Defining Outcomes of Hepatocellular Carcinoma therapy
HCC Treatment Options

• Surgical Treatment
  – Liver transplantation
  – Resection

• Imaging guided interventions
  – Percutaneous ethanol injection (PEI)
  – Ablation (RFA, MWA, Cryo))
  – Chemoembolization (TACE, DebTACE)
  – Radioembolization (TARE) Yttrium 90
  – External beam radiation (SBRT)

• Systemic therapy
  – Tyrosine kinase inhibitors
  – Immunotherapy

Potentially curative
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
HCC Diagnosis: Dynamic Imaging With LI-RADS/ OPTN

- HCCs are hypervascular
- Tumor blood supply
  - 100% hepatic artery
- Liver parenchymal blood supply
  - 30% hepatic artery
  - 70% portal vein
- Dynamic imaging (MRI, CT) follows tumor density with time after IV contrast bolus
  - Requires both arterial enhancement and washout

During early arterial phase on CT, HCC appears brighter than surrounding liver

In later portal venous phase, HCC appears darker than surrounding liver (washout)

HCC Resection
Liver Transplant for HCC in cirrhosis
Milan Criteria (Stage I+II)

- Single, not > 5cm
- Up to 3, none > 3cm

+ Absence of Macroscopic Vascular Invasion
  Absence of Extrahepatic Spread

A 14 gauge needle is directed into the tumor by ultrasound or CT guidance and an alternating current is applied, similar to microwave. Best in tumors less than 5 cm.
Liver cancer

Radiofrequency Ablation

High-frequency alternating current flows from electrical probe through tissue to ground

- Ionic agitation results in frictional heating and coagulation of surrounding tissue

- Probe insertion
- Extension of prongs
- RF current application
**HCC Ablation: RFA**

- **Theoretical advantages over RFA**
  - Larger zone of active heating
    - Possibly better performance near blood vessels
  - Hotter temperature
  - Use of multiple probes

HCC Ablation: Cryo
HCC Ablation: MWA

Microwave Ablation

Theoretical advantages over RFA

- Larger zone of active heating
  - Possibly better performance near blood vessels
- Hotter temperature
- Use of multiple probes

Trans arterial embolic therapy: procedure

- interventional radiology
- performed by angiography
- gaining percutaneous access to hepatic artery
- passing catheter into branch supplying tumor.
- selective angiogram performed
- distal most branches supplying the tumor(s) identified
- embolic particles gel foam/microspheres are injected
- At completion catheter and removed & bleeding from punctured artery controlled by applying pressure to the entry site
HCC: DEB TACE

Drug eluting beads-TACE/DEB-TACE

• Replace lipiodol with microspheres (100-300um)
• Slow release of drugs
• Enhances local therapeutic efficacy
• Less systemic side effects
HCC: TARE

Y-90 embolisation

Liver
Tumour
Microspheres with Y-90
Aorta
Catheter
AASLD Diagnostic Criteria for HCC

Mass on surveillance US or high AFP in a cirrhotic liver

- **< 1 cm**
  - Repeat US every 3-4 mos
  - Stable > 18-24 mos
  - Enlarging
    - Return to surveillance every 6-12 mos
    - Proceed according to lesion size

- **1-2 cm**
  - 1 dynamic imaging study
    - Typical vascular pattern
    - Diagnostic of HCC
    - Biopsy
    - Repeat biopsy or imaging follow-up
      - Change in size/profile
    - Repeat imaging and/or biopsy

- **> 2 cm**
  - 1 dynamic imaging technique
    - Atypical vascular pattern with both techniques
    - Diagnostic of HCC
    - Biopsy
    - Repeat biopsy or imaging follow-up
      - Change in size/profile
    - Repeat imaging and/or biopsy

- **Typical vascular pattern on dynamic imaging**
  - Typical vascular pattern
  - Treat as HCC

- **Nondiagnostic of HCC**
  - Repeat imaging and/or biopsy

- **Other diagnosis**
  - Other diagnosis

Diagnosis of HCC: To Biopsy or Not?

