Tyrosine Kinase Inhibitors in BCLC-B Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) represents an entity of poor prognosis, especially in cases of delayed diagnosis. Tyrosine kinase inhibitors (TKIs) have multiple anti-tumor effects and are widely used in several types of cancers. They down-regulate different molecular pathways that take part in carcinogenesis. The primary targets are the tyrosine kinase receptors (RTKs), key proteins that regulate cancer growth and metastasis. Specifically, TKIs block the phosphorylation of tyrosine kinases and the subsequent signaling pathways, slowing down cancer growth. Some of the inhibited networks are the rat sarcoma (RAS)/mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (Pi3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR), phospholipase C (PLC)/Ca2+/calmodulin-dependent protein kinase-protein kinase C (CaMK-PKC), Janus kinase (JAK)/signal transducer and activator of transcription protein family (STAT), epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), hepatocyte growth factor receptor (HGFR, Met), and RAF kinases. Due to their multiple actions, TKIs were the standard treatment of care in advanced HCC over the last 15 years, but after the induction of IO, they now comprise the second-line option.

Keywords: hepatocellular carcinoma ; liver cancer ; intermediate stage ; BCLC-B

1. Sorafenib

Sorafenib is a small molecular inhibitor of several RTK pathways, including VEGFR 1–3, RAF (CRAF, BRAF, mutant BRAF), PDGFR (PDGFR-β), and MAPK [1]. Its approval as a first-line systemic treatment against advanced, unresectable HCC was received from the FDA in 2008 [2] and EMA in 2009 after the results of the SHARP trial, a multicenter, phase 3, double-blind, randomized, sorafenib- versus placebo-controlled clinical trial [1]. The study included patients with PS less than or equal to 2, compensated liver disease Child–Pugh (C-P) A, adequate hematologic and renal function, and a life expectancy of at least 12 weeks. Subjects with viral and non-viral liver disease were equally distributed in both groups, and the vast majority of them were categorized in the BCLC-C group (82% in the sorafenib group and 83% in the placebo group versus 18% and 17% of BCLC-B, respectively, in the two groups). The study met its primary endpoint, as the median OS was significantly higher in sorafenib compared to the placebo group (10.7 vs. 7.9 months; HR: 0.69; 95% CI: 0.55–0.87, $p < 0.001$), representing a 31% lower risk of death. The study also showed a significantly prolonged time to radiological progression in the sorafenib group vs. placebo (5.5 vs. 2.8 months; HR: 0.58; 95% CI: 0.45–0.74, $p < 0.001$), while 2% of patients in the former group experienced partial response versus 1% in the latter. Regarding safety profile, the overall incidence of treatment-related AEs was 80% in sorafenib compared to 50% in the placebo, with the most common sorafenib-induced AEs being gastrointestinal, constitutional, or dermatologic (grades 1 and 2), while diarrhea was the most common grade 3 AE (8% in the sorafenib group). Discontinuation rates due to AEs were similar between the two groups (close to 38%).

Afterward, in 2016, the GIDEON study prospectively showed a significant difference in OS between C-P A and C-P B sorafenib-treated patients (13.6 vs. 5.2 months, respectively), without significant differences in type and severity of AE [3]. In line with that, McNamara et al. conducted a meta-analysis of 30 studies, with 8678 C-P A/B patients receiving sorafenib as a first-line systemic treatment for advanced HCC [4]. The authors demonstrated that treatment discontinuation rates without HCC progression as well as treatment-related deaths did not significantly differ between C-P A and B patients. However, C-P B stage was an independent factor of poor prognosis (4.6 months survival in C-P B vs. 8.8 in CP-A, $p < 0.0001$). The results from this meta-analysis as well as those from the GIDEON study illustrated a worse prognosis in cases of treatment initiation after the development of liver decompensation. Unfortunately, a sub-analysis investigating differences in OS between BCLC-B and BCLC-C patients was not performed in any of the aforementioned studies.

