Therapeutic advances in the management of advance HCC

Deva Mahalingam MD PhD
Associate Professor of Medicine
Leader Gastrointestinal Malignancies Program
UTHSCSA

Educational objectives

• Recognize the recent increase in incidence and mortality of HCC in the US/south Texas
• Understand risk factor & diagnosis of HCC.
• Identify the standard of care therapy for advanced HCC
• Learn the outcomes of recently published studies and future drugs in advanced HCC

2016 Estimated US Cancer Deaths

Men 314,290
Lung & bronchus 27%
Prostate 8%
Colorectal 8%
Liver & intrahepatic bile duct 6%
Leukemia 4%
Eosophagus 4%
Urinary bladder 4%
Non-Hodgkin’s lymphoma 4%
Brain/other nervous system 3%
All other sites 20%

Women 281,400
Lung & bronchus 26%
Breast 14%
Colon & rectum 8%
Pancreas 5%
Ovary 4%
Uterine corpus 4%
Leukemia 4%
Liver & intrahepatic bile duct 3%
Non-Hodgkin’s lymphoma 3%
Brain/other nervous system 2%
All other sites 24%

• Liver cancer in 2016 estimated as:
  – The #5 cancer killer in men (up from #7 in 2005)
  – The #8 cancer killer in women (not among top 10 in 2005)

LIVER/INTRAHEPATIC BILE DUCT CANCER IN SOUTH TEXAS

Incidence 2005-2009
- South Texas 12.2 cases
- Rest of Texas 8.4 cases
- Nationwide 7.3 cases
- South TX Hispanics/ non-Hispanic whites rate ratio 2.4
- South TX Males 19.5 cases vs. 6.2 for Females

Figure © Springer Science + Business Media 2013

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
LIVER/INTRAHEPATIC BILE DUCT CANCER IN SOUTH TEXAS

Incidence in South Texas by age/ethnicity, 2005-2009

Source: TCR, Cancer Epidemiology and Surveillance Branch, Texas DSHS

HCC IN SOUTH TEXAS vs. U.S. LATINOS

Annual Age-Adjusted HCC Incidence


Association of Glucose and Lipid Metabolism With HCC Pathogenesis


This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Complications of Cirrhosis

- Variceal bleeding
- Ascites/hepatorenal syndrome
- Hepatic encephalopathy
- HCC

HCC Surveillance

AASLD Practice Guidelines for Screening & Surveillance

- AASLD recommends surveillance using US every 6 months for at-risk patient groups:
  - Hepatitis B carriers
    - All cirrhotic hepatitis B carriers
    - Family history of HCC
    - Africans/North American Blacks
    - Asian males ≥45 years
    - Asian females ≥50 years
  - Stage 4 primary biliary cirrhosis
  - Cirrhosis due to hepatitis C, alpha-1 antitrypsin deficiency, genetic hemochromatosis, or other causes
- Surveillance should be conducted every 6 months using ultrasound alone

Prognosis scoring and staging – Cirrhosis and advance HCC

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
**Child-Pugh Score**

<table>
<thead>
<tr>
<th>Measure</th>
<th>1 Point Each</th>
<th>2 Points Each</th>
<th>3 Points Each</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2.0</td>
<td>2.0-3.0</td>
<td>&gt; 3.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>2.8-3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>1.0-3.0</td>
<td>4.0-6.0</td>
<td>&gt; 6.0</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
<td>I-II</td>
<td>III-IV</td>
</tr>
</tbody>
</table>

**Grade** | **Total Points** | **Surgical Risk**
---|------------------|-------------------
A       | 5-6              | Good              |
B       | 7-9              | Moderate          |
C       | 10-15            | Poor              |


**Survival of Cirrhotic Patients**

- Child-Pugh classification also important
  - Child-Pugh class A disease had better 1- and 2-year survival
- Median 1- and 2-year survival by Child-Pugh class
  - Class A: 95% and 90%, respectively
  - Class B: 80% and 70%, respectively
  - Class C: 45% and 38%, respectively