- **Yes**
  - Positive biopsy provides
    - Diagnostic certainty if imaging is inconsistent with HCC
    - Prognostic information
  - Avoids inappropriate treatment and misleading “cure”
  - May be required for experimental treatments
  - May permit personalized therapy based on tumor gene expression

- **No**
  - Not always feasible
  - Not needed if high diagnostic certainty based on imaging
  - Risk
    - Hemorrhage
    - Tumor seeding (2.7% overall incidence)
  - False negatives (up to 1/3 of biopsies) may delay treatment


Slide credit: clinicaloptions.com
Case 5

• Presentation
  – Chronic HCV infection with prior early cessation of IFN/RBV in 2001 due to cytopenias
  – Presents for DAA therapy
  – Ultrasound shows a 3.7-cm right lobe mass
• Past medical history: HTN, porphyria cutanea tarda

• Social history
  – Smokes 1 PPD; quitting
  – No alcohol

• Physical exam
  – Vital signs normal, except BP 147/92 mm Hg
  – No peripheral stigmata of advanced liver disease, no hepatosplenomegaly
Case 5

- **Further studies**
  - MRI corroborates a 3.4-cm arterial enhancing segment 5/8 mass with washout and pseudocapsule on delayed phases
  - There are no imaging, biochemical, or clinical findings of cirrhosis
  - Platelets, 147,000; INR, 1.0; Na 140; creatinine, 1.0; albumin, 4.1; total bilirubin, 0.8; AFP, 2
## Potentially Curative Treatments

### Resection
- **Noncirrhotics**
  - Choice of therapy
- **Cirrhotics**
  - Reserved for CTP A
  - No Portal HTN
- Best for solitary HCC
- < 30% eligible

### Ablation
- Effective when < 3 cm
- Multiple modalities
  - Thermal
  - Chemical
  - Stereotactic radiation
- Minimally invasive

### Transplant
- Cures both HCC and cirrhosis
- MELD exception
  - Milan criteria
  - Downsizing
- Demand > supply

### Survival
- **Resection**
  - 5 yrs: 70%
- **Ablation**
  - 5 yrs: 40% to 50%
- **Transplant**
  - 5 yrs: > 70%

### Recurrence
- **Resection**
  - 5 yrs: 70%
- **Ablation**
  - 5 yrs: 70%
- **Transplant**
  - 5 yrs: 15%

---

Survival After Resection for HCC

- Of 1265 HCC pts evaluated, only 35 were ideal candidates for resection


Slide credit: clinicaloptions.com
Case 5

- Biopsy of tumor and parenchyma
  - Well-differentiated HCC
  - Metavir stage III fibrosis
- The surgeon noted the liver to be nodular; the left lobe was small
  - Laparoscopic ablation was performed
Case 5

- 1-mo follow-up MRI showed ablation of the mass without evidence of recurrent or residual disease
- 3-mo MRI showed the same
  - He started a course of SOF/LDV 4 mos postablation and attained SVR
- Quarterly MRIs showed no recurrence until 10 mos after attaining SVR12
- 2 masses adjacent to the cavity were noted
  - 2.1 cm and 1.8 cm

Image courtesy of MTC Design, LLC. Slide credit: clinicaloptions.com
Biologically Aggressive HCC

**Features**
- Microvascular invasion
- Satellite nodules
- Diffuse infiltrating growth
- Poorly differentiated
- Mixed cholangiocarcinoma
- Bad molecular signature
- FDG-PET scan positive
- High AFP and AFP-L3%
- Rapid growth

**Associated with**
- Early metastasis
- High risk of recurrence after resection or liver transplantation
- Failure of local control with RFA/TACE
- Poor prognosis
- There is no consensus on how to incorporate biology into tumor staging

References in slide notes. 

