Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Abou-Alfa GK, Meyer T, Cheng A-L, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63. DOI: 10.1056/NEJMoa1717002

SUPPLEMENTARY APPENDIX

Abou-Alfa GK, Meyer T, Cheng LI, et al. Cabozantinib versus placebo in previously treated patients with advanced hepatocellular carcinoma.

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Study Investigators

The following investigators enrolled patients in CELESTIAL

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Inclusion and Exclusion Criteria

Inclusion Criteria

1. Histological or cytological diagnosis of HCC (results of a previous biopsy were accepted)
2. The subject had disease that was not amenable to a curative treatment approach (eg, transplant, surgery, radiofrequency ablation)
3. Received prior sorafenib
4. Progression following at least 1 prior systemic treatment for HCC
5. Recovery to ≤ Grade 1 from toxicities related to any prior treatments, unless the AEs were clinically nonsignificant and/or stable on supportive therapy
6. Age ≥ 18 years old on the day of consent
7. Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
8. Adequate hematologic function, based upon meeting the following laboratory criteria within 7 days before randomization:
    a. Absolute neutrophil count (ANC) ≥ 1200/mm^3 (≥ 1.2×10^9/L)
    b. Platelets ≥ 60,000/mm^3 (≥ 60×10^9/L)
    c. Hemoglobin ≥ 8 g/dL (≥ 80 g/L)
9. Adequate renal function, based upon meeting the following laboratory criteria within 7 days before randomization:
    a. Serum creatinine ≤ 1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault equation: (140 – age) × weight (kg)/(serum creatinine × 72 [mg/dL]) for males. (For females multiplied by 0.85)

    AND

    b. Urine protein/creatinine ratio (UPCR) ≤ 1 mg/mg (≤ 113.1 mg/mmol) or 24-hour urine protein < 1 g
10. Child-Pugh Score of A
11. Total bilirubin ≤ 2 mg/dL (≤ 34.2 µmol/L) within 7 days before randomization
12. Serum albumin ≥ 2.8 g/dL (≥ 28 g/L) within 7 days before randomization
13. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 5.0 × ULN within 7 days before randomization
14. Hemoglobin A1c (HbA1c) ≤ 8% within 28 days before randomization (if HbA1c results were unavailable [eg, hemoglobin variant], a fasting serum glucose ≤ 160 mg/dL)
15. Antiviral therapy per local standard of care if active hepatitis B virus (HBV) infection
16. Capable of understanding and complying with the protocol requirements and signed informed consent
17. Sexually active fertile subjects and their partners must have agreed to use medically accepted methods of contraception (eg, barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 4 months after the last dose of study treatment

18. Female subjects of childbearing potential must not have been pregnant at screening. Females of childbearing potential were defined as premenopausal females capable of becoming pregnant (ie, females who had any evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy). However, women who had been amenorrheic for 12 or more months were still considered to be of childbearing potential if the amenorrhea was possibly due to prior chemotherapy, antiestrogens, ovarian suppression, low body weight, or other reasons.

Exclusion Criteria

1. Fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma
2. Receipt of more than 2 prior systemic therapies for advanced HCC. Additional prior systemic therapies used as adjuvant or local therapy were allowed.
3. Any type of anticancer agent (including investigational) within 2 weeks before randomization
4. Radiation therapy within 4 weeks (2 weeks for radiation for bone metastases) or radionuclide treatment (eg, I-131 or Y-90) within 6 weeks of randomization (subject was excluded if there were any clinically relevant ongoing complications from prior radiation therapy)
5. Prior cabozantinib treatment
6. Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery (including radiosurgery) and stable for at least 3 months before randomization. Eligible subjects must have been without corticosteroid treatment at the time of randomization.
7. Concomitant anticoagulation, at therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, low molecular weight heparin (LMWH), thrombin or coagulation factor X (FXa) inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin for cardioprotection (per local applicable guidelines), low-dose warfarin (≤ 1 mg/day), and low-dose LMWH were permitted.
8. The subject had uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:
    a. Cardiovascular disorders including
        i. Symptomatic congestive heart failure, unstable angina pectoris, or serious cardiac arrhythmias
        ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic BP (SBP), or > 100 mm Hg diastolic BP (DBP) despite optimal antihypertensive treatment
        iii. Stroke (including transient ischemic attack), myocardial infarction, or other ischemic event within 6 months before randomization
        iv. Thromboembolic event within 3 months before randomization. Subjects with thromboses of portal/hepatic vasculature attributed to underlying liver disease and/or liver tumor were eligible
    b. Gastrointestinal (GI) disorders including those associated with a high risk of perforation or fistula formation:
        i. Tumors invading the GI tract, active peptic ulcer disease, inflammatory bowel disease (eg, Crohn's disease), diverticulitis, cholecystitis, symptomatic cholangitis or appendicitis, acute pancreatitis or acute obstruction of the pancreatic duct or common bile duct, or gastric outlet obstruction

ii. Abdominal fistula, GI perforation, bowel obstruction, intra-abdominal abscess within 6 months before randomization

