Treatment Landscape Comparison Guide

Scientific Background

- Primary liver cancer is the 6th most common cancer and 3rd most common cause of cancer-related deaths worldwide[1]
- Hepatocellular carcinoma (HCC) accounts for 75-85% of all primary liver cancer cases[1]
- Sorafenib is a recommended first-line treatment for patients with unresectable, intermediate- to advanced-stage HCC[2,3]
- Following treatment with sorafenib, recommended second-line therapies include pembrolizumab, cabozantinib, ramucirumab, and regorafenib, among others[2,3]

Purpose of This Guide

- To provide an overview of second-line systemic therapy options for HCC following treatment with sorafenib
- To summarize efficacy and safety data from key phase 3 trials of four drugs used in second-line treatment of HCC
- To compare primary and secondary endpoints across these clinical trials

How to Use This Guide

- For an optimal viewing experience, please open this PDF on a desktop or laptop. Select the single-page layout option in your PDF viewer to ensure full interactivity
- From the **Overview page**, click on a study name to view the trial summary or on an endpoint to view a comparison chart
- Use the interactive links provided on each page to navigate between trial summaries and endpoint comparison charts

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

1. Sung H, et al. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660. 2. Vogel A, et al. *Ann Oncol*. 2025;36(5):491-506. doi:10.1016/j.annonc.2025.02.006. 3. Benson AB, et al. *J Natl Compr Canc Netw*. 2021;19(5):541-565. doi:10.6004/jnccn.2021.0022

Overview: Key Phase 3 Trials in the Treatment of Unresectable HCC Following First-Line Sorafenib

THERAPEUTIC AGENTS	**Pembrolizumab** Monoclonal antibody (anti-PD-1)[1]	**Cabozantinib** Tyrosine kinase inhibitor (against VEGFR, MET, AXL)[2]	**Ramucirumab** Monoclonal antibody (anti-VEGFR2)[3]	**Regorafenib** Multikinase inhibitor (against VEGFR1-3, PDGFRB, KIT, RET, RAF-1)[4,5]
PHASE 3 STUDIES	KEYNOTE-240	CELESTIAL	REACH-2	RESORCE
	 PubMed Link	 PubMed Link	 PubMed Link	 PubMed Link
COMPARE ENDPOINTS	OS	PFS	TTP	RESPONSE RATES

HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

1. Merle P, et al. *Liver Cancer*. 2023;12(4):309-320. doi:10.1159/000529636. 2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002. 3. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9. 4. Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9. 5 Benson AB, et al. *J Natl Compr Canc Netw*. 2021;19(5):541-565. doi:10.6004/jnccn.2021.0022

KEYNOTE-240

Pembrolizumab vs placebo

Study Information

Title: Study of Pembrolizumab (MK-3475) vs. Best Supportive Care in Participants With Previously Systemically Treated Advanced Hepatocellular Carcinoma (MK-3475-240/KEYNOTE-240)[1]
ID: NCT02702401[1]
Sponsor: Merck Sharp & Dohme LLC[1]
Enrolment: May 31, 2016 to Nov 23, 2017[2]
Study Design: Phase 3, randomized, double-blind, placebo-controlled study conducted at 119 medical centers in 27 countries[2]

Intervention[2]

Randomized Population (2:1): N=413[a]
Pembrolizumab (200 mg IV q3w): n=278
Placebo (IV q3w): n=135

[a] All patients received sorafenib as the only prior systemic therapy for HCC, which was discontinued because of intolerance or radiographic progression.

Patient Characteristics[2]

Age: 67 vs 65 years
Male: 81.3 vs 83%
BCLC Stage
- B: 20.1 vs 21.5%
- C: 79.9 vs 78.5%

Child-Pugh Score
- A5: 63.3 vs 63.7%
- A6: 36.3 vs 34.8%
- B7: 0.4 vs 1.5%

ECOG PS
- 0: 58.3 vs 52.6%
- 1: 41.7 vs 47.4%

Region
- Asia w/o Japan: 24.1 vs 23.0%
- European Union: 34.5 vs 31.9%
- Japan: 14.4 vs 14.1%
- United States: 7.6 vs 11.9%
- Other[b]: 19.4 vs 19.3%

[b] Includes Argentina, Australia, Canada, Chile, Colombia, Israel, Mexico, Norway, Russian Federation, and Turkey

Patient Characteristics (cont'd)[2]

Etiology
- HBV: 25.9 vs 21.5%
- HCV: 15.5 vs 15.6%
- Alcohol use: 57.2 vs 58.5%

Extrahepatic disease
- Yes: 70.1 vs 68.9%

MVI
- Yes: 12.9 vs 11.9%

Baseline AFP, ng/mL
- <200: 53.6 vs 57.0%
- ≥200: 46.4 vs 43.0%

Ascites
- None: 100 vs 100%

Duration of Prior Sorafenib Treatment[2]

Median (range): 4.6 (0.1-56.6) vs 4.9 (0.3-101.4) months

Reason for Discontinuation of Sorafenib
- Intolerance: 12.9 vs 13.3%
- PD: 87.1 vs 86.7%

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; PD, progressive disease.

