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# Targeted Therapy and Immunotherapy are Novel Treatment Plans of Hepatocellular Carcinoma that is not Amenable to Surgical Resection: Emerging Trends in Combined Treatment Strategies

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**Abstract:** Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide, with advanced unresectable disease presenting a significant therapeutic challenge. The treatment paradigm has undergone a fundamental transformation, shifting from tyrosine kinase inhibitor (TKI) monotherapy to combination strategies integrating targeted therapy with immunotherapy. Atezolizumab plus bevacizumab, combining programmed cell death ligand 1 (PD-L1) blockade with anti-vascular endothelial growth factor (VEGF) therapy, established itself as the standard first-line regimen following the landmark IMbrave150 trial, with median overall survival of approximately 19.7 months. Durvalumab plus tremelimumab (STRIDE), a dual immune checkpoint inhibitor regimen, has emerged as an alternative first-line option with unprecedented long-term survival data. Emerging combination strategies include PD-1 inhibitors paired with multitargeted TKIs, bispecific antibodies, and novel therapeutic approaches. Network meta-analyses and real-world evidence suggest comparable efficacy among these regimens, with differential safety profiles facilitating individualized treatment selection. However, significant challenges persist, including the lack of reliable predictive biomarkers for patient stratification, with only approximately one-third of patients responding to current regimens. Emerging biomarkers such as circulating tumor DNA dynamics, interferon-γ signaling signatures, imaging-based radiomic features, and machine learning-based prognostic models show promise in predicting treatment response. The optimal integration of combination immunotherapy with locoregional therapies such as transarterial chemoembolization and radiotherapy remains an area of active investigation. This review synthesizes current evidence on targeted therapy combined with immunotherapy for advanced unresectable HCC, emphasizing combination treatment strategies, comparative efficacy, predictive biomarkers, and future research directions to optimize patient outcomes.

**Keywords:** Hepatocellular Carcinoma; Immunotherapy; Immune Checkpoint Inhibitors; Combination Therapy; Atezolizumab; Bevacizumab; Biomarkers; Overall Survival.

## 1. Introduction

The third cause of cancer-related mortality across the world is hepatocellular carcinoma (HCC), which is one of the most lethal cancers, making its treatment increasingly difficult [1,2]. Over the past few years, tyrosine kinase inhibitors (TKIs) have been employed as the drugs of choice to treat advanced unresectable HCC beginning with sorafenib (2007) where they demonstrated some benefit in terms of survival [2,3]. The first-line therapy addition was rather small and restricted until lenvatinib was approved as a substitute to sorafenib in 2018, which could not be regarded as inferior [3]. The new paradigm of therapy, immune checkpoint inhibition, a new paradigm based on the tumor microenvironment and immune evasion mechanisms was introduced as a paradigm shift in therapy [4].

Immune checkpoint inhibitors (ICIs) such as programmed cell death protein 1 (PD-1), its ligand PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) are transforming the care of advanced HCC [3,4]. Combination of atezolizumab (a PD-L1 blocker) with an anti-vascular endothelial growth factor (VEGF) treatment, bevacizumab, proved superior to sorafenib in the famous IMbrave150 trial and is now the first immunotherapy to replace the previous standard first-line therapy [1,2]. The most recent addition to the therapeutic arsenal, STRIDE regimen, comprising of durvalumab and tremelimumab, has offered another armamentarium to the therapeutic repertoire and has never reported any information on survival [4]. In their wake, numerous combination programs like the combination of PD-1 inhibitors with multi-targeted TKIs, bispecific antibodies and locoregional therapies have been suggested since then [5,6].

Although these achievements have been made, there are a lot of significant challenges that remain in the present context. The available combination regimen is ineffective in most of the patients and predictive biomarkers are available to select patients [7,8]. There is no clear sequence of therapies after first-line progression to be established and immune-related adverse reactions should be monitored carefully particularly in patients with underlying liver diseases [9,10]. Combined use of immunotherapy and locoregional interventions, such as transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and radiotherapy remains an active area of research and more recent research shows superior antitumor effectiveness [11-13]. An overview of this review will provide updated insight into targeted therapy and its role in combination treatments with immunotherapy in unresectable HCC as well as the findings of their combination programs in patients.

