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# HCC EXPERTS ROUND TABLE (AMERICAS & EU)

# OVERVIEW OF KEY DATA

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**April 2020**

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This content is supported by an Independent Educational Grant from Roche.

**Disclosures:**

Prof. Dr. Peter Galle has received honoraria from the following: Bayer, Bristol-Myers Squibb, MSD, AstraZeneca, Lilly, Ipsen, Roche, Sirtex, SillaJen.

# EXECUTIVE SUMMARY

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- The **HCC Experts Round Table** took place as a virtual meeting on **16 April 2020**
- With **7 Experts from the Americas and EU:**
  - 1x HCC patient advocate
  - 1x Payer/health economics expert
  - 5x Physicians (representing hepatology, oncology, and radiology)
- **21 questions** discussed:
  - 6 questions related to **standard of care in advanced 1L HCC** (sorafenib and lenvatinib)
  - 6 questions related to the **management of advanced HCC patients** (e.g. clinical setting, management tumour board)
  - 8 questions related to **IMbrave150 data** and potential impact in clinical practice
  - 1 question requesting **additional comments**
- **Next step:** Building a manuscript to reflect consensus outcomes

1L, first-line; HCC, hepatocellular carcinoma

# INTRODUCTION AND TREATMENT OVERVIEW OF ADVANCED HCC

# HEPATOCELLULAR CARCINOMA (HCC): OVERVIEW

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- The **fourth most common** cause of cancer-related death worldwide[1]
- HCC accounts for **>80% of primary liver cancers** worldwide[1]
- Chronic HBV and HCV infection are the most important causes of HCC and account for **80% of HCC cases globally**[1]
- Alcoholic cirrhosis is the **second most common risk factor** for HCC in the USA and Europe[1]
- **Staging of HCC** is important to determine outcome and planning of optimal therapy and **BCLC is the current accepted staging system** as follows:[2]

| | BCLC staging | Survival rate without therapy | Standard of care treatment |
|---|---|---|---|
| Early and intermediate HCC | Stage 0-A | >5 years | Ablation, resection, transplantation |
| | Stage B | >2.5 years | Chemoembolisation (TACE) |
| Advanced HCC | Stage C | >1 year | Systemic therapy |
| | Stage D | 3 months | Best supportive care |

BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolisation


1. Yang JD, et al. Nat Rev Gastroenterol Hepatol 2019;16:589-604
2. Bruix J, et al. Nat Rev Gastroenterol Hepatol 2019;16:617-30

# SYSTEMIC TREATMENT SEQUENCING FOR BCLC STAGE C ADVANCED HCC

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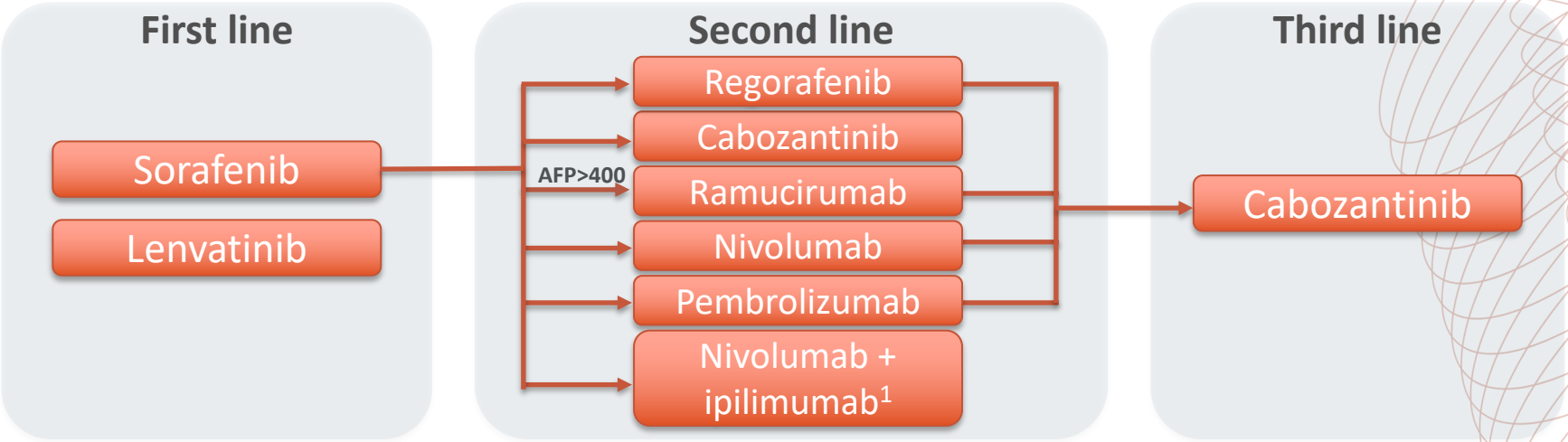
- **Targeted first-line therapies**
  - Oral multikinase inhibitors: **sorafenib** and **lenvatinib**
- **Targeted second-line therapies**
  - Multikinase inhibitor: **regorafenib** = standard of care
  - Multikinase inhibitor: **cabozantinib**
  - Human immunoglobulin G1 monoclonal antibody against VEGFR-2: **ramucirumab**
  - PD-1/PD-L1 inhibitors: **nivolumab, pembrolizumab**
  - Immune therapy combination: **nivolumab + ipilimumab**[1]




