Introduction

The results of the phase III CELESTIAL trial of cabozantinib were presented by Prof. Ghassan Abou-Alfa at the ASCO Gastrointestinal Cancer Symposium held in San Francisco from January 18 to 20, 2018 [1]. Although most of the previous clinical trials of second-line agents, except regorafenib [2], failed [3–8], the CELESTIAL trial yielded positive results in line with most expectations and produced a fourth molecular-targeted drug option for hepatocellular carcinoma (HCC). Based on this trial, cabozantinib can be added as a second-line option to the first-line drugs sorafenib [9, 10] and lenvatinib [11] and the second-line drug regorafenib [2] (Table 1).

Phase II Trial of Cabozantinib

The structural formula of cabozantinib is relatively similar to that of regorafenib [12, 13] (Fig. 1), although the kinase inhibitory activity (IC_{50}) of cabozantinib is different. Cabozantinib was originally identified as a dual inhibitor of VEGFR-2 and c-MET [14, 15], whereas current data suggest that it is a more potent inhibitor of MET, AXL, RET, FLT3, and TIE-2 than regorafenib (Tables 2, 3). VEGF, MET, and AXL are involved in tumor proliferation and angiogenesis, and MET and AXL are involved in the acquisition of resistance to antiangiogenic drugs [14–18]. VEGF, MET, or AXL expression is considered a poor prognostic factor [14–18].
A waterfall plot from the phase II trial showed tumor shrinkage in a large proportion of patients. Progression-free survival (PFS) was 4.2 months in sorafenib-naïve patients and 5.5 months in sorafenib-pretreated patients, and overall survival (OS) was 11.5 months [15] (Table 4). The overall response rate (ORR) was 5%, the disease control rate was 81%, and PFS was 5.2 months (Table 4). Considering that some patients in the cabozantinib trial received first-line therapy, the results were not very good compared with the results of the phase II trial of regorafenib [19] (Table 4). Cabozantinib was also associated with a higher incidence of adverse events (AEs) than regorafenib (Table 5).
Phase III CELESTIAL Trial

In light of these results, a phase III trial of cabozantinib was conducted (Fig. 2). The trial design was not as sophisticated as that of the RESORCE trial [2, 20]. For example, vascular invasion and/or extrahepatic spread was included as a stratification factor, which may result in an unfavorable imbalance regarding patients with vascular invasion. In fact, this unfavorable imbalance was present in the BRISK-PS trial and resulted in negative results [3]. The BRISK-PS trial did not include alpha-fetoprotein as a stratification factor, which caused an unfavorable balance against the trial drug similar to that seen in the REFLECT trial [11]. The RESORCE trial led to the inclusion of vascular invasion as an independent stratification factor.
and alpha-fetoprotein as a stratification factor in the design of trials of second-line drugs [21]. However, the CELESTIAL trial had a conventional design with few strategic elements (Table 6) and did not even exclude sorafenib-intolerant patients as in the RESORCE trial [2, 20, 21]. The only inclusion criteria regarding prior treatment were (a) prior sorafenib treatment, (b) progression following at least 1 prior systemic treatment for HCC, and (c) up to 2 prior systemic regimens for advanced HCC; the exact number of sorafenib-intolerant patients enrolled remains unclear.

Between September 2013 and September 2017, the trial enrolled 773 patients with unresectable HCC showing disease progression after at least 1 prior systemic chemotherapy regimen containing sorafenib. The second interim analysis performed in January 2016 demonstrated the superiority of cabozantinib in terms of the primary endpoint of OS. There was an imbalance in baseline patient characteristics between the cabozantinib and placebo groups caused by the failure to include vascular invasion and extrahepatic spread as independent stratification factors; namely, the rate of vascular invasion was only 27% in the cabozantinib group compared with 34% in the placebo group, which favored the cabozantinib
Table 6. Phase III clinical trials: advanced stage second line versus placebo