Note: Complete healing of an intra-abdominal abscess must have been confirmed prior to randomization

c. Major surgery within 2 months before randomization. Complete healing from major surgery must have occurred 1 month before randomization. Complete healing from minor surgery (eg, simple excision, tooth extraction) must have occurred at least 7 days before randomization. Subjects with clinically relevant complications from prior surgery were not eligible

d. Cavitating pulmonary lesion(s) or endobronchial disease

e. Lesion invading a major blood vessel including, but not limited to: inferior vena cava, pulmonary artery, or aorta. Subjects with lesions invading the portal vasculature were eligible.

f. Clinically significant bleeding risk including the following within 3 months of randomization: hematuria, hematemesis, hemoptysis of > 0.5 teaspoon (> 2.5 mL) of red blood, or other signs indicative of pulmonary hemorrhage, or history of other significant bleeding if not due to reversible external factors

g. Other clinically significant disorders such as:

i. Active infection requiring systemic treatment, known infection with human immunodeficiency virus (HIV), or known acquired immunodeficiency syndrome (AIDS)-related illness. Subjects with active hepatitis virus infection controlled with antiviral therapy were eligible.

ii. Serious non-healing wound/ulcer/bone fracture

iii. Malabsorption syndrome

iv. Uncompensated/symptomatic hypothyroidism

v. Requirement for hemodialysis or peritoneal dialysis

vi. History of solid organ transplantation

9. Subjects with untreated or incompletely treated varices with bleeding or high risk for bleeding. Subjects treated with adequate endoscopic therapy (in accordance with institutional standards) without any episodes of recurrent GI bleeding requiring transfusion or hospitalization for at least 6 months prior to study entry were eligible.

10. Moderate or severe ascites

11. Corrected QT interval calculated by the Fridericia formula (QTcF) > 500 ms within 7 days before randomization

Note: If the QTcF was > 500 ms in the first ECG, a total of 3 ECGs were to be performed. If the average of these 3 consecutive results for QTcF was ≤ 500 ms, the subject met eligibility in this regard.

12. Inability to swallow tablets

13. Previously identified allergy or hypersensitivity to components of the study treatment formulations

14. Pregnant or lactating females

15. Diagnosis of another malignancy within 2 years before randomization, except for superficial skin cancers, or localized, low-grade tumors deemed cured and not treated with systemic therapy

Table S1. Baseline Characteristics In Detail

	Cabozantinib (N = 470)	Placebo (N = 237)
Age, median (range), years	64 (22-86)	64 (24-86)
Sex, n (%)		
Male	379 (81)	202 (85)
Female	91 (19)	35 (15)
Geographic region, n (%)		
Asia*	116 (25)	59 (25)
Europe	231 (49)	108 (46)
North America (Canada/United States)	108 (23)	59 (25)
Australia/New Zealand	15 (3)	11 (5)
Race, n (%)[†]		
White	264 (56)	130 (55)
Asian	159 (34)	82 (35)
Black	8 (2)	11 (5)
Other	8 (2)	2 (1)
Not reported	31 (7)	12 (5)
ECOG performance status, n (%)		
0	245 (52)	131 (55)
1	224 (48)	106 (45)
2[‡]	1 (<1)	0
Etiology of disease, n (%)[§]		
HBV	178 (38)	89 (38)
HCV	113 (24)	55 (23)
Dual HBV and HCV infection	8 (2)	4 (2)
Alcohol_	112 (24)	39 (16)
Nonalcoholic steatohepatitis	43 (9)	23 (10)
Other	24 (5)	16 (7)
Unknown	75 (16)	47 (20)
Child-Pugh class, n (%)		
A	462 (98)	235 (99)
B[‡]	7 (1)	2 (1)
Missing	1 (<1)	0
BCLC stage, n (%)[‖]		