**Staging Strategy and Treatment for HCC**

**Barcelona Clinic Liver Cancer (BCLC)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early stage</td>
<td>PEN (if available) or PEI/RF + DAA (sorafenib) (if available, not contraindicated)</td>
</tr>
<tr>
<td>Early stage</td>
<td>PEN, PEI/RF + DAA (sorafenib) (if available, not contraindicated)</td>
</tr>
<tr>
<td>Intermediate stage</td>
<td>PEN, PEI/RF + DAA (sorafenib) (if available, not contraindicated)</td>
</tr>
<tr>
<td>Advanced stage</td>
<td>Liver transplantation, PEI/RF + DAA (sorafenib) (if available, not contraindicated)</td>
</tr>
</tbody>
</table>

**Surgical treatments:** applicable overall to 10% to 15% of HCC at first diagnosis and 2% to 5% of recurrent HCC

**Nonsurgical treatments:** applicable overall to 65% to 75% of HCC at first diagnosis and 50% to 75% of recurrent HCC

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Case: 1

- 62-yr-old man referred to your clinic with history of self-administered tattoos
- Saw a television ad about HCV and decided to see his physician; found to be positive for HCV
- Screening MRI: splenomegaly, hepatic nodularity consistent with cirrhosis, and 2.6-cm lesion in right lobe of liver that showed rapid arterial enhancement with significant washout on delayed images

What further testing should be done in order to make the diagnosis of HCC?

A. Biopsy for histologic examination
B. AFP first; if normal, proceed to biopsy
C. CEA or CA19-9 to rule out other histologies
D. No further testing
E. CT scan or ultrasound to further examine vascular characteristics

HCC are vascular tumors

Case: Management of Large Solitary HCC

- A 32-yr-old woman recently emigrated from Shanghai infected with HBV since childhood
- Upon evaluation for a new job, she is found to have abnormal liver transaminases
  - Follow-up imaging shows a 6-cm well-circumscribed lesion within the left lobe of her liver with vascular characteristics consistent with HCC; no stigmata of cirrhosis are noted
- Serum bilirubin, albumin, platelets, and INR are normal, and AFP is elevated at 1769 ng/mL
- CT of the torso shows no evidence of other lesions
Which of the following is the optimal next step in the management of this pt?

A. Biopsy of the lesion  
B. Full evaluation for potential transplantation  
C. Follow the lesion to determine the rate of growth  
D. Immediate resection when feasible  
E. Chemoembolization or radioembolization  
F. Local treatment to the mass to reduce the size followed by resection

Case: Multifocal HCC With Esophageal Varices
- A 59-yr-old man with a history of alcohol abuse, who quit drinking 11 yrs ago, presents to the ED with hematemesis
- On evaluation, he is found to have bleeding esophageal varices, ascites, splenomegaly, and a platelet count of 61,000
- MRI shows 2 lesions—2.7 cm and 2.1 cm—within the right lobe. These both show peripheral enhancement on the arterial phase with central washout and peripheral enhancement on delayed images
  - Splenomegaly, ascites, and small perigastric varices are also seen

Once he has been treated, stabilized, and discharged, further management of this pt should include which of the following?

A. Referral to liver service for possible cadaveric or live donor transplantation  
B. Referral to hepatobiliary surgery for potential right hepatectomy  
C. Immediate chemoembolization  
D. Thermal or cryoablation to the 2 individual lesions  
E. PET scan to look for metastatic lesions  
F. Systemic treatment with sorafenib

Curative Treatments

<table>
<thead>
<tr>
<th>Resection</th>
<th>Ablation</th>
<th>Transplant</th>
</tr>
</thead>
</table>
| • Noncirrhosis  
  - Choice of therapy  
  • Cirrhosis  
  - Reserve for CTP A  
  - Avoid right hepatectomy  
  • Best for solitary HCC  
  • Only 5% to 15% eligible  
  • Survival  
  - 1 yr: 95%  
  - 3 yrs: 85%  
  - 5 yrs: 50%  
  • Recurrence  
  - 5 yrs: 70%  | • Effective when ≤ 3 cm  
  • Multiple modalities  
  - Thermal  
  - Chemical  
  • Minimally invasive  
  • Survival  
  - 1 yr: 90%  
  - 3 yrs: 75%  
  - 5 yrs: 60% to 70%  
  • Recurrence  
  - 5 yrs: 70%  | • Cures both cirrhosis and HCC  
  • MELD exception  
  - Milan criteria  
  - Downstaging  
  • Demand > supply  
  • Survival  
  - 1 yr: 91%  
  - 2 yrs: 75%  
  - 5 yrs: > 70%  
  • Recurrence  
  - 5 yrs: < 15%  |