AFP, Alpha-Fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; USPI, US prescribing information; VEGFR-2, vascular endothelial growth factor receptor 2
Source: Bruix J, et al. Nat Rev Gastroenterol Hepatol 2019;16:617-30
[1]nivolumab + ipilimumab combination was approved by the US FDA in March 2020 (refer to the USPI of the respective drugs)

# SORAFENIB / LENVATINIB EFFICACY AND SAFETY DATA IN 1L FOR ADVANCED HCC PATIENTS

# SORAFENIB EFFICACY DATA

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**Based on results from:**

**SHARP** (NCT00105443): phase 3, international, multi-centre, randomised, double blind, placebo-controlled study in 602 patients with hepatocellular carcinoma

**Primary endpoint:** OS **Secondary endpoint:** TTP

**Population enrolled:** BCLC stage (stage B: 18.1% vs. 16.8%; stage C: 81.6% vs. 83.2%; stage D: <1% vs. 0%) in sorafenib and placebo respectively

| Efficacy parameter | Sorafenib (n=299) | Placebo (n=303) | P-value | HR (95% CI) |
|---|---|---|---|---|
| Median OS, months (95% CI) | 10.7 (9.4, 13.3) | 7.9 (6.8, 9.1) | 0.00058 | 0.69 (0.55, 0.87) |
| Median TTP, months (95% CI) | 5.5 (4.1, 6.9) | 2.8 (2.7, 3.9) | 0.000007 | 0.58 (045, 0.74) |

**Formulation:** Film-coated tablets 200 mg

**Recommended daily dose:** 400 mg (2 x 200 mg tablets) twice daily

BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HR, hazard ratio; OS, overall survival; SmPC, summary of product characteristics; TTP, time to progression; USPI, US prescribing information

Sources: Sorafenib SmPC November 2019, sorafenib USPI April 2020

# LENVATINIB EFFICACY DATA

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## Based on results from:

**REFLECT** (NCT01761266): phase 3, international, multi-centre, open-label, randomised study in 954 patients with hepatocellular carcinoma

→ Non inferiority assessment of lenvatinib vs. sorafenib for OS

**Primary endpoint:**

OS

**Secondary endpoints:**

PFS, ORR (mRECIST and RECIST v1.1)

**Population enrolled:**

BCLC stage B: 20%; stage C: 80%

**Formulation:**

Hard capsules 4 mg or 10 mg

**Recommended dose daily:**

12 mg (body weight ≥60 kg)

or 8 mg (<60 kg)

