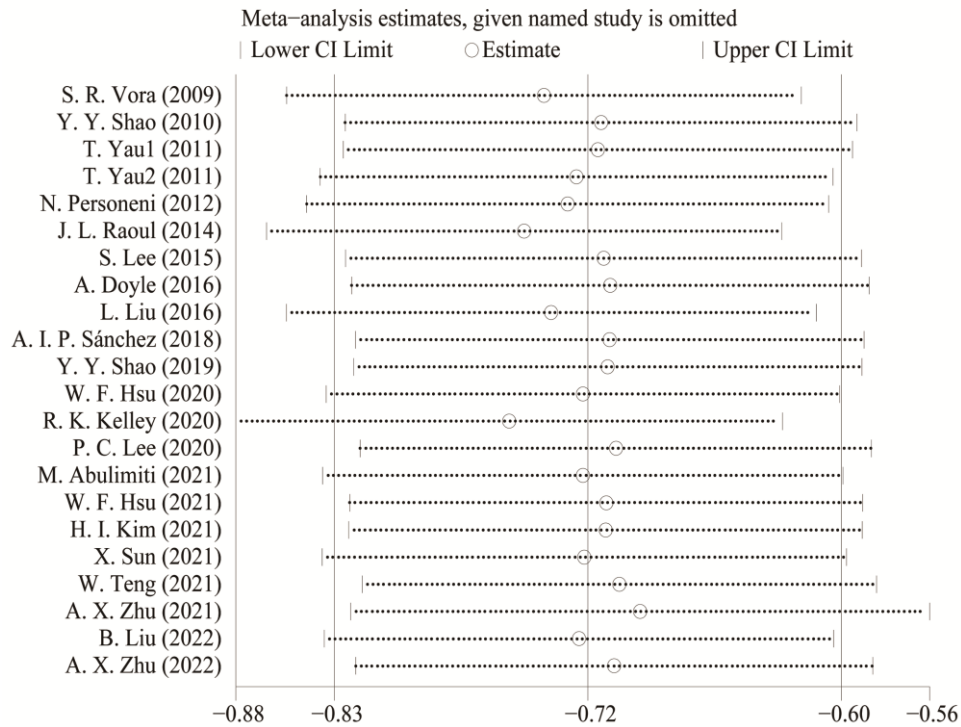


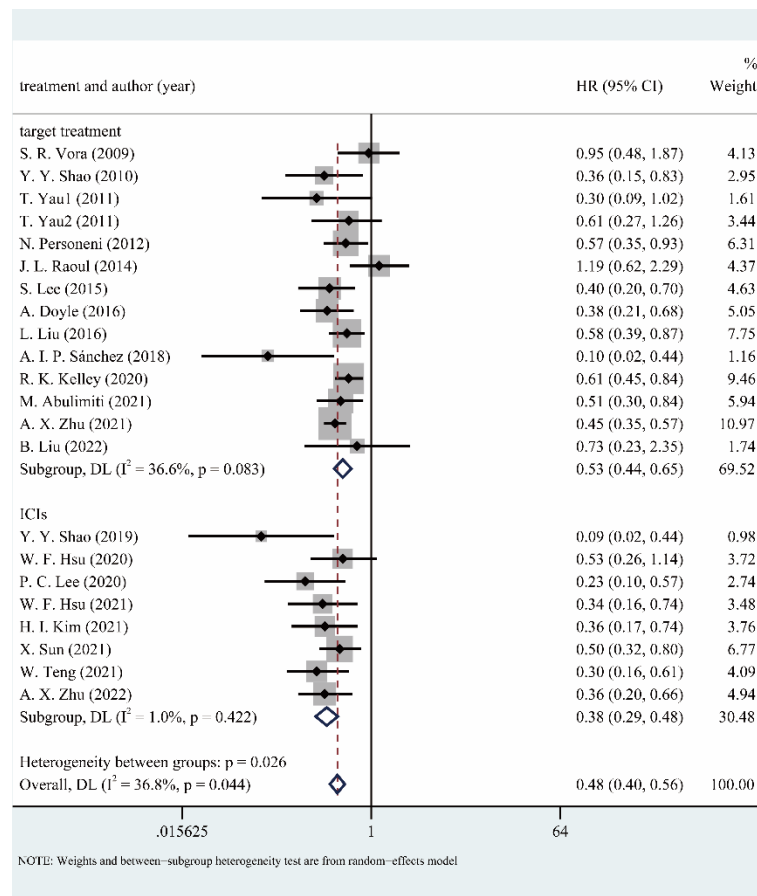
## Supplementary Information

### Inventory of Supplementary Information

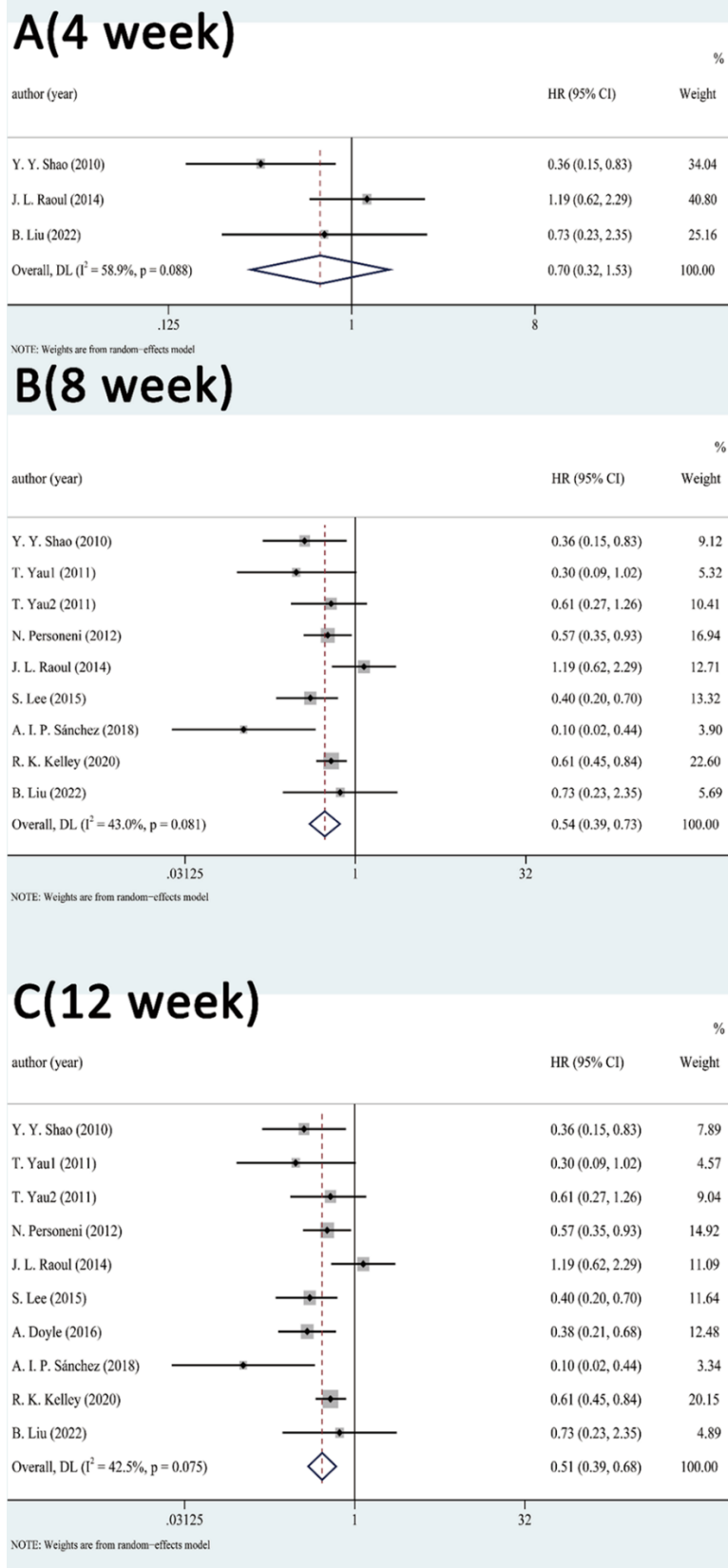
|                               |            |
|-------------------------------|------------|
| 1. Supplementary Figures..... | Pages 2-8  |