This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Case: Large Solitary HCC With Preserved Liver Function

- A 71-yr-old asymptomatic man with a history of hemochromatosis goes to a new gastroenterologist and is found to have a 7-cm mass in the right lobe consistent with HCC.
- He is not a surgical candidate because of significant cardiovascular disease but has relatively well-preserved hepatic function.

Which of the following treatment options would be most suitable for this pt?

A. Radiofrequency ablation
B. Stereotactic body radiotherapy
C. Chemoembolization or radioembolization
D. Referral for potential liver transplantation
E. Sorafenib

Radioembolization in HCC Pts With vs Without Portal Vein Thrombosis

- Radioembolization achieved survival benefit independent of PVT.

Survival Functions

- PVT
  - Not present
  - Present
  - Not present-censored
  - Present-censored

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Case: Newly Diagnosed Metastatic HCC

- A 68-yr-old man with PMH significant only for diabetes presents with back pain and is found to have a lytic lesion at T11
- CT scan of the torso shows multiple metastases up to 3 cm in size throughout both lungs and an 8-cm lesion within the liver. Several bony metastases are also seen
- ECOG PS is 1 and lab tests are relatively well preserved
- Liver biopsy demonstrates well-differentiated HCC. The pt strongly desires systemic therapy following the completion of radiation to his back. He refuses to participate in clinical trials

Which of the following is the best choice for this pt?

A. Sorafenib  
B. Gemcitabine plus cisplatin or oxaliplatin  
C. Nivolumab  
D. Capecitabine  
E. Best supportive care

Targeted Therapy: Sorafenib

Multispecific, blocks tyrosine kinase receptors regulating tumor proliferation and angiogenesis

This presentation is the intellectual property of the author.  
Contact them for permission to reprint and/or distribute.
Phase III SHARP Trial Study Design

- Primary end-points: Overall survival
  Time to symptomatic progression (FHSI8-TSP)
- Secondary end-points: Time to progression (independent review)

Stratification:
- Macroscopic vascular invasion and/or extrahepatic spread
- ECOG PS
- Geographical region

602 patients

Sorafenib (n=299) 400 mg po bid
Discontinue therapy Radiologic progression AND
FHSI8-TSP worsening

Placebo (n=303) 400 mg po bid

Key SHARP Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Sorafenib (299)</th>
<th>Placebo (303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>HBV</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>EtOH</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Other</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>ECOG PS (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Child’s Pugh (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>SCLC (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B (Intermediate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (Advanced)</td>
<td>82</td>
<td>85</td>
</tr>
</tbody>
</table>

Adverse events of Sorafenib.

- What do you typically see in your practice?
Among 88 patients, median OS (95% CI) = 15.8 (7.9, 18.4) months.

Among 88 patients, median PFS (95% CI) = 6.0 (3.8, 8.5) months.

Efficacy data patients treated on Nexavar based on dosage.

Among 82 patients, median OS (95% CI). For 400 mg = 10.0 (4.8, 18.3) months. For 800 mg = 15.9 (7.8, 28.1) months. Log-rank p=0.04
So why the difference in survival between Asian vs West?

Hyperactivation of RAS/RAF/MEK/ERK and PI3K/AKT/mTOR signalling and epithelial to mesenchymal transition (EMT) process are more prevalent in the Western population; however, fibroblast growth factor (FGF), transforming growth factor β (TGFβ) and Notch pathways seems to be more relevant in Asian population.

What about other agents that target VEGF pathway?

