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AN EXPLORATORY SUBGROUP ANALYSIS OF A PHASE II/III TRIAL OF DONAFENIB VERSUS SORAFENIB IN THE FIRST-LINE TREATMENT OF ADVANCED HEPATOCELLULAR CARCINOMA

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BACKGROUND

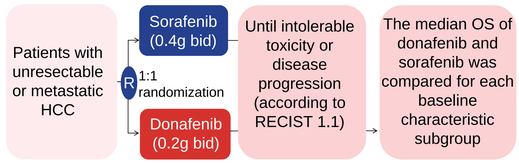
- In 2020, there were 410,000 new cases of liver cancer in China accounting for 45% of global cases (910,000), and its mortality rate was the second highest among all cancers in China with 391,200 deaths[1].
- Donafenib is a novel multikinase inhibitor, and it showed potential benefits in a previous phase Ib study in hepatocellular carcinoma (HCC)[2].
- An open-label, randomized, multicentre phase II/III trial (ZGDH3) has demonstrated that compared with sorafenib, donafenib significantly prolonged the overall survival (OS) of patients with advanced HCC[3].
- Donafenib also showed a better survival benefit than sorafenib in the prespecified subgroup analysis[3-4].

AIM

This article aimed to further explore whether the baseline characteristics of patients other than the predefined subgroups were related to the better OS benefit of donafenib.

METHOD

Figure 1. Study Design



Analytical Method

- The statistical analysis for this report was based on the intention-to-treat (ITT) population of ZGDH3 study (which included 334 patients receiving donafenib and 334 patients receiving sorafenib).
- The median OS of donafenib and sorafenib of each subgroup was assessed by the Kaplan-Meier method. The stratified Cox proportional hazard model was used to calculate the hazard ratio and its 95% confidence interval.

RESULTS

- A total of 668 patients were included in the analysis (334 in each group). The baseline characteristics of patients in subgroups involved in this analysis included ECOG PS score, Child Pugh score, alanine aminotransferase (ALT), aspartate transaminase (AST), alfa-Fetoprotein (AFP), with or without prior interventional therapy, lung target lesion, lymph node target lesion, primary liver lesion, age, BMI, and number of target lesions (Figure 2).
- The result showed that donafenib was associated with a trend of improved OS benefit when compared with sorafenib in most subgroups (HR < 1) (Figure 2).

Figure 2. Exploratory subgroup comparison of donafenib *vs.* sorafenib in OS

Subgroup	Events/Patients		Median (months)		HR (95% CI)	*p* value
	Donafenib	Sorafenib	Donafenib	Sorafenib	Donafenib *vs.* Sorafenib	
ECOG PS						
0	98/132	87/111	12.4	11.4	0.919 (0.687, 1.229)	0.5687
1	157/202	189/223	11.7	9.6	0.804 (0.649, 0.996)	0.0462
Child Pugh						
5	196/267	210/262	13.0	11.8	0.857 (0.705, 1.042)	0.1217
6	55/63	54/59	7.9	8.0	0.774 (0.528, 1.135)	0.1892
ALT						
Normal	189/255	204/251	12.5	10.9	0.839 (0.688, 1.023)	0.0831
Abnoraml	66/79	72/83	9.2	9.2	0.857 (0.611, 1.204)	0.3739
AST						
Normal	123/177	134/173	15.7	13.5	0.776 (0.606, 0.993)	0.0439
Abnoraml	132/157	142/161	8.6	8.8	0.947 (0.746, 1.200)	0.6501
AFP						
≥200μg/L	160/192	168/191	9.5	8.9	0.852 (0.686, 1.059)	0.1488
<200μg/L	95/142	108/143	18.1	15.4	0.786 (0.595, 1.038)	0.0893
Prior Interventional Therapy						
Yes	160/210	183/221	12.1	10.6	0.889 (0.719, 1.099)	0.2768
No	95/124	93/113	11.5	8.8	0.741 (0.554, 0.991)	0.0433
Lung Target Lesion						
Yes	72/83	60/74	8.1	10.5	1.198 (0.841, 1.707)	0.3178
No	183/251	216/260	13.0	10.1	0.758 (0.622, 0.925)	0.0062
Lymph Node Target Lesion						
Yes	34/42	47/50	7.9	7.2	0.599 (0.380, 0.945)	0.0277
No	221/292	229/284	12.3	11.3	0.898 (0.747, 1.081)	0.2564
Age						
≥65	29/41	43/51	12.1	8.9	0.516 (0.315, 0.847)	0.0089
<65	226/293	233/283	11.8	10.3	0.901 (0.750, 1.082)	0.2630
BMI						
≥25	60/80	68/89	13.3	15.8	1.069 (0.751, 1.521)	0.7109
<25	195/254	208/245	11.2	9.1	0.757 (0.622, 0.921)	0.0054
Primary Liver Lesion						
Yes	164/208	170/204	11.2	9.3	0.817 (0.659, 1.014)	0.0663
No	91/126	106/130	13.1	12.6	0.875 (0.659, 1.161)	0.3542
Number of Targe Lesions						
1	78/118	92/121	17.6	13.5	0.779 (0.573, 1.057)	0.1089
2	115/147	122/147	11.6	9.6	0.840 (0.650, 1.087)	0.1847
≥3	62/69	62/66	7.4	7.6	0.922 (0.645, 1.317)	0.6546