Ogasawara S et al. in 2014 and Arizumi T et al. in 2015 first evaluated the efficacy of sorafenib in BCLC-B hepatocellular carcinoma as being refractory to TACE [5][6]. The former group of investigators retrospectively reviewed 509 patients treated with TACE, 122 of whom had refractory HCC. After excluding patients with a C-P score of ≥8 (patients with C-P C and C-P B/8 were excluded) and/or advanced-stage BCLC-C, 20 out of 122 patients converted to sorafenib, and 36 continued with TACE. Interestingly, the time to disease progression (TTP), defined as the time towards the development of C-P C or advanced BCLC-C stage, was 22.3 months in the conversion group and 7.7 months in the non-conversion group (p = 0.001), while the OS was significantly higher in the former compared to the latter group (25.4 vs. 11.5 months, respectively, p = 0.003) [6]. Likewise, Arizumi et al., among 56 non-responders to TACE patients, retrospectively found a median OS of 24.7 months in those who switched to sorafenib (n = 32) compared to 13.6 months (p = 0.002) in those who continued with TACE (n = 24) [6]. The above evidence demonstrated the necessity of shifting from TACE to systemic treatment without delay in cases where TACE was ineffective.

Later on, Ren et al. compared the efficacy of TACE versus sorafenib plus TACE in patients with unresectable HCC. A total of 308 patients (247 in TACE monotherapy and 61 in TACE/sorafenib) were retrospectively evaluated. In the overall analysis including all patients, the median OS was significantly longer in the combination group than in the TACE monotherapy group (29 ± 7.2 vs. 14.9 ± 1.1 months; p = 0.008). In the propensity matching cohort (61 subjects receiving TACE/sorafenib and 122 receiving only TACE), the median OS was 29 ± 7.2 months in the combination group and 14.9 ± 1.5 in the TACE group (HR 0.684, 95% CI: 0.470–0.997; p = 0.018). Exclusively in BCLC-B subjects, the median OS after matching was 33 ± 9.8 months in the combination arm and 25.3 ± 6.7 months in the arm of TACE monotherapy (HR 0.620, 95% CI: 0.345–1.114; p = 0.041) [7]. These findings were in opposition to the results provided by Meyer et al. The latter group of investigators, in a randomized, placebo-controlled, double-blind, phase 3 trial, randomly assigned 313 C-P A patients with unresectable HCC to TACE plus sorafenib (n = 157) or TACE plus a placebo (n = 156). Interestingly, no significant difference was determined between the sorafenib and the placebo group regarding the PFS (238 days (95% CI: 221–281) vs. 235 days (95% CI: 209–322), respectively) (HR 0.99; 95% CI: 0.77–1.27, p = 0.94) [8]. Recently, Kudo et al. established the superiority of TACE/sorafenib compared to TACE alone in a randomized, open-label, multicenter, prospective research that included a large proportion of BCLC-B HCCs (n = 44/80 (55%) in the first group and n = 34/76 (45%) in the second) as well as a significant number of BCLC-A cases (33.8% and 43.4%, respectively; patients with single tumor but unresectable due to size > 5 cm). Although TACE plus sorafenib did not show significant OS benefit over TACE alone (median OS 36.2 months in TACE/sorafenib vs. 30.8 months in TACE monotherapy; HR 0.861; 95% CI: 0.607–1.223; p = 0.40), the combination offered a clinically meaningful prolongation of OS (ΔOS 5.4 months) and a significantly improved PFS (22.8 vs. 13.5 months in TACE/sorafenib vs. TACE alone, respectively) (HR 0.661; 95% CI: 0.466–0.938; p = 0.02) [9]. Additionally, time to vascular invasion, time to extrahepatic spread, and time to stage progression were significantly longer in the combination group, whereas a post hoc analysis revealed PFS and OS benefits in HCC patients with tumor burden beyond the up-to-seven criteria.