Molecular targets in HCC angiogenesis with the growth factors and receptors

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Which of the following has demonstrated superior OS in phase III trials when compared with sorafenib in the first-line setting for metastatic HCC?

A. Sunitinib  
B. Brivanib  
C. Linifanib  
D. Erlotinib plus sorafenib  
E. Doxorubicin plus sorafenib  
F. None of the above

### Phase III First-line Targeted Drug Trials for HCC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>OS vs Sorafenib, Mos</th>
<th>Trial Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib[1]</td>
<td>VEGFR, PDGFR, FLT3, KIT, RET</td>
<td>7.9 vs 10.2</td>
<td>NCT00699374</td>
</tr>
<tr>
<td>Brivanib[2]</td>
<td>VEGFR, FGFR</td>
<td>9.5 vs 9.9</td>
<td>NCT00858871</td>
</tr>
<tr>
<td>Linifanib[3]</td>
<td>VEGFR, PDGFR</td>
<td>9.1 vs 9.8</td>
<td>NCT01009593</td>
</tr>
<tr>
<td>Erlotinib/Sor[4]</td>
<td>EGFR</td>
<td>9.5 vs 8.5</td>
<td>NCT00901901</td>
</tr>
<tr>
<td>Doxorubicin/Sor[5]</td>
<td>Topoisomerase II, intercalation</td>
<td>9.3 vs 10.5</td>
<td>NCT01015833</td>
</tr>
<tr>
<td>Lenvatinib[6]</td>
<td>VEGFR2, VEGFR3, RET</td>
<td>Ongoing</td>
<td>NCT01761266</td>
</tr>
<tr>
<td>Nivolumab[7]</td>
<td>PD-1</td>
<td>Ongoing</td>
<td>NCT02576509</td>
</tr>
</tbody>
</table>

[1]References listed in slide notes.

---

**Case: Management Following Progression on Sorafenib**

- The pt described above (a 66-yr-old diabetic man with HCC metastatic to the lungs and bone) was treated with sorafenib.
- After slowly advancing the initial dose, he was able to tolerate a dose of 400 mg twice daily for the first 3 wks; because of fatigue, the dose was reduced to a total of 600 mg/day.
- After a total of 8 wks, he was re-evaluated because of worsening fatigue, decreased appetite, and an AFP that had risen from 1589 to 4623 ng/mL while on therapy.
- CT scan showed that his lung metastases had increased in both size and number, with the largest now being 4.5 cm. The solitary liver lesion increased from 8 to 9 cm in longest diameter, and the bone lesions appeared stable. He had no pain or shortness of breath and felt that most of his complaints stemmed from the sorafenib; ECOG PS remained at 1.

Which of the following agents was shown in a phase III trial to improve OS in pts who have disease progression following treatment with sorafenib?

A. Nivolumab  
B. Everolimus  
C. Brivanib  
D. Regorafenib  
E. Ramucirumab  
F. None of the above

This presentation is the intellectual property of the author.
Contact them for permission to reprint and/or distribute.
### Phase III Second-line Targeted Drug Trials for HCC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>OS vs PBO, Mos</th>
<th>Trial Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regorafenib(^1)-(^3)</td>
<td>VEGFR, RET, PDGFR, FGFR, BRAF</td>
<td>10.6 vs 7.8</td>
<td>NCT01774344</td>
</tr>
<tr>
<td>Ramucirumab(^2)-(^3)</td>
<td>VEGFR2</td>
<td>9.2 vs 7.6</td>
<td>NCT01140347</td>
</tr>
<tr>
<td>Everolimus(^2)-(^3)</td>
<td>mTOR</td>
<td>7.6 vs 7.3</td>
<td>NCT01035229</td>
</tr>
<tr>
<td>Tivantinib(^2)-(^3)</td>
<td>c-MET</td>
<td>Ongoing</td>
<td>NCT01755767</td>
</tr>
<tr>
<td>Brivanib(^2)-(^3)</td>
<td>VEGFR, FGFR</td>
<td>9.4 vs 8.2</td>
<td>NCT00825955</td>
</tr>
<tr>
<td>Cabozantinib(^2)-(^3)</td>
<td>c-MET</td>
<td>Ongoing</td>
<td>NCT01908426</td>
</tr>
<tr>
<td>Tivantinib(^2)-(^3)</td>
<td>c-MET, tubulin</td>
<td>Ongoing</td>
<td>NCT01755767</td>
</tr>
<tr>
<td>Ramucirumab(^2)-(^3)</td>
<td>VEGFR2</td>
<td>Ongoing, AFP &gt; 400</td>
<td>NCT02435433</td>
</tr>
<tr>
<td>Apatinib(^2)-(^3)</td>
<td>VEGFR2</td>
<td>Ongoing</td>
<td>NCT02329860</td>
</tr>
</tbody>
</table>