| Study          | Agent       | Intolerance of sorafenib, % | Stratification factor                                                                 |
|----------------|-------------|----------------------------|---------------------------------------------------------------------------------------|
| BRISK-PS       | Brivanib    | 12–13                      | Reason for sorafenib discontinuation, ECOS-PS score, Extrahepatic spread, and/or vascular invasion |
| EVOLVE-1       | Everolimus  | 18.5–20                    | Region, Cause of liver disease (HBV, HCV, other)                                       |
| REACH          | Ramucirumab | 13–15                      | Medical institutions, Extrahepatic metastasis and/or vascular invasion                 |
| S-CUBE SI      | Regorafenib | 30.6–33.8                  | Region, ECOG-PS score, Extrahepatic spread, Vascular invasion                         |
| RESOURCE       | Tivantinib  | 0                          | Region, Vascular invasion                                                            |
| METIV-HVV      | Pembrolizum | 17–21                      | Region, Disease etiology (HBV, HCV, other), Extrahepatic metastasis and/or vascular invasion |
| CELESTIAL      | Cabozantinib| N/A                        |                                                                                      |

After the BRISK-PS trial, where there was an imbalance of AFP and MVI in the testing arm, AFP and MVI started to be included as independent stratification factors in most trials, but not in the CELESTIAL trial. Modified from [1–6]. AFP, alpha-fetoprotein; MVI, macrovascular invasion.

Table 7. Baseline characteristics

|                    | Cabozantinib (n = 470) | Placebo (n=237) |
|--------------------|------------------------|-----------------|
| Median (range) age, years | 64 (22–86)             | 64 (24–86)      |
| Male, %            | 81                     | 85              |
| ECOG performance status 0/1, % | 52/48                 | 55/45           |
| AFP ≥400 ng/mL, %  | 41                     | 43              |
| Enrollment region, % | 25/49/23/3            | 25/46/25/5      |
| Asia/Europe/North America/Pacific |                    |                 |
| Etiology of HCC, % |                        |                 |
| HBV                | 38                     | 38              |
| HCV                | 22                     | 22              |
| Other              | 40                     | 41              |
| Extrahepatic spread of disease, % | 79                    | 77              |
| Macrovascular invasion, % | 27                   | 34              |
| Extrahepatic spread and/or macrovascular invasion, % | 85             | 84              |

Asia: Hong Kong, South Korea, Singapore, Taiwan; Pacific: Australia and New Zealand. Cited from [1]. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

This resulted in significantly better OS in the cabozantinib group (10.2 months, 95% CI: 9.1–12.0) than in the placebo group (8.2 months, 95% CI: 9.1–12.0) and consequently in a positive result for the clinical trial. PFS, the secondary endpoint, was also better in the cabozantinib group (5.2 months, 95% CI: 4.0–5.5) than in the placebo group (1.9 months, 95% CI: 1.9–1.9) (Table 8). PFS of 1.9 months in the placebo arm in the CELESTIAL trial was similar to that of 1.5 months in the placebo arm in the RESORCE trial (Fig. 3). Moreover, ORR was superior in the cabozantinib group (4 vs. 0.4%; p = 0.0086) (Table 9). Post-trial treatment was performed in a comparably low proportion of patients in the cabozantinib and placebo groups (25 vs. 30%), demonstrating the poor condition of the patient population. In summary, although the relative number of sorafenib-intolerant patients in the trial was not reported, it can be inferred from the trial results that the proportion was relatively low (Table 10).
Regorafenib and cabozantinib had comparable efficacy in terms of OS, ORR, and PFS (Tables 8, 9). Patients who received prior treatment with sorafenib alone showed slightly better outcomes (Table 10), which were comparable to those of regorafenib.

The duration of treatment with cabozantinib was 3.8 months, which was comparable to the 3.6 months for regorafenib and indicates acceptable tolerability, similar to that of regorafenib.

**Comparison between Regorafenib and Cabozantinib: Efficacy and Safety**
Dose reduction or discontinuation because of treatment-related AEs was more common with cabozantinib than with regorafenib. Specific AEs such as palmar-plantar erythrodysesisia, diarrhea, and asthenia were more common with cabozantinib than with regorafenib, indicating that cabozantinib may have a slightly higher toxicity than regorafenib (Table 11).