## 2. Evolving Landscape of First-Line Combination Regimens for Advanced HCC

### 2.1. Atezolizumab plus Bevacizumab: Establishment of the Current First-Line Standard of Care

The combination of atezolizumab (anti-PD-L1 monoclonal antibody), bevacizumab (humanized anti-VEGF antibody) has become the foundation of current first line therapy of advanced HCC [1,3]. According to the results of the IMbrave150 phase III trial, this combination proved superior to sorafenib in terms of overall survival and progression free survival and has established a new therapeutic benchmark [2,12]. The clinical benefit of Atezolizumab and Bevacizumab extends beyond the simple survival outcome but offers a favourable health-related quality of life score relative to the sorafenib [14]. The effectiveness of this regimen has also been demonstrated through real-life experience with larger and more prospectively studied groups who had an average overall survival of approximately 19.7 months and 36 months survival of 30% in the Italian ARTE database [15].

The administration of atezolizumab and bevacizumab has also been optimized in its introduction into clinical use. One big population-based study in Japan on 1507 patients determined the association between the body surface area-adjusted administration of bevacizumab, which was defined by the body surface area index of bevacizumab (BBI), and clinical outcomes in Japan [16]. The optimal value of BBI was found using restricted cubic spline analysis and it was 106-121 percent, and the patients who were in this target range had significantly higher progression-free survival (10.3 vs. 6.5 months), and overall survival (24.9 vs. 19.2 months) than those who were not in target range without additional toxicity [16]. These findings imply the potential of improving the efficacy of bevacizumab portion through optimization of the dose.

European Society of Medical Oncology-Magnitude of Clinical Benefit Score (ESMO-MCBS) assessed the Atezolizumab-bevacizumab combination to be 5 suggesting a high level of clinical benefit [1]. It is not necessarily the best choice. The outcome of a study in Spain found that the outcome was significantly lower than in the IMbrave150 study, where the overall survival rate was 381 days and the dropout rate due to adverse effects was 39.1 percent indicating the importance of selective patient selection in clinical practice [17].

### 2.2. Durvalumab plus Tremelimumab (STRIDE) and Its Incorporation into Clinical Guidelines

According to the HIMALAYA trial, another first-line treatment option for advanced HCC was double immune checkpoint inhibition using tremelimumab (anti-CTLA-4) and durvalumab (anti-PD-L1) [1,4]. It has been shown that the STRIDE regimen was more effective compared to sorafenib and had the highest survival rates in the long term ever reported [4]. A regimen of one dose of tremelimumab with durvalumab is included in the American Association of the Study of liver disease guidance document and the National Comprehensive Cancer Network [1]. It is particularly helpful in these cases when the risk of gastrointestinal bleeding is high because it lacks the anti-angiogenic component that increases the risk of bleeding when atezolizumab and bevacizumab are used concurrently [1]. The combination of durvalumab and tremelimumab was also rated by ESMO-MCBS at 5 points which means that it has substantial clinical utility [1].

### 2.3. Emerging PD-1 Inhibitor plus Anti-Angiogenic Tyrosine Kinase Inhibitor Combinations

The combination of PD-1 inhibitors and multitargeted TKIs have been one of the treatment options in advanced HCC [3,6]. The combination of sintilimab (anti-PD-1 antibody) and IBI305 (a bevacizumab biosimilar), has scored 5 on the ESMO-MCBS, which means that the combination is much more clinically useful than atezolizumab and bevacizumab [1]. Apart from this regimen, there are additional forms of immunotherapy combined with anti-angiogenic therapy, which can be particularly beneficial in areas where atezolizumab with bevacizumab is not accessible.

Camrelizumab (anti-PD-1 monoclonal antibody), rivoceranib (VEGFR-2 TKI) are extremely effective, but they were found to be significantly more likely to induce treatment-related side effects compared to atezolizumab/bevacizumab in network meta-analyses (relative risk 1.59) [1]. The safety signal should also be taken into account when selecting a treatment plan.

The interaction between lenvatinib and PD-1 inhibitors has been extensively studied. The bi-specific antibody KN046 and lenvatinib were evaluated in multicenter phase II trials in 55 patients with advanced unresectable HCC (18). The response rate was 45.5 percent and the median progression-free survival was 11.0 months and the median overall survival was 16.4 months and overall survival rate is 60 at 12 months (18). There was an association between the pre-third round circulating tumor DNA status and prognosis, which can be seen as one of the possible uses of this dynamism in biomarker monitoring [18]. Despite the encouraging effectiveness of lenvatinib combinations, they cannot be directly compared with atezolizumab and bevacizumab regimens prospectively, and retrospective findings suggest that initial use of lenvatinib will not always be inferior to ICI combinations in certain groups of patients [6].

