Hepatocellular Carcinoma (HCC)

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Agenda

• Epidemiology
• Screening & Diagnosis
• Staging & Treatment
  – Early stage
  – Intermediate stage
  – Advanced stage & terminal stage
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Epidemiologie des HCC

• 5th most common malignancy, 2\textsuperscript{nd} most common cause of cancer-related death
• >90% have underlying liver cirrhosis
• Most common etiologies: HBV, HCV, Alkohol, NAFLD
• Annual HCC incidence in cirrhotics: 1-8%
• 1/3 develop HCC during their life-time

EASL-EORTC HCC practice guidelines. J Hepatol 2012;56:908
http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp.
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Screening

• 6-monthly US (sens: 58-89%, spec: >90%)
  – AFP only increases sensitivity by 6-8%, but reduces cost-effectiveness

• Target population:
  – CP A/B cirrhotics
  – CP C listed for transplantation
  – HbsAg+ with active disease of family history
  – HCV+ with advanced fibrosis (F3)

J Hepatol 2012;56:908
Diagnosis

Mass/Nodule on US

<1 cm
- Repeat US at 4 mo
  - Growing/changing character
    - Investigate according to size
  - Stable

1-2 cm
- 4-phase CT/dynamic contrast enhanced MRI
  - 1 or 2 positive techniques*: HCC radiological hallmarks**
    - Yes
      - HCC
    - No
      - Biopsy

>2 cm
- 4-phase CT or dynamic contrast enhanced MRI
  - 1 positive technique: HCC radiological hallmarks**
    - Yes
      - HCC
    - No
      - Biopsy

Inconclusive

J Hepatol 2012;56:908
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BCLC staging & treatment
(Bruix et al. Gastroenterology 2016;150:835)
Resection

• Solitary tumor & well-preserved liver function

• Assessment of liver function:
  – Indocyanine green retention rate at 15 min.
    • Major resection: ≤14%
    • Extend if est. remnant liver volume sufficient: 15-20%

  – Portal hypertension:
    • Hepatic vein catheterization: HVPG <10mmHg
    • Alternatively: GI varices or platelets <100x10⁹/L+ splenomegaly

Clinically significant portal hypertension (CSPH), bilirubin & post-resection 5-year-survival rate

Cut-off 10 mmHg excludes ~25% of patients who would benefit from surgery without short- to mid-term postoperative complications (J Hepatol 2016;64:79).

Push limits?????

No CSPH, 74%

CSPH & Bili ≥1mg/dl, 25%
Local ablation

- Tumors ≤3 (5cm), Child-Pugh A-B
- RFA preferred over PEI:
  - Better survival, CR rate and TTP
  - <2cm: no sign. difference

J Hepatol 2010;52:380.
J Hepatol 2012;56:908.
ESMO Open 2016;1:e000042.

Gastroenterology 2005;129:122
Liver transplantation

Expand

**UCSF criteria** (Hepatology 2001;33:1394):
- 1 tumor ≤6.5 cm, ≤3 tumors ≤4.5 cm and cumulative size ≤8 cm
- UCSF (pathology): 5-year survival rate, 75%

- Milan vs. UCSF (imaging): 5-year post-transplant survival, 79% vs. 64%; *P*=0.061 (Ann Surg 2007;246:502)
- Would increase proportion available for OLT by only ~5% (Liver Transplant 2011:17 (suppl 2):S81)

**Up-to 7 criteria** (Lancet Oncol 2009;10:35):
- 7 = result of the sum of size (cm) and number of tumors
- Milan vs. Up-to-7 (pathology): 5-year post OLT survival, 73% vs 71%
Metro ticket

Bridging therapy (TACE/RFA)

• To reduce drop-out and recurrence, and improve survival

• EASL: consider if expected waiting time exceeds 6 months

  – Bridging LRT group (n=686) vs. no LRT (2108), all Milan in
  – lower recurrence
  – longer median OS

  – n=4197, all Milan in
  – Drop-out rate Risk factors: AFP, MELD, max. tumor size
  – At 6 and 12 months of untreated vs. any ablation:
    10.1% vs. 8.0% and 11.8 vs. 11.2%
Response to neoadjuvant treatment and outcome after OLT
(Finkenstedt et al. Liver Int 2016;36:688)