| Efficacy parameters | lenvatinib | sorafenib |
|---|---|---|
| | N= 478 | N=476 |
| **Overall Survival** | | |
| Number of deaths (%) | 351 (73) | 350 (74) |
| Median OS in months (95% CI) | 13.6 (12.1, 14.9) | 12.3 (10.4, 13.9) |
| Hazard Ratio (95% CI) | 0.92 (0.79, 1.06) | |
| **Progression-Free Survival (mRECIST)** | | |
| Number of Events (%) | 311 (65) | 323 (68) |
| Median PFS in months (95% CI) | 7.3 (5.6, 7.5) | 3.6 (3.6, 3.7) |
| Hazard Ratio (95% CI) and P-value | 0.64 (0.55, 0.75) ; p<0.001 | |
| **Objective Response Rate (mRECIST)** | | |
| Objective response rate | 41% | 12% |
| Complete responses, n (%) | 10 (2.1) | 4 (0.8) |
| Partial responses, n (%) | 184 (38.5) | 55 (11.6) |
| 95% CI | (36%, 45%) | (10%, 16%) |
| P-value | p<0.001 | |
| **Progression-Free Survival (RECIST 1.1)** | | |
| Number of Events (%) | 307 (64) | 320 (67) |
| Median PFS in months (95% CI) | 7.3 (5.6, 7.5) | 3.6 (3.6, 3.9) |
| Hazard Ratio (95% CI) | 0.65 (0.56, 0.77) | |
| **Objective Response Rate (RECIST 1.1)** | | |
| Objective response rate | 19% | 7% |
| Complete responses, n (%) | 2 (0.4) | 1 (0.2) |
| Partial responses, n (%) | 88 (18.4) | 30 (6.3) |
| 95% CI | (15%, 22%) | (4%, 9%) |

CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; mRECIST, modified Response evaluation criteria in solid tumours; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response evaluation criteria in solid tumours

Sources: Lenvatinib SmPC November 2019, lenvatinib USPI February 2020

# SORAFENIB AND LENVATINIB SAFETY DATA IN HCC PATIENTS

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| Most common adverse reactions (≥20%) | |
|---|---|
| Sorafenib-treated patients in **SHARP** trial | diarrhoea – fatigue – hand-foot skin reaction – rash – weight loss – decreased appetite – nausea – abdominal pain |
| Lenvatinib-treated patients in **REFLECT** trial | hypertension – fatigue – diarrhoea – decreased appetite – arthralgia/myalgia – decreased weight - abdominal pain – palmar-plantar erythrodysesthesia syndrome – proteinuria – dysphonia – haemorrhagic events – hypothyroidism – nausea |

**Further and more detailed information about the safety profile of both products and their management can be found in the European SmPC and USPI**

HCC, hepatocellular carcinoma; SmPC, summary of product characteristics; USPI, US prescribing information

Sources: Sorafenib SmPC November 2019, sorafenib USPI April 2020, lenvatinib SmPC November 2019, lenvatinib USPI February 2020

# IMbrave150:
# A STUDY OF ATEZOLIZUMAB IN COMBINATION WITH BEVACIZUMAB COMPARED WITH SORAFENIB IN PATIENTS WITH UNTREATED LOCALLY ADVANCED OR METASTATIC HEPATOCELLULAR CARCINOMA

**ClinicalTrials.gov Identifier: NCT03434379**

# IMbrave150 CLINICAL TRIAL DESIGN

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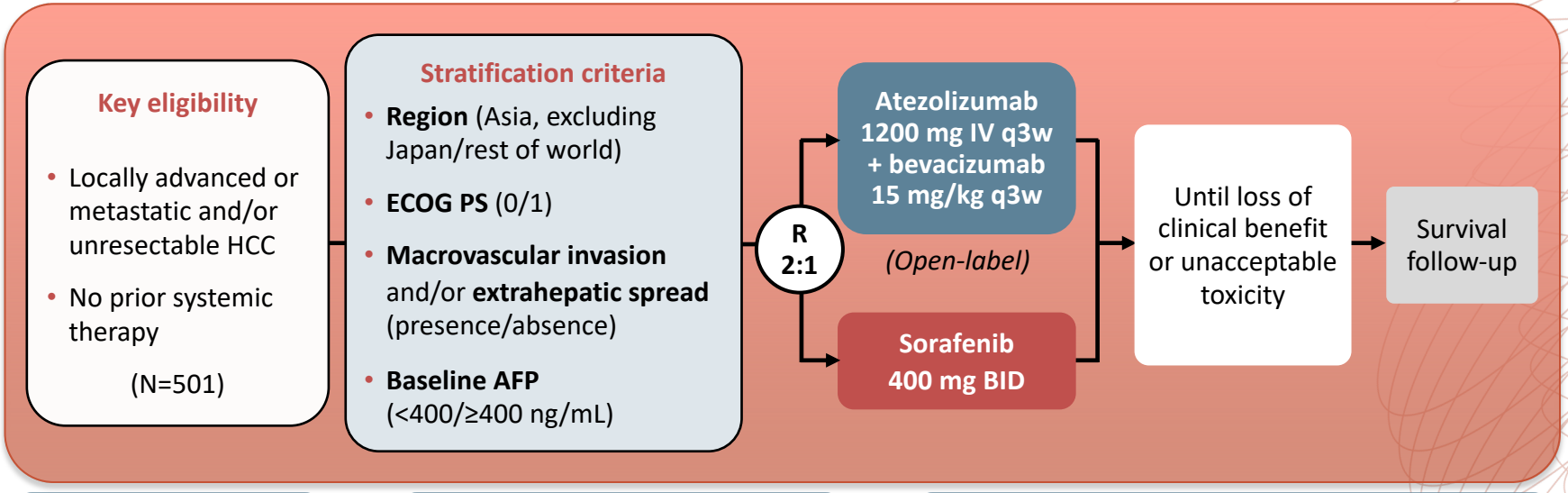
- Phase 3 trial assessing combination therapy with the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab vs. standard of care sorafenib in 1L advanced HCC