- There were significant differences in the following subgroups (p<0.05): ECOG PS score of 1, normal AST, no prior interventional therapy, lung target lesion absent, lymph node target lesion present, age ≥ 65 years, and BMI < 25 (Figure 2-9).
- Among patients ≥ 65 years of age, the median OS of the donafenib group and the sorafenib group was 12.1 and 8.9 months, respectively, representing the most significant benefit in the donafenib group (HR 0.516, 95% CI 0.315–0.847) (Figure 8).

Figure 3. K-M plots of OS by ECOG PS 0 and 1 for donafenib *vs.* sorafenib

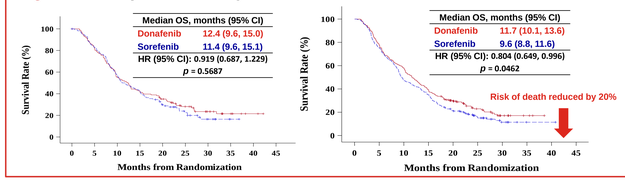


Figure 4. K-M plots of OS by AST normal and abnormal for donafenib *vs.* sorafenib

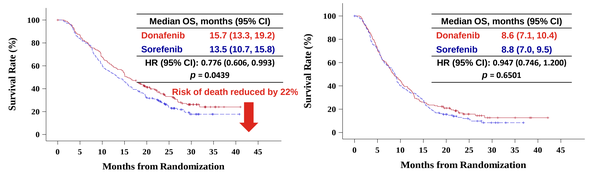


Figure 5. K-M plots of OS by prior interventional therapy and no prior interventional therapy for donafenib *vs.* sorafenib

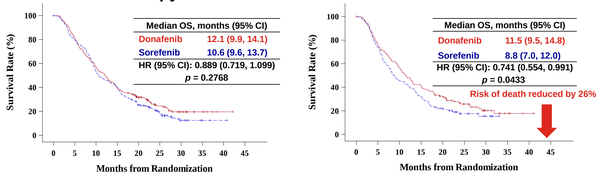


Figure 6. K-M plots of OS by presence and absence of lung target lesion for donafenib *vs.* sorafenib

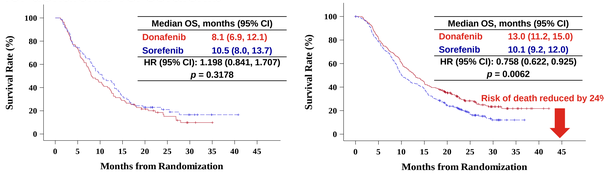


Figure 7. K-M plots of OS by presence and absence of lymph node target lesion for donafenib *vs.* sorafenib

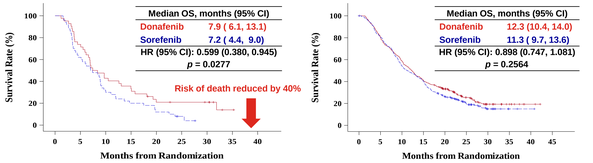


Figure 8. K-M plots of OS by age ≥65 and < 65 for donafenib *vs.* sorafenib

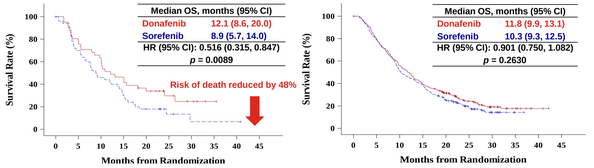
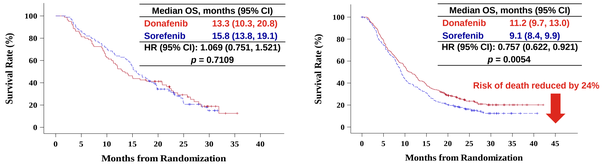


Figure 9. K-M plots of OS by BMI ≥25 and < 25 for donafenib *vs.* sorafenib



CONCLUSION

- Donafenib exhibited a better survival benefit than sorafenib in most of the baseline characteristic subgroups, and among them, there were significant differences in patients with ECOG PS score of 1, normal AST, no prior interventional therapy, lung target lesion absent, lymph node target lesion present, age ≥ 65 years, and BMI < 25.
- The survival benefit in the subgroups further confirmed the excellent efficacy of donafenib in the first-line treatment of advanced HCC.

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