### 2.4. Novel Bispecific Antibody-Based Combinations

This concept of bispecific antibodies has become a relatively fresh approach in enhancing the activity of immune checkpoint blockades. As stated in the aforementioned phase II trial which demonstrated encouraging efficacy with a good safety profile when lenvatinib and KN046 (bispecific antibody to PD-L1 and CTLA-4) were given together [18]. Grade >= 3 treatment-related adverse events were recorded in 47.3 percent of patients and grade >= 3 immunotherapy-related adverse events in 5.5 percent of patients which is an acceptable tolerance [18]. The protocol is a common instance of the engineering of antibodies that might enable binding to multiple checkpoints of the immune system without endangering safety during the process of use.

### 2.5. Investigational First-Line Options: Regorafenib plus Pembrolizumab

A multicenter dose-defining/expansion study has assessed

the regimen of regorafenib (multitargeted TKI) and pembrolizumab (anti-PD-1 antibody) as the first line therapy [19]. At the end of this, it was found that the regorafenib dose of 120 mg/day and the pembrolizumab dose of 200 mg every 3 weeks are safe to administer. Out of the 54 patients who were evaluable to determine response, the objective response rate was 31 and the disease control rate was 89 [19]. The findings that showed that low angiogenesis and transforming growth factor-β signaling before the treatment correlated with the response, which is the initial sign of predictive biomarkers were explanatory [19]. This finding indicates that such a combination should be investigated in the first-line scenario.

# 3. Comparative Efficacy of Combination Therapies: Meta-Analyses and Real-World Evidence

## 3.1. Network Meta-Analyses Comparing Atezolizumab plus Bevacizumab, Lenvatinib, and Sorafenib

The network meta-analyses were used because there do not exist head-to-head randomized trials of all the available treatments in first line to offer information about the treatment alternatives. The combination of atezolizumab and bevacizumab, lenvatinib and sorafenib effectiveness has been assessed in eleven studies and network meta-analysis indicated no significant difference in overall survival between the three therapies, hazard ratios of 0.98 of atezolizumab and bevacizumab compared to lenvatinib and 1.4 compared to sorafenib [20]. According to the SUCRA analysis, it was most probable that the initial choice would be made with atezolizumab plus bevacizumab with the subsequent options being lenvatinib and sorafenib [20]. These findings suggest that in clinical practice, atezolizumab plus bevacizumab is preferred, but it is not statistically significant.

Another systematic review and synthesis of 12 retrospective studies (6,620 patients) was performed to compare lenvatinib and atezolizumab combined with bevacizumab [21]. Both of the regimens had the same overall survival, progression-free survival, objective response rate and disease control rate [21]. Assessments of viral and non-viral etiological groups showed the same outcome that is, lenvatinib can also be applied in other etiologies of HCC [21]. Loss of appetite, diarrhea, fatigue and hand-foot syndrome were significantly more frequent in patients receiving lenvatinib compared to those given atezolizumab plus bevacizumab whereas high aspartate aminotransferase level was more prevalent with atezolizumab plus bevacizumab [21]. All the different toxicity profiles can be used to select a therapy using an individual.

## 3.2. Real-World Comparative Studies of Combination Immunotherapy versus TKI Monotherapy

The actual experience of large populations of patients has contributed to filling the gaps of what it is that works in clinical trials by applying the information of clinical trials into the real world setting. A retrospective multicenter study in Korea was carried out to compare lenvatinib or sorafenib as second-line therapy after the failure of treatment with atezolizumab and bevacizumab [22]. In 126 patients, it was observed that lenvatinib was associated with superior progression-free survival (3.5 months) compared to sorafenib (1.8 months), greater disease control rates (66.7% vs. 22.2%) as well as comparable overall survival (10.3 months vs. 7.5 months) [22]. It demonstrates that lenvatinib may serve as a TKI of choice in the case where the first-line therapy cannot be administered due to immunotherapy.

This is a retrospective investigation of 52 patients to be compared regarding the effectiveness of atezolizumab and bevacizumab and lenvatinib in the treatment of patients with portal vein tumor thrombosis (PVTT). Average overall survival in atezolizumab and bevacizumab was 10.8 months and 5.8 months on average in lenvatinib, which were not statistically different (adjusted hazard ratio 0.71) [23]. Also, the progression-free survival and disease control rates of the two regimens were similar [23]. The results suggest that two possible treatment alternatives can be utilized to treat HCC patients with PVTT although the better numerically survival rate of the population of patients given atezolizumab plus bevacizumab needs to be studied more.