	Cabozantinib (N = 470)	Placebo (N = 237)
B (intermediate)	42 (9)	23 (10)
C (advanced)	427 (91)	214 (90)
Extrahepatic spread of disease, n (%)	369 (79)	182 (77)
Macrovascular invasion, n (%)	129 (27)	81 (34)
Extrahepatic spread of disease and/or macrovascular invasion, n (%)	398 (85)	200 (84)
Sites of disease, n (%)		
Liver**	395 (84)	216 (91)
Bone	60 (13)	34 (14)
Visceral (excluding liver)	215 (46)	105 (44)
Lung	184 (39)	91 (38)
Adrenal gland	51 (11)	24 (10)
Lymph Node	155 (33)	71 (30)
Number of sites (including liver)		
1	144 (31)	72 (30)
2	172 (37)	91 (38)
≥3	154 (33)	74 (31)
Alpha-fetoprotein (ng/mL), n (%)		
< 400	278 (59)	136 (57)
≥ 400	192 (41)	101 (43)
Number of prior systemic anticancer regimens for advanced HCC, n (%)		
0¶	3 (1)	0
1	335 (71)	174 (73)
2	130 (28)	62 (26)
≥3	2 (<1)	1 (<1)
Prior systemic anticancer therapy, n (%)		
Sorafenib	470 (100)	237 (100)
Regorafenib	6 (1)	2 (1)
Lenvatinib	0	1 (<1)
Tivantinib	1 (<1)	2 (1)
Ramucirumab	8 (2)	1 (<1)
Anti-PD-1/PD-L1	14 (3)	3 (1)

	Cabozantinib (N = 470)	Placebo (N = 237)
Cytotoxic chemotherapy	41 (9)	30 (13)
Doxorubicin	22 (5)	10(4)
Investigational agent	60 (13)	20 (8)
Local liver-directed non-radiation anticancer therapy, n (%)	209 (44)	113 (48)
Time from initial pathologic diagnosis of HCC to randomization, median, years	1.5	1.3
Total duration of treatment on prior sorafenib, median, months[#]	5.3	4.8
Time from the end of most recent systemic anticancer agent for HCC to randomization, median, months[#]	1.4	1.2

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; PD-1, programmed death-1; PD-L1, programmed death-ligand 1.
Significant differences between treatment groups are indicated by _ for P < 0.05 and ** for P < 0.01.
*Asia included Hong Kong, South Korea, Singapore, and Taiwan.
†Race was self reported by the patients.
‡Although patients were required to have ECOG performance status of 0 or 1 and Child-Pugh class A, a few patients had ECOG performance status of 2 or Child-Pugh class B.
[§]Etiology per case report form. Some patients had more than one disease etiology category.
[‖]BCLC status[1] was assigned retrospectively, using macrovascular invasion as a surrogate for portal vein invasion. One patient in the cabozantinib group had unknown BCLC status.
[¶]Three subjects in the cabozantinib group received prior systemic anticancer therapy that was administered for adjuvant treatment but not for advanced hepatocellular carcinoma treatment.
[#]Time from initial pathologic diagnosis of HCC to randomization missing for 1 patient in the cabozantinib group and 2 patients in the placebo group. Total duration of treatment on prior sorafenib missing for 1 patient in the cabozantinib group.

Table S2. Kaplan-Meier Landmark Estimates of Overall Survival

Landmark	Estimate of % of Patients Alive (95% CI)	
	Cabozantinib (N = 470)	Placebo (N = 237)
6 months	72 (67-76)	61 (54-67)
12 months	46 (41-50)	34 (28-41)
18 months	32 (27-37)	18 (12-24)
24 months	18 (14-22)	13 (8-18)

CI, confidence interval.

Table S3. Subsequent Anticancer Therapy

	Cabozantinib (N=470)	Placebo (N=237)
Any non-radiation systemic or local liver-directed anticancer therapy, n (%)	123 (26)	78 (33)
Any systemic anticancer therapy, %	117 (25)	70 (30)
Sorafenib	19 (4)	4 (2)
Regorafenib	11 (2)	3 (1)
Anti-PD-1/PD-L1	23 (5)	15 (6)
Lenvatinib	1 (<1)	0
Cytotoxic chemotherapy	57 (12)	40 (17)
Investigational agent	28 (6)	17 (7)
Any non-radiation local liver-directed anticancer therapy, n (%)	15 (3)	13 (5)

PD-1, programmed death-1; PD-L1, programmed death-ligand 1.

Table S4. Tumor Response

	Cabozantinib (N = 470)	**Placebo (N = 237)**
Objective response rate, % (95% CI)[*,†]	4 (2 - 6)	<1 (0 - 2)
Best overall response, n (%)		
Complete response	0	0
Partial response	18 (4)	1 (<1)
Stable disease	282 (60)	78 (33)
Progressive disease	98 (21)	131 (55)
Not evaluable or missing	72 (15)	27 (11)

Tumor response was assessed by investigator per RECIST version 1.1.