| 2. Supplementary Tables.....  | Pages 9-17 |



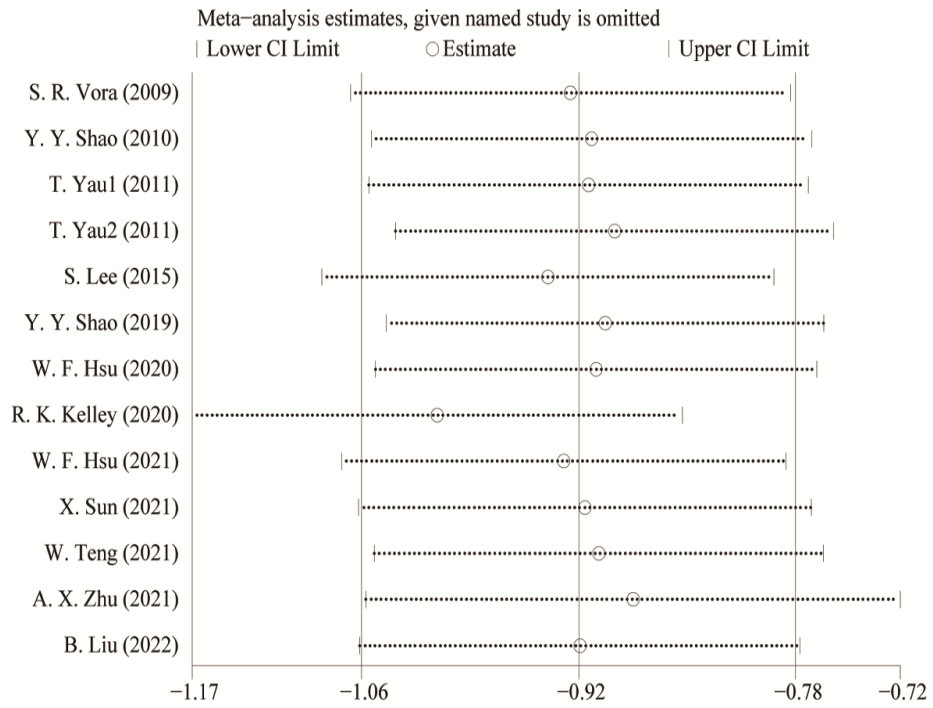
**Supplementary Fig1.** Sensitivity analysis for OS in HCC patients with AFP response.



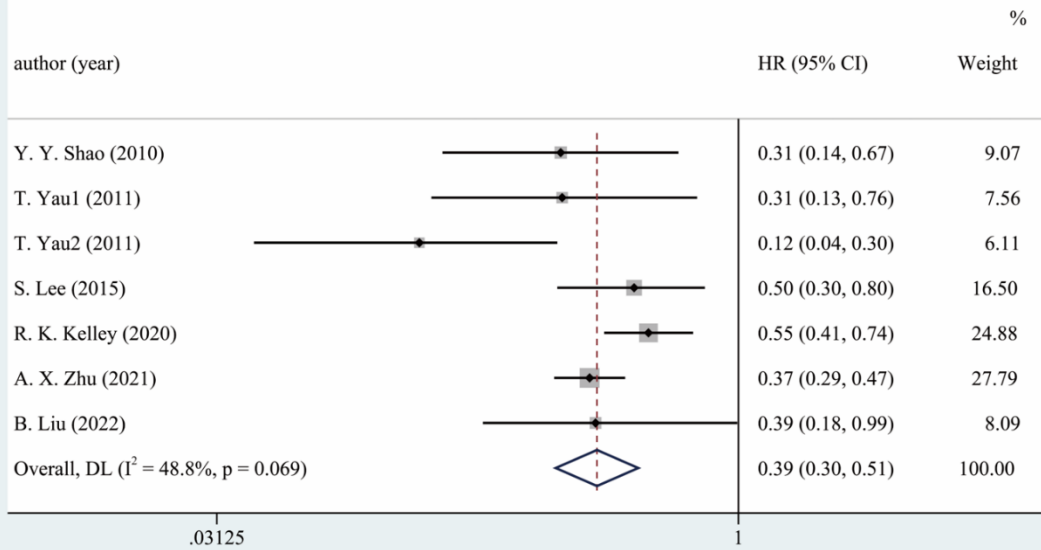
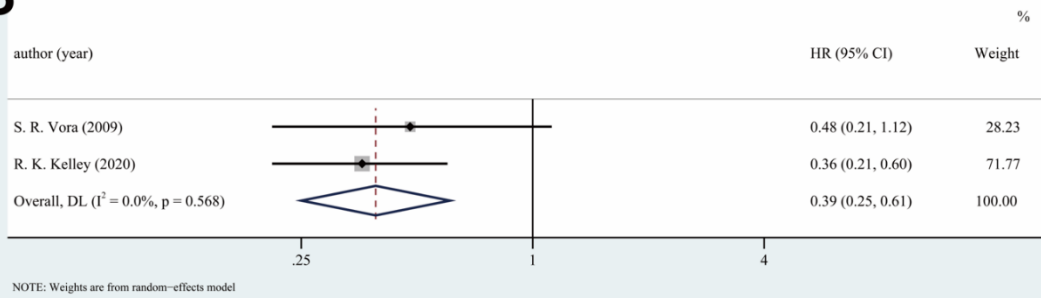
**Supplementary Fig2.** Forest plots of OS in HCC patients with AFP response in treatment subgroup.



