Speaker, consultancy and advisory role:
- Roche, Bayer, Sanofi, BMS, Lilly, Novartis, Eisai, AstraZeneca, Merck, Incyte, Medac, Ipsen, Servier, PierreFabre, MSD, BTG, Janssen

Research funding:
- Servier
CURRENT STANDARDS AND PRACTICE
CHANGING STUDIES IN
HEPATOCELLULAR AND BILIARY TRACT
CARCINOMA
ESMO GUIDELINE HCC

BCLC 0-A
- Resection* [III, A]
- Ablation* [III, A]
- TACE [I, B]
- SBRT* Brachytherapy* [III, C]

BCLC B
- LTx Resection [III, A]
- TACE* [I, A]
- SIRT [III, C]

BCLC C
- Sorafenib* [I, A]
- Lenvatinib* [I, A; MCBS 4]
- TACE failure/ refractoriness
- Systemic therapy [I, A]
- Regorafenib [I, A; MCBS 4]
- Cabozantinib [I, A; MCBS 3]
- Ramucirumab [I, A]

BCLC D
- BSC [III, A]

Vogel et al. ESMO CPG 2019, eUpdate
**EVIDENCE FOR TACE**

**Phase-III Study**
- 950 patients screened, 70% ≥ 2 tumors, ~ 5cm, Median: 2,8 treatmetns

**Real life**
- Systematic review of 101 studies (n=10,108) Patients treated with lipiodol TACE

17,9 (BSC!) vs. 28,7 months

mOS: 19.4 months

---

Llovet et al., Lancet 2002

Lencioni et al. Hepatology 2016
PATIENT SELEKTION FOR TACE IS KEY!

HAP score to identify patients that benefit from TACE

- Albumin < 36 g/dl
- Bilirubin > 17 μmol/l
- AFP > 400 ng/ml
- Max. tumour > 7 cm

HAP Points
- HAP A 0
- HAP B 1
- HAP C 2
- HAP D >2

N= 1714
A: 33
B: 26
C: 17
D: 9

T. Labeur/ Vogel/ Johnson; Hepatology 2019
DEFINE THE TIME TO STOP TACE!

Response matters!

18.4 months (95% C.I. 17.6, 19.2) ranging from 12.9 to 33.8

Survival by mRECIST response

Stop TACE, if there is no response after 2 treatments
Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial


Median overall survival duration (months; 95% CI)

- Lenvatinib: 13.6 (12.1-14.9)
- Sorafenib: 12.3 (10.4-13.9)

HR 0.92 (95% CI 0.79-1.06)

Median progression-free survival duration (months; 95% CI)

- Lenvatinib: 7.4 (6.9-8.8)
- Sorafenib: 3.7 (3.6-4.6)

HR 0.66 (95% CI 0.57-0.77), Log-rank p<0.0001
SECOND LINE THERAPY IN HCC

PATIENT CHARACTERISTICAS

**Regorafenib**
- 2nd line, Sorafenib discontinued due to PD
- Tolerated at least 400mg of Sorafenib for 4 weeks

**Cabozantinib**
- 2nd or 3rd line, Sorafenib discontinued due to PD or Intolerance

**Ramucirumab**
- 2nd line, Sorafenib discontinued due to PD or Intolerance
- Baseline AFP over 400 ng/ml

---

2\textsuperscript{ND} LINE THERAPY IN HCC

Increasing options!