**Co-primary endpoints**
- OS
- IRF-assessed PFS per RECIST 1.1

**Secondary endpoints include**
- IRF-assessed ORR per RECIST 1.1 and HCC mRECIST
- PROs

**Exploratory PRO endpoints**
- TTD of symptoms
- Patients (%) with clinically meaningful deterioration in QoL, physical and role functioning

1L, first line; AFP, alpha-fetoprotein; BID, twice a day; ECOG PS; Eastern Cooperative Oncology Group performance status; HCC; hepatocellular carcinoma; IFR; independent review facility; IV, intravenous; mRECIST, modified RECIST; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression free survival; PRO: patients-reported outcome; q3w, every 3 weeks; QoL, quality of life; RECIST, response evaluation criteria in solid tumours; TTD, time to treatment discontinuation; VEGF, vascular endothelial growth factor

Galle PR, et al. J Clin Oncol 2020;38(suppl 4:abstract 476)

# IMbrave150 CLINICAL TRIAL EFFICACY RESULTS

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- Data cut-off date: 29 August 2019; median survival follow-up: 8.6 months

| | Atezolizumab + bevacizumab | Sorafenib |
|---|---|---|
| Median OS, months (95% CI) | NE | 13.2 (10.4-NE) |
| OS, HR (95% CI) | 0.58 (0.42, 0.79) | |
| P-value | 0.0006 | |
| Median PFS, months (95% CI) IRF RECIST v1.1 | 6.8 (5.7, 8.3) | 4.3 (4.0, 5.6) |
| PFS, HR (95% CI) | 0.59 (0.47, 0.76) | |
| P-value | <0.0001 | |
| ORR, IRF RECIST v1.1 | 27% | 12% |
| P-value | <0.0001 | |

CI, confidence interval; HR, hazard ratio; IRF, independent review facility; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours

Cheng A-L, et al. Ann Oncol 2019;30(suppl 9;abstract LBA3); Galle PR, et al. J Clin Oncol 2020;38(suppl 4:abstract 476)

# IMbrave150 CLINICAL TRIAL SAFETY AND QOL RESULTS

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- Safety Data presented by Cheng et al. at ESMO Asia in 2019

| | Atezolizumab + bevacizumab | Sorafenib |
|---|---|---|
| Grade 3-4 AEs | 57% | 55% |
| Grade 5 AEs | 5% | 6% |

- PRO endpoints data presented by Galle et al. at ASCO GI in 2020:
  - Three QoL instruments were used EORTC QLQ-C30, EORTC QLQ-HCC18 and EQ-5D-5L:
    - QoL
    - Functioning: physical, role
    - Symptoms: fatigue, pain, appetite loss, diarrhoea, jaundice
  - Conclusion: Clinically meaningful benefits in key aspects of the patient experience (QoL, functioning, key symptoms) with atezolizumab + bevacizumab vs. sorafenib

AE, adverse event; ASCO GI, Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology; EORTC, European Organisation for Research and Treatment of Cancer; ESMO, European Society for Medical Oncology; PRO, patient-reported outcome; QLC-C30, cancer-specific quality of life questionnaire; QLQ-HCC18, hepatocellular-carcinoma-specific quality of life questionnaire; QoL, quality of life