**Supplementary Fig3.** A. Forest plots of OS in HCC patients receiving targeted therapy with AFP decrease >20% within 4 weeks; B. Forest plots of OS in HCC patients receiving targeted therapy with AFP decrease >20% within 8 weeks; C. Forest plots of OS in HCC patients receiving targeted therapy with AFP decrease >20% within 12 weeks.

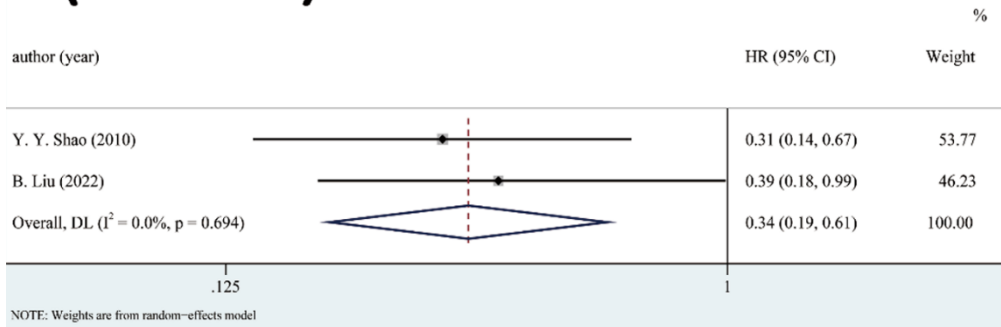


**Supplementary Fig4.** Sensitivity analysis for PFS in HCC patients with AFP response.

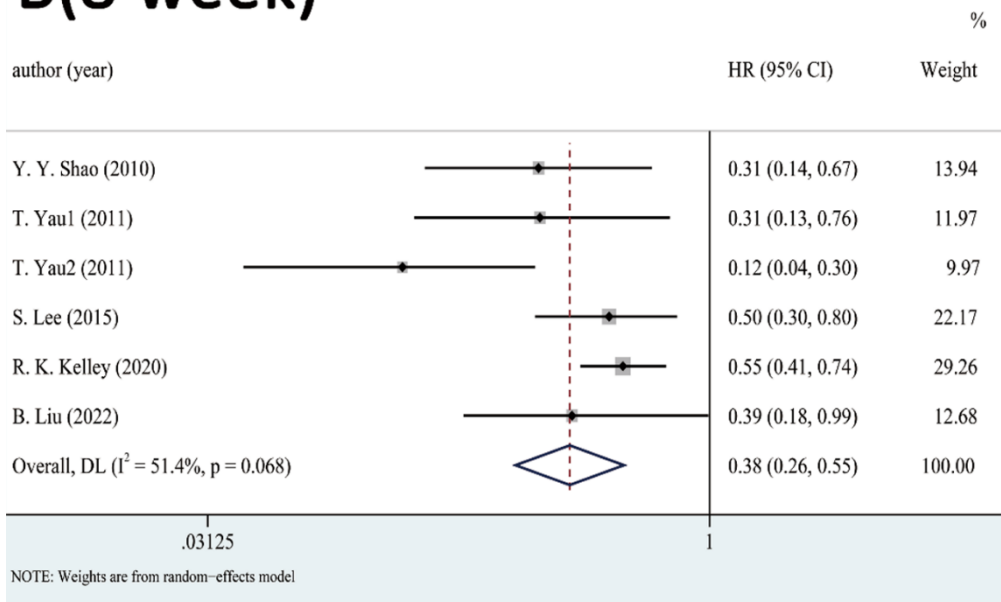
**A****B**

**Supplementary Fig5.** A. Forest plots of PFS in HCC patients receiving targeted therapy with AFP decrease>20%. B. Forest plots of PFS in HCC patients receiving targeted therapy with AFP decrease>50%.

