CHEMOTHERPY IN HEPATIC TUMORS-ADVANCES IN TARGETED THERAPY
• Liver cancer
  • Fifth most common cancer
  • Second most frequent cause of cancer-related death globally
    • 854,000 new cases and 810,000 deaths per year
    • 7% of all cancers

• HCC - 85-90% of primary liver cancers

• Cholangiocarcinoma 10%
• Fibrolamellar carcinoma 0.5 - 1%

• Mesenchymal Cancers of the Liver
  • Angiosarcoma of the liver
  • Epithelioid haemangioendothelioma

• Secondary liver cancer - Tumors metastatic to the liver - more common than primary tumors

• Akinyemiju T, et al. JAMA Oncol 2017;3:1683–91;
• EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019
Liver Cancer Incidence and Mortality are Increasing

![Graph showing increasing liver cancer incidence and mortality rates from 1975 to 2017.

- Rate of New Cases
- Death Rate

SEER Database.]
Most HCC - Setting of Cirrhosis

Hep B infection
Hep C infection
Alcoholic liver disease
Nonalcoholic steatohepatitis
BCLC Staging System + Treatment Recommendations

Patient Population

- Early (BCLC A)
- Intermediate (BCLC B)
- Advanced (BCLC C)
- Terminal (BCLC D)

Treatment Recommendations

- Resection
- Transplant
- Ablation SBRT
- TACE or TARE
- First-line systemic therapy
- Second-line systemic therapy
- BSC

Unsuitable

Recurrence

Therapeutic options:

- Immune checkpoint inhibitors (ICI)
- Adoptive transfer of immune cells
- Bispecific antibodies
- Vaccines
- Oncolytic viruses

- **HCC** - Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- **Advanced CCA** - PD-1 ICl antitumor responses in a minority of select patients. Adoptive transfer- promise in trials of met disease
Hepatocellular Carcinoma - The Challenge of the Tumor Microenvironment

- **Low tumor mutational burden** - Fewer somatic mutations within the tumor, reduced number of tumor-specific neoantigens lesser adaptive immune response (Nat. Genet. 2016, 48, 500–509.)

- **Immunosuppressive microenvironment** that facilitates tumor development. “immune-tolerant” environment due to its need to be accepting of new antigens encountered from food and microbial antigens delivered from the gastrointestinal tract (Crispe, I.N. The liver as a lymphoid organ. Annu. Rev. Immunol. 2009, 27, 147–163.)

- **Anti-inflammatory mediators** can be increased in patients with cirrhosis (Cancer Res. 2005, 65, 2457–2464.)
Fig. 1  Overview of the targeted agents approved for HCC. ATEZO atezolizumab, BEV bevacizumab, CAM camrelizumab, LEN lenvatinib, PEM pembrolizumab, NIV nivolumab, IPI ipilimumab
SHARP: Frontline Sorafenib Improves Survival for Advanced HCC

- Randomized, double-blind phase III trial of sorafenib vs placebo for patients with advanced HCC, Child-Pugh A (N = 602)

**OS**

- Median OS: **10.7** vs **7.9** mos
- HR: 0.69 (95% CI: 0.55-0.87; \( P < .001 \))

**Time to Radiologic Progression**

- \( P < .001 \)
FDA-Approved Systemic Therapy for Advanced HCC

**First Line**
- Lenvatinib
- Atezolizumab + bevacizumab

**Second Line and Beyond**
- Regorafenib
- Nivolumab*
- Pembrolizumab*
- Cabozantinib
- Ramucirumab
- Nivolumab ± ipilimumab*

*Accelerated approval.
REFLECT: Frontline Lenvatinib Is Noninferior to Sorafenib for OS but Provides Better Response Rates

- Randomized, open-label, noninferiority phase III trial of lenvatinib vs sorafenib for patients with unresectable HCC, Child-Pugh A/BCLC stage B or C (N = 954)

<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</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</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</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 < .0001 vs sorafenib.

CheckMate 459: Nivolumab vs Sorafenib as First-line Therapy for Advanced HCC

- International, open-label, randomized phase III trial (minimum follow-up: 22.8 mos)

- Adults with advanced HCC; ineligible for or PD after surgical and/or locoregional therapies; Child-Pugh class A; ECOG PS 0/1; no prior systemic therapy for HCC (N = 743)

- Primary endpoint: OS
  - Predefined threshold for statistical significance: HR of 0.84 (P = .0419)

- Secondary endpoints: PFS, ORR, association between PD-L1 expression and efficacy

Nivolumab 240 mg IV Q2W (n = 371)

Sorafenib 400 mg PO BID (n = 372)

Until PD, unacceptable toxicity, consent withdrawal, or end of study


Slide credit: clinicaloptions.com
The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit.