## 3.3. Efficacy of Combination Therapy in Special Populations: Portal Vein Tumor Thrombosis

PVTT is a severe manifestation of HCC, and it has been related to unfavorable prognosis and restricted treatment alternatives [5]. In HCC with PVTT, treatments have not been standardized across the globe with systemic therapy being recommended but it was found out that this therapy is not effective [5]. Recent findings indicate that locoregional or local interventions like liver resection, radiotherapy, HAIC, TACE, and transarterial radioembolization (TARE) may also be useful to some patients with PVTT [5]. This is a new concept of incorporating these locoregional approaches with systemic targeted-immunotherapy, which can be used in this difficult-to-treat group of patients [5,23].

## 3.4. Health-Related Quality of Life Integrated with Survival Outcomes Across First-Line Regimens

Health-related quality of life (HR-QoL) has been used as a secondary outcome in the selection of treatment other than survival. A network meta-analysis was conducted to determine the HR-QoL reduction of the first-line regimens within nine randomized clinical trials of 9,425 patients [14]. According to SUCRA scores, the combination of atezolizumab and bevacizumab had the highest probability of increasing the overall health status and quality of life (85%) and the abdominal swelling (95%), jaundice (89), and pain (86)[14]. A combination of atezolizumab and bevacizumab was found to be better than any other treatment in all measurements of the measured items combined with overall survival [14]. Such a thorough review of the outcomes of the survival and the quality of life adds another patient-focused attitude to the choice of a treatment in medical practice.

# 4. Combination of Targeted-Immunotherapy with Locoregional and Interventional Therapies

## 4.1. Transarterial Chemoembolization Combined with Lenvatinib plus PD-1 Inhibitors as Triple Therapy

The combination of TACE and lenvatinib with PD-1 inhibitors may also be a potential treatment in advanced HCC,

particularly in cases where the tumor load is extremely high. Retrospective analysis of 40 patients with Barcelona Clinic Liver Cancer stage C HCC who underwent the combined treatment of lenvatinib, sintilimab and TACE demonstrated encouraging results with 3, 6, and 12-month overall survival rates of 100 (3/40), 88.5 (7/40), and 22.5 (3/40), respectively [11]. The overall response rate was 45% and the disease control rate was 90 percent (which was tolerably toxic, i.e., grade 3 adverse events were recorded in 15 percent of the patients) [11]. These findings are consistent with the appropriateness and appropriateness of triple therapy in advanced HCC.

GUIDANCE001 was a multi-center trial comparing TACE alone versus TACE with an immune checkpoint and a tyrosine kinase inhibitor as conversion therapy in unresectable HCC [13]. Triple conversion therapy was found to be significantly more effective in overall survival (hazard ratio 0.43) and median progression-free survival (15.9 vs. 8.0 months) than TACE only in 802 patients [13]. It has shown its effectiveness in the middle and later stages as well as in the early stages of the disease. The ratio of hepatectomy after conversion among those who received triple therapy was significantly higher (36.4% vs. 23.5%) and of those who underwent surgery, there were more patients with complete tumor response (32.1% vs. 11.1%) [13]. There were also significantly more serious adverse events in patients undergoing triple therapy (35.6% vs. 27.0), which highlights why it is important to select and monitor patients carefully [13].

### 4.2. Hepatic Arterial Infusion Chemotherapy-Based Triple Regimens for Conversion Therapy

It has been reported that HAIC-based combination chemotherapy can be successfully applied as a treatment of initially non-resectable HCC that is converted into a more tractable disease. In 12 patients with HAIC and sintilimab/bevacizumab, a significant decrease in the tumor size (11.4-7.6cm) and alpha-fetoprotein levels (73,471-2,374ng/mL) was observed [24]. Six out of fourteen patients were converted to resectability of which six were treated with curative resection and four reached pathological complete response [24].

In this larger study, tislelizumab was evaluated in combination with lenvatinib and FOLFOX4-HAIC as a first-line conversion therapy in 18 patients [25]. The objective response rate was 94.4 and conversion was obtained in 61.1 percent of the patients and the conversion resection rate was 38.9 percent [25]. Of those who underwent surgery, there was a pathological complete response of 57.1 percent [25]. Progression-free survival had a median of 17.8 months and the 6- and 9-month progression-free survival were 83.3 percent and 66.7 percent respectively [25]. This implies that triple regimens based on HAIC are a highly efficient conversion therapy of unresectable HCC.

### 4.3. Transarterial Radioembolization plus Atezolizumab and Bevacizumab

TARE with yttrium-90 has been explored in a preliminary pilot study of 10 patients with intermediate and advanced stage HCC, as a combined therapy of atezolizumab and bevacizumab [12]. All the treated target lesions with TARE achieved tumor control and 75 percent of the patients with intermediate-stage disease were downstaged to satisfy the Milan criteria [12]. Six-month overall survival rate and 12-month overall survival rate were found to be 90.0 and 77.1 percent respectively with tolerable toxicity [12]. The findings confirm the assertion that it is safe to administer atezolizumab and bevacizumab with TARE, however, additional prospective research is needed.

