HEPATOMA CASE DISCUSSION

According to ESMO guidelines

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Disclosures

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- Research funding: BMS, Sirtex
- Non-financial: ESMO Asia Local Chair
CASE STUDY 1

76y male
Hepatitis B-related CP A6 liver cirrhosis
  - Albumin low 29 g/L
  - Bilirubin 30umol/L normal
Solitary 4cm seg8 HCC
CASE STUDY 1

Diagnostic workup

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Hep B</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>AFP</td>
<td>1231</td>
<td>YES</td>
</tr>
<tr>
<td>Imaging</td>
<td>Triphasic CT showing</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>typical HCC changes</td>
<td></td>
</tr>
</tbody>
</table>

No histology required

STAGING: 4cm solitary, no vascular invasion; CP A, ECOG 0
BCLC stage B
T1bN0M0 (stage 1B)
BCLC staging and treatment outcomes

Barcelona Clinic Liver Cancer (BCLC) Staging and Treatment Strategy

ASIA-PACIFIC HCC GUIDELINES (APASL)
2017 update
5-year OS Transplantation for HCC

4482 patients with HCC

Intention to treat
5 year overall survival
Within Milan  61%
Outside Milan  32%

Actually transplanted
5 year overall survival
Within Milan  65%
Outside Milan  38%

Pelletier et al. 2009,
Liver Transplantation

Figure 6. Overall intent-to-treat survival of patients listed for hepatocellular carcinoma according to the utilized criteria. There was a significant difference in survival among those that met the Milan criteria (black line) compared to those who exceeded the Milan criteria (black dotted line). The P value was <0.0001.
# TAE/TACE vs Best Supportive Care: 2-year Survival

<table>
<thead>
<tr>
<th>Author, journal year</th>
<th>Patients</th>
<th>Odds ratio (95% CI)</th>
<th>Random effects model (DerSimonian and Laird)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, Gastroenterology 1998</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GETCH, NEJM 1995</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruix, Hepatology 1998</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelletier, J Hepatol 1998</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lo, Hepatology 2002</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Llovet, Lancet 2002</td>
<td>112</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>503</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis of 7 RCTs showed survival benefit with TACE, OR 0.53, RR 35%

**Heterogeneity p=0.14**

**Author, journal year**
- Lin, Gastroenterology 1998
- GETCH, NEJM 1995
- Bruix, Hepatology 1998
- Pelletier, J Hepatol 1998
- Lo, Hepatology 2002
- Llovet, Lancet 2002

**Patients**
- 63
- 96
- 80
- 73
- 79
- 112
- 503

**Random effects model (DerSimonian and Laird)**

- **z=–2.3**
- **p=0.017**
**Conventional TACE vs DCBeads TACE**

- **PRECISION V Trial:**
  - Phase 2 randomised, Europe, n=200
  - Arm 1: TACE with doxorubicin
  - Arm 2: DC Beads with doxorubicin (150mg)  
    - Up to 3 times at 0,2,4mths
  - Primary endpoint was  
    - RR at 6 months

Results:

- Less liver toxicity (p<0.001) and less doxorubicin toxicity (p=0.0001) with DC Beads.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DC Bead (n=102)</th>
<th>cTACE (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean (sd)</td>
<td>67.0 years (±9.2)</td>
<td>67.3 years (±8.8)</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>88/14</td>
<td>97/13</td>
</tr>
<tr>
<td>Aetiology</td>
<td>20/14/41/27</td>
<td>12/13/52/33</td>
</tr>
<tr>
<td>Okuda (VII)</td>
<td>88/14</td>
<td>104/6</td>
</tr>
<tr>
<td>BCLC (A/B/C)</td>
<td>26/76/0</td>
<td>29/81/0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>DC Bead</strong></th>
<th><strong>cTACE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>52%</td>
<td>44% p not sig</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>63%</td>
<td>52% p not sig</td>
</tr>
<tr>
<td></td>
<td>SARAH</td>
<td>SIRveNIB</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Sample size</td>
<td>467</td>
<td>360</td>
</tr>
<tr>
<td>Main PVT</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>Etiology</td>
<td>Alcohol. 68%</td>
<td>HBV 51%</td>
</tr>
<tr>
<td></td>
<td>HCV. 25%</td>
<td>HCV 14.3%</td>
</tr>
<tr>
<td></td>
<td>NASH. 23%</td>
<td>Both HBV+HCV 2.2%</td>
</tr>
<tr>
<td>BCLC stage A/B/C</td>
<td>3.8/ 27.8/ 68.4%</td>
<td>0/ 54.9/ 44.5%</td>
</tr>
<tr>
<td>OS</td>
<td>SIRT 8m vs sorafenib 9.9m</td>
<td>SIRT 8.9m vs soraf 10m</td>
</tr>
<tr>
<td></td>
<td>HR 1.15, p=0.18</td>
<td>HR1.12 , p=0.36</td>
</tr>
<tr>
<td>PFS/ TTP</td>
<td>PFS 4.3 vs 3.7m</td>
<td>TTP 6.08 vs 5.36m</td>
</tr>
<tr>
<td></td>
<td>HR0.97, p=0.77</td>
<td>HR 0.88, p=0.287</td>
</tr>
<tr>
<td>ORR ( CR + PR)</td>
<td>19% vs 11.6%, p=0.042</td>
<td>16.5% vs 1.7% , p&lt;0.0001</td>
</tr>
</tbody>
</table>
SORAMIC Trial: Schema