- **ORR:** nivolumab, 15%; sorafenib, 7%
CheckMate 040: Nivolumab for Advanced HCC

Phase I/II study of Nivolumab in advanced HCC and CP B cirrhosis

- **Advanced HCC**: Child-Pugh class B7–B8
  - 49 patients (25 sorafenib naive)

- **Efficacy**
  - Tumor response (%)
    - Child-Pugh B: Response rate = 12%, Disease control rate = 55%
    - Child-Pugh A: Response rate = 20%, Disease control rate = 61%

- **Safety**
  - Treatment-related adverse events (%)
    - Grade 3/4: Child-Pugh B = 24%, Child-Pugh A = 23%
    - Leading to discontinuation: Child-Pugh B = 4%, Child-Pugh A = 6%
IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-line Treatment of HCC

- Multicenter, randomized, open-label phase III trial[1]
  - GO30140: randomized phase Ib study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)[2]

Patients with locally advanced or metastatic and/or unresectable HCC with no previous systemic therapy, Child-Pugh A, and ECOG PS ≤ 1* (N = 501)

**Atezolizumab 1200 mg Q3W + Bevacizumab 15 mg/kg Q3W**
(n = 336)

**Sorafenib 400 mg BD**
(n = 165)

- Coprimary endpoints: OS and PFS

*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ~ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

IMbrave150: OS, PFS, and Response

- **ORR by HCC-specific modified RECIST with atezolizumab + bevacizumab vs sorafenib:** 33.2% vs 13.3%; CR rate, 10.2% vs 1.9%

Median follow-up: 8.6 mos.

Finn. NEJM. 2020;382:1894.
IMbrave150: Quality of Life (Patient Reported)

Quality of life
Median TTD, Mos (95% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median TTD, Mos</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezo + bev (n = 336)</td>
<td>11.2</td>
<td>(6.0 - NE)</td>
</tr>
<tr>
<td>Sorafenib (n = 165)</td>
<td>3.6</td>
<td>(3.0 - 7.0)</td>
</tr>
</tbody>
</table>

HR: 0.63 (95% CI: 0.46-0.85)
IMbrave150: Safety

- EGD within 6 mos of initiating treatment required to evaluate for varices; varices of any size according to local standards of care.

- Upper GI bleeding rate in atezo + bev vs sorafenib groups: 7% vs 4.5%; this was consistent with historical data in other studies of bevacizumab in HCC.

≥ 10% frequency in either arm and > 5% difference between arms.

Key Warnings and Precautions for First-Line Atezolizumab/Bevacizumab

- **Atezolizumab**[^1]
  - Immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies

- **Patients with Child-Pugh B/C cirrhosis or prior organ transplant were excluded from IMbrave150**

- **Bevacizumab**[^2]
  - GI perforations
  - Surgery in last 28 days; incompletely healed wound
  - Recent hemoptysis or major bleed (variceal bleeding)
  - Fistula
  - Uncontrolled hypertension
  - > 2 g proteinuria
  - Congestive heart failure

[^1]: Atezolizumab PI.
[^2]: Bevacizumab PI.
CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

- Open-label phase I/II trial of 3 different dosing schemes of nivolumab + ipilimumab for patients with advanced HCC and prior sorafenib treatment; uninfected or infected with HBV or HCV; CP score A5-A6; ECOG PS 0/1

<table>
<thead>
<tr>
<th>Response</th>
<th>Arm A NIVO1/IPI3 Q3W (n = 50)</th>
<th>Arm B NIVO3/IPI1 Q3W (n = 49)</th>
<th>Arm C NIVO3 Q2W/IPI1 Q6W (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>16 (32)</td>
<td>15 (31)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>BOR, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4 (8)</td>
<td>3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>12 (24)</td>
<td>12 (24)</td>
<td>15 (31)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (18)</td>
<td>5 (10)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>PD</td>
<td>20 (40)</td>
<td>24 (49)</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>3 (6)</td>
<td>4 (8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>DCR, n (%)</td>
<td>27 (54)</td>
<td>21 (43)</td>
<td>24 (49)</td>
</tr>
<tr>
<td>Median TTR, mos (range)</td>
<td>2.0 (1.1-12.8)</td>
<td>2.6 (1.2-5.5)</td>
<td>2.7 (1.2-8.7)</td>
</tr>
<tr>
<td>Median DoR, mos (range)</td>
<td>17.5 (4.6 to 30.5+)</td>
<td>22.2 (4.2 to 29.9+)</td>
<td>16.6 (4.1+ to 32.0+)</td>
</tr>
</tbody>
</table>