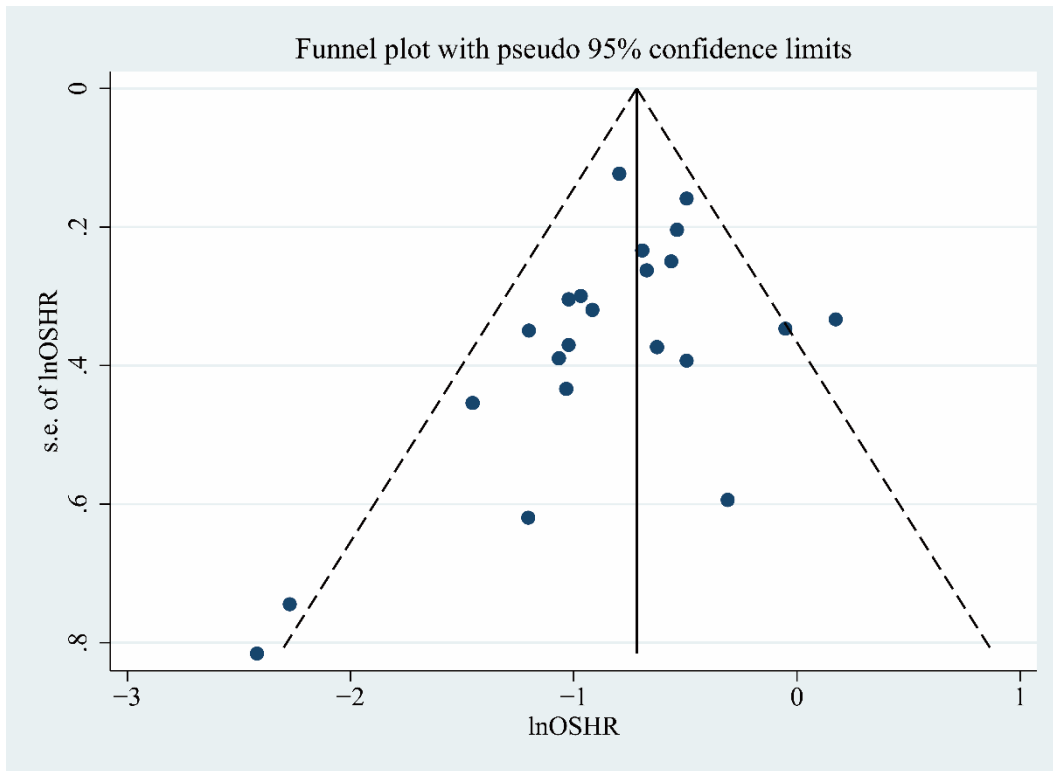
# A(4 week)



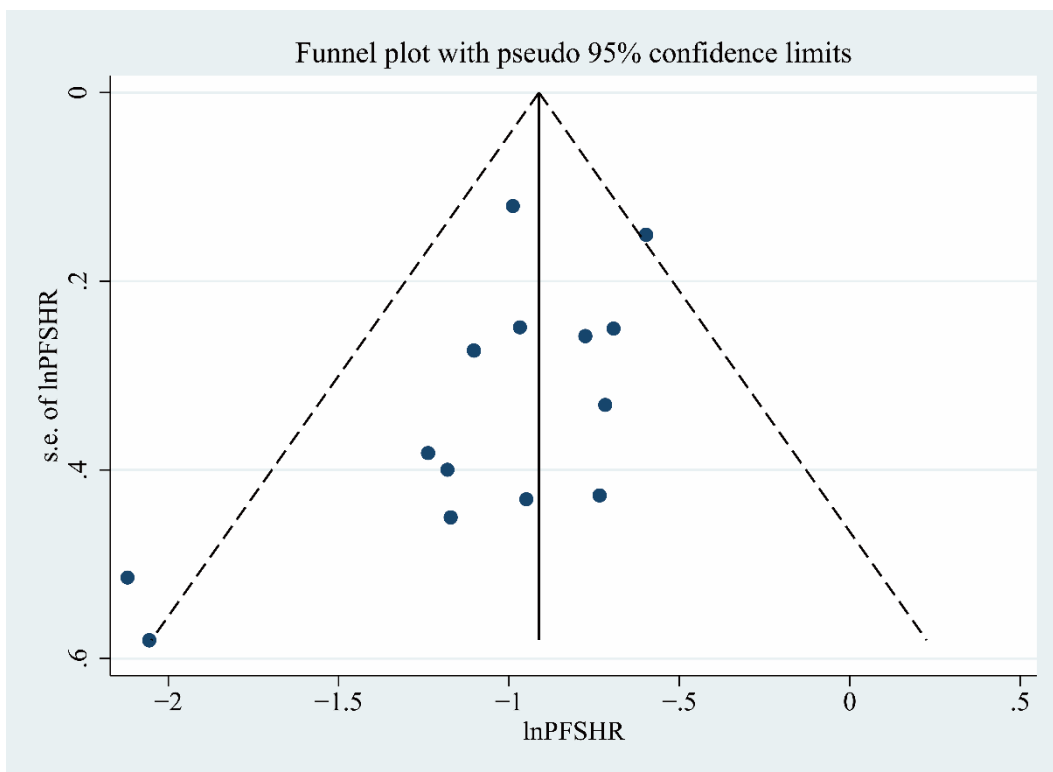
# B(8 week)



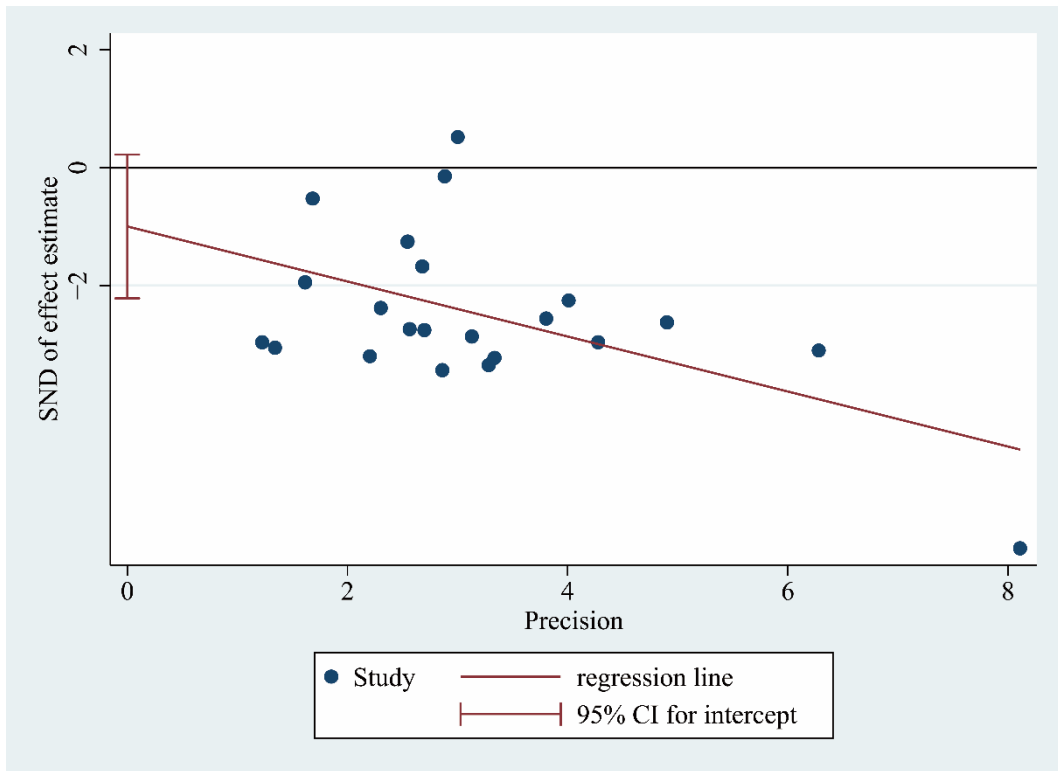
**Supplementary Fig6. A.** Forest plots of PFS in HCC patients receiving targeted therapy with AFP decrease >20% within 4 weeks; **B.** Forest plots of PFS in HCC patients receiving targeted therapy with AFP decrease >20% within 8 weeks.