NEGATIVE trial
SIRT + sorafenib vs sorafenib: OS
12.1m vs 11.5m
Clinical outcome of SBRT for HCC

<table>
<thead>
<tr>
<th>First author (country)</th>
<th>Sample size</th>
<th>SBRT schedule</th>
<th>Local control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andolino (United States)</td>
<td>60 patients</td>
<td>24–48 Gy, 3–5 fx</td>
<td>90% at 2 y</td>
</tr>
<tr>
<td>Dewas (France)</td>
<td>42 patients, 48 lesions</td>
<td>Median 45 Gy, 3 fx</td>
<td>91% at 2 y</td>
</tr>
<tr>
<td>Honda (Japan)</td>
<td>30 patients*</td>
<td>Median 48 Gy, 4 fx</td>
<td>94% at 2 y</td>
</tr>
<tr>
<td>Jang (Korea)</td>
<td>82 patients, 95 lesions</td>
<td>&lt;45 Gy, 3 fx (n = 11) 45–54 Gy, 3 fx (n = 47) &gt;54 Gy, 3 fx (n = 57)</td>
<td>87% at 2 y</td>
</tr>
<tr>
<td>Kang (Korea)</td>
<td>47 patients</td>
<td>Risk-adapted, 3 fx</td>
<td>95% at 2 y</td>
</tr>
<tr>
<td>Kwon (Korea)</td>
<td>42 patients</td>
<td>Median 33 Gy, 3 fx</td>
<td>68% at 3 y</td>
</tr>
<tr>
<td>Sanuki (Japan)</td>
<td>185 patients</td>
<td>35 Gy, 5 fx (n = 48) 40 Gy, 5 fx (n = 137)</td>
<td>91% at 3 y</td>
</tr>
<tr>
<td>Wahl (United States)</td>
<td>63 patients, 83 lesions</td>
<td>27–60 Gy, 3–5 fx</td>
<td>84% at 2 y</td>
</tr>
</tbody>
</table>

Ohri et al, NCI HCC Working Group, JNCI 2016
SBRT as a bridge to liver transplantation-2

- SBRT may be as effective as TACE or RFA for bridge Tx to liver transplantation.

Sapisochin et al., J Hepatol 2017
ROLE of SIRT and SBRT in ESMO guidelines

“SIRT is not recommended as first-line therapy for patients in intermediate or advanced stage [I,E]
What would you do now?

A. Surgery (inadequate liver reserve) TRANSPLANT?
B. Radiofrequency ablation (open/ percutaneous)
C. Microwave ablation (open/ percutaneous)
D. TACE (lipiodol, doxorubicin-embedded beads)
E. Selective internal irradiation (SIR) alone – no head to head comparison with TACE; both SIRveNIB and SARAH were negative trials
F. SIR with sorafenib – SORAMIC trial was negative
G. SBRT- no level 1 evidence

- Best for 3cm or less. MWA has limited data though may have more predictable ablation zone

MDT review – for local ablation. Enrolled into trial of microwave (MWA) vs RFA (randomized to MWA)
Since June 2014: Caudate lobe recurrences

- June 2014: Caudate lobe recurrence on CT
- MDT: Not for surgery due to borderline liver reserve
- **What would you do now?**
  A. Surgery *(Transplant?)*
  B. TACE
  C. SBRT
  D. Open ablation X
  E. SIR +/- sorafenib X
June 2014-Oct 2017: TACE x 4- responded? Is this TACE failure?