Slide credit: clinicaloptions.com
Case 5

- The pt undergoes selective DEB-TACE of the 2 viable lesions
- His performance status and synthetic function remain excellent
- 1 mo following TACE, there is no viable tumor on follow-up MRI
# Liver Embolotherapy Techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Mechanism</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAE</td>
<td>Ischemic necrosis induced at arteriolar level via permanent embolic (eg, small particles)</td>
<td>Low cost, no chemotherapy adverse events</td>
<td>Postembolization syndrome may cause PEs</td>
</tr>
<tr>
<td>Conventional TACE (cTACE)</td>
<td>Intrahepatic chemotherapy with embolization by ethiodized oil</td>
<td>Strongest evidence supporting benefit from RCT data</td>
<td>Intraoperator technical variation (cTACE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systemic release of chemotherapy (cTACE)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Postembolization syndrome</td>
</tr>
<tr>
<td>DEB-TACE</td>
<td>Intrahepatic chemotherapy + embolization with slow-release drug-eluting beads</td>
<td>More standardized than cTACE, less systemic release of chemotherapy</td>
<td>More expensive than cTACE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Postembolization syndrome</td>
</tr>
<tr>
<td>Radio-Embolization (TARE)</td>
<td>Radiation necrosis induced by beta-emitting Yttrium-90 microspheres</td>
<td>May improve TTP, Fewer sessions required, No postembolization syndrome, May be safer in adv disease with PVT, Radiation segmentectomy may be curative, FLR hypertrophy from radiation lobectomy can provide tumor control and facilitate resection</td>
<td>Cost: 2-3x more expensive, Requires multidisciplinary coordination, Nontarget delivery may cause severe ulceration, Potential biliary toxicity, Radiation-induced liver disease</td>
</tr>
</tbody>
</table>
Palliative TACE Prolongs Survival in Unresectable HCC

- **Graph**: Kaplan-Meier survival curves showing the probability of survival over months since randomization.
  - **Log-rank test**: $P < .009$.
  - **Pts at Risk, n**:
    - Chemoembolization (n = 40): 40, 29, 14, 4, 2
    - Control (n = 35): 35, 19, 7, 3, 0

- **Random Effects Model (DerSimonian & Laird)**:
  - OR (95% CI) with $z = 2.3$ and $P = .017$.

- **References**:

Slide credit: clinicaloptions.com
Case 5

- The pt undergoes transplant evaluation at a Transplant Center.
- His performance status and synthetic function remain excellent.
- He is listed with MELD 22; 6 mos later, he remains recurrence free, and his MELD is increased per HCC MELD exception protocol to 28.
- He is transplanted at MELD 31, approximately 9 mos following listing.
Palliation of HCC: Sorafenib

- Prior to 2007, no therapy was of benefit in advanced HCC
- SHARP trial: CTP A pts with advanced HCC randomized to sorafenib 400 BID vs placebo
- Sorafenib delayed progression and prolonged survival from 7.9 to 10.7 mos
- Led to approval by the FDA in 2007 for palliation of advanced-stage HCC
- It remains the only approved first-line systemic therapy for HCC

Case 6

- A 57-yr-old male is diagnosed with BCLC stage B HCC based on compensated cirrhosis (Child-Pugh A), liver-only disease, and ECOG PS 0
- After 2 TACE sessions, angiography revealed obstructed hepatic artery blood flow to the tumor and surrounding sites with disseminated disease
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>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>Brivanib vs sorafenib (BRISK-FL)[3]</td>
<td>VEGFR2, FGFR[4]</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>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>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>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](http://clinicaloptions.com)
Case: Progression After TACE

- The pt is started on systemic therapy with sorafenib
- After 8 days of sorafenib, the pt develops a hand–foot skin reaction, starting with mild pain in his feet that progressed to severe pain with blistering by Day 14
- The dose of sorafenib was reduced by one half and the pt was able to tolerate the reduced dose
- After 15 mos of stable disease on 400 mg/day of sorafenib, progressive disease with extrahepatic dissemination in the lymph nodes is detected
**Tyrosine Kinase Inhibitors**