Down-staging to Milan criteria (status must be maintained for at least 3-6 months) is NOT endorsed by guidelines due to lack of robust data

Bruix et al. Gastroenterology 2016;150:835
OS according to treatment & tumor size

**Updated – very early HCC (≤2cm):**

- **RFA first-line** (similar long-term survival, less post-surgical morbidity)
- Resection, if candidate for OLT (tissue to identify high risk for recurrence; e.g., VI, satellite nodules) or risk of LF similar to RFA (good liver function, superficial tumor)
- **OLT** as salvage therapy for recurrence or liver failure


Kutlu et al. Cancer 2017
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BCLC staging & treatment

(Bruix et al. Gastroenterology 2016;150:835)
TACE effective in intermediate HCC

- Metaanalysis of RCT, TACE vs. BSC
- Intermediate HCC:
  - No EHS
  - Asymptomatic (PS 0)
- Median OS TACE vs. BSC: 20 vs. 16 months
- Increased 2-year survival rate (OR, 0.53)

Llovet et al. Hepatology 2003; 37:429
TACE
TACE – candidates & techniques

• Best candidates (BCLC stage B):
  – Asymtomatic (PS 0), large (<10cm) or multifocal HCC, no MVI or extrahepatic metastases, Child-Pugh A-B7 (no ascites)

• cTACE vs. DEB-TACE:
  – Technique:
    • cTACE: CHT/lipiodol + embolizing agent (e.g., gelatine sponge)
    • DEB-TACE: CHT-loaded embolic microspheres
  – Efficacy: equally effective
  – DEB-TACE: slow drug release -> high local, low systemic CHT levels -> less systemic side effects

TACE - contraindications

**Absolute:**
- Decompensated cirrhosis (CP B8)
- Impaired portal vein flow (PVT, hepatofungal flow)
- Large diffuse HCC
- MVI
- Technical CI (e.g., untreatable AV fistula)
- Crea ≥2mg/ml or crea clearance <30ml/min.

**Relative:**
- Untreated varices with high bleeding risk
- Tumor >10cm
- Severe comorbidities
- Biliary (e.g., dilation, incompetent papilla)

Proposed stopping guidelines for TACE

- Fehlendes radiologisches Ansprechen nach 2 aufeinanderfolgenden TACE
  - "non-response"

- Entwicklung von Kontraindikationen für TACE
  - Gefäßinvasion
  - Extrahepatische Metastasen
  - Klinische Progression zu ECOG PS ≥ 2
  - Anhaltender Aszites
  - Anhaltendes Child-Pugh B Stadium
  - Thrombozyten <60,000/µL
  - "BCLC-stage progression"
  - "Impairment of liver function"

Retreatment with TACE, Vienna retrospective cohort (ART score)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall survival</th>
<th>ART-score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95%CI</td>
<td>B</td>
</tr>
<tr>
<td>Child-Pugh score increase</td>
<td>Absent</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>+ 1 point</td>
<td>2.0</td>
<td>1.2-3.5</td>
</tr>
<tr>
<td></td>
<td>+ ≥2 points</td>
<td><strong>4.4</strong></td>
<td>2.0-9.6</td>
</tr>
<tr>
<td>AST increase &gt;25%</td>
<td>Absent</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td><strong>8.4</strong></td>
<td>4.5-15.5</td>
</tr>
<tr>
<td>Radiologic tumor response</td>
<td>Present</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1.7</td>
<td>1.1-2.6</td>
</tr>
</tbody>
</table>

Sieghart W et al. Hepatology 2013
TACE & liver function (ART score)

<table>
<thead>
<tr>
<th>ART Score Points</th>
<th>Training Cohort</th>
<th>0-1.5</th>
<th>&gt; 2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE ≥ grade 3 within 4 weeks after first TACE</td>
<td>Absent</td>
<td>57 (95)</td>
<td>32 (87)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>3 (5)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>AE ≥ grade 3 within 4 weeks after second TACE</td>
<td>Absent</td>
<td>56 (93)</td>
<td>27 (73)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>4 (7)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Unscheduled hospitalizations after second TACE</td>
<td>Absent</td>
<td>58 (97)</td>
<td>29 (78)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>2 (3)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>30-day mortality after second TACE</td>
<td>Alive</td>
<td>59 (98)</td>
<td>34 (92)</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td>0</td>
<td>3 (8)</td>
</tr>
<tr>
<td></td>
<td>Censored</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

log-rank p = 0.0001
Timely switch to systemic treatment avoids irreversible harm of liver function