2. Regorafenib

The RESORCE trial demonstrated the role of regorafenib in HCC treatment. The primary endpoint of OS in the treatment group was favorable, with an HR of 0.63 relative to the placebo (p < 0.0001). Specifically, regorafenib compared to the placebo significantly extended the median OS (10.6 vs. 7.8 months, respectively), whereas it prolonged the PFS by 1.6 months (3.1 vs. 1.5 months, respectively). Additionally, TTP was 3.2 months in regorafenib and 1.5 months in the placebo group (HR: 0.44; 95% CI: 0.36–0.55, p < 0.001), while the disease control rate (DCR) and overall response rate (ORR) were 65.2% and 10.6% in regorafenib and 36.1% and 4.1% in the placebo, respectively. AEs were reported in all 374 regorafenib recipients (100%) and 179/193 (93%) of placebo recipients. In this trial, 14% of patients in the regorafenib group and 11% in the placebo group had BCLC-B HCC. However, a sub-analysis merely in BCLC-B was not performed, probably due to the small number of included patients [10].

Later on, the REFINE study recruited 500 patients with HCC, of whom 482 (97%) had been previously treated with sorafenib. Regorafenib was the second-line treatment in 81% of patients (n = 403), third-line or higher in 17% (n = 87), and first-line in only 2% (n = 8). The investigators evaluated the OS in patients who had previously received sorafenib, taking into account the C-P stage and the albumin–bilirubin (ALBI) grade at the entry. The median OS was 16 months in C-P A versus 8 months in C-P B subjects. The median OS among those with ALBI grades 1, 2, and 3 was 19.6 months (95% CI, 14.8–19.6), 10.5 (95% CI, 8.7–16.0), and 3.1 months (95% CI, 1.6–8.7), respectively. These results underlined the importance of switching to second-line treatments without delay when the first-line treatment is found to be ineffective, and furthermore, they showed that the better the liver function at the time of conversion, the better the survival [11]. Subsequently, several studies evaluated the effect of regorafenib on OS, PFS, or ORR [12][13][14] but without estimating the effect of regorafenib in patients with BCLC-B HCCs exclusively. Recently, Han Y et al., in a retrospective real-world study,

tried to explore the benefits and tolerability of TACE combined with regorafenib in patients with unresectable HCC who had failed in the first-line treatment with sorafenib. Eighteen BCLC-B and twenty BCLC-C patients were included. After a median follow-up of 5.6 months (range: 0.7–17), the median OS, PFS, and TTP were 14.3, 9.1, and 9.1 months, respectively. The PFS and TTP were found to be associated with AFP levels, tumor size, dose of regorafenib, and degree of response (complete response (CR) vs. partial response (PR) vs. stable disease (SD)), while the OS was associated only with regorafenib's dose and degree of response. The BCLC stage was not found to correlate with OS, PFS, and TTP in the Cox regression analysis [15]. Afterwards, Lee et al., in a retrospective study of 108 patients (BCLC stage B/C: 18.5%/81.5%; albumin–bilirubin (ALBI) grade 1/2/3: 40.7%/58.3%/0.9%; C-P A/B: 84.3%/15.7%) with unresectable HCC treated with regorafenib after sorafenib failure, found no significant difference in PFS between BCLC-B and BCLC-C stages; however, the ALBI grading was associated with OS (2–3/1: HR 2.758, 95% CI: 1.458–5.216, $p = 0.002$) and post-progression survival (ALBI 2/1: HR 4.499, 95% CI: 1.541–13.137, $p = 0.006$ and 3/1: HR 26.926, 95% CI: 6.638–109.227, $p < 0.001$) [13]. Obviously, the study did not detect any improvement in PFS by using regorafenib earlier regarding the BCLC stage, but it clarified an association between the severity of liver dysfunction at the time of regorafenib induction and patients' outcome.