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1. NCT02702401. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02702401. Accessed August 23, 2025. 2. Finn RS, et al. *J Clin Oncol*. 2020;38(3):193-202. doi:10.1200/JCO.19.01307

KEYNOTE-240

Pembrolizumab vs placebo

OS (Co-1° endpoint) — Compare

Median: 13.9 vs 10.6 months
HR 0.771; 95% CI, 0.617-0.964[a]
Median follow-up: 39.6 vs 39.8 months

Prespecified statistical significance criteria for OS superiority compared with placebo were not met at the final analysis.

24-month OS rate: 28.8 vs 20.4%
36-month OS rate: 17.7 vs 11.7%

Subgroup Analysis by Baseline Characteristics
HRs for OS favoured pembrolizumab over placebo and were generally consistent across predefined subgroups.

[a] Estimated using stratified Cox regression; p-value from stratified log-rank test. 95% CIs are descriptive.

PFS[b] (Co-1° endpoint) — Compare

Median: 3.0 vs 2.8 months
HR 0.718; 95% CI, 0.571-0.903[c]

Prespecified statistical significance criteria for PFS superiority compared with placebo were not met at the final analysis.

24-month PFS rate: 11.6 vs 4.8%
36-month PFS rate: 8.9 vs 0%

Subgroup Analysis by Baseline Characteristics
HRs for PFS favoured pembrolizumab over placebo and were generally consistent across predefined subgroups.

[b] Per RECIST v1.1 by BICR.
[c] For PD or death. Estimated using stratified Cox regression; p-value from stratified log-rank test. 95% CIs are descriptive.

TTP[d] (2° endpoint) — Compare

Median (range): 3.8 (2.8-4.4) vs 2.8 (1.6-2.9) months

24-month TTP rate: 14.6 vs 6.8%
36-month TTP rate: 11.2 vs 0%

[d] Per RECIST v1.1 by BICR.

Response Rates[e] (2° endpoint) — Compare

Pembrolizumab (n=278) vs placebo (n=135)
ORR: 18.3 vs 4.4%
- CR: 3.6 vs 0%
- PR: 14.7 vs 4.4%

SD: 43.9 vs 48.9%
DCR: 62.2 vs 53.3%
PD: 32.7 vs 42.2%

Median TTR (range): 2.7 (1.2-16.9) vs 2.9 (1.1-6.9) months

[e] Per RECIST v1.1 by BICR.

DOR (2° endpoint)

Median (range): 13.9 (1.5-41.9) vs 15.2 (2.8-21.9) months[f]

DOR ≥12 months: 53.7 vs 50.0%[g]

[f] Assessed in responders who had a best overall response as confirmed CR or PR by product-limit (Kaplan-Meier) method for censored data.
[g] From product-limit (Kaplan-Meier) method for censored data for patients with confirmed response.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTP, time to progression; TTR, time to response.

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Merle P, et al. *Liver Cancer*. 2023;12(4):309-320. doi:10.1159/000529636

KEYNOTE-240

Pembrolizumab vs placebo

Safety

Safety Population
Pembrolizumab (n=279) vs placebo (n=134)

Median Duration of Treatment
Pembrolizumab 3.48 (range, 0.03-37.1) months
Placebo 2.83 (range, 0.03-24.2) months

Any-Grade All-Cause AE: 96.8 vs 91.0%

Grade 3 or 4 All-Cause AE: 53.4 vs 46.3%

Most Common All-Cause Grade 3 or 4 AE
(reported in ≥5% of patients in either arm)
Increased AST 13.6 vs 7.5%
Increased blood bilirubin 7.5 vs 6.0%
Anemia 3.9 vs 9.0%
Increased ALT 6.8 vs 3.0%
Ascites 7.9 vs 6.0%

Rate of Discontinuation Due to All-Cause AE:
18.6 vs 9.7%

Most Common AE Leading to Discontinuation
Ascites 4.7 vs 2.2%
Increased AST 1.8 vs 0.7%
Increased blood bilirubin 1.4 vs 1.5%
Esophageal varices hemorrhage 1.4 vs 0%