**Key Factors Contributing to the Success of the CELESTIAL Trial**

The following 5 factors may have contributed to the success of the CELESTIAL trial of cabozantinib despite the unsophisticated trial design compared with that of the RESORCE trial and the drug's slightly higher toxicity (Table 12).

1. Cabozantinib has a sufficiently potent antitumor activity.
2. Toxicity and tolerability were clinically acceptable.
3. An imbalance in vascular invasion favored cabozantinib.
4. The short time to progression in the placebo arm and low proportion of patients having post-trial treatment indicate low enrollment of sorafenib-intolerant patients, which was similar to no enrollment of sorafenib-intolerant patients in the RESORCE trial.

5. The sample size of 470 patients was considerably higher than that of other second-line trials and provided sufficient power to eliminate the effect of the small imbalance and detect small differences as significant (Table 13).

**Paradigm Shift in the Treatment Strategy for HCC**

Sorafenib was the only HCC drug available between 2007 and 2016. Between 2017 and 2018, 5 drugs, sorafenib, lenvatinib, regorafenib, cabozantinib, and nivolumab, became available. Therefore, it is necessary to establish how these drugs should be used in clinical practice (Fig. 4). Combinations of immune checkpoint inhibitors and molecular-targeted drugs or molecular-targeted drugs and established locoregional therapies [22] are particularly likely to produce a paradigm shift in the treatment of HCC. The treatment landscape for...
Table 13. Phase III trials in a second line setting

|                      | CELESTIAL cabozantinib arm (n = 470) | RESORCE regorafenib arm (n = 379) | BRISK-PS brivanib arm (n = 263) | EVOLVE-1 everolimus arm (n = 362) | REACH ramucirumab arm (n = 283) |
|----------------------|-------------------------------------|----------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Male, %              | 81                                  | 88                               | 82                              | 84                              | 83                              |
| Median age (range), years | 64 (22–86)                         | 64 (19–85)                      | 64 (19–89)                     | 67 (21–86)                     | 64 (28–87)                     |
| Asian race, %        | 25                                  | 41                               | 48                              | 38                              | 46                              |
| ECOG PS 0/1, %       | 52/48                               | 65/35                            | 57/39                           | 59/36                           | 56/44                           |
| Child Pugh A, %      | NA                                  | 98                               | 92                              | 98                              | 98                              |
| BCLC stage, B/C, %   | NA                                  | 14/86                            | 9/87                            | 14/87                           | 12/88                           |
| AFP ≥400 ng/mL, %    | 41                                  | 43                               | 50a                             | 47a                             | 42                              |
| MVI, %               | 27                                  | 29                               | 31                              | 33                              | 29                              |
| EHS, %               | 79                                  | 70                               | 65                              | 74                              | 73                              |
| Etiology, %          | Alcohol                             | NA                               | 24                              | 23                              | 18                              | –
| HBV                  | 38                                  | 38                               | 39                              | 25                              | 35                              |
| HCV                  | 22                                  | 21                               | 28                              | 26                              | 27                              |
| NASH                 | NA                                  | 7                                | –                               | 4                               | –                               |
| Intolerance of sorafenib, % | –                              | 0                                | 13                              | 19                              | 13                              |
| Median total duration of prior sorafenib, months | 5.3                              | 7.8                              | –                               | –                               | –                               |
| Median time from disease progression to randomization, months | 1.6                              | 0.9                              | –                               | –                               | –                               |

AFP, alpha-fetoprotein; MVI, macrovascular invasion; EHS, extrahepatic spread; NASH, non-alcoholic steatohepatitis.

Fig. 4. New treatment landscape in HCC associated with the emergence of multiple molecular-targeted agents. Identification of the subgroup that easily develops to TACE failure/refractory may be important. BSC, best supportive care.
Liver Cancer

Kudo: Cabozantinib as a Second-Line Agent in Advanced Hepatocellular Carcinoma

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HCC will soon undergo major changes as systemic therapy is integrated into the treatment for all stages, from early to intermediate to advanced, which could drastically improve the prognosis of patients with HCC.

Conclusion

The success of the clinical trial of cabozantinib increased the treatment options for HCC, and combination treatment with immunotherapy may soon improve the prognosis of patients with HCC.

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