**Objective response rate**

- Pembrolizumab
- Regorafenib
- Cabozantinib
- Ramucirumab

**Overall survival (months)**

- Pembrolizumab
- Cabozantinib
- Regorafenib
- Ramucirumab

IMMUNOTHERAPY IN HCC:
PHASE IB DATA: ATEZOLIZUMAB + BEVACIZUMAB

Data cut-off: 26 July 2018
*Data from four patients (6%) not evaluable or missing
§Baseline EHS/MVI data from one patient missing
EHS, extrahepatic spread; MVI, macrovascular invasion
NE, not evaluable or missing; SLD, sum of longest diameter

BOR (INV-RECIST v1.1) (n=73)

<table>
<thead>
<tr>
<th>Response</th>
<th>ORR, n (%)*</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>22 (30)</td>
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<tr>
<td>SD</td>
<td>33 (45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>13 (18)</td>
<td></td>
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</tr>
</tbody>
</table>

By aetiology, n/n (%)

- HBV: 11/36 (31)
- HCV: 10/23 (43)
- Non-viral: 2/14 (14)

By EHS/MVI, n/n (%)

- EHS and/or MVI: 18/64 (28)
- MVI negative: 13/32 (41)
- EHS negative: 9/22 (41)
- Neither EHS nor MVI: 5/8 (63)
IMMUNOTHERAPY IN HCC:
IMBRAVE150 PHASE III: OVERALL SURVIVAL

6-mo OS rate: 85%
6-mo OS rate: 72%
mOS: 13.2 mo
mOS: NE

Median OS (95% CI), mo:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + Bev</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>13.2 (10.4, NE)</td>
<td>13.2 mo</td>
</tr>
</tbody>
</table>

HR, 0.58 (95% CI: 0.42, 0.79)
P = 0.0006

Cheng AL et al. @EMSO Asia 2019
## Evolution of OS in advanced HCC

### mOS IN FIRST LINE TRIALS IN HCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Experimental mOS</th>
<th>Sorafenib mOS</th>
<th>Sorafenib mPFS/ mTTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHARP</td>
<td>10.2</td>
<td>9.9</td>
<td>n.r.</td>
</tr>
<tr>
<td>AP</td>
<td>7.2</td>
<td>7.2</td>
<td>3.8</td>
</tr>
<tr>
<td>SUN</td>
<td>10.2</td>
<td>9.9</td>
<td>9.9</td>
</tr>
<tr>
<td>BRISK-FL</td>
<td>9.1</td>
<td>9.1</td>
<td>9.1</td>
</tr>
<tr>
<td>LIGHT</td>
<td>9.8</td>
<td>9.8</td>
<td>8.5</td>
</tr>
<tr>
<td>SEARCH</td>
<td>8.5</td>
<td>8.5</td>
<td>8.5</td>
</tr>
<tr>
<td>CALGB 0092</td>
<td>9.9</td>
<td>9.9</td>
<td>9.0</td>
</tr>
<tr>
<td>SARAH</td>
<td>9.9</td>
<td>9.9</td>
<td>9.9</td>
</tr>
<tr>
<td>SRINEB</td>
<td>10.1</td>
<td>10.1</td>
<td>10.2</td>
</tr>
<tr>
<td>SORAMIC</td>
<td>12.1</td>
<td>12.1</td>
<td>12.1</td>
</tr>
<tr>
<td>STAH</td>
<td>12.8</td>
<td>12.8</td>
<td>12.8</td>
</tr>
<tr>
<td>REFLECT</td>
<td>13.6</td>
<td>13.6</td>
<td>13.6</td>
</tr>
<tr>
<td>CHECKMATE-459</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
</tr>
<tr>
<td>IMBRAVE150</td>
<td>17.3</td>
<td>17.3</td>
<td>17.3</td>
</tr>
</tbody>
</table>

**Note:** m OS/ months
IMMUNOTHERAPY IN HCC: many combinations on the horizon
Lenva and Pembro Phase Ib

mPFS: 9.3 months
mOS: 22.1 months

Llovet et al, ESMO 2019
SYSTEMIC HCC THERAPY IN 2020

1st line

- **Sorafenib**
  - OS: 10.7 mo (SHARP)
  - TTP: 5.5 mo (SHARP)
  - good efficacy in HCV-induced HCC and liver-limited disease