### 4.4. Radiotherapy in Combination with Atezolizumab plus Bevacizumab

A small retrospective group of seven patients with advanced HCC has been treated with radiation therapy and atezolizumab and bevacizumab [26]. The average dose of radiation prescribed was 35 Gy, and average follow up time was 14.2 months and none had a locally progression-free survival rate [26]. At the end of one year, 60 percent of them had not developed a local progression and no hematological adverse effects of grade =3 or higher [26]. The preliminary findings suggest that radiotherapy combined with atezolizumab and bevacizumab can be feasible with possibly favorable effect on local control.

### 4.5. Conversion Therapy Strategies Enabling Curative Resection in Initially Unresectable HCC

The goal of the conversion therapy is to convert unresectable tumors into resectable tumors through a particular combination of local and systemic treatments [13,24,25]. The conversion therapy can be deemed effective when the decrease in tumor size is adequate and, ideally, there would be a connection between this reduction and pathological complete response and excellent long-term outcomes [25, 27]. Of the three discussed therapies, in particular HAIC, it has been shown to have very high conversion rate percentages and pathological cure rates, which allows one of the subgroups of patients with initially unresectable disease to be given curative opportunities [13,24,25]. There is an ongoing research on what is the best duration of neoadjuvant treatment, what is the most suitable time to perform surgery, and what is the function of adjuvant therapy after the conversion surgery.

## 5. Treatment Sequencing After First-Line Combination Therapy Failure

### 5.1. TKI Monotherapy After Atezolizumab plus Bevacizumab Progression

One of the areas of ongoing investigation is the most suitable second-line treatment when atezolizumab with bevacizumab fails. As it has been reported in the earlier multicenter Korean study [22], the efficacy of both sorafenib and lenvatinib as second-line therapy of the discussed condition was compared. Lenvatinib was found to be more effective in terms of progression-free survival and disease control rate, however, the overall survival rates were not significantly different [22]. Such results suggest that lenvatinib can be the least favored TKI after a first-line immunotherapeutic-based therapy since it is likely to inhibit more kinases and have other mechanisms of resistance.

### 5.2. Regorafenib plus PD-1 Inhibitors as Second-Line Therapy

The application of regorafenib and PD-1 inhibitors to serve as a second line therapy has also been investigated in several reports due to its feasibility in clinical settings. In a

multicenter retrospective study of 133 patients, regorafenib with PD-1 inhibitors was compared with regorafenib alone [28]. As well, the combination group had a higher objective response rate (25.53% versus 10.26%), disease control rate (87.23 versus 66.67) and median progression-free survival (9.0 versus 4.0 months) [28]. There was no significant difference regarding overall survival between two groups (14.0 vs. 12.0 months) and the incidence of adverse effects due to the treatment was the same [28]. These findings support the fact that the combination of regorafenib and PD-1 inhibitors could be used as a second line therapy particularly among those patients who have not undergone immunotherapy previously.

After reviewing a clinical trial involving 76 patients who received regorafenib and PD-1 blockage, it was noted that the objective response rate was 21.1 percent and the disease control rate was 56.6 percent and the median progression-free survival was 6.8 months [29]. The commonest adverse events of grade 3 or above were reported in 31.6% of patients, and the typical adverse events were hand-foot syndrome, loss of appetite and abdominal distension [29]. These results support the idea that this combination can also be used as the second line.

### 5.3. Evidence-Based Frameworks for Sequencing Beyond Second-Line Treatment

The advanced systemic therapy of HCC has altered the linear and stepwise algorithm of treatments that were once given to the multi-dimension treatment due to treatment response, liver function, and accessibility of therapies [30]. The inclusion of the Barcelona Clinic Liver Cancer stage name after response (BCLC-UR) improves the correctness of the classification in the people who have reached a high response or conversion rate, and the stages correlate with the current trends in the treatment [30]. A different definition of sequencing in terms of a patient-centered and adaptive process, which also takes into consideration toxicity, feasibility, and patient values, in addition to efficacy, is a CUSE model (i.e., Complexity, Uncertainty, Subjectivity, and Emotion) [30]. Other combinations based on immunity are also still active and have a median overall survival of approximately 10-11 months and continued function of the liver decides whether treatment is still feasible and whether it can be survived after progression [30]. The sequence of HCC will not end at second-line therapy as conversion therapy and drug-off therapy with full or partial responses is establishing new boundaries [30].