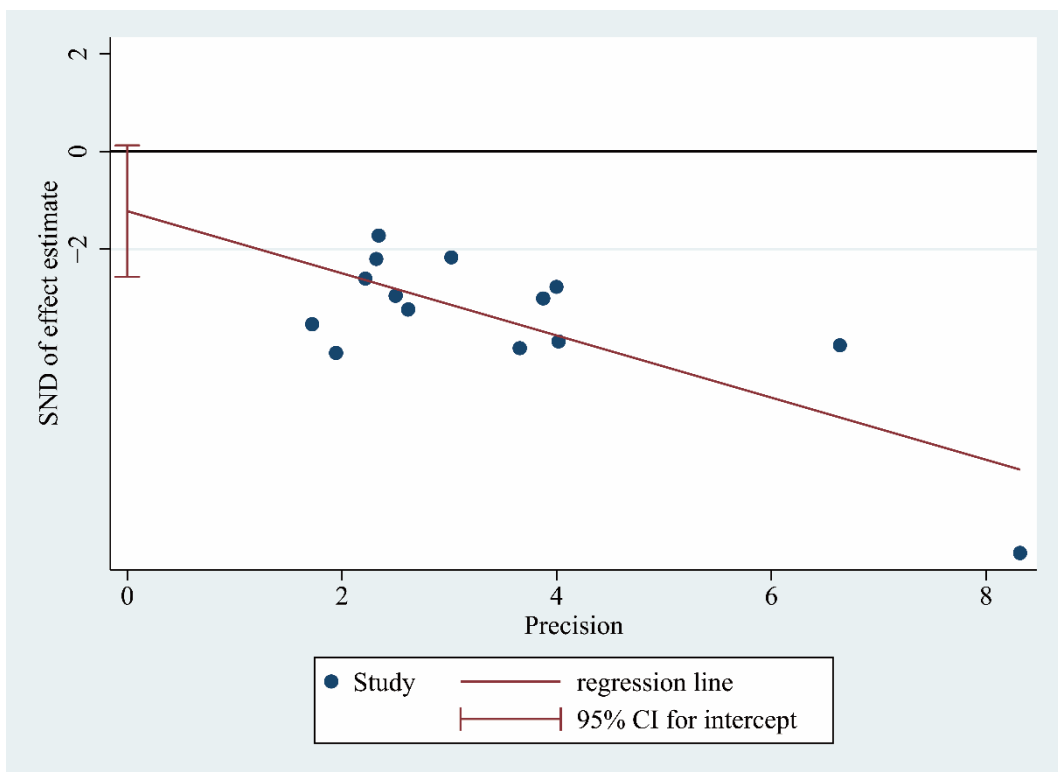
**Supplementary Fig7.** Funnel plots of OS in HCC patients with AFP response.



**Supplementary Fig8.** Funnel plots of PFS in HCC patients with AFP response.



**Supplementary Fig9.** Egger's test of OS in HCC patients with AFP response.



**Supplementary Fig10.** Egger's test of PFS in HCC patients with AFP response.



**Supplementary Table: Database-specific search strategy**

|                   |   |   |
|-------------------|---|---|
| P (population)    | Keywords searched for in abstract and title             | "Carcinoma, Hepatocellular" OR "hepatocellular carcinoma*" OR "hepatocellular cancer" OR "hepatocellular cancer" OR "hepatic carcinoma*" OR HCC OR "liver cancer" OR "liver carcinoma*" OR "hepatoma"   |
| I (intervention)  | Keywords searched for in abstract and title             | (Immunotherapy OR "immune checkpoint inhibitors" OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR camrelizumab OR SHR-1210 OR durvalumab OR bevacizumab OR ipilimumab OR tislelizumab OR toripalimab OR penpulimab) OR ("targeted therapy" OR "targeted drug therapies" OR sorafenib OR Lenvatinib OR regorafenib OR cabozantinib OR ramucirumab OR brivanib OR everolimus OR tivantinib OR sunitinib OR erlotinib) |
| C (comparison)    | Keywords searched for in abstract, title                | ("alpha-Fetoproteins" OR alpha-Fetoprotein* OR "alpha Fetoprotein*" OR AFP OR "alpha fetal protein" OR alpha-fetal-protein) AND (response OR change OR increase OR decrease OR responses OR changes)  |
| O (outcome)       | Limits to overall survival or progression free survival |   |
| S (study design)  | none  |   |
| Additional limits | Limits to English language only                         |   |