Deaths Due to All-Cause AE: 2.5 vs 3.0%

Safety (cont'd)

Any-Grade TRAE: 61.3 vs 48.5%

Most Common Any-Grade TRAE
(reported in ≥10% of patients in either arm)
Pruritus 14.0 vs 5.2%
Fatigue 10.0 vs 14.2%

Grade 3 or 4 TRAE: 19.4 vs 7.5%

Most Common Grade 3 or 4 TRAE
(reported in ≥1.5% of patients in either arm)
Increased ALT 5.7 vs 1.5%
Increased AST 3.9 vs 1.5%

Rate of Discontinuation Due to TRAE: 6.8 vs 0.7%

Most Common TRAE Leading to Discontinuation in the Pembrolizumab Arm
Increased ALT 0.7%
Increased AST 0.7%
Increased blood bilirubin 0.7%
Immune-mediated hepatitis 0.7%
Interstitial lung disease 0.7%

The only TRAE that led to discontinuation in the placebo arm was anemia.

No TRAE that led to death occurred in the follow-up period.

Safety (cont'd)

Any-Grade All-Cause Immune-Mediated AE:
17.9 vs 8.2%

Grade 3 or 4 All-Cause Immune-Mediated AE:
7.2 vs 0.7%

Most Common Any-Grade All-Cause Immune-Mediated AE
(reported in ≥3% of patients in either arm)
Hypothyroidism 5.0 vs 5.2%
Pneumonitis 3.6 vs 0.7%

Rate of Discontinuation Due to Immune-Mediated AE: 3.6 vs 0%

Administration of Steroids for Possible Immune-mediated AE: 8.2 vs 0.7%

Immune-mediated Hepatitis Events: 3.6 vs 0%
No viral hepatitis flare events were reported.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

Merle P, et al. *Liver Cancer*. 2023;12(4):309-320. doi:10.1159/000529636

CELESTIAL

Cabozantinib vs placebo

Study Information

Title: Study of Cabozantinib (XL184) vs Placebo in Subjects With Hepatocellular Carcinoma Who Have Received Prior Sorafenib (CELESTIAL)[1]
ID: NCT01908426[1]
Sponsor: Exelixis[1]
Enrolment: Sept 2013 to Sept 2017[2]
Study Design: Phase 3, randomized, double-blind, placebo-controlled study conducted at 95 medical centers in 19 countries[2]

Intervention[2]

Randomized Population (2:1): N=707[a]
Cabozantinib (60 mg po qd): n=470
Placebo (po qd): n=237

[a] All patients received previous treatment with sorafenib and had disease progression after at least one systemic treatment for HCC. Patients could have received up to two previous systemic treatments.

Patient Characteristics[2]

Age: 64 vs 64 years
Male: 81 vs 85%
BCLC Stage
- B: 9 vs 10%
- C: 91 vs 90%

Child-Pugh Score
- A: 98 vs 99%
- B: 1 vs 1%
- Missing: <1 vs 0%

ECOG PS
- 0: 52 vs 55%
- 1: 48 vs 45%
- 2: <1 vs 0%

Region
- Asia[b]: 25 vs 25%
- Europe: 49 vs 46%
- Canada and United States: 23 vs 25%
- Australia and New Zealand: 3 vs 5%

Etiology
- HBV: 38 vs 38%
- HCV: 24 vs 23%
- HBV and HCV: 2 vs 2%
- Alcohol use: 24 vs 16%
- Non-alcoholic steatohepatitis: 9 vs 10%

[b] Includes Hong Kong, South Korea, Singapore, and Taiwan

Patient Characteristics (cont'd)[2]

Extrahepatic disease
- Yes: 79 vs 77%

MVI
- Yes: 27 vs 34%

AFP, ng/mL
- <400: 59 vs 57%
- ≥400: 41 vs 43%

Number of prior systemic treatments for advanced HCC
- 0: 1 vs 0%
- 1: 71 vs 73%
- 2: 28 vs 26%
- ≥3: <1 vs <1%

Duration of Prior Sorafenib Treatment[2]

Median: 5.3 vs 4.8 months

Reason for Discontinuation of Sorafenib
- PD: 100 vs 100%

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MVI, macrovascular invasion; PD, progressive disease.

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1. NCT01908426. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT01908426. Accessed August 23, 2025. 2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002

CELESTIAL

Cabozantinib vs placebo

OS[a] (1° endpoint) — Compare

Median: 10.2 vs 8.0 months
HR 0.76; 95% CI, 0.63-0.92; p=0.005[b]
Median follow-up: Not explicitly reported

Subgroup Analysis by Baseline Characteristics
HRs for OS across predefined subgroups were variable.