*References listed in slide notes.*

### RESORCE: Regorafenib in HCC After Progression on Sorafenib

- Randomized, double-blind phase III trial
- **Randomized 2:1**
- **All pts treated until PD, death, or unacceptable toxicity**

- **Pts with BCLC stage B or C HCC; documented PD on sorafenib ≥ 20 days at ≥ 400 mg/day; Child-Pugh A liver function; ECOG PS 0-1 (N = 573)**

- **Primary endpoint: OS (ITT)**
- **Secondary endpoints: PFS, TTP, RR, DCR**

### RESORCE: Efficacy of Regorafenib vs Placebo

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Regorafenib (n = 379)</th>
<th>Placebo (n = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>10.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>3.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Median TTP</td>
<td>3.2(^1)</td>
<td>1.5(^1)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>10.6(^1)</td>
<td>4.1(^1)</td>
</tr>
</tbody>
</table>

*HR 0.44; 95% CI: 0.36-0.55; P < .001; 1P = .005
* 38% reduction in risk of death (HR: 0.62; 95% CI: 0.50-0.78; P < .001)
* 54% reduction in risk of progression or death (HR: 0.46; 95% CI: 0.37-0.56; P < .001)
* DCR (CR + PR + SD): 65.2% vs 36.1% (P < .001)


### RESORCE: Safety

<table>
<thead>
<tr>
<th>AE, %</th>
<th>Regorafenib (n = 379)</th>
<th>Placebo (n = 194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ≥ grade 3 AE</td>
<td>79.7</td>
<td>58.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15.2</td>
<td>4.7</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>12.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.2</td>
<td>0</td>
</tr>
<tr>
<td>Dose modifications due to AEs</td>
<td>68.2</td>
<td>31.1</td>
</tr>
<tr>
<td>Deaths occurring ≤ 30 days after last dose</td>
<td>13.4</td>
<td>19.7</td>
</tr>
</tbody>
</table>


This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Checkpoint Inhibitors in Advanced HCC

T-Cell Response: Accelerate or Brake?

Activating Signals
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Signals
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

T-Cell Stimulation

T-Cell Inhibition

Biomarkers to Determine Response
- Convergent biomarkers of PD-1 pathway blockade response
  - PD-L1 expression
  - Mutational load
  - CD8+ T cell density
- PD-L1 expression patterns across cancer types

PD-1/PD-L1 Axis in HCC

<table>
<thead>
<tr>
<th>PD-L1</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expression level</td>
<td>45% to 100%</td>
</tr>
<tr>
<td>Expression location</td>
<td>HCC microenvironment (e.g., Kupffer cells, tumor-associated macrophages)</td>
</tr>
<tr>
<td>Expression correlated with</td>
<td>HCC stage, HBV infection, inflammation</td>
</tr>
<tr>
<td>Clinical outcome of elevated expression</td>
<td>DFS, OS</td>
</tr>
<tr>
<td>Blockade outcome</td>
<td>Tumor cell death in murine models</td>
</tr>
</tbody>
</table>

Biomarkers to Determine Response

- PD-L1 expression across cancer types


Slide credit: clinicaloptions.com
Checkpoint Inhibitors in Advanced HCC:
Clinical studies