May 2018: SBRT

Sep 2018: multifocal HCC

- Attempted #5 TACE: No hypervascular lesions. High-grade stenosis near origin of RIGHT hepatic artery.
- AFP slowly rose between 20-80ug/L. Observed
- May 2018: AFP rose to 503
- CT: exophytic seg 6 recurrence
- SBRT given. AFP returned to 16-20ug/L
- Sept 2018: AFP = 125ug/L. platelet: 98 x 10^9/L

What are his options now?
A. Sorafenib
B. Immune checkpoint inhibitor
C. RFA/ MW
D. SIRT
E. SBRT again (< 4 months from last RT)

Lenvantinib is an alternative to sorafenib
CASE STUDY 2

- 59y Hep B related HCC
- s/p Resection x 2 + RFA
- Now multifocal HCC  CP A
- Feb 2016: CT shows seg II/III, III, Iva and VII recurrences.
- **What would you do now?**
  
  A. TACE
  
  B. Sorafenib
  
  C. Immune Checkpoint inhibitor
  
  D. SIRT +/- sorafenib

ECOG status?
PV patent?
Definition of TACE failure/refractoriness (JSH Criteria)\(^1\)

Intrahepatic lesion

i. **Two or more consecutive insufficient responses of the treated tumor (viable lesion >50\%)** even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having **adequately performed selective TACE**

ii. **Two or more consecutive progressions in the liver (tumor number increases** as compared to tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having **adequately performed selective TACE**

\(^1\)Kudo M, et al. TACE Failure criteria JSH guideline. Dig Dis 2011;29:339-364
CASE STUDY 2

Patient received TACE x1#

- Eventually progressed. CP A6
- Is this TACE failure?

What next?
- TACE
- SIRT
- systemic therapy – sorafenib? Lenvantinb? IO?
- Clinical trial
OPTIMIS: patients not indicated for TACE given TACE

Conditions Not Indicated by International Guidelines for Initial TACE

Patients (%)

- Overall
- ECOG PS≥1
- BCLC C or D
- Advanced Liver Disease
- Vascular Invasion
- Extrahepatic Spread

TACE is used in certain patients where systemic therapy is more appropriate

M Peck-Radosavlijevic 2018
# 1st Line treatment of advanced HCC

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Lenvatinib</th>
</tr>
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<tbody>
<tr>
<td>FDA approval</td>
<td>2007</td>
<td>Aug 2018</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Raf-mek</td>
<td>VEGf, FGF1-3, ret</td>
</tr>
<tr>
<td>Level of evidence</td>
<td>Phase III vs placebo</td>
<td>Phase III non-inferiority</td>
</tr>
<tr>
<td>Dosing</td>
<td>400mg BD</td>
<td>8mg OM if &lt; 60kg; 12mg OM if &gt; 60kg</td>
</tr>
<tr>
<td>Median OS</td>
<td>6.5/10.7 m (2007); 12.3mths (2017)</td>
<td>13.6m</td>
</tr>
<tr>
<td>Median PFS</td>
<td>3.6m</td>
<td>7.3m</td>
</tr>
<tr>
<td>Response Rates</td>
<td>3% (2007) 7% (2017)</td>
<td>19%</td>
</tr>
<tr>
<td>Common toxicities</td>
<td>HFS, fatigue</td>
<td>Hypertension, fatigue</td>
</tr>
</tbody>
</table>
Phase III Trial of Lenvatinib vs Sorafenib in 1L Treatment of Patients with Unresectable HCC

Patients with unresectable HCC (N = 954)
- No prior systemic therapy for unresectable HCC
- 1 Measurable target lesion per 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)
- MPVI and/or EHS: (yes or no)
- ECOG PS: (0 or 1)
- Body weight: (< 60 kg or ≥ 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

Dose was around half of that for other cancers

Excluded a subgroup of poor-prognostic patients.

NON-inferiority trial: predefined non-inferiority margin for OS was 1.08
CASE STUDY 2

- Tolerated sorafenib but after 4 months progressed in the liver and lungs. AFP > 2200

What next?
- Lenvatinib
- Nivolumab
- Regorafenib
- Cabozantinib
- Ramucirumab
- Prembrolizumab
ESMO GUIDELINES FOR HCC

BCLC 0-A
- Resectiona
- LTX
  - [III, A]
- Ablationa
  - [III, A]

BCLC B
- LTX Resection
  - [III, A]
- TACE
  - [I, A]
- TACE failure/ refractoriness

BCLC C
- Sorafenib
  - [I, A]
- Regorafenib
  - [I, A]
- Cabozantinibb
- Ramucirumab
  - [I, A]
- Nivolumab
- Pembrolizumab
  - [III, B]
- SIRTa
  - [III, C]
- BSC
  - [III, A]
**Clinical Presentation**

- Inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only

**Treatment**

**Options**

- Locoregional therapy preferred
  - Ablation
  - Arterially directed therapies
  - Radiation therapy
- Systemic therapy
  - Sorafenib (Child-Pugh Class A [category 1] or B)
  - Lenvatinib (Child-Pugh Class A only)
- Chemotherapy
  - Systemic (category 2B)
  - Intra-arterial
- Clinical trial
- Best supportive care

**Options**

- If progression on or after sorafenib:
  - Regorafenib (Child-Pugh Class A only)
  - Nivolumab (Child-Pugh Class A or B7 only)
  - Cabozantinib (Child-Pugh Class A only)

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**Note:**

- See Principles of Biopsy (HCC-B).