In patients whose only previous systemic therapy was sorafenib, median OS

Only previous systemic therapy was sorafenib
Median: 11.3 vs 7.2 months
HR 0.70; 95% CI, 0.55-0.88

[a] Defined as time from randomization to death from any cause.
[b] Estimated using univariate Cox regression; p-value from stratified log-rank test.

PFS[c] (2° endpoint) — Compare

Median: 5.2 vs 1.9 months
HR 0.44; 95% CI, 0.36-0.52; p<0.001[d]

Subgroup Analysis by Baseline Characteristics
HRs for PFS favoured cabozantinib over placebo and were consistent across predefined subgroups.

Only previous systemic therapy was sorafenib
Median: 5.5 vs 1.9 months
HR 0.40; 95% CI, 0.32-0.50

[c] Determined by the investigator according to RECIST v1.1.
[d] Estimated using univariate Cox regression; p-value from stratified log-rank test.

Response Rates[e] (2° endpoint) — Compare

Cabozantinib (n=470) vs placebo (n=237)
ORR: 4 vs <1%; p=0.009[f]
- CR: 0 vs 0%
- PR: 4 vs <1%

SD: 60 vs 33%
DCR: 64 vs 33%
PD: 21 vs 55%
NE: 15 vs 11%

[e] Determined by the investigator according to RECIST v1.1.
[f] Per Cochran-Mantel-Haenszel test.

CI, confidence interval; HR, hazard ratio; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

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Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002

CELESTIAL

Cabozantinib vs placebo

Safety

Safety Population
Cabozantinib (n=467) vs placebo (n=237)

Median Duration of Treatment
Cabozantinib 3.8 months
Placebo 2.0 months

Rate of Discontinuation Due to TRAE: 16 vs 3%

Most Common AE Leading to Discontinuation
(reported in >1.0% of patients in the cabozantinib arm; actual values not reported)
PPE
Fatigue
Decreased appetite
Diarrhea
Nausea

Any-Grade Any-Cause AE: 99 vs 92%

Grade 3 or 4 Any-Cause AE: 68 vs 36%

Most Common Grade 3 or 4 Any-Cause AE
(reported in ≥10% of patients in either arm)
PPE 17 vs 0%
Hypertension 16 vs 2%
Increased AST 12 vs 7%
Fatigue 10 vs 4%
Diarrhea 10 vs 2%

Safety (cont'd)

Serious Any-Grade Any-Cause AE: 50 vs 37%

Deaths for any reason within 30 days of treatment discontinuation:
Cabozantinib: 55 patients (12%)
Placebo: 28 patients (12%)

Deaths were most commonly related to disease progression.

Deaths Due to TRAE:
Cabozantinib: 6 patients
Hepatic failure, n=1
Bronchoesophageal fistula, n=1
Portal-vein thrombosis, n=1
Upper gastrointestinal hemorrhage, n=1
Pulmonary embolism, n=1
Hepatorenal syndrome, n=1

Placebo: 1 patient
Hepatic failure, n=1

AE, adverse event; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; TRAE, treatment-related adverse event.

Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002

REACH-2

Ramucirumab vs placebo

Study Information

Title: A Study of Ramucirumab (LY3009806) Versus Placebo in Participants With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (REACH-2)[1]
ID: NCT02435433[1]
Sponsor: Eli Lilly and Company[1]
Enrolment: July 26, 2015 to Aug 30, 2017[2]
Study Design: Phase 3, randomized, double-blind, placebo-controlled study conducted at 92 hospitals, clinics, and medical centers in 20 countries[2]

Intervention[2]

Randomized Population (2:1): N=292[a]
Ramucirumab (8 mg/kg IV q14d): n=197
Placebo (IV q14d): n=95

[a] All patients received sorafenib as the only prior systemic therapy for HCC, which was discontinued because of intolerance or disease progression.

Patient Characteristics[2]

Age: 64 vs 64 years
Male: 78 vs 83%
BCLC Stage
- B: 17 vs 21%
- C: 83 vs 79%

Child-Pugh Score
- A5: 62 vs 57%
- A6: 38 vs 43%

ECOG PS
- 0: 57 vs 58%
- 1: 43 vs 42%

Region
- Americas, Europe, Australia, Israel: 51 vs 53%
- Asia excluding Japan: 28 vs 28%
- Japan: 21 vs 19%

Etiology
- HBV: 36 vs 38%
- HCV: 24 vs 29%
- Alcohol use: 24 vs 22%
- Non-alcoholic steatohepatitis: 10 vs 4%

Patient Characteristics (cont'd)[2]

Extrahepatic disease
- Yes: 72 vs 74%

MVI
- Yes: 36 vs 35%

Median AFP (IQR), ng/mL[b]
- Ramucirumab: 3920 (range, 1175-20,000)
- Placebo: 2741 (range, 1178-11,681)

Ascites
- None: 94 vs 93%
- Mild: 6 vs 7%

[b] Potential imbalance between groups was noted by the authors.