## 6. Safety Management of Combination Targeted-Immunotherapy

### 6.1. Spectrum, Incidence, and Management of Immune-Related Adverse Events

Immune checkpoint inhibitors can cause hyperactivation of the immune system, which can result in immune-related adverse effects (irAEs) that can affect numerous organs including the skin, gastrointestinal tract, liver, endocrine glands, lungs, and heart [9]. Patients with HCC have a high probability of having an underlying liver disease such as chronic hepatitis or cirrhosis and thus are at greater risk of developing hepatic irAEs compared to other cancers [9]. IrAEs pathophysiology consists of increased T-cell activity, the failure to tolerate the immune response, the disturbance of cytokines, the elicitation of complement-induced toxicity, and the activation of innate immunity [9]. The decision regarding continuing or discontinuing the use of ICIs, or administering corticosteroids and/or immunosuppressants should be based on the level of toxicity [9].

An actual-life study involving a Latin American multinational group of 99 patients who received atezolizumab in combination with bevacizumab showed an incidence rate of irAEs of 2.1 per 100 person-months and a cumulative incidence of 18.1% [31]. The most frequent irAEs were hepatitis and thyroiditis with a median duration of 2.3 months to develop the condition [31]. The initial alpha-fetoprotein value of >=400 ng/mL has proven to be a strong independent predictor of irAE development [31]. IrAEs are not associated with survival outcomes of this population, thus most irAEs can be successfully treated with proper treatment [31].

### 6.2. Hepatic Decompensation and Preservation of Liver Function During Combination Therapy

The hepatic decompensation is one of the leading factors of mortality among patients with HCC undergoing combination immunotherapy. In a multicenter study of 571 patients in the AB-real observational study, the authors found that the presence of a hepatic decompensation was an independent predictor of overall survival at a hazard ratio of 19.04 which was significantly higher than that of the tumor progression (hazard ratio 9.91) [10]. Decompensation was linked to pre-treatment albumin-bilirubin (ALBI) grades 2/3, but viral etiology was also protective [10]. The successful treatment of viruses reduced the probability of decompensation in patients with viral etiology dramatically, and this remark shows the importance of the multidisciplinary approach to the treatment of these patients [10]. The findings underline the critical importance of ensuring that the liver can maintain its activity during the combined therapy to bring about the best outcomes.

### 6.3. Bleeding Risk and Hepatic Safety Assessment Tools for Patient Stratification

Bleeding, particularly variceal bleeding, can also be a complication of treatments containing bevacizumab. To provide prediction of clinically meaningful portal hypertension and prognosis, hepatic safety score based on machine learning (MHSS) was applied to 2,026 unresectable HCC patients [32]. The MHSS also had a strong predictive ability in predicting hepatic decompensation (AUROC 0.840) and the high-risk patients had much higher risk of hepatic decompensation (hazard ratio 3.25), variceal bleeding (hazard ratio 4.90), and mortality (hazard ratio 2.21) [32]. However, despite the fact that atezolizumab-bevacizumab had higher survival rates in low-risk patients, it also had a high risk of severe bleeding and no survival advantage over other regimens in high-risk patients. Hypothetical treatment options using MHSS demonstrated that hepatic decompensation (24 percent), variceal bleeding (40 percent), and mortality (26 percent) were reduced [32]. These findings point to a good performance of risk stratification measures in order to establish if bevacizumab-containing or any other regimens need to be implemented.

### 6.4. Long-Term Safety Data from Real-World Cohorts

Safety information on combination immunotherapy can be considered useful because it gives a broad notion of a duration and tolerance that were accessible to a real-life group. Of the 538 patients in the Italian ARTE database that received atezolizumab and bevacizumab, 36.8 per cent experienced grade ≥3 adverse events (5 late-onset severe toxicities were reported after 24 months) [15]. Also, 14.1 per cent of the patients had liver decompensation that was not related to tumor progression [15]. It should be also emphasized that among 14.9 per cent of patients who underwent surgery or locoregional treatment after the start of atezolizumab and bevacizumab therapy, 4.4 per cent achieved disease-free status without drugs [15]. The findings suggest the need to take an interdisciplinary and integrated approach to management of advanced HCC and rigorous long-term monitoring to determine late-onset toxicities.

## 7. Biomarkers and Prediction Tools for Patient Selection in Combination Therapy

### 7.1. Circulating Tumor DNA Dynamics During Combination Treatment

The circulating tumor DNA (ctDNA) is a very good non-invasive marker of response to treatment and development of the disease in HCC [33,34]. Testing of 772 plasma samples of 173 patients with HCC revealed that the percentage of ctDNA mutations increased with increasing tumor stage and the presence of mutations in ctDNA was linked to progression on imaging in patients treated with atezolizumab-bevacizumab (63.6% vs. 36.4% disappearance) [34]. Patients treated with KN046 combined with lenvatinib had a pre-third treatment cycle ctDNA level that was related to the prognosis [18]. These findings support the clinical relevance of ctDNA as a dynamic biomarker of therapy surveillance and early resistance identification.