**Checkmate-040 Study Design:**
Assessing Nivolumab in Pts With Advanced HCC

- A phase I dose escalation study of 3 pt cohorts in advanced HCC

<table>
<thead>
<tr>
<th>Uninfected pts: sorafenib progressors (n = 50 planned) sorafenib naive (n = 50 planned)</th>
<th>3 + 3 Dose-Escalation Phase</th>
<th>Ongoing Expansion Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 0.1-10 mg/kg q2w for up to 2 yrs (n = 21)</td>
<td>Nivolumab 3 mg/kg q2w for up to 2 yrs (n = 3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCV-infected pts (n = 50 planned)</th>
<th>Nivolumab 0.1-10 mg/kg q2w for up to 2 yrs (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 3 mg/kg q2w for up to 2 yrs (n = 3)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBV-infected pts (n = 50 planned)</th>
<th>Nivolumab 0.1-10 mg/kg q2w for up to 2 yrs (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab dose TBD q2w for up to 2 yrs (n = 0)</td>
<td></td>
</tr>
</tbody>
</table>


---

**CheckMate-040: Treatment-Related Adverse Events**

<table>
<thead>
<tr>
<th>Treatment-Related AEs in ≥10% of Pts, n (%)</th>
<th>All Dose Escalation Pts (n = 48)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>11 (23)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AST elevation</td>
<td>10 (21)</td>
<td>5 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Lipase elevation</td>
<td>10 (21)</td>
<td>6 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Amylase elevation</td>
<td>9 (19)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>7 (15)</td>
<td>3 (6)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Safety profile of nivolumab in HCC similar to other tumors except greater frequency of AST/ALT elevation


---

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Immune-Related AEs With Immunotherapy

- Pulmonary: Pneumonitis, Interstitial lung disease, Acute interstitial pneumonitis
- Neurologic: Autoimmune neuropathy, Demyelinating polyneuropathy, Guillain-Barré, Myasthenia gravis–like syndrome
- Hepatic: Hepatitis, autoimmune
- Gastrointestinal: Colitis, Enterocolitis, Necrotizing colitis, GI perforation
- Endocrine: Hypothyroidism, Hyperthyroidism, Adrenal insufficiency, Hypophysitis
- Eye: Uveitis, Iritis
- Renal: Nephritis, autoimmune
- Skin: Dermatitis, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Vitiligo, Alopecia

If not vigilant, may result in more serious immune-related AEs

Distribution of Immune-Related AEs With CTLA-4, PD-1, and PD-L1 Inhibition

CheckMate-040: Change in Target Lesions in Expansion Cohort

CheckMate-040: Nivolumab Response Kinetics
This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Are there any other pathways we may target in HCC?

**Modulation of autophagy**
- Autophagy is a bulk lysosomal mediated degradation pathway, that degrades unwanted proteins and defective organelles.
- Evidence now suggest that therapy-induced autophagy promotes cancer cell survival, and thus diminish the efficacy of some therapeutic agents.
- Studies have shown that SOR treatment in HCC cells induced the morphological and biochemical hallmarks of autophagy, for example, the generation of autophagosomes, GFP-LC3 redistribution and LC3-II accumulation. Thus, blocking of autophagy mediated survival by SOR-targeted therapy should be a rational approach to overcome resistance to SOR.

---

**Autophagy inhibitors to enhance cancer therapeutics**
- Choroquine (CQ) and its derivatives, such as hydroxychloroquine (HCQ), functions as weak bases and are trapped in acidic cellular compartments, including lysosomes. This deacidification of lysosomes by CQ and its derivatives impairs the activity of most lysosomal enzymes due to their strict pH requirements.
- When autophagy is inhibited by CQ, cells dependent on autophagy for survival increase the generation of autophagosomes and undergo either apoptotic or non-apoptotic cell death.

---

*This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.*
**Efficacy of SAHA + HCQ**

N = 19

mOS 6.7 months (95% CI: 4.63-NR).
(95% CI: 1.63-8.16)

mPFS 2.8 months

Five patients (26%) had stable disease ≥ 12 weeks.