Point of TACE failure/deterioration of liver function

Adapted from Kudo M, Liver Cancer 2016;5:235–244
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BCLC staging & treatment
(Bruix et al. Gastroenterology 2016;150:835)
Sorafenib in advanced HCC phase III (SHARP) trial

Radiological response (RECIST):
- PR: 2 vs. 1%
- DCR: 43 vs. 32%
- Median TTP: 5.5 vs. 2.8 mo; p<0.001

Most common AEs (%):
- Diarrhea: 39 vs. 11
- Fatigue: 22 vs. 16
- HFS: 21 vs. 3
- Rash: 16 vs. 11
- Anorexia: 14 vs. 3
- Hypertension: 5 vs. 2

Sorafenib in Asia-Pacific region (phase III)

Median OS: 6.5 vs. 4.2 mo, p=0.014


Only patients with well-preserved liver function (Child-Pugh class A) included!

Child-Pugh B????????

Sorafenib and Child-Pugh stage

GIDEON (phase IV observational study)

Ongoing phase III (BOOST) in patients with Child-Pugh B (NCT01405573)

Marrero et al. J Hepatol 2016;65:1140
# Negative 1st-line phase III studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Main drug targets</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib vs. sora (SUN)</td>
<td>VEGFR, PDGFR, c-KIT, RET</td>
<td>7.2 vs. 10.2, p=0.001</td>
</tr>
<tr>
<td>Brivanib vs. sora (BRISK-FL)</td>
<td>VEGFR, FGFR</td>
<td>9.5 vs. 9.9, n.s.*</td>
</tr>
<tr>
<td>Linifanib vs. sora (LIGHT)</td>
<td>VEGFR, PDGFR</td>
<td>9.1 vs. 9.8, n.s.*</td>
</tr>
<tr>
<td>Sora ± erlotinib vs. sora (SEARCH)</td>
<td>EGFR</td>
<td>9.5 vs. 8.5, n.s.</td>
</tr>
</tbody>
</table>

*Noninferiority

Phase II results - TKIs

Phase III trial (Study 304) achieved its primary endpoint non-inferiority of OS with lenvatinib vs. sorafenib

(Eisai, Press release Jan 25, 2017)

### Negative 2nd-line phase III studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Main drug targets</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivanib vs. Placebo (BRISK-PS)</td>
<td>VEGFR, FGFR</td>
<td>9.4 vs. 8.2, n.s.</td>
</tr>
<tr>
<td>Everolimus vs. Placebo (EVOLVE-1)</td>
<td>mTOR</td>
<td>7.6 vs. 7.3, n.s.</td>
</tr>
<tr>
<td>Ramucirumab vs. Placebo (REACH)</td>
<td>VEGFR-2</td>
<td>9.2 vs. 7.6, n.s.</td>
</tr>
<tr>
<td>ADI-peg 20 vs. Placebo</td>
<td>Depletion of external arginine</td>
<td>7.8 vs. 7.4, n.s.</td>
</tr>
</tbody>
</table>

Regorafenib 2nd-line phase III (RESORCE)

Radiological response (mRECIST):
• ORR: 11 vs. 4%
• DCR: 65 vs. 36%
• Median TTP: 3.2 vs. 1.5 mo; p<0.0001

Clinically most relevant AEs (%):
• HFS: 53 vs. 8%
• Diarrhea: 41 vs. 15%
• Fatigue: 40 vs. 32%
• Hypertension: 31 vs. 6%

• Median time on sorafenib: 7.8 mo (both)
• Median time from sora discont. to treatment start: 0.9 mo (both)

Note:
• Child-Pugh A only
• Prior sorafenib tolerance required

Bruix et al. Lancet 2017; 389: 56
Was ist möglich mit systemischer Therapie

<table>
<thead>
<tr>
<th>Time from start of sorafenib to death on study drug</th>
<th>Regorafenib (n=374)</th>
<th>Placebo (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95%CI), months</td>
<td>26.0 (22.6-28.1)</td>
<td>19.2 (16.3-22.8)</td>
</tr>
</tbody>
</table>