### 7.2. Imaging-Based Biomarkers: Rim Arterial-Phase Enhancement and Radiomic Signatures

The imaging properties may serve as a non-invasive biomarker to predict the treatment response. Aggressive characteristics of tumors have been linked to HCC and rim arterial phase enhancement (APHE) computed tomography or magnetic resonance imaging [35]. Another study of 51 patients taking atezolizumab and bevacizumab revealed that patients who did not have rim APHE were less responsive and had median progression-free survival than patients who had rim APHE [35]. A biopsy of liver tumors showed a significant proportion of CD8+ tumor infiltrating lymphocytes in HCC patients with rim APHE, which means that there was an active tumor microenvironment [35].

Radiomic signature has demonstrated the intratumoral heterogeneity and the forecasting ability of the response to TACE with immunotherapy and targeted therapy. The composite global tumor region-intratumor heterogeneity score which had excellent discrimination (area under the receiver operating characteristic curve scores = 0.94 in training set and 0.83 in independent test sets) was developed by the 742-patient multicenter cohort [36]. All low-risk patients had significantly better progression free survival and overall survival and this low risk patient population had an immune inflammatory micro environment with high plasma cell and M1 macrophage frequencies [36].

The concept of deep learning has been applied to evaluate MRI tumor radiomic dynamics in order to predict pathologic complete response after immunotherapy and subsequent hepatectomy in HCC (27). The delta radiomic model, as a measure of change in imaging properties between the baseline and post-treatment images, proved highly superior to the baseline and pre-surgery models concerning lesion-level pathological complete response with areas under the curve of 0.835 in test set and 0.783 in validation set (27). Prediction of the outcome improved with delta radiomics and alpha-fetoprotein response which had area under the curve values of 0.920 and 0.857 in the test and validation set respectively (27).

### 7.3. Circulating Inflammatory, Cytokine, and Immune-Cell Markers

One of the most accessible biomarkers, the neutrophil-to-lymphocyte ratio (NLR), has proven to be prognostically significant in HCC. In 69 atezolizumab plus bevacizumab-treated patients, it was found that the predictive value of NLR less than 2.04 (3 weeks after beginning treatment) had a statistical significance (area under the curve 0.77) [37]. Multivariate analysis indicated that the NLR at 3 weeks and non-viral infection were independent predictors of developing irAEs [37]. The general response rates (75.0/28.1 percent) and progression-free survival (12.1/6.0 months) were also significantly greater among patients with irAEs, which is why the occurrence of irAEs may be an indicator of a more effective anti-tumor immunity [37].

The initial NLR was also found valuable in the stratification of the prognosis in the patients with Child-Pugh B liver function who were treated with atezolizumab and bevacizumab [38]. A total of 105 patients were assessed and the ones with low NLR (lower than 2.56) had better overall survival and it was a prognostic factor in Child-Pugh A and B patients [38]. The degree of hepatic reserve was prognistic and even though objective response was highly associated with survival in Child-Pugh A patients, the disease stabilization was clinically meaningful in Child-Pugh B patients [38].

Cytokine analysis has indicated potential predictive biomarkers of immunotherapy combinations. Analysis of 56 patients, who were given either ICIs alone or with bevacizumab, demonstrated that combination therapy was also linked to significant decrease in the fold change of various cytokines, including sCD40L, macrophage inflammatory protein-1beta (MIP-1beta) and monokine induced by interferon- gamma, and interleukin-1RA [39]. Baseline MIP-1beta values above the median were associated with poor clinical outcomes, and baseline IL-6 and IL-12p40 values were associated with better progression-free survival in combination therapy of ICI and bevacizumab compared to ICI alone [39]. Clinical improvements were associated with decreased levels of IL-1Ra, IL-8, IL-18 and VEGF-A after the treatment [39].

### 7.4. Machine Learning-Based Prognostic Models and Composite Clinical Scores

The created machine learning techniques are also applied to forecast the outcome of the treatment with atezolizumab and bevacizumab. Fourteen supervised machine-learning

models based on 44 baseline clinical characteristics were trained with a retrospective cohort of 774 patients in 24 centers in eight countries [7]. Ensemble model to predict overall survival had a significantly lower area under the receiver operating characteristic curve of 0.75 in the external validation set than all the eight clinical bench marker variables (BCLC stage, alpha-fetoprotein concentration, ALBI grade, and NLR) that were assessed [7]. Median overall survival in the low-risk group was also significantly increased (16.4 months vs. 4.8 months), thus, making it possible to use machine learning as a potential tool to come up with personalized treatment strategies [7].

