Hepatocellular cancer therapy in patients with HIV infection: Disparities in cancer care, trials enrolment, and cancer-related research

Francesca Negri a,⁎,1, Gabriele Missale b,c,2, Anna Degli Antoni b,3, Camillo Porta d,e,4

a Medical Oncology Unit, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci 14, 43126 Parma, Italy
b Unit of Infectious Diseases and Hepatology, Azienda Ospedaliero-Università di Parma, Via Gramsci 14, 43126 Parma, Italy
c Department of Medicine and Surgery, University of Parma, Via Gramsci 14, 43126 Parma, Italy
d Chair of Oncology, Department of Biomedical Sciences and Human Oncology, University of Bari ‘A. Moro’, Piazza G. Cesare 11, 70124 Bari, Italy
e Division of Medical Oncology, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Piazza G. Cesare 11, 70124 Bari, Italy

⁎ Corresponding author.
E-mail address: fnegri@ao.pr.it (F. Negri).

Abstract

In the highly active antiretroviral therapy (HAART) era, hepatocellular carcinoma (HCC) is arising as a common late complication of human immunodeficiency virus (HIV) infection, with a great impact on morbidity and mortality. Though HIV infection alone may not be sufficient to promote hepatocarcinogenesis, the complex interaction of HIV with hepatitis is a main aspect influencing HCC morbidity and mortality.

Data about sorafenib effectiveness and safety in HIV-infected patients are limited, particularly for patients who are on HAART. However, in properly selected subgroups, outcomes may be comparable to those of HIV-uninfected patients. Scarce data are available for those other systemic treatments, either tyrosine kinase inhibitors, as well as immune checkpoint inhibitors (ICIs), which have been added to our therapeutic armamentarium. This review examines the influence of HIV infection on HCC development and natural history, summarizes main data on systemic therapies, offers some insight into possible mechanisms of T cell exhaustion and reversal of HIV latency with ICIs and issues about clinical trials enrollment. Nowadays, routine exclusion of HIV-infected patients from clinical trial participation is totally inappropriate, since it leaves a number of patients deprived of life-prolonging therapies.

Keywords:
Human immunodeficiency virus
Hepatocellular carcinoma
Sorafenib
Immunotherapy
Clinical trial

Human immunodeficiency virus (HIV) infection and natural history of stage-stratified HCC

The early 21st century has witnessed both an increasing biological and immunological knowledge of the human immunodeficiency virus (HIV) epidemic, as well as a huge evolution of medical treatments available for HIV-infected patients. The advent of highly active antiretroviral therapy (HAART) has considerably extended the life expectancy of these subjects [12], and has converted HIV infection into a chronic disease [12,109]. HAART can restore immune function, lower plasma viral RNA load, and decrease morbidity and mortality of acquired immune deficiency syndrome (AIDS)-related complications [121,94]. As a consequence of this positive impact on survival, the occurrence of other chronic, non AIDS-related, morbidities has increased [121,94,16,171,91]. Previously published data on HIV-infected patients receiving medical care in Europe showed that leading causes of mortality are: AIDS-related cancers (29%), non-AIDS-defining cancers (15%), liver diseases (13%), and cardiovascular diseases (11%) [151].