Finn et al. ASCO GI 2017 abstr #344.
Tissue biomarkers for treatment decisions in solid tumors

- **Breast cancer**
  - HR – hormonal therapy
  - Her2/neu - trastuzumab

- **Colon cancer**
  - KRAS wt - cetuximab

- **Lung cancer**
  - EGFR mutat. – anti-EGFR
  - ALK fusion - crizotinib

- **Melanoma**
  - BRAF mutat. – vemurafenib

- **CML:**
  - BRC-ABL fusion - imatinib

NSCLC - Biomarker-driven therapy

**Unselected**
- Kuroto et al. Lancet Oncol 2008
  - 15%

**Mutated EGFR**
- Maemondo et al. NEJM 2010
  - 42%

**ALK-Positive**
- Solomon et al. NEJM 2014
  - 47%

**PD-L1-Positive**
- Reck et al. NEJM 2016
  - 47%
Tivantinib 2nd-line phase II

Intention-to-treat:
- **Primary endpoint met**: median TTP, 1.6 vs. 1.4 months; HR, 0.64; p=0.04
- **Secondary endpoint**: median OS, 6.6 vs. 6.2 months; HR, 0.90; p=0.63

Phase III in patients with MET-high (NCT01755767) **NEGATIV!**

*Daiichi Sankyo, Press release Feb 17, 2017*

Santoro et al. Lancet Oncol 2013;14:55
Ramucirumab (monoklonaler VEGFR2 Ab)  
2nd-line, Patienten mit AFP≥400ng/mL  

Laufende Phase III 2nd-line bei Patienten mit hohem AFP (NCT02435433)  

Rationale für Immunotherapie beim HCC

• Immunogen, spontane Regressionen beschrieben (mit systemischer Entzündungsreaktion einhergehend)

• HCC mit chronischer Entzündung assoziiert -> Hochregulation von Checkpoint Molekülen und Akkumulation von immunsuppressiven Zellen

• Immun-Checkpoint Moleküle (z.B.: PD-L1) helfen bei der Immunevasion des HCC, Hochregulation durch Sorafenib

• Leber fördert Immuntoleranz (z.B.: PD-L1 on LSEC)

• Immunotherapeutika nicht über Leber metabolisiert (prädiktives pharmakologisches Profil bei Leberzirrhosikern)

Immunotherapy

Greten et al., Clin Cancer Res 2013;19:6678

JX-594

Nivolumab, Tremelimumab, Pembrolizumab
Checkpoint blockers

# Phase II results - Immunotherapy

<table>
<thead>
<tr>
<th>Drug (main target)</th>
<th>Design, N</th>
<th>Common AEs</th>
<th>ORR/D CR %</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sangro 2013</td>
<td>Tremelimumab (anti-CTLA-4)</td>
<td>Phase II, 21</td>
<td>Rash, fatigue, anorexia</td>
<td>18/76</td>
</tr>
<tr>
<td>Sangro 2016 (AASLD)</td>
<td>Nivolumab (anti-PD-1)</td>
<td>Phase I/II, 48/214</td>
<td>Fatigue, pruritus, rash, diarrhea</td>
<td>16/68</td>
</tr>
</tbody>
</table>

## Drugs tested in phase III

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Setting</th>
<th>Identifier</th>
<th>Primary completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Anti-PD-1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line</td>
<td>NCT02576509</td>
<td>Q3 2017</td>
</tr>
<tr>
<td>JX-594 + SOR</td>
<td>Oncolytic virus</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line</td>
<td>NCT02562755</td>
<td>Q4 2017</td>
</tr>
<tr>
<td>Donafenib</td>
<td>VEGF, PDGF, Raf, KIT, FLT3</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line</td>
<td>NCT02645981</td>
<td>Q1 2019</td>
</tr>
<tr>
<td>Doxo + SOR</td>
<td>DNA replication</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line</td>
<td>NCT01015833</td>
<td>Q2 2017</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>MET, VEGFR2, FLT3, KIT, RET</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line</td>
<td>NCT01908426</td>
<td>Q4 2016</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>Anti-VEGFR2</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line</td>
<td>NCT02435433</td>
<td>Q4 2017</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Anti-PD-1</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line</td>
<td>NCT02702401</td>
<td>Q1 2019</td>
</tr>
<tr>
<td>Doxo Transdrug</td>
<td>DNA replication</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line</td>
<td>NCT01655693</td>
<td>Q3 2017</td>
</tr>
</tbody>
</table>
Radioembolization (RE)