## Supplementary Retrieval Methods

### Pubmed Search Method:

("alpha-Fetoproteins" OR alpha-Fetoprotein\* OR "alpha Fetoprotein\*" OR AFP OR "alpha fetal protein" OR alpha-fetal-protein) AND ("Carcinoma, Hepatocellular" OR "hepatocellular carcinoma\*" OR "hepatocellular cancer" OR "hepatocellular cancer" OR "hepatic carcinoma\*" OR HCC OR "liver cancer" OR "liver carcinoma\*" OR "hepatoma") AND (response OR change OR increase OR decrease OR responses OR changes) AND ((immunotherapy OR "immune checkpoint inhibitors" OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR camrelizumab OR SHR-1210 OR durvalumab OR bevacizumab OR ipilimumab OR tislelizumab OR toripalimab OR penpulimab) OR ("targeted therapy" OR "targeted drug therapies" OR sorafenib OR Lenvatinib OR regorafenib OR cabozantinib OR ramucirumab OR brivanib OR everolimus OR tivantinib OR sunitinib OR erlotinib))

Result: 562 April 20, 2022

### Embase Search Method:

('alpha-fetoproteins'/exp OR 'alpha-fetoproteins' OR 'alpha fetoprotein\*' OR afp OR 'alpha fetal protein') AND ('carcinoma, hepatocellular'/exp OR 'carcinoma, hepatocellular' OR 'hepatocellular carcinoma\*' OR 'hepatocellular cancer' OR 'hepatic carcinoma\*' OR hcc OR 'liver cancer'/exp OR 'liver cancer' OR 'liver carcinoma\*' OR 'hepatoma\*') AND ('response'/exp OR response OR 'change'/exp OR change OR increase OR decrease OR responses OR changes) AND ('immunotherapy'/exp OR immunotherapy OR 'immune checkpoint inhibitors'/exp OR 'immune checkpoint inhibitors' OR 'nivolumab'/exp OR nivolumab OR 'pembrolizumab'/exp OR pembrolizumab OR 'atezolizumab'/exp OR atezolizumab OR 'avelumab'/exp OR avelumab OR 'camrelizumab'/exp OR camrelizumab OR 'shr 1210'/exp OR 'shr 1210' OR 'durvalumab'/exp OR durvalumab OR 'bevacizumab'/exp OR bevacizumab OR 'ipilimumab'/exp OR ipilimumab OR 'tislelizumab'/exp OR tislelizumab OR 'toripalimab'/exp OR toripalimab OR 'penpulimab'/exp OR penpulimab OR 'targeted therapy'/exp OR 'targeted therapy' OR 'targeted drug therapies' OR 'sorafenib'/exp OR sorafenib OR 'lenvatinib'/exp OR lenvatinib OR 'regorafenib'/exp OR regorafenib OR 'cabozantinib'/exp OR cabozantinib OR 'ramucirumab'/exp OR ramucirumab OR 'brivanib'/exp OR brivanib OR 'everolimus'/exp OR everolimus OR 'tivantinib'/exp OR tivantinib OR 'sunitinib'/exp OR sunitinib OR 'erlotinib'/exp OR erlotinib)

Result: 1747 April 20, 2022

### Web of Science Search Method:

TS=(response OR change OR increase OR decrease OR responses OR changes) AND TS=(immunotherapy OR "immune checkpoint inhibitors" OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR camrelizumab OR SHR-1210 OR durvalumab OR bevacizumab OR ipilimumab OR tislelizumab OR toripalimab OR penpulimab OR "targeted therapy" OR "targeted drug therapies" OR sorafenib OR Lenvatinib OR regorafenib OR cabozantinib OR ramucirumab OR britanin OR everolimus OR tivantinib OR sunitinib OR erlotinib) AND TS=("Carcinoma, Hepatocellular" OR "hepatocellular carcinoma\*" OR "hepatocellular cancer" OR "hepatocellular cancer" OR "hepatic carcinoma\*" OR HCC OR "liver cancer" OR "liver carcinoma\*" OR "hepatoma\*") AND TS=("alpha-Fetoproteins" OR alpha-Fetoprotein\* OR "alpha Fetoprotein\*" OR AFP OR "alpha fetal protein" OR alpha-fetal-protein)

Result:981 April 20, 2022

### Cochrane library database Search Method:

("alpha-Fetoproteins" OR "alpha Fetoprotein" OR AFP OR "alpha fetal protein" OR alpha-fetal-protein) AND ("hepatocellular carcinoma\*" OR "hepatocellular cancer" OR

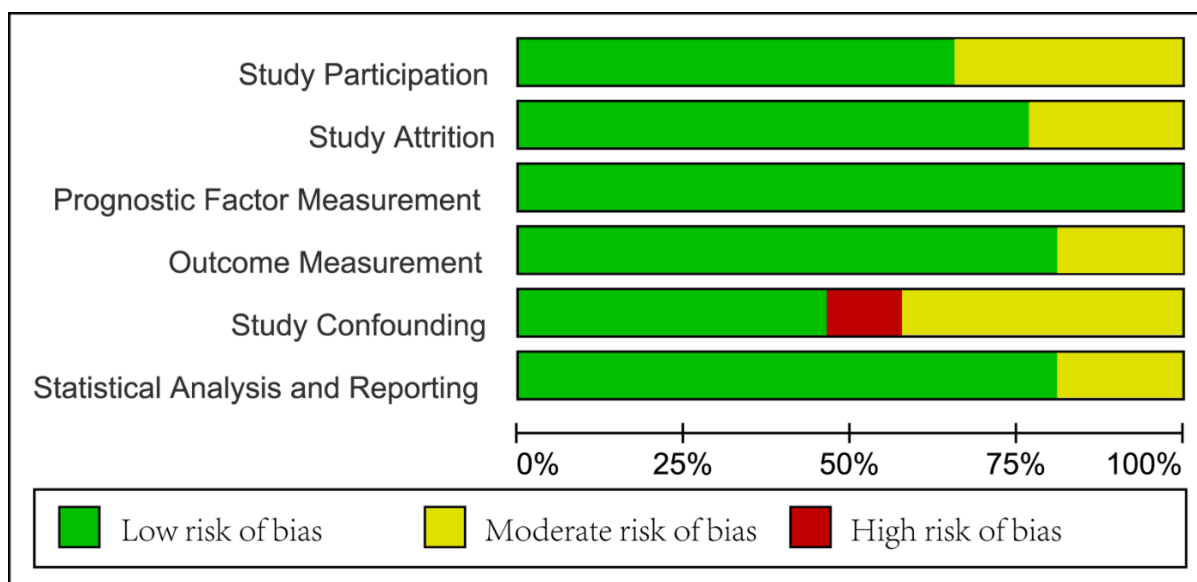
"hepatocellular cancer" OR "hepatic carcinoma" OR HCC OR "liver cancer" OR "liver carcinoma" OR "hepatoma\*") AND (response OR change OR increase OR decrease OR responses OR changes) AND ((immunotherapy OR "immune checkpoint inhibitors" OR nivolumab OR pembrolizumab OR atezolizumab OR avelumab OR camrelizumab OR SHR-1210 OR durvalumab OR bevacizumab OR ipilimumab OR tislelizumab OR toripalimab OR penpulimab) OR ("targeted therapy" OR "targeted drug therapies" OR sorafenib OR Lenvatinib OR regorafenib OR cabozantinib OR ramucirumab OR brivanib OR everolimus OR tivantinib OR sunitinib OR erlotinib))