CRAPT-M model was developed using a 456-patient cohort and validated with a 205-patient sample to identify five independent variables that could be predicted as follows: C-reactive protein >=1.0 mg/dL, albumin <=3.5 g/dL, protein induced by the vitamin K absence or antagonist-II >=1500 mAU/mL, total bilirubin >=1.0 mg/dL, and macrovascular invasion [40]. Groups with low-risk, intermediate-risk, and high-risk were formed with median overall survival of 22.4, 12.9 and 6.7 months respectively [40]. It was found that the predictive accuracy of the CRAPT-M model was significantly greater than that of the CRAFITY model and the time-dependent area under the receiver operating characteristic was 0.785, 0.737 and 0.742 (12, 24 and 36 months) [40].

### 7.5. Molecular Signatures Associated with Immunotherapy Response

Molecular examination of tumor tissue has shown that the profiles of immune-related gene expression are associated with the reaction to anti-PD1 therapy. When investigating 111 tumors of patients with advanced HCC who were treated with anti-PD1 antibodies it was found that, following the introduction of the agent in the front line setting, the indicators of responder treatment indicated that there was an up-regulation of interferon-? signaling and antigen presentation of major histocompatibility complex II [8]. It has been observed that a set of eleven genes (IFNAP) could represent such molecular properties that would determine response and survival of those who were in the frontline and received anti-PD1 and was used in another set of HCC patients and over 240 patients with various forms of solid cancers [8]. The signature also had no predictive value regarding response on archival tissue in patients treated with frontline TKIs suggesting the importance of re-biopsy before immunotherapy [8].

Transcriptomic analysis of individual cells in tumors of patients with advanced HCC treated with atezolizumab and bevacizumab revealed that among the patients with durable responses the tumors contained PDL1+ CXCL10+ macrophages and expressed high levels of CXCL9/10/11 [41]. It was supposed that these tumors would draw in CXCR3+ CD8+ effector-memory T cells to peripheral regions, which are more readily able to become PD1- CD45RA+ effector-memory CD8+ T cells containing a large amount of cytotoxicity [41]. The findings provide a mechanistic understanding of the causes of the influence of specific factors on the outcome of the cocktail immunotherapy.

## 8. Conclusion and Future Perspectives

The implementation of targeted therapy in immunotherapy has led to the revolution of the advanced unresectable HCC treatment area. At present, atezolizumab with bevacizumab and durvalumab with tremelimumab are regarded as the new standards of care in first-line treatment and the old idea of TKI monotherapy is being replaced [1, 2, 4]. Other combinations of PD-1 inhibitors and anti-angiogenic TKIs, bispecific antibodies therapy and inclusion of local-regional treatments into the systemic immunotherapy armamentarium have also been published [11,13,18,25]. Network meta-analyses and real world studies are comparative studies that demonstrate that the two regimes are effective but have different safety properties which might be utilized to tailor the treatment choice upon them [20,21].

A lot of significant problems have been identified. It is essential to consider indirect information and patient-related indicators when deciding on treatment due to the fact that it is not possible to compare every first-line choice directly [1,42]. Useful predictive biomarkers to stratify patients were not part of routine clinical practice, but have advanced considerably in the form of dynamic ctDNA, image-based radiomic signatures, presence of circulating inflammatory markers, and machine-learning based prognostic models [7,8,27,34,36,40]. First-line progression perfect treatment sequence is not well described, and the capacity to preserve liver function in combination therapy is among the factors that determine the outcome [10,30].

Here are the major themes that should be discussed in the future. Firstly, the novel biomarker should be examined in large and diverse populations of patients to enable the implementation of precision medicine strategy [8, 33]. The third component is the efficacy of the superior integration of locoregional treatment and systemic immunotherapy, particularly in conversion therapy with a well-done clinical trial [13]. Thirdly, development of novel combination regimens, like bispecific antibodies or novel immune checkpoint targets may also prove useful [18]. Fifthly, it is necessary to study the treatment of immune-mediated side effects more thoroughly, particularly in patients who have other liver disorders [9,32]. Finally, the use of early systemic therapeutic interventions in the disease, which may impact the course of further treatment, is a potential approach [2,42]. To solve these issues, there needs to be a high number of various fields and extended commitment to translational research such that people with advanced HCC are given top-notch care.

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