3. Lenvatinib

Lenvatinib is an orally acting antiangiogenic agent that inhibits VEGFR 1–3, FGFR 1–4, PDGFR-α, and RET and KIT tyrosine kinases. In a phase 3 trial (REFLECT), lenvatinib, as a treatment of unresectable HCC, was found to be non-inferior to sorafenib in terms of OS. The trial demonstrated the clinical significance of lenvatinib over sorafenib regarding PFS, TTP, and ORR [16]. In 2019, Kudo et al. conducted a proof-of-concept study to compare lenvatinib versus TACE to explore whether the former is more favorable for intermediate-stage HCC with large or multinodular tumors exceeding the up-to-seven criteria. Among 176 eligible subjects (unresectable HCC, beyond the up-to-seven criteria, no prior TACE/systemic therapy, no vascular invasion, no extrahepatic spread, and C-P A), 30 were treated with lenvatinib and 60 with TACE after propensity score matching for patients' demographics. Change in ALBI score from the baseline to the end of treatment was from −2.61 to −2.61 in lenvatinib patients ($p = 0.254$) and from −2.66 to −2.09 in TACE patients ($p < 0.01$), respectively. The lenvatinib group showed significantly higher ORR (73.3% vs. 33.3%; $p < 0.001$), significantly longer median PFS (16 vs. 3 months; $p < 0.001$), and significantly longer OS compared to TACE (37.9 vs. 21.3 months; HR: 0.48, $p < 0.01$) [17].

Subsequently, Kobayashi et al. prospectively investigated whether treatment with lenvatinib improved survival in TACE-naïve patients with BCLC substage B2 HCC and preserved liver function. Thirty-one patients were enrolled, and substage B2 was defined as C-P score 5–6, beyond the up-to-seven criteria, PS 0, and no portal vein thrombosis. By reviewing the studies published to date, the authors concluded that the median OS and the 1-year survival rates for substage B2 patients treated with TACE were between 15.6 and 26.9 months and 59.2 and 75.5%, respectively [18][19][20][21][22][23]. Given values as historical controls, the threshold of 1-year survival rate after TACE was set to 60%, and this was expected to further increase to 78% after treatment with lenvatinib instead of TACE in patients with substage B2 disease. According to the results, the authors found a median OS of 17.0 months and 1-year survival rate of 71.0%. The 2-year survival rate was 32.3%, the median PFS was 10.4 months, and the 1-year PFS rate was 42%. In addition, according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1), an ORR of 22.6% and a DCR of 90.3% were revealed, which were 70% and 90.3%, according to the modified RECIST (m-RECIST), respectively [24]. The overall lenvatinib safety profile was comparable to that observed in the REFLECT trial [16]. The authors performed a sub-group analysis to determine the prognostic factors in lenvatinib-treated patients, taking into account the age (≥ or <75 years), the AFP level (≥ or <400 ng/mL), the tumor diameter (≥ or <50 mm), the number of liver tumors (≥ or <10), and the C-P score (5 or 6). Interestingly, the C-P score was found to affect the prognosis, with a median OS of 21.5 months in C-P 5 compared to 13.2 months in C-P 6 (HR: 3.206; 95% CI: 1.081–9.509). Obviously, lenvatinib was found to be more effective in treatment-naïve BCLC B2 substage HCCs compared to TACE, especially in patients with C-P A/5 [24].

The significance of BCLC and C-P stage was also identified in the study of Patwala et al. In a real-world Australian multicenter cohort of 155 patients (BCLC stage C (69.7%) and BCLC stage B (27.7%); C-P A/B/C: 78.8%/19.7%/1.5%), the authors retrospectively showed that patients treated with lenvatinib had median OS and PFS of 7.7 months and 5.3 months, respectively. In Kaplan–Meier analysis, improved OS was noticed in patients who had developed hypertension or diarrhea or had proceeded in dose reduction compared to patients who had not presented the above AEs (median OS: 16.2 vs. 9.4 months, $p = 0.02$; 17.5 vs. 10.1 months, $p = 0.08$; 19.6 vs. 7.8 months, $p < 0.01$, respectively). Conversely, patients with more severe liver disease were associated with worse OS (C-P B/C vs. C-P A: median OS 5.6 vs. 12.5 months; $p < 0.01$). The development of AEs was attributed to a more potent action of lenvatinib, which positively affected the OS, while on the other hand, the advanced C-P stage (B/C) resulted in worse outcome due to less hepatic reserve.