Cheng A-L, et al. Ann Oncol 2019;30(suppl 9;abstract LBA3); Galle PR, et al. J Clin Oncol 2020;38(suppl 4:abstract 476)

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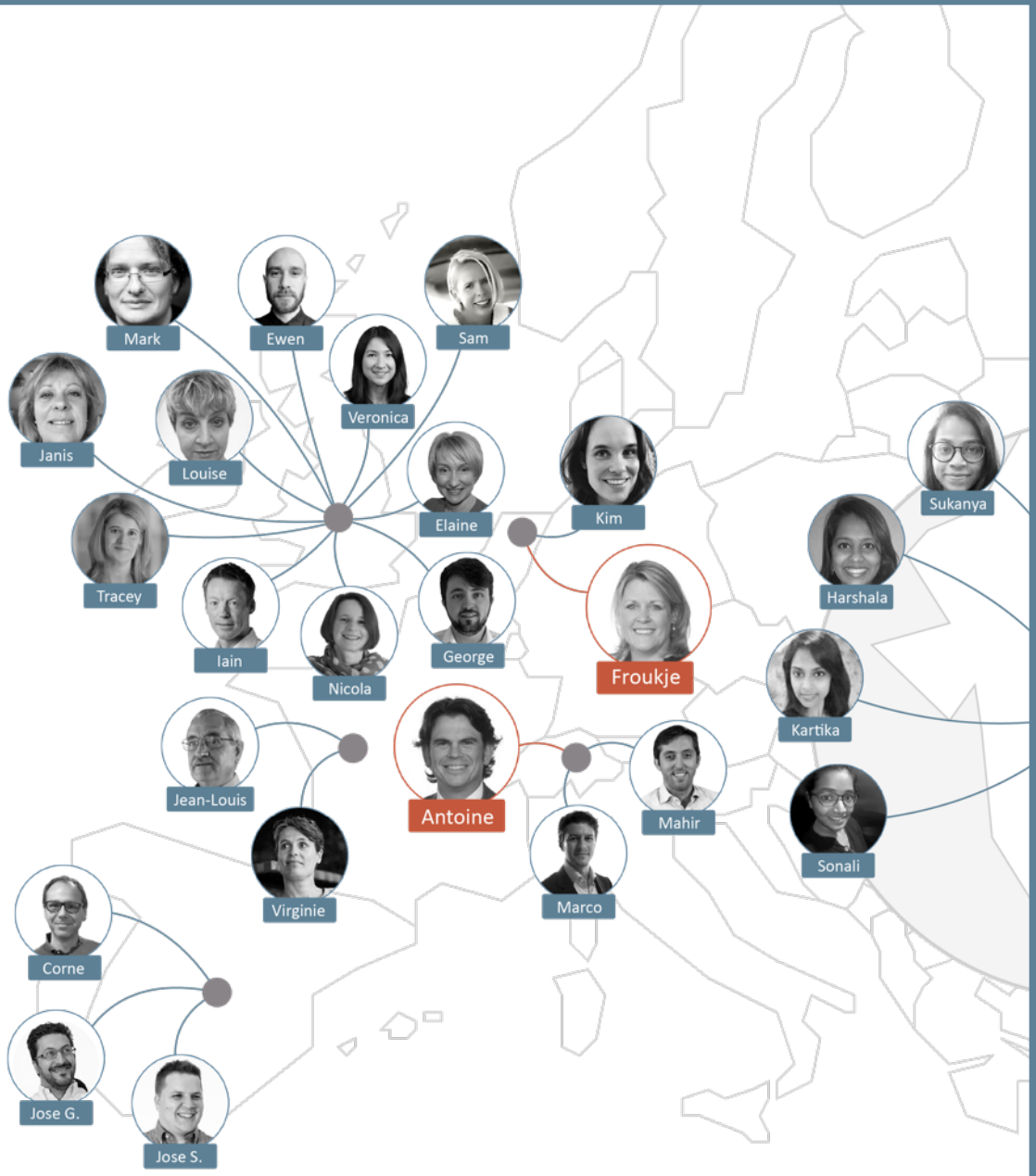


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