**Result:172 April 20, 2022**

**Supplementary Table 1:** Details of Quality in Prognosis Studies

|                       | <b>Study Participation</b> | <b>Study Attrition</b> | <b>Prognostic Factor Measurement</b> | <b>Outcome Measurement</b> | <b>Study Confounding</b> | <b>Statistical Analysis and Reporting</b> |
|-----------------------|----------------------------|------------------------|--------------------------------------|----------------------------|--------------------------|---|
| S. R. Vora-2009       | Moderate                   | Low                    | Low                                  | Moderate                   | Moderate                 | Low                                       |
| Y. Y. Shao-2010       | Low                        | Low                    | Low                                  | Low                        | Low                      | Low                                       |
| T. Kuzuya-2011        | Moderate                   | Low                    | Low                                  | Low                        | High                     | Moderate                                  |
| T. Yau-2011           | Low                        | Low                    | Low                                  | Low                        | Low                      | Low                                       |
| T. Kawaoka-2012       | Moderate                   | Moderate               | Low                                  | Moderate                   | Low                      | Low                                       |
| N. Personeni-2012     | Low                        | Low                    | Low                                  | Low                        | Moderate                 | Low                                       |
| T. Nakazawa-2013      | Moderate                   | Low                    | Low                                  | Low                        | Low                      | Low                                       |
| J. L. Raoul-2014      | Low                        | Low                    | Low                                  | Low                        | High                     | Moderate                                  |
| T. Kuzuya-2015        | Low                        | Low                    | Low                                  | Moderate                   | Moderate                 | Low                                       |
| S. Lee-2015           | Low                        | Low                    | Low                                  | Low                        | Moderate                 | Low                                       |
| A. Doyle-2016         | Low                        | Moderate               | Low                                  | Moderate                   | Low                      | Moderate                                  |
| L. Liu-2016           | Low                        | Moderate               | Low                                  | Low                        | Moderate                 | Moderate                                  |
| A. I. P. Sánchez-2018 | Moderate                   | Low                    | Low                                  | Low                        | Moderate                 | Low                                       |
| Y. Y. Shao-2019       | Moderate                   | Low                    | Low                                  | Low                        | Low                      | Low                                       |
| W. F. Hsu-2020        | Moderate                   | Low                    | Low                                  | Low                        | Low                      | Low                                       |

|                   |          |          |     |          |          |          |
|-------------------|----------|----------|-----|----------|----------|----------|
| R. K. Kelley-2020 | Low      | Moderate | Low | Low      | Low      | Low      |
| P. C. Lee-2020    | Low      | Low      | Low | Low      | Low      | Low      |
| M. Abulimiti-2021 | Moderate | Low      | Low | Low      | Moderate | Low      |
| W. F. Hsu-2021    | Low      | Moderate | Low | Low      | Low      | Low      |
| H. I. Kim-2021    | Low      | Moderate | Low | Low      | Moderate | Low      |
| X. Sun-2021       | Low      | Low      | Low | Low      | Moderate | Low      |
| W. Teng-2021      | Low      | Low      | Low | Low      | Low      | Low      |
| A. X. Zhu-2021    | Low      | Low      | Low | Moderate | High     | Moderate |
| P.-Y. Hsu-2022    | Low      | Low      | Low | Low      | Moderate | Low      |
| B. Liu-2022       | Moderate | Low      | Low | Low      | Low      | Low      |
| A. X. Zhu-2022    | Low      | Low      | Low | Low      | Moderate | Low      |



**Supplementary Fig. Risk of bias summary**

**Supplementary Table 2: Details of analysis type and adjusted major confounders**

|                       | <b>Analysis type</b>  | <b>Adjusted major confounders</b>  |
|-----------------------|-----------------------|--|
| S. R. Vora-2009       | Multivariate Analysis | age, ECOG performance status score, and serum total bilirubin  |
| Y. Y. Shao-2010       | Multivariate Analysis | treatment cohort, age, sex, performance status, hepatitis etiology, vascular invasion, extrahepatic involvement, metastatic sites, CLIP score, Okuda stage and BCLC stage  |
| T. Kuzuya-2011        | Univariate Analysis   | NA   |
| T. Yau-2011           | Multivariate Analysis | age, sex, large or diffuse tumor, bilobar involvement, portal vein invasion, presence of distant metastases, HBV status, HCV status, the use of antiviral therapy, presence of baseline ascites, baseline liver function and ECOG performance status |
| T. Kawaoka-2012       | Multivariate Analysis | age, gender, etiology, platelet count, Child-Pugh, tumor volume, metastasis, tumor thrombosis  |
| N. Personeni-2012     | Multivariate Analysis | CLIP stage and alanine transaminase  |
| T. Nakazawa-2013      | Multivariate Analysis | age, sex, hepatitis etiology, Child-Pugh score, BCLC stage, intrahepatic vascular invasion, distant metastasis, performance status and early increases in DCP  |
| J. L. Raoul-2014      | Univariate Analysis   | NA   |
| T. Kuzuya-2015        | Multivariate Analysis | disappearance of arterial tumor enhancement on CE-CT and two or more increments in the CP score  |
| S. Lee-2015           | Multivariate Analysis | ECOG, Child-Pugh, Tumor size and portal vein invasion  |
| A. Doyle-2016         | Multivariate Analysis | BCLC stage, Child-Pugh class, ECOG, baseline AFP, macrovascular invasion, extrahepatic metastases, starting dose, dose reduction due to irAEs, diarrhea, hand-foot skin reaction, nausea and hypertension  |
| L. Liu-2016           | Multivariate Analysis | ECOG and PVTT  |
| A. I. P. Sánchez-2018 | Multivariate Analysis | age, ECOG performance status, Child-Pugh class and basal AFP   |
| Y. Y. Shao-2019       | Multivariate Analysis | age, sex, HBV, HCV, macrovascular invasion, extrahepatic metastasis, AFP>400 ng/mL, combination therapy and previous lines of systemic therapy   |