Arm A mOS: 22.8 mos (95% CI: 9.4-NE)
Arm B mOS: 12.5 mos (95% CI: 7.6-16.4)
Arm C mOS: 12.7 mos (95% CI: 7.4-33.0)

KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

- KEYNOTE-224: open-label, single arm, phase II trial showed potential efficacy of pembrolizumab for patients with advanced HCC and previous sorafenib (ORR 17%)\(^1\)

- KEYNOTE 240: randomized, double-blind phase III trial\(^2\)

Patients with advanced HCC with intolerance to or PD on or after sorafenib; Child-Pugh A; BCLC stage B/C; ECOG PS ≤ 1; no invasion of main portal vein (N = 413)

- Pembrolizumab 200 mg Q3W + BSC (n = 278)
- Placebo + BSC (n = 135)

- Coprimary endpoints: PFS,* OS
  - Efficacy boundaries: PFS at first interim cutoff, \(P = .0020\) (primary analysis for PFS); OS at final analysis cutoff, \(P = .0174\)

- Secondary endpoints: ORR,* DoR, DCR, TTP, safety

*PFS, secondary response outcomes centrally reviewed.

Failed to reach prespecified level of statistical significance for OS and PFS

- ORR was significantly higher with pembrolizumab vs placebo (18.3% vs 4.4%; *P* = .00007), median DoR was 13.8 mos with pembrolizumab

*Primary analysis.
Finn. JCO. 2020;38:193.
## Key Phase III Trials With Immunotherapy Combinations for First-line Treatment of Advanced HCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Key Supporting Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAP-002</td>
<td>Lenvatinib + pembrolizumab vs lenvatinib</td>
<td>▪ KEYNOTE-524 (phase Ib study*): ORR 36%, † mOS 22 mos with lenvatinib + pembrolizumab (N = 104)&lt;sup&gt;[1]&lt;/sup&gt;</td>
</tr>
<tr>
<td>HIMALAYA</td>
<td>Durvalumab ± tremelimumab vs sorafenib</td>
<td>▪ Study 22 (phase I/II study*): ORR 24%, † mOS 19 mos with a single dose of tremelimumab 300 mg followed by monthly durvalumab (N = 332)&lt;sup&gt;[2]&lt;/sup&gt;</td>
</tr>
<tr>
<td>COSMIC-312</td>
<td>Cabozantinib + atezolizumab vs sorafenib</td>
<td>▪ Cabozantinib active 2L and 3L therapy for HCC (phase III CELESTIAL study); early studies in solid tumors suggest efficacy of combination&lt;sup&gt;[3,4]&lt;/sup&gt;</td>
</tr>
<tr>
<td>CheckMate 9DW</td>
<td>Nivolumab + ipilimumab vs sorafenib or lenvatinib</td>
<td>▪ CheckMate 040 (phase Ib study*): ORR up to 32%, † mOS up to 23 mos (N = 148)&lt;sup&gt;[5]&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Patients previously treated with systemic therapy included. †RECIST v1.1.

HIMALAYA TRIAL – STRIDE Tremelimumab (T) and durvalumab (D) as first-line therapy

- HIMALAYA open-label, multicentre, phase 3 study, in which pts with uHCC and no prior systemic therapy.