Duration of Prior Sorafenib Treatment[2]

Median (IQR): 4.1 (2.3-8.4) vs 4.1 (2.8-7.2) months

Reason for Discontinuation of Sorafenib
- Intolerance: 16 vs 20%
- PD: 84 vs 80%

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; MVI, macrovascular invasion; PD, progressive disease.

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1. NCT02435433. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02435433. Accessed August 23, 2025. 2. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9

REACH-2

Ramucirumab vs placebo

OS[a] (1° endpoint) — Compare

Median: 8.5 vs 7.3 months
HR: 0.710; 95% CI, 0.531-0.949; p=0.0199[b]
Median follow-up: 7.6 months (IQR, 4.0-12.5)

Subgroup Analysis by Baseline Characteristics
Most subgroups analyzed for OS showed a benefit with ramucirumab compared with placebo, except for that in female patients, which included only 16 patients in the placebo group.

Post-hoc Analysis by Baseline AFP
When adjusted for baseline AFP, median OS was significantly longer in the ramucirumab arm vs placebo, indicating that AFP remained a strong negative prognostic factor for OS.

[a] Defined as time from randomization to death from any cause.
[b] Estimated using stratified Cox regression; p-value from stratified log-rank test.

PFS[c] (2° endpoint) — Compare

Median: 2.8 vs 1.6 months
HR: 0.452; 95% CI, 0.339-0.603; p<0.0001[d]

Subgroup Analysis by Baseline Characteristics
All subgroup analyses for PFS favoured treatment with ramucirumab compared with placebo.

[c] Defined as the time from randomization to investigator-assessed radiographic progression or death.
[d] Estimated using stratified Cox regression; p-value from stratified log-rank test.

TTP[e] (2° endpoint) — Compare

Median (95% CI): 3.0 (2.8-4.2) vs 1.6 (1.5-2.7) months
HR: 0.427; 95% CI, 0.313-0.582; p<0.0001[f]

[e] Radiographic progression determined by RECIST v1.1.
[f] Per stratified log-rank test.

Response Rates[g] (2° endpoint) — Compare

Ramucirumab (n=197) vs placebo (n=95)
ORR: 5 vs 1%; p=0.1697[h]
DCR: 59.9 vs 38.9%; p=0.0006[h]

[g] Determined locally by the investigator according to RECIST v1.1.
[h] Per exact Cochran-Mantel-Haenszel test.

Patient-Reported Disease-Related Symptoms (2° endpoint)

FHSI-8 Scores[i]
Median TTD: 3.7 (2.8-4.4) vs 2.8 (1.6-2.9) months
HR: 0.799; 95% CI, 0.545-1.171; p=0.238

ECOG PS[j]
Median TTD: HR: 1.082; 95% CI, 0.639-1.832; p=0.77[k]

[i] Time from randomization to the first clinically meaningful deterioration (≥3 points) in total FHSI-8 scores.
[j] Time from randomization to recording of a performance status of 2 or higher.
[k] The number of events was insufficient for meaningful statistical assessment of deterioration.

AFP, α-fetoprotein; CI, confidence interval; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; FHSI-8, Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8; HR, hazard ratio; IQR, interquartile range; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTD, time to deterioration; TTP, time to progression.

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Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9

REACH-2

Ramucirumab vs placebo

Safety

Safety Population
Ramucirumab (n=197) vs placebo (n=95)

Median Duration of Treatment
Ramucirumab 12 weeks (IQR, 6-28)
Placebo 8 weeks (IQR, 6-13)

Rate of Discontinuation Due to Any AE: 18 vs 11%

Rate of Discontinuation Due to TRAE: 11 vs 3%

Most Common Any-Grade TEAE
(reported in ≥20% of patients in either arm)
Fatigue 27 vs 18%
Peripheral oedema 25 vs 14%
Decreased appetite 23 vs 20%

Most Common Grade ≥3 TEAE
(reported in ≥5% of patients in either arm)
Hypertension 13 vs 5%
Hyponatremia 6 vs 0%
Increased AST 3 vs 5%