### Systemic Therapy in Advanced HCC

*PeerView Oncology*

### TKIs / Targeted Agents

<table>
<thead>
<tr>
<th>Agent Indication/Status</th>
<th>Dosage</th>
<th>Future Directions</th>
</tr>
</thead>
</table>
| **Sorafenib**<sup>1</sup>  
First-line treatment of unresectable HCC  
*Approved* | 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 | **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.**  
- Multiple combination strategies with locoregional therapy (Y-90, SBRT, TACE, or others)<sup>7</sup>  
- Combinations with immune checkpoint inhibitors<sup>8</sup>  
- Other next-generation TKIs are also being explored<sup>9</sup> |
| **Lenvatinib**<sup>2</sup>  
First-line treatment of unresectable HCC  
*Approved* | 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 |
| **Regorafenib**<sup>3</sup>  
Second-line setting following treatment with sorafenib  
*Approved* | 160 mg orally; 3 wks on, 1 wk off (4-wk cycle) |
| **Cabozantinib**<sup>4,5</sup>  
Efficacy evidence in advanced HCC after progression with ≥1 prior therapy, including sorafenib  
*Phase 3* | 60 mg/d (dose studied in phase 2 and 3 trials) |
| **Ramucirumab**<sup>6</sup>  
Evidence in second-line setting following treatment with sorafenib for advanced HCC  
*Phase 3* | 8 mg/kg IV every other wk (dose studied in phase 3 trial) |
Immune Checkpoint Inhibitors

**Immune Checkpoint Inhibitors**

### Agent Indication/Status

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication/Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab$^{b,1}$</td>
<td>Second-line setting following treatment with sorafenib</td>
</tr>
<tr>
<td>Approved</td>
<td></td>
</tr>
<tr>
<td>Phase 3 testing (CheckMate-459; NCT02576509) as first-line treatment</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab$^{b,1}$</td>
<td>Second-line setting following treatment with sorafenib</td>
</tr>
<tr>
<td>Priority review</td>
<td></td>
</tr>
<tr>
<td>Durvalumab$^{a,1}$</td>
<td>HCC (Child-Pugh class A)</td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab + bevacizumab$^{a,2}$</td>
<td>First-line treatment of advanced or metastatic HCC</td>
</tr>
<tr>
<td>Breakthrough therapy designation</td>
<td></td>
</tr>
</tbody>
</table>

### Dosage

<table>
<thead>
<tr>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>240 mg every 2 wk or 480 mg every 4 wk</td>
</tr>
<tr>
<td>200 mg every 3 wk (dose studied in phase 1/2 trial)</td>
</tr>
<tr>
<td>10 mg/kg IV every other wk (dose studied in phase 1/2 trial)</td>
</tr>
<tr>
<td>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)</td>
</tr>
</tbody>
</table>

### 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)$^{a,3}$
- Combinations with TKIs and with locoregional therapy$^{a,2}$

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This Practice Aid has been provided as a quick reference to help learners apply the information to their daily practice and care of patients.
Adverse Event Management 1

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

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

Why do irAEs occur?

The precise pathophysiology is unknown, but traditional studies have shown that T-cell activity 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 (skin, pruritus, rash), endocrine (thyroiditis), hepatic (pancreatitis), and ocular (uveitis, retinopathy, retinal ischemia) toxicities.

How should irAEs be diagnosed and managed?

IrAEs should be diagnosed and managed as a medical emergency. Grade 3 or 4 irAEs necessitate cessation of immunotherapy and emergent medical management.

General management principles include the following:

- IrAEs should be diagnosed and managed as a medical emergency.
- Cease the immunotherapy as soon as possible.
- Supportive care is essential.
- If an irAE requires hospitalization, consult with an oncologist.
- Immune checkpoint inhibitors should be discontinued immediately.