|                   |                       |   |
|-------------------|-----------------------|---|
| W. F. Hsu-2020    | Multivariate Analysis | age, sex, alcohol, HBV, HCV, irAEs, TTV, tumor number, MVI, EHM, CLIP, AFP, NLR, AST, ALT, Child-Pugh, ALBI, prior therapy and concurrent therapy     |
| R. K. Kelley-2020 | Multivariate Analysis | baseline AFP level, ECOG PS, macrovascular invasion, extrahepatic spread, age, gender and etiology  |
| P. C. Lee-2020    | Multivariate Analysis | tumor size, tumor volume, portal vein invasion, AFP, ALT, AST and Child-Pugh class  |
| M. Abulimiti-2021 | Multivariate Analysis | gender, Child-Pugh, AFP levels, radiation dose, overall response and sorafenib  |
| W. F. Hsu-2021    | Multivariate Analysis | sex, DM, irAEs, TTV, MVI, AFP, AST, ALT, NLR, Child-Pugh class, ALBI grade and combination therapy  |
| H. I. Kim-2021    | Multivariate Analysis | HBV, Child-Pugh class, portal vein invasion and first-line of systemic treatment  |
| X. Sun-2021       | Multivariate Analysis | vascular invasion, extrahepatic metastasis, ALBI grade PIVKA- II reduction and baseline AFP level   |
| W. Teng-2021      | Multivariate Analysis | age, sex, viral infection, ALBI grade, platelet count, portal vein thrombosis, extrahepatic metastasis, AFP, BCLC stage, first line therapy and irAEs |
| A. X. Zhu-2021    | Univariate Analysis   | NA  |
| P.-Y. Hsu-2022    | Multivariate Analysis | ALBI grade, macrovascular invasion, AFP and extrahepatic metastasis   |
| B. Liu-2022       | Multivariate Analysis | age, ALBI grade, ECOG PS, extrahepatic metastasis and portal vein metastasis  |
| A. X. Zhu-2022    | Multivariate Analysis | age, baseline AFP and etiology  |

**Supplementary Table 3: Details of the previous treatment of the patients**

|                   | <b>Intervention</b>             | <b>Patient No.</b> | <b>Previous treatment</b>   |
|-------------------|---------------------------------|--------------------|---|
| S. R. Vora-2009   | Targeted therapy                | 107                | Prior treatment with two or fewer systemic agents/regimens was permitted. |
| Y. Y. Shao-2010   | Antiangiogenic Targeted Therapy | 72                 | Partially allow prior TACE  |
| T. Kuzuya-2011    | Sorafenib                       | 48                 | Initial therapy(6) /therapy for recurrence(42)                            |
| T. Yau-2011       | Sorafenib                       | 94                 | Surgical treatment(31) /TACE(36) / RFA(15) /chemotherapy(9)               |
| T. Kawaoka-2012   | Sorafenib                       | 66                 | TACE(21) /HAIC(16) /systemic chemotherapy(10)                             |
| N. Personeni-2012 | Sorafenib                       | 85                 | Sorafenib as first-line treatment   |
| T. Nakazawa-2013  | Sorafenib                       | 59                 | Previous treatments: presence(54) /absence(5)                             |
| J. L. Raoul-2014  | Brivanib alaninate              | 70                 | Prior local treatment: 49% for cohortA /83% for cohortB                   |
| T. Kuzuya-2015    | Sorafenib                       | 57                 | Initial therapy(9) /therapy for recurrence(48)                            |
| S. Lee-2015       | Sorafenib                       | 126                | Previous treatment history: 94  |
| A. Doyle-2016     | Sorafenib                       | 92                 | Prior treatment: 64%  |
| L. Liu-2016       | Sorafenib with TACE             | 118                | Sorafenib before TACE(52) /TACE before sorafenib(62) /meanwhile(4)        |



|                       |  |     |   |
|-----------------------|--|-----|---|
| A. I. P. Sánchez-2018 | Sorafenib                                    | 167 | Locoregional therapy(64) /surgical resection(18) /liver transplants(7) /not any treatment(53) /no information(25) |
| Y. Y. Shao-2019       | ICIs(mainly PD-1 blockade)                   | 43  | Prior lines of systemic therapy: 0(12) /1(17) /≥2(14)   |
| W. F. Hsu-2020        | Nivolumab                                    | 87  | Sorafenib(43) /lenvatinib(7) /TACE(49) /TARE(2) /radiotherapy(44) /surgery(16) /RFA(15) /PEI(4)                   |
| R. K. Kelley-2020     | Cabozantinib                                 | 236 | Must have received prior sorafenib and could have received up to two prior systemic regimens                      |
| P. C. Lee-2020        | ICIs(nivolumab or pembrolizumab)             | 95  | Surgical resection(35) /RFA(31) /PEIT(9) /MWA(1)/TACE(55) /RT(23) /TARE(5)  |
| H. I. Kim-2021        | ICIs(nivolumab, atezolizumab or bevacizumab) | 108 | Treatment-naïve(4) /surgical resection(54) /locoregional treatment(80) /systemic treatment(81)                    |
| X. Sun-2021           | Anti-PD-1 therapy                            | 235 | Targeted drugs(52) /locoregional treatments(71) /targeted drugs+locoregional treatments(94)                       |
| W. Teng-2021          | Nivolumab                                    | 90  | Prior locoregional therapy: resection(27)/ RFA or TACE(44)  |
| A. X. Zhu-2021        | Ramucirumab                                  | 542 | Most have received previous treatment   |