Most Common Any-Grade TEAE of Special Interest
(more frequent in ramucirumab vs placebo)
Hypertension 25 vs 13%
Liver injury or failure 40 vs 29%
Proteinuria 20 vs 4%
Infusion-related reactions 9 vs 3%
Bleeding or haemorrhage 24 vs 13%

Safety (cont'd)

Serious Any-Grade Any-Cause AE: 35 vs 29%

Any-Grade TRAE: 11 vs 5%

Most Common Any-Grade TRAE
(reported in ≥10% of patients in either arm)
Fatigue 14 vs 5%
Decreased appetite 11 vs 4%
Bleeding or haemorrhage events 11 vs 5%
Proteinuria 14 vs 3%

Serious Any-Grade TRAE:
Dyspnoea 1 vs 0%
Hepatic encephalopathy 1 vs 0%

Post-hoc Analysis
Patients with mild ascites at baseline treated with ramucirumab (n=12) or placebo (n=7) showed no increased risk of clinically important adverse events of special interest.

Safety (cont'd)

Deaths for any reason while on therapy or within 30 days of treatment discontinuation:
Ramucirumab: 39 patients (20%)
Placebo: 16 patients (17%)

Deaths Due to AE:
Ramucirumab: 6 patients (3%)
Acute kidney injury, n=1
Generalised oedema, n=1
Hepatorenal syndrome, n=1
Myocardial infarction, n=1
Pneumonia, n=1
Renal failure, n=1

Placebo: 3 patients (3%)
Lung disorder, n=1
Myocardial infarction, n=1
Respiratory tract infection, n=1

Deaths Due to TRAE:
Ramucirumab: 3 patients
Acute kidney injury, n=1
Hepatorenal syndrome, n=1
Renal failure, n=1

AE, adverse event; AST, aspartate aminotransferase; IQR, interquartile range; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9

RESORCE

Regorafenib vs placebo

Study Information

Title: Study of Regorafenib After Sorafenib in Patients With Hepatocellular Carcinoma (RESORCE)[1]
ID: NCT01774344[1]
Sponsor: Bayer[1]
Enrolment: May 14, 2013 to Dec 31, 2015[2]
Study Design: Phase 3, randomized, double-blind, placebo-controlled international study conducted at 152 centers in 21 countries in North America, South America, Europe, Asia, and Australia[2]

Intervention[2]

Randomized Population (2:1): N=573[a]
Regorafenib (160 mg po qd, weeks 1-3 of each 4-week cycle): n=379
Placebo (po qd, weeks 1-3 of each 4-week cycle): n=194

[a] All patients received sorafenib as the only prior systemic therapy for HCC, which was discontinued because of documented radiological progression. Patients were excluded from the study if they discontinued sorafenib for toxicity.

Patient Characteristics[2]

Age: 64 vs 62 years
Male: 88 vs 88%
BCLC Stage
- A: <1 vs 0%
- B: 14 vs 11%
- C: 86 vs 89%

Child-Pugh Score[b]
- A: 98 vs 97%
- B: 1 vs 3%

ECOG PS
- 0: 65 vs 67%
- 1: 35 vs 33%

Region
- Rest of world: 62 vs 62%
- Asia: 38 vs 38%

Pattern of Progression on Prior Treatment with Sorafenib
- New extrahepatic lesion: 40 vs 41%
- New intrahepatic lesion: 44 vs 45%
- Growth of intrahepatic or extrahepatic lesions, or both: 81 vs 80%

[b] Child-Pugh score was missing in one patient in the regorafenib arm.

Patient Characteristics (cont'd)[2]

Etiology
- HBV: 38 vs 38%
- HCV: 21 vs 21%
- Alcohol use: 24 vs 28%
- Non-alcoholic steatohepatitis: 7 vs 7%

Extrahepatic disease
- Yes: 70 vs 76%

MVI
- Yes: 29 vs 28%

AFP, ng/mL
- ≥400: 43 vs 45%

Duration of Prior Sorafenib Treatment[2]

Median (IQR): 7.8 (4.2-14.5) vs 7.8 (4.4-14.7) months

Reason for Discontinuation of Sorafenib
- PD: 100 vs 100%

AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MVI, macrovascular invasion.

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1. NCT01774344. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT01774344. Accessed August 23, 2025. 2. Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9

RESORCE

Regorafenib vs placebo

OS[a] (1° endpoint) — Compare

Median: 10.6 vs 7.8 months
HR: 0.63; 95% CI, 0.50-0.79; one-sided p<0.0001[b]
Median follow-up: 7.0 months (IQR, 3.7-12.6)

Subgroup Analysis by Baseline Characteristics
Predefined subgroup analyses for OS showed consistent benefit of regorafenib compared with placebo.