For organ-specific assessment and management of irAEs, please see the ASCO guidelines.

Additional resources available on the ASCO website.
### 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</td>
<td>Continue</td>
<td>Weekly or more</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</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>3</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</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>

- **Monitor AST, ALT, and bilirubin prior to each infusion**
- **Counsel patients**
- **Rule out other causes**
AE Management 3

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

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**
- Hot water, direct sunlight, restrictive footwear, excessive friction, vigorous activity, and contact with cleaning products with strong chemicals
- Calluses and hyperkeratotic regions
- Moisturizers, cold pack (indirectly) for 20 min/d, wear thick cotton gloves and socks, gently pat hands/feet dry after washing

<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 with pain, 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 1/0 → 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 27 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

Management of AEs Associated With TKIs

**Diarrhea**

- **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**

- **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

Access the activity, “Surveying the View From the Driver’s Seat in Hepatocellular Carcinoma: Bringing Into Focus Hepatology’s Key Role In Guiding HCC Care Down the Path to Improved Outcomes,” at www.peerview.com/WDR40.
# 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</td>
<td>IgG1 Ab to VEGFR2</td>
<td>3.5 vs 2.6 HR: 0.59</td>
<td>9.2 vs 7.6 HR 0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI: 0.49-0.72;</td>
<td>(95% CI: 0.72-1.05;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .0001)</td>
<td>P = .14)</td>
</tr>
<tr>
<td>Brivanib vs placebo</td>
<td>VEGFR2, FGFR</td>
<td>4.2 vs 2.7 HR: 0.56</td>
<td>9.4 vs 8.2 HR: 0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI: 0.42-0.76;</td>
<td>(95% CI: 0.69-1.15;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .001)</td>
<td>P = .3307)</td>
</tr>
<tr>
<td>Everolimus vs placebo</td>
<td>mTOR</td>
<td>3.0 vs 2.6 HR: 0.93</td>
<td>7.6 vs 7.3 HR: 1.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI: 0.75-1.15;</td>
<td>(95% CI: 0.86-1.27;</td>
</tr>
<tr>
<td></td>
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<td>P = NR*)</td>
<td>P = .68)</td>
</tr>
<tr>
<td>Tivantinib vs placebo</td>
<td>cMet</td>
<td>2.4 vs 3.0 HR: 0.96</td>
<td>8.4 vs 9.1 HR 0.97</td>
</tr>
<tr>
<td></td>
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<td>(95% CI: 0.74-1.25;</td>
<td>(95% CI 0.75-1.25;</td>
</tr>
<tr>
<td></td>
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<td>P = .76)</td>
<td>P = .81)</td>
</tr>
</tbody>
</table>

*Difference not statistically tested per prespecified analysis plan.

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.

Slide credit: clinicaloptions.com
Lenvatinib: Study 304: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Lenvatinib (n = 478)</th>
<th>Sorafenib (n = 476)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS, 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>mPFS, 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>mTTP, 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 (24.1)*</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

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

Slide credit: clinicaloptions.com
Immune-Based Approaches in HCC

- Antibody
- Dendritic cells
- Peptides
- Cytokines
- CTL mediated lysis
- T-cell activation
- T-cell function
- Foxp3+ Treg
- MDSC
- IL-10, TGF-β
- Oncolytic virus
- Antibody
- Cancer vaccines
- Cytokines (GM-CSF, IL-2, IFN-γ, etc)
- Checkpoint blockade
- Elimination of suppressor cells
- Blockade of immunosuppressive cytokines
Phase I/II CheckMate 040: Nivolumab in Advanced HCC

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

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
- Advanced-stage HCC may be palliated with
  - TACE or TARE
  - Systemic Therapies
  - Clinical Trials
    - Combination systemic therapies
    - Combination locoregional / systemic
- Local measures often fail in tumors with aggressive biology
- Application of therapies may be limited by severity of cirrhosis
- Choosing the optimal treatment requires collaboration of multiple specialties
Thank you!