- Randomisation:
  - STRIDE (T 300 mg plus D 1500 mg [one dose] plus D 1500 mg every 4 weeks [Q4W]), STRIDE (N=393)
  - D (1500 mg Q4W), D (N=389),
  - S (400 mg twice daily), S (N=389)
  - or T 75 mg Q4W (4 doses) plus D 1500 mg Q4W (T75+D).
HIMALAYA TRIAL

- The primary objective - overall survival (OS) for STRIDE vs S.
- The secondary objective was OS noninferiority (NI) of D to S.
- Secondary endpoints - PFS, ORR; RECIST v.1.1, DoR, safety

RESULTS:

- OS was significantly improved for STRIDE vs S (hazard ratio [HR], 0.78; 96% [CI], 0.65–0.92; p=0.0035).
- D met the objective of OS NI to S (HR, 0.86; 96% CI, 0.73–1.03).
- ORRs were higher for STRIDE (20.1%) and D (17.0%) than for S (5.1%).
# HIMALAYA TRIAL

<table>
<thead>
<tr>
<th></th>
<th>STRIDE (n=393)</th>
<th>D (n=389)</th>
<th>S (n=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, mo</td>
<td>16.1</td>
<td>16.5</td>
<td>13.3</td>
</tr>
<tr>
<td>Deaths at DCO, %</td>
<td>66.7</td>
<td>72.0</td>
<td>75.3</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>16.4 (14.2–19.6)</td>
<td>16.6 (14.1–19.1)</td>
<td>13.8 (12.3–16.1)</td>
</tr>
<tr>
<td>24/36-mo OS rate, %</td>
<td>40.5/30.7</td>
<td>39.6/24.7</td>
<td>32.6/20.2</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>3.8 (3.7–5.3)</td>
<td>3.7 (3.2–3.8)</td>
<td>4.1 (3.8–5.5)</td>
</tr>
<tr>
<td>ORR, %</td>
<td>20.1</td>
<td>17.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Median DoR, mo</td>
<td>22.3</td>
<td>16.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Grade 3/4 TRAE, %</td>
<td>25.8</td>
<td>12.9</td>
<td>36.9</td>
</tr>
<tr>
<td>Serious TRAE, %</td>
<td>17.5</td>
<td>8.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Grade 5 TRAE, %</td>
<td>2.3</td>
<td>0.0</td>
<td>0.8</td>
</tr>
<tr>
<td>TRAE leading to discontinuation, %</td>
<td>8.2</td>
<td>4.1</td>
<td>11.0</td>
</tr>
</tbody>
</table>

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### Targeted Therapies for Patients Previously Treated With Sorafenib: Positive Phase III Trials

<table>
<thead>
<tr>
<th>Drug; Trial Name</th>
<th>Mode of Action</th>
<th>N</th>
<th>Median OS, Mos (vs Placebo)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regorafenib (RESORCE)[1]</td>
<td>Multitargeted TKI</td>
<td>573</td>
<td>10.6 vs 7.8</td>
<td>0.63 (0.50-0.79)</td>
</tr>
<tr>
<td>Cabozantinib (CELESTIAL)[2]</td>
<td>Multitargeted TKI</td>
<td>707</td>
<td>10.2 vs 8.0</td>
<td>0.76 (0.63-0.92)</td>
</tr>
<tr>
<td>Ramucirumab (REACH-2)[3]</td>
<td>Anti-VEGFR2 mAb</td>
<td>292</td>
<td>8.5 vs 7.3</td>
<td>0.71 (0.53-0.95)</td>
</tr>
<tr>
<td>Apatinib (AHELP)[4]</td>
<td>VEGFR2 inhibitor</td>
<td>393</td>
<td>8.7 vs 6.8</td>
<td>0.785 (0.617-0.998)</td>
</tr>
</tbody>
</table>

What Patients Might Be Optimal Candidates for Second-line Immunotherapy?

Based on RCTs
- Regorafenib
- Cabozantinib
- Ramucirumab
- Nivolumab
- Pembrolizumab
- Nivolumab + ipilimumab

Based on non-randomized trials or lacking prospective trial data
- Atezo + bev
- Sorafenib
- Lenvatinib
- Apatinib
Army hospital data (Jan 21 – June 22)

<table>
<thead>
<tr>
<th></th>
<th>HCC</th>
<th>Metastatic Ca GB</th>
<th>Hilar Cholangio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Outcomes in Biliary Cancers


Therapies at Hand

First-line treatment - gemcitabine with cisplatin (superior to gemcitabine monotherapy)

Triple combination therapy with folinic acid, 5-FU, and oxaliplatin more promising regimen but more toxic

Second-line therapies - combinations of chemotherapy and/or small-molecule inhibitors including VEGF inhibitors / IDH1 inhibitors / FGFR2 inhibitors
Anti-PD-1 ICIs have not yet demonstrated robust utility for CCA and GBC.