Significantly, the multivariate analysis demonstrated that the BCLC stage (HR: 2.50, 95% CI: 1.40–4.45, $p < 0.01$), the baseline albumin (HR: 0.89, 95% CI: 0.86–0.93, $p < 0.01$), the development of hypertension (HR: 0.42, 95% CI: 0.24–0.73, $p < 0.01$) or diarrhea (HR: 0.47, 95% CI: 0.25–0.88, $p = 0.01$), and the dose reduction (HR: 0.41, 95% CI: 0.24–0.69, $p < 0.01$) were independently associated with OS. Similarly, dose reduction (HR: 0.45, 95% CI: 0.29–0.68, $p < 0.01$), older age (HR: 0.96, 95% CI: 0.94–0.98, $p < 0.01$), and higher baseline C-P score (HR: 1.24, 95% CI: 1.01–1.52, $p = 0.04$) were independent predictors of PFS [25]. Clearly, the above results indicated that lower C-P score and milder BCLC stage at the beginning of treatment both predispose towards a better prognosis.

The effectiveness of lenvatinib's earlier induction was also confirmed by the research of Hiraoka et al. This was a multicenter, retrospective study that aimed to determine whether the cause of liver cirrhosis (NAFLD vs. non-NAFLD) had any additional impact on the OS and PFS in lenvatinib-treated HCC patients. Interestingly, the Cox regression analysis revealed that elevated ALT (≥30 U/L) (HR 1.247, $p = 0.029$), modified ALBI grade 2b (HR 1.236, $p = 0.047$), and elevated AFP (≥400 ng/mL) (HR 1.294, $p = 0.014$) and NAFLD (HR 0.763, $p = 0.036$) were significant prognostic factors of PFS. Furthermore, higher AFP (≥400 ng/mL) (HR 1.402, $p = 0.009$), BCLC-C stage (HR 1.297, $p = 0.035$), later introduction of lenvatinib (HR 0.737, $p = 0.014$), and modified ALBI grade 2b (HR 1.875, $p < 0.001$) were independently associated with OS [26].

Except for lenvatinib's efficacy as monotherapy in patients with BCLC-B HCC, some investigators explored the role of lenvatinib plus TACE as a combination treatment. Hence, Ando et al. collected 88 BCLC-B subjects previously controlled by taking lenvatinib and divided them into two groups. Thirty patients, who continued with lenvatinib plus TACE comprised the first group, and fifty-eight patients who remained on lenvatinib monotherapy comprised the second. After matching, the two groups had similar characteristics (BCLC stage B (100%); beyond up-to-seven criteria (68.4% vs. 63.16%); ALBI grade 2 (31.58% vs. 31.58%)). No significant difference in ORR was found between the two groups (63.2% vs. 63.2%). However, the multivariate analysis identified that the TACE (HR: 0.264, 95% CI: 0.087–0.802, $p = 0.019$) and C-P score 5 (HR: 0.223, 95% CI: 0.070–0.704, $p = 0.011$) were independent significant predictors of PFS when added. The median PFS was 11.6 months in the first group and 10.1 months in the second, while CR was detected in 15.8% of the former and 10.5% of the latter group. The survival rate was significantly higher in the lenvatinib–TACE group compared to the lenvatinib group (median survival time; not reached vs. 16.9 months, $p = 0.007$). Furthermore, lenvatinib-associated AEs were equally presented in two groups [27]. Almost simultaneously, a retrospective study was conducted to evaluate whether the addition of lenvatinib in TACE-treated patients improved prognosis in comparison to TACE alone. The 1-year and 2-year OS findings were significantly higher in TACE + lenvatinib (88.4% and 79.8%) than TACE alone (79.2% and 49.2%, $p = 0.047$). Similarly, the former group had better PFS rates (1-year PFS rate: 78.4% vs. 64.7%; 2-year PFS rate: 45.5% vs. 38.0%, $p < 0.001$, respectively). The ORR was also higher in the TACE/lenvatinib group (ORR: 68.3% vs. 31.7%, $p < 0.001$). Interestingly, there were no significantly different rates of hepatic deterioration (increase in C-P stage) between the two groups. When the analysis was limited only to BCLC-B patients, the combination group showed better ORR (69.7% vs. 38.5%, $p = 0.016$), higher PFS (HR: 0.149; 95% CI: 0.059–0.379, $p < 0.001$), and a trend toward higher OS (HR: 0.28; 95% CI: 0.092–0.853, $p = 0.07$) [28].