[a] Defined as the time from randomization to death from any cause.
[b] Estimated using stratified Cox regression; p-value from stratified log-rank test.

PFS[c] (2° endpoint) — Compare

Median: 3.1 vs 1.5 months
HR: 0.46; 95% CI, 0.37-0.56; one-sided p<0.0001[d]

Subgroup Analysis by Baseline Characteristics
Predefined subgroup analyses for PFS showed consistent benefit of regorafenib compared with placebo.

[c] Defined as the time from randomization to radiological or clinical disease progression or death. Assessed by investigators using mRECIST.
[d] Per stratified log-rank test.

TTP[e] (2° endpoint) — Compare

Median: 3.2 vs 1.5 months
HR: 0.44; 95% CI, 0.36-0.55; one-sided p<0.0001[f]

[e] Defined as the time from randomization to radiological or clinical disease progression or death. Assessed by investigators using mRECIST.
[f] Per stratified log-rank test.

Response Rates[g] (2° endpoint) — Compare

Regorafenib (n=379) vs placebo (n=194)
ORR: 11 vs 4% (one-sided p=0.0047)[h]
- CR: 1 vs 0%
- PR: 10 vs 4%

SD: 54 vs 32%
DCR: 65 vs 36% (one-sided p<0.0001)[h]
PD: 23 vs 56%

Tumour shrinkage[i]: 49 vs 23%

[g] Assessed by investigators using mRECIST.
[h] Per Cochran-Mantel-Haenszel test.
[i] Any decrease in the sum of diameters of target lesions.

HRQoL (2° endpoint)

FACT-Hep
Changes from baseline: Similar in both arms

LSM time-adjusted AUC analysis: Scores were lower in regorafenib arm vs placebo

Total Scores: Statistically lower in regorafenib arm vs placebo (p=0.0006)[j]

Trial Outcome Index Scores: Statistically lower in regorafenib arm vs placebo (p<0.0001)[j]

EQ-5D
Changes from baseline: Similar in both arms

LSM time-adjusted AUC analysis: Scores were lower in regorafenib arm vs placebo

[j] Minimally important thresholds for the differences as established in the literature were not met.

AUC, area under the curve; CI, confidence interval; CR, complete response; DCR, disease control rate; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary; HR, hazard ratio; HRQoL, health-related quality of life; IQR, interquartile range; LSM, least-squares mean; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression.

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Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9

RESORCE

Regorafenib vs placebo

Safety

Safety Population
Regorafenib (n=374) vs placebo (n=193)

Median Duration of Treatment
Regorafenib 3.6 months (IQR, 1.6-7.6)
Placebo 1.9 (IQR, 1.4-3.9)

Rate of Discontinuation Due to AE: 25 vs 19%

Rate of Discontinuation Due to Drug-Related TEAE: 10 vs 4%

Most Common TEAE Leading to Discontinuation
Increased AST 2 vs 3%
Hand-foot skin reaction 2 vs 0%
Increased ALT 1 vs 0%

Safety (cont'd)

Any-Grade TEAE: 100 vs 93%

Possibly Drug-Related TEAE: 93 vs 52%

Most Common Clinically Relevant Grade 3 or 4 TEAE
Hypertension 15 vs 5%
Hand-foot skin reaction 13 vs 1%
Fatigue 9 vs 5%
Diarrhea 3 vs 0%
Hepatobiliary disorders 11 vs 18%

Serious TEAE: 44 vs 47%

Serious Drug-Related TEAE: 10 vs 3%

Grade ≥3 Treatment-Emergent Bleeding Events: 6 vs 8%

Deaths from Any Cause: 13 vs 20%

Deaths Related to Treatment: 2 vs 1%[a]

[a] All patients (n=2) in the placebo arm had hepatic failure.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; TEAE, treatment-emergent adverse event.

Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9

OS

	KEYNOTE-240[1]		CELESTIAL[2]		REACH-2[3]		RESORCE[4]	
	Pembrolizumab n=278	Placebo n=135	Cabozantinib n=470	Placebo n=237	Ramucirumab n=197	Placebo n=95	Regorafenib n=379	Placebo n=194
Median OS (months)	13.9	10.6	10.2	8.0	8.5	7.3	10.6	7.8
HR	0.771		0.76		0.710		0.63	
(95% CI)	(0.617-0.964) Prespecified statistical significance criteria not met[a]		(0.63-0.92) p=0.005[b]		(0.531-0.949) p=0.0199[c]		(0.50-0.79) one-sided p<0.0001[c]	

[a] Estimated using stratified Cox regression; p-value from stratified log-rank test. 95% CIs are descriptive. [b] Estimated using univariate Cox regression; p-value from stratified log-rank test.
[c] Estimated using stratified Cox regression; p-value from stratified log-rank test.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

1. Merle P, et al. *Liver Cancer*. 2023;12(4):309-320. doi:10.1159/000529636. 2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002. 3. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9. 4. Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9

PFS

	KEYNOTE-240[1,a]		CELESTIAL[2,b]		REACH-2[3,c]		RESORCE[4,d]	
	Pembrolizumab n=278	Placebo n=135	Cabozantinib n=470	Placebo n=237	Ramucirumab n=197	Placebo n=95	Regorafenib n=379	Placebo n=194
Median PFS (months)	3.0	2.8	5.2	1.9	2.8	1.6	3.1	1.5
HR	0.718		0.44		0.452		0.46	
(95% CI)	(0.571-0.903) Prespecified statistical significance criteria not met[e]		(0.36-0.52) p<0.001[f]		(0.339-0.603) p<0.0001[g]		(0.37-0.56) one-sided p<0.0001[h]	

[a] Per RECIST v1.1 by BICR. [b] Determined by the investigator according to RECIST v1.1. [c] Defined as the time from randomization to investigator-assessed radiographic progression or death. [d] Defined as the time from randomization to radiological or clinical disease progression or death. Assessed by investigators using mRECIST. [e] Estimated using stratified Cox regression; p-value from stratified log-rank test. 95% CIs are descriptive. [f] Estimated using univariate Cox regression; p-value from stratified log-rank test. [g] Estimated using stratified Cox regression; p-value from stratified log-rank test. [h] Per stratified log-rank test.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Merle P, et al. *Liver Cancer*. 2023;12(4):309-320. doi:10.1159/000529636. 2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002. 3. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9. 4. Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9

TTP

	KEYNOTE-240[1,a]		CELESTIAL[2]		REACH-2[3,b]		RESORCE[4,c]	
	Pembrolizumab n=278	Placebo n=135	Cabozantinib n=470	Placebo n=237	Ramucirumab n=197	Placebo n=95	Regorafenib n=379	Placebo n=194
Median TTP (months)	3.8	2.8	NR	NR	3.0	1.6	3.2	1.5
HR (95% CI)	NR		NR		0.427 (0.313-0.582) p<0.0001[d]		0.44 (0.36-0.55) one-sided p<0.0001[d]	

[a] Per RECIST v1.1 by BICR. [b] Radiographic progression determined by RECIST v1.1. [c] Defined as the time from randomization to radiological or clinical disease progression or death. Assessed by investigators using mRECIST. [d] Per stratified log-rank test.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NR, not reported; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

1. Merle P, et al. *Liver Cancer*. 2023;12(4):309-320. doi:10.1159/000529636. 2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002. 3. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9. 4. Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9

RESPONSE RATES

	KEYNOTE-240[1,a]		CELESTIAL[2,b]		REACH-2[3,c]		RESORCE[4,d]	
	Pembrolizumab n=278	Placebo n=135	Cabozantinib n=470	Placebo n=237	Ramucirumab n=197	Placebo n=95	Regorafenib n=379	Placebo n=194
ORR	18.3%	4.4%	4%	<1% p=0.009[e]	5%	1% p=0.1697[f]	11%	4% one-sided p<0.0047[e]
CR	3.6%	0%	0%	0%	NR	NR	1%	0%
PR	14.7%	4.4%	4%	<1%	NR	NR	10%	4%
SD	43.9%	48.9%	60%	33%	NR	NR	54%	32%
DCR	62.2%	53.3%	64%	33%	59.9%	38.9% p=0.0006[f]	65%	36% one-sided p<0.0001[e]
PD	32.7%	42.2%	21%	55%	NR	NR	23%	56%
DOR	13.9 months	15.2 months	NR	NR	NR	NR	NR	NR

[a] Per RECIST v1.1 by BICR. [b] Determined by the investigator according to RECIST v1.1. [c] Determined locally by the investigator according to RECIST v1.1. [d] Assessed by investigators using mRECIST.
[e] Per Cochran-Mantel-Haenszel test. [f] Per exact Cochran-Mantel-Haenszel test.

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NR, not reported; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

1. Merle P, et al. *Liver Cancer*. 2023;12(4):309-320. doi:10.1159/000529636. 2. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002. 3. Zhu AX, et al. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9. 4. Bruix J, et al. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9