Phase II study (NCT02628067) / phase Ib study (NCT02054806) - pembrolizumab in advanced biliary tract cancer, durable antitumor activity was only noted among 6–13% of patients.

(Results from the KEYNOTE-158 and KEYNOTE-028 studies. Int. J. Cancer 2020, 147, 2190–2198)

Phase II trial (NCT02829918) - Nivolumab for advanced, refractory biliary tract cancer -- modest ORR of 11%, including one partial response, and a disease control rate of 50%.

(A Phase 2 Multi-institutional Study of Nivolumab for Patients with Advanced Refractory Biliary Tract Cancer. JAMA Oncol. 2020, 6, 888–894).
Table 1. Completed clinical trials assessing the use of immune checkpoint inhibitors (ICIs) for the treatment of biliary tract cancer.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Agent</th>
<th>Target</th>
<th>Phase</th>
<th>Patients</th>
<th>Setting</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02829918</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>2</td>
<td>54</td>
<td>Second line and subsequent</td>
<td>mPFS 3.68 months mOS 14.2 months ORR 22%</td>
</tr>
<tr>
<td>JapicCTI-153098</td>
<td>Nivolumab</td>
<td>PD-1</td>
<td>1</td>
<td>30</td>
<td>Second line and subsequent</td>
<td>mPFS 1.4 months mOS 5.2 months ORR 3%</td>
</tr>
<tr>
<td>KEYNOTE-028</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>1b</td>
<td>24</td>
<td>Pretreated (PD-L1 positive tumors)</td>
<td>mPFS 1.8 months mOS 5.7 months ORR 13%</td>
</tr>
<tr>
<td>KEYNOTE-158</td>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>2</td>
<td>104</td>
<td>Second line and subsequent</td>
<td>mPFS 2 months mOS 7.4 months ORR 5.8%</td>
</tr>
<tr>
<td>NCT01938612</td>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>1</td>
<td>42</td>
<td>Second line and subsequent</td>
<td>mPFS 2 months mOS 8.1 months ORR 4.8%</td>
</tr>
<tr>
<td>CA209-538</td>
<td>Nivolumab + Ipilimumab</td>
<td>PD-1 + CTLA4</td>
<td>2</td>
<td>39</td>
<td>Second line and subsequent</td>
<td>mPFS 2.9 months mOS 5.7 months ORR 23%</td>
</tr>
<tr>
<td>NCT01938612</td>
<td>Durvalumab + Tremelimumab</td>
<td>PD-L1 + CTLA4</td>
<td>2</td>
<td>65</td>
<td>Second line and subsequent</td>
<td>mOS 10.1 months ORR 10.8%</td>
</tr>
<tr>
<td>NCT02699514</td>
<td>Bintrafusp alfa</td>
<td>PD-L1</td>
<td>1</td>
<td>30</td>
<td>Second line and subsequent</td>
<td>mPFS 2.5 months mOS 12.5 months ORR 20%</td>
</tr>
<tr>
<td>NCT03833661</td>
<td>Bintrafusp alfa</td>
<td>PD-L1</td>
<td>2</td>
<td>159</td>
<td>Second line and subsequent</td>
<td>ORR 10.1%</td>
</tr>
<tr>
<td>JapicCTI-153098</td>
<td>Nivolumab + cisplatin/gemcitabine</td>
<td>PD-1</td>
<td>2</td>
<td>30</td>
<td>First line</td>
<td>mPFS 4.2 months mOS 15.4 months ORR 37%</td>
</tr>
</tbody>
</table>
Way ahead - BTC

- Approx 45% of biliary tract tumors express high levels of immune checkpoint inhibitors such as IDO-1, LAG-3, HAVCR2, TNFRSF9, BTLA, CD274, PDCD1, and TNFRSF4.
Future Directions and Novel Approaches

Immunotherapy beyond ICIs
- adoptive cell transfer (ACT) of immune cells.
- cytokine-induced killer (CIK)
- CAR-T immunotherapy
In Conclusion

The aggressive tumor biology, reduced tumor mutational burden, and immunosuppressive tumor microenvironment characteristic of hepatobiliary cancers have significantly delayed the development and adoption of novel immunotherapies.

ICIs are now standard of care in patients with unresectable or metastatic HCC.

Immunotherapy - valuable treatment option in select patients with CCA and GBC

Immunotherapy represents a potential avenue for developing new treatments,
THANK YOU