4. Cabozantinib

Cabozantinib is an oral multi-kinase inhibitor that inhibits the activity of VEGF, cMET, RET, AXL, TIE2, and FLT3. The survival-prolonging effects of cabozantinib, as a second-line agent for patients with HCC refractory/intolerant to sorafenib treatment, compared to the placebo control were presented at the CELESTIAL trial. This was a double-blind, phase 3 trial that randomized patients with HCC refractory to prior sorafenib treatment in a 2:1 ratio of cabozantinib 60 mg/day versus the matching placebo. Patients had C-P A liver function and PS 0–1. Among 707 subjects, 470 were assigned to cabozantinib and 237 to the placebo. Most of them had BCLC-C HCC (91% and 90% in the two groups, respectively). At the end of the trial, cabozantinib had significantly improved the OS, PFS, and ORR compared to the placebo. The median OS was 10.2 months in the cabozantinib arm versus 8 months in the placebo arm (HR 0.76; 95% CI: 0.63–0.92; $p = 0.005$), with a median PFS of 5.2 versus 1.9 months, respectively (HR 0.44; 95% CI: 0.36–0.52; $p < 0.001$). In the cabozantinib arm, the ORR was 4%, and the DCR was 64%, while the placebo arm offered an ORR of <1% and a DCR of 33%. AEs of any grade were reported in 99% of patients treated with cabozantinib and in 92% of those treated with the placebo, with rates of 68% and 36% for grade 3/4 AE, respectively [29]. Of note, a separate analysis of cabozantinib's efficacy exclusively on BCLC-B HCC was not conducted, probably due to the small number of participants at that stage. Likewise, several studies that followed the CELESTIAL trial did not evaluate the potential role of cabozantinib in patients with BCLC-B HCC exclusively [12][30][31][32].

Regarding the combination of cabozantinib with ICIs, a multicenter, open-label, randomized, phase 3 trial (COSMIC-312) enrolled 837 individuals with HCC not amenable to curative or locoregional therapy and not previously treated with any

kind of systemic treatment. These patients were randomly assigned to a combination treatment of cabozantinib plus atezolizumab (n = 432), sorafenib monotherapy (n = 217), or cabozantinib monotherapy (n = 188). At the end of the follow-up (median period of 15.8 months), the PFS was more significantly prolonged in the combination treatment than in sorafenib monotherapy (6.8 vs. 4.2 months, respectively; HR 0.63; 99% CI: 0.44–0.91, $p = 0.0012$), but the OS (interim analysis) did not differ between the two groups (15.4 vs. 15.5 months, respectively; HR 0.90; 95% CI: 0.69–1.18, $p = 0.44$). Importantly, a sub-analysis exclusively on BCLC-B patients was not performed, even though these patients comprised 30% of each group [33]. Thus, the efficacy of cabozantinib/atezolizumab combination treatment in BCLC-B stage was not evaluated.