Patel S, Hurez V, Nawrocki ST, Gora M, Michalek J, Sarantopoulos J, Gurlo T, Mahalingam D. 
Oncotarget. 2016 Sep 13;7(37):59087-59097

**Phase 1 study of Sorafenib/HCQ in advanced cancer – PI: Curiel**

Treatment results in reduction in Tregs and T-cell exhaustion markers and improved T-effector function.

Patel S, Hurez V, Nawrocki ST, Gora M, Michalek J, Sarantopoulos J, Gurlo T, Mahalingam D. 
Oncotarget. 2016 Sep 13;7(37):59087-59097

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Phase 2 study of modulation of sorafenib induced autophagy in HCC:

**Study design:**

![Study design diagram]

**Mutation Portrait of HCC**

<table>
<thead>
<tr>
<th>Genes Frequently Mutated in HCC</th>
<th>Estimated Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TERT promoter</td>
<td>80</td>
</tr>
<tr>
<td>TP53</td>
<td>20-30</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>15-25</td>
</tr>
<tr>
<td>ARID1A</td>
<td>10-16</td>
</tr>
<tr>
<td>PTN</td>
<td>4-10</td>
</tr>
<tr>
<td>APEX1</td>
<td>6-10</td>
</tr>
<tr>
<td>JAK1</td>
<td>0-9</td>
</tr>
<tr>
<td>AKR1</td>
<td>4-8</td>
</tr>
<tr>
<td>ARID2</td>
<td>5-7</td>
</tr>
<tr>
<td>KEAP1</td>
<td>3-8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genes Frequently Mutated in Other Solid Tumors but Rarely in HCC</th>
<th>Estimated Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH1, IDH2</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>NAPDH1</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>EGFR</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>BRAF</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>KRAS, NRAS</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>PTEN</td>
<td>&lt; 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Pathway/Gene Function</th>
<th>Estimated Frequency, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TERT promoter</td>
<td>Telomere stability</td>
<td>80</td>
</tr>
<tr>
<td>TP53</td>
<td>Genome integrity</td>
<td>20-30</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>WNT signaling</td>
<td>15-25</td>
</tr>
<tr>
<td>ARID1A</td>
<td>Chromatin remodeling</td>
<td>10-16</td>
</tr>
<tr>
<td>PTN</td>
<td>Chromosome segregation</td>
<td>4-10</td>
</tr>
<tr>
<td>APEX1</td>
<td>Oxidative stress</td>
<td>6-10</td>
</tr>
<tr>
<td>JAK1</td>
<td>JAK/STAT signaling</td>
<td>0-9</td>
</tr>
<tr>
<td>AKR1</td>
<td>WNT signaling</td>
<td>4-8</td>
</tr>
<tr>
<td>ARID2</td>
<td>Chromatin remodeling</td>
<td>5-7</td>
</tr>
<tr>
<td>KEAP1</td>
<td>Ubiquilinination</td>
<td>3-8</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com

**Personalized medicine in HCC**

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Conclusions

- Evolving local and systemic therapies for HCC. Effective anti-HCV therapy.
- Immunotherapy has emerged as an exciting therapeutic strategy.
- We need to enrich the clinical experience of checkpoint inhibitors in HCC.
- Assessing the molecular biomarkers that are important in predicting treatment response, resistance, and treatment-related AEs.
- Combination strategies to improve the efficacy of checkpoint inhibitors under investigation.
- Evaluating driver mutations and tailoring specific therapies.

Acknowledgement

Texas Liver Tumor Center Partnership

- One stop shop for Liver Tumors
- All-day clinic visit
- AM: Labs (in clinic) & Radiology (off-site transportation arranged) if needed
- Team schedules all procedure dates, times, additional testing, follow up clinic meetings
- Leave with a written plan and contact numbers
- Referring physician is sent a summary and packet of patient’s records
- Clinic Location: CTRC

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.
Texas Liver Tumor Center

Patient Referrals:
Phone: 210.743.4306 or Toll-free 1.888.3363963
Fax: 210.702.4233

Thank you

This presentation is the intellectual property of the author. Contact them for permission to reprint and/or distribute.