- Yttrium-90-microspheres
- Small beads -> no substantial ischemia -> less post-embolization syndrome, but
- RE-induced liver disease (= form of sinusoidal obstruction syndrome) in up to 20%:
  - 4-8 weeks after treatment
  - Jaundice, moderate cholestasis, mild ascites
- Median survival in BCLC stage B: 15-18 months
- Lack of RCT comparing RE with TACE or sorafenib -> thus still considered experimental

Bruix et al. Gastroenterology 2016;150:835
Yttrium-90-RE for HCC
(Sangro et al. Hepatology 2011;54:868)

- Retrospective, 8 EU centers, n=325
- Median OS, 12.8 (95%CI, 10.9-15.7) months
- Prognostic factors: ECOG PS, tumor burden, INR, EHS
- Common ASs: fatigue, nausea/vomiting, abdominal pain
Y-90-RE vs. Sorafenib in HCC

(Gramenzi et al. Liver Int 2015;35:1036)

Propensity score matched survival (retrospective, single center)
Y-90-RE vs. cTACE
Salem et al. Gastroenterology 2015;151:1155

Phase II randomized trial

TTP: 26 vs. 6.8 months, p=0.0012

OS: 18.6 vs. 17.7 months, p=n.s.
Conclusion (1)

- Surveillance every 6 months with US
- Diagnosis – imaging only - no tissue biomarker
- Early HCC, BCLC stage 0-A:
  - RFA first-line in very early HCC (≤2cm)
  - Resection if HCC >3cm
  - HCC >2-3cm: RFA or resection (individual patient)
  - OLT if within Milan and resection not possible
    - Bridging if expected waiting time >6 months
- Intermediate HCC, BCLC stage B:
  - TACE: Cave: subtle liver function deterioration
Conclusion (2)

• Advanced HCC, BCLC C:
  – 1\textsuperscript{st}-line systemic therapy: sorafenib and lenvatinib (very likely)
  – 2\textsuperscript{nd}-line systemic therapy: regorafenib (very likely)
  – New treatments, e.g., immunotherapy & ramucirumab in subgroups
  – Still no biomarker-driven approach

• Terminal stage, BCLC D:
  – Supportive therapy
Vielen Dank!
## Potential drivers of molecular hepatocarcinogenesis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Pathways/Gene Functions Involved</th>
<th>Estimated Frequency Based on Deep-sequencing Studies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Driver Genes Frequently Mutated in HCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TERT promoter</td>
<td>telomere stability</td>
<td>60</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>TTN</td>
<td>chromosome segregation</td>
<td>4–10</td>
</tr>
<tr>
<td>NFE2L2</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><strong>Oncogenes/Tumor Suppressors Rarely Mutated in HCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1, IDH2</td>
<td>NAPDH metabolism</td>
<td>&lt;5</td>
</tr>
<tr>
<td>EGFR</td>
<td>growth factor signaling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>BRAF</td>
<td>RAS/MAPK signaling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>KRAS, NRAS</td>
<td>RAS/MAPK signaling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>AKT signaling</td>
<td>&lt;5</td>
</tr>
<tr>
<td>PTEN</td>
<td>AKT signaling</td>
<td>&lt;5</td>
</tr>
<tr>
<td><strong>Oncogenes Contained in High-Level Amplifications in HCC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGF19</td>
<td>FGF signaling</td>
<td>5–10</td>
</tr>
<tr>
<td>CCND1</td>
<td>cell cycle</td>
<td>5–10</td>
</tr>
<tr>
<td>VEGFA</td>
<td>HGF signaling/angiogenesis</td>
<td>7–10</td>
</tr>
</tbody>
</table>

Modified from Llovet and Hernandez-Gea (2014).

Oncogene addiction loop → proof-of-principle/concept trial