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**Additional Information:**

- See Evidence Blocks on HCC-6A.
How does one decide on 2L Treatment of HCC if CP A

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>REGORAFENIB</th>
<th>NIVOLUMAB</th>
<th>CABOZANTINIB</th>
<th>RAMUCIRUMAB</th>
<th>pembrolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multitarget TKI</td>
<td>Anti-PD1</td>
<td>Multitarget TKI</td>
<td>Antibody against</td>
<td>Anti-PD1</td>
<td></td>
</tr>
<tr>
<td>(?Raf)</td>
<td></td>
<td>(c-met, AXL)</td>
<td>VEGFR2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Evidence        | Phase 3 RCT vs    | Phase I/II      | Phase 3 RCT vs   | Phase 3 RCT vs   |
|-----------------| placeholder       |                 | placebo          | placebo          |

| Patient         | Sorafenib tolerant + radiological progression | Sorafenib experienced (no limit to prior lines) | Sorafenib experienced (≤2 lines) | Sorafenib experienced (1 prior line only) with AFP ≥400ng/ml |
| characteristics |                                                |                                              |                                |                                                             |

| Efficacy : OS   | 7.8 to 10.6m      | 15.6m           | 8.0 to 10.2m     | 7.3 to 8.5m      |
|                 | 1.5 to 3.1m       | 37% at 6m       | 1.9 to 5.2m      | 1.6 to 2.8m      |
| PFS             | 12.9m             |                 | 7.3 to 8.5m      |                 |
|                 | 4.9m              |                 | 1.6 to 2.8m      |                 |

| ORR (CR + PR)   | 4 to 11%          | 20%             | 0.4 to 4%        | 1.1 to 4.6%      |
|                 |                   |                 |                  |                  |
|                 | 17%               |                 |                  |                  |

| Toxicities      | Hypertension; diarrhea | Immune-related AEs | HFS, diarrhea | Hypertension, bleeding proteinuria | irAEs |

| COSTs?          |
**CheckMate 040 Child-Pugh B Cohort Study**

**Design**

**Child-Pugh B7–B8 Cohort (N = 50)**

- Advanced HCC
- Sorafenib-naïve or -treated intolerant or progressors
- Nivolumab 240 mg flat dose IV for 30 min Q2W
- Follow-up visit 1 and 2 and survival follow-up

Treat until RECIST v1.1–defined progression or unacceptable toxicity

Median follow-up: 11.8 months (range, 6.4–18.0 months)

**Study Endpoints**

**Primary**
- ORR based on investigator assessment

**Secondary**
- Disease control rate
- Duration of response
- Time to response
- Time to progression
- Progression-free survival
- Overall survival

**Other**
- BOR and ORR based on BICR-assessed tumor response

**AASLD 2018: Masatoshi Kudo, Ana Matilla, Armando Santoro, Ignacio Melero, Antonio Gracian, Mirelis Rivera Acosta, Su-Pin Choo, Anthony B. El-Khoueiry, Ryoko Kuromatsu, Bassel El-Rayes, Kazushi Numata, Yoshito Itoh, Francesco Di Costanzo, Oxana Crysler, Maria Reig, Yun Shen, Jaclyn Neely, Christine dela Cruz, Carlos Baccan, Bruno Sangro**
### Hepatic Treatment-Related AEs

<table>
<thead>
<tr>
<th></th>
<th>Child-Pugh B</th>
<th></th>
<th>Child-Pugh A&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;sup&gt;n (%)&lt;/sup&gt;</td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase increased</td>
<td>2 (4.1)</td>
<td>2 (4.1)</td>
<td>21 (8.0)</td>
<td>8 (3.1)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>2 (4.1)</td>
<td>2 (4.1)</td>
<td>27 (10.3)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>2 (4.1)</td>
<td>1 (2.0)</td>
<td>19 (7.3)</td>
<td>15 (5.7)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>1 (2.0)</td>
<td>0</td>
<td>26 (9.9)</td>
<td>10 (3.8)</td>
</tr>
<tr>
<td>Liver function test increased</td>
<td>1 (2.0)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertransaminasaemia</td>
<td>2 (4.1)</td>
<td>2 (4.1)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hepatic function abnormal</td>
<td>1 (2.0)</td>
<td>1 (2.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>1 (2.0)</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data from CheckMate 040 cohorts 1 and 2, in which almost all patients had Child-Pugh A status, are presented for comparison.

- Only 2 patients with hepatotoxicity had a treatment-related AE leading to discontinuation in the Child-Pugh B cohort.
Thank you