- **Lenvatinib**
  - OS: 13.6 mo (REFLECT)
  - TTP: 8.9 mo (REFLECT)
  - ORR and PFS significantly improved compared to sorafenib

- **Atezolizumab/Bevacizumab**
  - OS: n.r. (IMBRAVE150)
  - PFS: 4.2 mo (IMBRAVE 150)
  - mOS significantly longer compared to sorafenib, better side effect and QoL profile

sequence lenvatinib: 2nd line (in 75% Sorafenib)
OS: 20.8 mo (REFLECT)

2nd line

- **Regorafenib**
  - OS: 10.6 mo (RESORCE)
  - TTP: 3.2 mo (RESORCE)
  - good tolerability of sorafenib; sequence sorafenib/regorafenib: OS 28 Mo

- **Cabozantinib**
  - OS: 10.2 mo (CELESTIAL)
  - TTP: 5.4 mo (CELESTIAL)
  - efficacy in 2nd and 3rd line independent of sorafenib tolerability

- **Ramucirumab**
  - OS: 8.5 mo (REACH II)
  - TTP: 3.02 mo (REACH II)
  - AFP > 400 ng/ml required; monoclonal antibody, different side effect profile than TKI

- **Nivolumab Pembrolizumab**
  - OS Nivo: 15.6 mo (Check-040)
  - OS Pemb: 13.9 mo (Key-240)
  - no positive phase-III study; approved by FDA

Vogel and Saborowski Cancer Treatment Reviews 2020
TAKE HOME

✓ Multidisciplinary evaluation is key!

✓ **TACE** is the current standard of care for early intermediate stage HCC; right time point to switch to systemic therapies should not be missed!

✓ **SIRT** is no rescue treatment after TACE, may be alternative to TACE

✓ **IMBRAVE150** marks the transition from TKI based monotherapies to IO based combinations in the future. Atezo/ Bev will be the next standard of care in fist line.

✓ **Regorafenib, Cabozantinib and Ramucirumab** (and Lenvatinib/ Sorafenib) are options in 2nd line. Most likely regardless of 1st line treatment (my view…)

✓ **High response** rates with current systemic therapies offer new opportunities: Downstaging to local therapies & Tx/ neoadjuvant strategies

✓ Survival will increase in the future with more systemic treatment option, but deterioration of liver function remains a significant challenge in HCC
ADJUVANT CHEMOTHERAPY: BILCAP

ABC-06

OS ITT

A Intention-to-treat analysis

Number at risk (number censored)

Capecitabine group
223 (0)

195 (6)

155 (7)

165 (25)

83 (39)

56 (53)

46 (47)

Observation group
224 (0)

193 (3)

132 (5)

95 (23)

67 (34)

46 (47)

OS Per-Protocol

B Per-protocol analysis

Number at risk (number censored)

Capecitabine group
210 (0)

199 (2)

152 (3)

105 (21)

83 (36)

56 (49)

Observation group
220 (0)

190 (3)

154 (5)

92 (25)

64 (34)

44 (47)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>51.1 months (34.6-59.1)</td>
<td>0.81 (0.63-1.04)</td>
</tr>
<tr>
<td>Observation</td>
<td>36.4 months (29.7-44.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>52.7 months (40.3-NR)</td>
<td>0.75 (0.58-0.97)</td>
</tr>
<tr>
<td>Observation</td>
<td>36.1 months (29.6-44.2)</td>
<td></td>
</tr>
</tbody>
</table>

Primrose et al, Lancet Oncology 2019
**STANDART OF CARE IN 1ST LINE BILIARY TRACT CANCER**

**ABC-02 trial**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC-02</td>
<td>Valle NEJM 2010</td>
<td>5.0</td>
<td>8.1</td>
</tr>
<tr>
<td>BT-22</td>
<td>Okusaka BJC 2010</td>
<td>3.7</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Valle et al. NEJM 2010
CHEMOTHERAPY IN 2ND LInIE:

ABC-06

- First randomized 2nd line Phase III
- ASC vs mFOLFOX

Subgroups that **benefited the most** from mFOLFOX

- Platinum resistant/refractory during 1st line
- Low albumin
- Metastatic disease

**Overall survival by trial arm**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (ASC alone)</th>
<th>Arm B (ASC + mFOLFOX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Hazard Ratio</td>
<td>0.69 (95% CI 0.50-0.97)</td>
<td>0.89 (95% CI 0.70-1.13)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.031</td>
<td>0.175</td>
</tr>
<tr>
<td>Median OS</td>
<td>5.3 months</td>
<td>6.2 months</td>
</tr>
<tr>
<td>6-month survival-rate</td>
<td>35.5%</td>
<td>50.6%</td>
</tr>
<tr>
<td>12-month survival-rate</td>
<td>11.4%</td>
<td>25.9%</td>
</tr>
</tbody>
</table>

**poor prognosis subgroups**

Lamarca @ ASCO 2019
GENOMIC ALTERATIONS IN BILIARY TRACT CANCER

Adapted from Silverman, ASCO 2019
## FGFR INHIBITION IN BTC

<table>
<thead>
<tr>
<th>Medikament</th>
<th>Phase</th>
<th>ORR</th>
<th>DCR</th>
<th>mPFS</th>
<th>Patients/GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infigratinib (BGJ398)</td>
<td>II</td>
<td>18.8% (fusion)</td>
<td>83.3% (fusion)</td>
<td>5.8 mo (4.3-7.6)</td>
<td>48 FGFR2 fusion 8 mutation 3 amplification Javle, JCO 2018</td>
</tr>
<tr>
<td>Derazantinib (ARQ087)</td>
<td>I/II</td>
<td>20.7%</td>
<td>82.8%</td>
<td>5.7 mo (4.04-9.2)</td>
<td>29 FGFR2 fusion Mazzaferro, BJC 2018</td>
</tr>
<tr>
<td>INCBO54828</td>
<td>II (FIGHT)</td>
<td>24% (fusion)</td>
<td></td>
<td>A.: 6.8 mo (3.6-9.2) B: 1.4 mo C: 1.5 mo</td>
<td>A: 47 FGFR2 fusion B: 22 other FGF/FGFR GA C: 8 no FGF/FGFR GA Hollebecque, ESMO 2018</td>
</tr>
</tbody>
</table>

**Javle @ ASCO 2019**

**Vogel A @ ESMO 2019**
ClarIDHy: Study design and endpoints

- **Primary endpoint**: PFS by blinded independent radiology center (IRC)
- **Secondary endpoints included**: safety and tolerability; PFS by local review; OS; objective response rate; quality of life (QoL); pharmacokinetics/pharmacodynamics
- Sample size of ~186 patients based on hazard ratio (HR)=0.5, 96% power, 1-sided alpha=0.025
- 780 patients were screened for IDH1 mutations across 49 sites and 6 countries

---

**Key eligibility criteria**
- ≥18 years of age
- Histologically confirmed diagnosis of cholangiocarcinoma
- Centrally confirmed mIDH1* status by NGS
- ECOG PS score 0 or 1
- 1-2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function

**Pre-screening for IDH1 mutation**

**2:1 double-blind randomization (n=185)**

**Ivosidenib**
- 500 mg QD orally in continuous 28-day (±2 days) cycles (n=124)

**Placebo**
- (n=61)

**Crossover permitted at radiographic disease progression**

An independent data monitoring committee monitored the safety data throughout the study.

---

*IDH1 mutation status prospectively confirmed by NGS-based Oncomine™ Focus Assay on formalin-fixed, paraffin-embedded tumor tissue in a Clinical Laboratory Improvement Amendments-certified laboratory.*

†Assessed using ECOG-PS, EORTC QLQ-C30, EORTC QLQ-BIL21, and PGI questions.

ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC=European Organisation for Research and Treatment of Cancer; EQ-5D-5L=5-level EuroQoL 5 Dimension questionnaire; FU=fluorouracil; NGS=next-generation sequencing; PGI=Patient Global Impression; QD=once daily; QLQ-BIL21=Cholangiocarcinoma and Gallbladder Cancer module; QLQ-C30=Quality of Life Questionnaire Core 30; RECIST=Response Evaluation Criteria in Solid Tumors.
ClarlDHy: PFS by IRC

HR=0.37 (95% CI 0.25, 0.54)  
P<0.001

<table>
<thead>
<tr>
<th></th>
<th>Ivosidenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, months</td>
<td>2.7</td>
<td>1.4</td>
</tr>
<tr>
<td>6-month rate</td>
<td>32%</td>
<td>NE</td>
</tr>
<tr>
<td>12-month rate</td>
<td>22%</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Disease control rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PR+SD)</td>
<td>53%</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>(2% PR, 51% SD)</td>
<td>(0% PR, 28% SD)</td>
</tr>
</tbody>
</table>

NE=not estimable; PR=partial response; SD=stable disease.
ClariDHy: OS by intent-to-treat (ITT)

- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs. 9.7 months)
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo
  - Rank-preserving structural failure time (RPSFT)\textsuperscript{1,2} method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib
  - With the RPSFT method, the median OS with placebo adjusts to 6 months

HR=0.69 (95% CI 0.44, 1.10); P=0.06
HR=0.46 (95% CI 0.28, 0.75); P<0.001 (RPSFT-adjusted)

Number of patients at risk:

<table>
<thead>
<tr>
<th>Survival (months)</th>
<th>Ivosidenib</th>
<th>Placebo</th>
<th>Placebo (RPSFT-adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>124</td>
<td>61</td>
<td>61</td>
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<tr>
<td>2</td>
<td>117</td>
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<td>5</td>
<td>75</td>
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<td>6</td>
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<td>9</td>
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<tr>
<td>23</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td>24</td>
<td>1</td>
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<td></td>
</tr>
</tbody>
</table>

*Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier.

IMMUNOTHERAPY IN BTC

KEYNOTE-158: Biliary tract cancer

Patients
- Unresectable and/or metastatic BTC
- Progression on or intolerance to standard therapy
- ECOG PS 0 or 1
- ≥1 measurable lesion

Pembrolizumab 200 mg IV Q3W

Treat for 2 years\(^a\) or until progression,\(^b\) intolerable toxicity, or study withdrawal

Survival follow-up

7% ORR

Ueno et al.\(^a\) ESMO 2018
KEYNOTE-158 & -164: PEMBROLIZUMAB IN MSI TUMORS

Colorectal Cancer

Median (95% CI), mo
NR (26.3-NR)

OS %

No. at risk
CRC 124 114 106 97 90 86 80 77 69 34 31 10 0

Time, months

Biliary Cancer

Median (95% CI), mo
24.3 (6.5-NR)

OS %

No. at risk
Biliary 22 20 18 15 11 9 7 4 4 1 1 0 0

Time, months

Pancreatic Cancer

Median (95% CI), mo
4.0 (2.1-9.8)

OS %

No. at risk
Pancreatic 22 15 8 8 5 4 3 2 1 1 1 0 0

Time, months

ESMO VIRTUAL SUMMIT RUSSIA

Diaz et al. ESMO 2019
TAKE HOME CCA......

Adjuvant therapy:
- Xeldo can be considered

Chemotherapy:
- CisGem ist SOC in 1st line
- FOLFOX is option for 2nd line. Studies with Irinotecan are initiated>

Targeted therapies:
- IDH1/2-, HER2-, FGFR2-, BRAF directed therapies are very promising

Immunotherapy:
- MSI patients are good candidates, but we need additional marker/ combinations
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