5. Immune Checkpoint Inhibitors (ICIs)

The vast majority of studies evaluating the efficacy of ICIs combined with anti-VEGFR monoclonal antibodies or TKIs have been carried out in populations predominantly consisting of BCLC-C patients [34]. In 2022, Hiraoka et al. retrospectively analyzed the results from 171 HCC patients treated with atezolizumab plus bevacizumab. The study included an adequate number of BCLC-B HCCs (n = 68, 40%) and showed an ORR and a DCR after 6 weeks of 10.6% and 79.6%, respectively. A similar response was observed in patients with or without a history of systemic treatment. In 111 patients who underwent a 6-week observation period, the ALBI score was significantly worsened 3 weeks after treatment introduction (−2.525 ± 0.419 vs. −2.323 ± 0.445, $p < 0.001$) but recovered at week 6 (−2.403 ± 0.452; $p = 0.001$ for comparison to ALBI score at week 3). Nonetheless, the study did not provide comparative data regarding the ORR and DCR between BCLC-B and BCLC-C patients [35]. One year later, the same group of investigators compared the efficacy of atezolizumab/bevacizumab versus lenvatinib as a first treatment for unresectable HCC (BCLC-B/C) and did not show significant differences in the response rates of two groups by using the m-RECIST criteria. Furthermore, the PFS and OS were comparable between the two groups, but after adjusting with inverse probability weighting, the atezolizumab/bevacizumab group showed better PFS (0.5/1/1.5 years: 56.6%/31.6%/non-estimable vs. 48.6%/20.4%/11.2%, $p < 0.0001$) and OS (0.5/1/1.5 years: 89.6%/67.2%/58.1% vs. 77.8%/66.2%/52.7%, $p = 0.002$) [36]. Concurrently, the impact of the combination of ICIs with TACE was assessed. Yang et al. compared the efficacy and safety of regorafenib plus ICIs and TACE (R+ICIs+TACE) versus regorafenib plus ICIs (R+ICIs) as a second-line treatment for patients with HCC. After propensity score matching, patients who received R+ICIs+TACE had higher ORR (34.8% vs. 4.3%, $p = 0.009$) and longer PFS (5.8 vs. 2.6 months, $p = 0.014$) compared to those who received R+ICIs. The Cox regression model showed that age (>50 vs. ≤50 years old) (HR 0.260, 95% CI: 0.112–0.605, $p = 0.002$), C-P stage (A6+B7 vs. A5) (HR 3.125, 95% CI: 1.293–7.555, $p = 0.011$), and treatment option (R+ICIs+TACE vs. R+ICIs) (HR 0.244, 95% CI: 0.096–0.622, $p = 0.003$) were independent prognostic factors of PFS, while AFP (>400 vs. ≤400 ng/mL) (HR 2.625, 95% CI: 1.194–5.770, $p = 0.016$), platelets/lymphocytes ratio (high vs. low) (HR 2.384, 95% CI: 1.006–5.648, $p = 0.048$), ALT (≤35 vs. >35 U/L) (HR 0.405, 95% CI: 0.176–0.932, $p = 0.034$), and treatment option (R+ICIs+TACE vs. R+ICIs) (HR 0.410, 95% CI: 0.170–0.988, $p = 0.047$) were independent prognostic factors of OS. On the contrary, the BCLC stage was not found to correlate with the PFS or OS [37].

Likewise, Liu et al. conducted a meta-analysis of five studies and 425 subjects to compare the efficacy and AEs between TACE plus TKIs plus ICIs versus TACE plus TKIs. It was clarified that the first option improved the ORR (RR 1.53, 95% CI: 1.27–1.85, $p < 0.01$) and extended the PFS (mean difference: 4.51 months, $p < 0.01$) and OS (mean difference: 5.75 months, $p < 0.01$). The fixed-effects model showed a significant difference in OS among C-P A patients considering the treatment option (TACE/TKIs/ICIs vs. TACE/TKIs: 22.6 vs. 15.1 months, $p = 0.05$). Similarly, the OS was significantly higher in TACE/TKIs/ICIs than TACE/TKIs among C-P B subjects (12.9 vs. 6.5 months, respectively, $p < 0.01$) [38].

Two ongoing studies are testing the efficacy and safety of atezolizumab in combination with bevacizumab compared to TACE in patients with intermediate-stage liver cancer. The NCT04803994 trial has been designed to evaluate the efficacy and safety of atezolizumab/bevacizumab plus TACE versus TACE alone, while the DEMAND trial (EUDRACT 2019–002430-36), a randomized, two-arm, non-comparative, phase II study, aims to assess the efficacy of atezolizumab/bevacizumab followed by on-demand selective TACE as well as the efficacy of the initial synchronous treatment of TACE plus atezolizumab/bevacizumab in patients with unresectable HCC.

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