<tr>
<td>GemOx+/Cetuximab</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>II</td>
<td>150</td>
<td>29% vs 23%</td>
<td>5.3 vs 6</td>
<td>12.4 vs 11</td>
<td>(14)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>II</td>
<td>42</td>
<td>8%</td>
<td>2.6</td>
<td>7.5</td>
<td>(18)</td>
</tr>
<tr>
<td><strong>HER-2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>II</td>
<td>17</td>
<td>0%</td>
<td>1.8</td>
<td>5.2</td>
<td>(19)</td>
</tr>
<tr>
<td><strong>MEK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selumitinib</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>II</td>
<td>56</td>
<td>12%</td>
<td>3.7</td>
<td>9.8</td>
<td>(3)</td>
</tr>
<tr>
<td>MEK 162</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;/2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>I</td>
<td>28</td>
<td>8%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>(6)</td>
</tr>
<tr>
<td><strong>VEGF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GemOx+/Bevacizumab</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>II</td>
<td>35</td>
<td>41%</td>
<td>7.6</td>
<td>14.2</td>
<td>(24)</td>
</tr>
</tbody>
</table>
11-20% of CCA have FGFR2 genetic alteration (translocation, fusion).

CBJ398 is a novel FGFR inhibitor being tested at UCLA.
<table>
<thead>
<tr>
<th>Non-Selective</th>
<th>Activity</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dovitinib</td>
<td>FLT3, c-KIT, FGFR1,3, VEGFR1,3</td>
<td>Gastric, urothelial, renal</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>ABL, PDGFRa, VEGFR2, FGFR1, c-SRC</td>
<td>Biliary, Advanced solid tumors</td>
</tr>
<tr>
<td>Lucitanib ARQ087</td>
<td>VEGFR1-2, FGFR 1-2 (83nM) FGFR 1-3 (1.8-4.5 nM), KIT, RET, PDGFRB</td>
<td>Breast, Lung CCA</td>
</tr>
<tr>
<td>AZD4547</td>
<td>FGFR1, 2, 3 (1-2.5nM)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Selective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BGJ398</td>
<td>FGFR1,2,3 (1nM) FGFR4 (60nM)</td>
<td>SCC, Bladder, Biliary</td>
</tr>
<tr>
<td>JNJ-42756493</td>
<td>FGFR1-4 (&lt;1nM)</td>
<td>Liver, bladder, NSCLC, Gastric</td>
</tr>
<tr>
<td>INCB054828 DEBIO 1347</td>
<td>FGFR 1-3, VEGFR2 FGFR 1-3</td>
<td></td>
</tr>
<tr>
<td>TAS-120 LY2874455</td>
<td>FGFR1-4 VEGFR2, FGFR 1-4</td>
<td>Solid tumors, CCA</td>
</tr>
<tr>
<td>AB Ligand Trap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FP-1039 FPA114</td>
<td>FGF2 FGFR2-IIb</td>
<td>Solid tumors</td>
</tr>
</tbody>
</table>
Conclusions

- Cholangiocarcinoma is a rare yet deadly malignancy
- Resectable disease can be cured in ~50% of patients
- Neo-adjuvant chemo-radiotherapy and liver transplantation are curative for highly selected patient with extra-hepatic CholangioCA
- Systemic Therapy and molecular characterization is necessary for treatment of advanced cholangiocarcinoma
- Clinical Trials are the key to improving survival of patients
Thank you !