[*]Confirmed complete and partial responses

[†]P = 0.009 (Cochran-Mantel-Haenszel test)

Table S5. Overall Survival and Progression-free Survival in Subgroups

	No. patients		Overall Survival			Progression-free Survival		
	Cabo	Pbo	mOS cabo, mo	mOS pbo, mo	HR (95% CI)	mPFS cabo, mo	mPFS pbo, mo	HR (95% CI)
Overall	470	237	10.2	8.0	0.76 (0.63-0.92)	5.2	1.9	0.44 (0.36-0.52)
Age								
<65	240	124	9.6	7.7	0.81 (0.62-1.05)	5.0	1.9	0.45 (0.35-0.57)
≥65	230	113	11.1	8.3	0.74 (0.56-0.97)	5.4	2.0	0.46 (0.35-0.59)
Sex								
Male	379	202	10.1	7.9	0.79 (0.64-0.97)	4.9	1.9	0.49 (0.40-0.59)
Female	91	35	11.1	8.9	0.68 (0.42-1.09)	5.5	1.9	0.31 (0.20-0.49)
ECOG PS								
0	245	131	12.4	9.3	0.69 (0.53-0.89)	5.6	1.9	0.39 (0.31-0.50)
1	224	106	8.6	6.4	0.87 (0.66-1.14)	3.7	1.9	0.54 (0.41-0.70)
AFP								
<400 ng/mL	278	136	13.9	10.3	0.81 (0.62-1.04)	5.5	1.9	0.47 (0.37-0.60)
≥400 ng/mL	192	101	8.5	5.2	0.71 (0.54-0.94)	3.9	1.9	0.42 (0.32-0.55)
Region								
Asia	116	59	10.9	10.2	1.01 (0.68-1.48)	5.4	1.8	0.46 (0.32-0.67)
Other Regions	354	178	10.2	7.8	0.71 (0.57-0.88)	5.2	1.9	0.45 (0.37-0.56)
Race								
Asian	159	82	9.7	8.5	0.86 (0.63-1.19)	5.4	1.8	0.43 (0.32-0.58)
Non-Asian	280	143	11.1	7.9	0.75 (0.59-0.96)	5.2	1.9	0.47 (0.38-0.59)
EHS and/or MVI								
Yes	398	200	9.5	7.3	0.73 (0.60-0.90)	5.0	1.9	0.45 (0.37-0.54)
No	72	37	14.0	14.7	0.99 (0.59-1.65)	5.6	2.0	0.46 (0.29-0.74)
EHS								
Yes	369	182	9.6	6.9	0.72 (0.58-0.89)	5.0	1.9	0.46 (0.37-0.56)
No	101	55	12.0	12.3	0.96 (0.63-1.46)	5.4	1.9	0.45 (0.31-0.66)
MVI								
Yes	129	81	7.6	5.3	0.75 (0.54-1.03)	3.7	1.8	0.42 (0.31-0.58)
No	339	156	12.4	9.7	0.80 (0.64-1.01)	5.5	1.9	0.48 (0.38-0.59)
Etiology								
HBV (with or without HCV)	178	89	9.7	6.1	0.69 (0.51-0.94)	4.4	1.8	0.31 (0.23-0.42)
HCV (without HBV)	105	51	11.1	11.4	1.11 (0.72-1.71)	4.1	1.9	0.61 (0.42-0.88)

	No. patients		Overall Survival			Progression-free Survival		
	Cabo	**Pbo**	**mOS cabo, mo**	**mOS pbo, mo**	**HR (95% CI)**	**mPFS cabo, mo**	**mPFS pbo, mo**	**HR (95% CI)**
Other	187	97	11.1	8.7	0.72 (0.54-0.96)	5.5	2.0	0.48 (0.36-0.63)
Prior systemic anticancer regimens for advanced HCC								
One	335	174	11.4	7.7	0.74 (0.59-0.92)	5.5	1.9	0.43 (0.35-0.52)
Two	130	62	8.6	8.6	0.90 (0.63-1.29)	3.7	1.9	0.58 (0.41-0.83)

AFP, α-fetoprotein; cabo, cabozantinib; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; MVI, macrovascular invasion; pbo, placebo.

Hazard ratios are stratified for the overall population and unstratified for the subgroups.One patient in cabozantinib group had ECOG performance status 2.

Thirty-one patients in the cabozantinib group and 12 patients in the placebo group had no race reported.

Two patients in the cabozantinib group had unknown MVI status.

Three patients in the cabozantinib group received prior systemic anticancer therapy that was administered for adjuvant treatment but not for advanced hepatocellular carcinoma treatment, and 2 patients in the cabozantinib group and 1 patient in the placebo group had ≥3 prior regimens.

References

1. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.