The observation that chronic liver disease is a significant cause of mortality in HIV-infected patients in the era of HAART is not unexpected. Indeed, co-infection with hepatitis B (HBV) or C (HCV) is quite common among HIV-infected patients, due to shared transmission modalities, although the prevalence of co-infection varies greatly according to the geographic origin of infected patients [145,158]. In Western countries, approximately 30% of HIV-positive subjects has HCV co-infection [158], and an increasing morbidity and mortality of
HIV-infected patients due to HCC has been reported, accounting for more than 40% of liver-related death [141]. As a well known complication of liver cirrhosis in more than 80% of incident cases, HCC is an extremely complex condition, due to the combined influence of different etiologic factors, severity of primary chronic liver disease, and extent of disease [126,140]. Co-infection of HIV with either HBV or HCV might be associated with rapidly progressive liver disease, and the risk of HCC increases when patients develop cirrhosis [91,151]. Available epidemiologic evidence suggests a seven-fold increase in the incidence of HCC in HIV-positive subjects with hepatitis, when compared with HIV-negative controls [127]. Traditionally, the increased risk associated with HIV infection has been explained by the synergistic oncogenic effect of hepatitis, leading to a faster progression of liver fibrosis in the context of immune-impairment [73], which can be further worsened by other associated factors, including increased oxidative stress from HAART [89], excessive alcohol consumption [99], impaired cell mediated immune response [73], and dysbiosis of the gut microbiota [170]. Indeed, the altered intestinal permeability triggered by HIV infection through depletion of mucosal CD4+ T lymphocytes, especially T helper 1 (Th17) cells, and altered epithelial function enables microbial translocation such as bacterial lipopolysaccharide, with secondary immune activation by interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [170, 153,120]. This protracted cytokine release enables the development of liver fibrosis, and can activate Toll-like receptors (TLR) –4 and –9 [119]. Consistently, compared with HIV-negative cases, HIV-associated HCCs have been shown to present at a younger age, and are often characterized by a higher tumor burden, supporting the hypothesis of an accelerated hepatocarcinogenesis [19,133]. Also, elevated levels of α-fetoprotein (AFP) are common in HIV/HCV coinfected patients, independently of HCC stage, and liver fibrosis severity [19,17]. Interestingly, patients with cirrhosis who are co-infected with HIV and HCV often present at radiologic diagnosis an infiltrative-type HCC, with portal vein thrombosis [92], which is usually characterized by considerably poorer long-term survival. Yet, diverging evidence shows that HIV seropositivity impacts on the outcome of patients with HCC [19,17, 132,10,93]. Case cohort analyses indicate that HIV co-infection does not have a detrimental effect on clinical outcome, provided the widespread use of standardized screening programs and the broader acceptance of the Barcelona Clinic Liver Cancer (BCLC) staging algorithm [93], likely the consequence of effective treatments, and of an extended access to anticancer drugs for HIV patients. Nevertheless, these conclusions may not be applicable to HIV+ patients with low CD4+ cell counts, or failure to maintain undetectable plasma viral load on HAART, as both conditions are recognized risk factors for end-stage liver disease. Remarkably, a multicenter case–control study showed that undetectable plasma HIV RNA, rather than CD4+ cell counts predicted longer survival in HCV-infected patients, suggesting that an adequate suppression of viral replication by HAART might reduce the influence of HIV on HCV-induced liver fibrosis, and slow the progression of fibrosis [18]. Conversely, in a recently reported global collaborative study, despite adequate antiretroviral treatment, HIV seropositivity adversely influenced the prognosis in a multicohort of patients with untreated HCC, where survival estimates were not biased by the effect of active anti-cancer treatment [128]. In an adjusted analysis, HIV infection increased the hazard ratio (HR) for death by 24% (P = .0333), independently of BCLC stage (P < .0001), Child-Turcotte-Pugh class (P < .0001), AFP level (P = .001), HCV genotype 1 (P = .02), and male sex (P = .08). Still, the clinical behavior of HCC in HIV-infected patients is not clearly defined [139], and different studies showed overall comparable survival rates regardless of HIV status, thus refuting HIV adverse prognostic association [19,132,10,93].

Probably, the survival heterogeneity within each BCLC stage, a recognized feature of HCC, may be even wider in HIV-infected patients with HCC [13,101,61,59], socioeconomic and geographical differences, as well as long-term HIV control, might also contribute to limit both access and eligibility to oncologic treatments, thus potentially affecting patients’ outcome, independently of any true immunobiologic effect of HIV [43]. Nevertheless, previously published studies have recognized anticancer treatment as a key prognostic factor in HIV-infected patients [124,164,48,49,110,44]. In one of the largest series ever reported [132], which demonstrated HIV to adversely influence the prognosis of HCC, 60% of the patients with HIV-associated HCC received best supportive care compared with 38% of the HIV-negative controls (P = .02), emphasizing that the unfavorable prognostic role of HIV infection might be at least partly related to an imbalance in treatment allocation across subgroups. Treatment imbalance is also a feature of another study [10], though a significantly higher proportion of HIV-positive patients received active anticancer treatment compared with HIV-negative patients (65.4%, vs 85.6%, respectively; P < .001). The study showed an unexpectedly high 12.8 months median OS in 27 consecutive HIV-infected patients with unresectable HCC treated with sorafenib. Yet, only 19% of patients harbored a BCLC stage C, which limits reproducibility of these data. Moreover, patients who were HIV-positive seemed disadvantaged by the lower probability of receiving treatment at recurrence (61% of HIV-positive patients vs 86.2% of HIV-negative cases, P < .001), underlining that the unfavorable prognostic role of HIV status might have been partially influenced by the different treatment allocation across patients’ subgroups. Moreover, available data describing the incidence and clinical outcome of HCC in the HAART era are often biased by small cohort size from single centers or tertiary referral hospitals, and short follow-up. Further studies exploring the immunobiology of HIV-associated HCC are straightaway required.

In this review, we highlight the role of HIV infection on HCC pathogenesis, summarize recent advances in medical knowledge and specific pathways involvement as well as latest report on immunotherapy. It also offers some insights on evidence-based data and clinical trial inclusion of HIV-positive patients.

**HIV infection and pathogenesis of HCC**

The role of HIV on HCC development has long been investigated. In vivo studies on murine models have reported the involvement of the HIV tyrosine aminotransferase (Tat) gene [116,33,4]. Tat promotes proliferation and protects cells from apoptosis [181,25], has angiogenic properties [53,2] and induces expression of several cytokines [147,172], growth factors [52], and transcription factors [41]. Transgenic mice bearing a Tat transgene showed a greater incidence of HCC and other extra-hepatic malignancies [103]. The relationship between HIV decreased immuno-surveillance, manifesting as a low CD4+ cell count, and HCC has gained increasing attention in recent studies [23,31]. A CD4+ count less than 200 cells/mmc has been significantly associated with HCC, but not with cirrhosis, suggesting that immune suppression may be directly involved in carcinogenesis [23,68]. A decreased cancer immuno-surveillance is of particular relevance in HIV/HCV co-infected patients treated with interferon-free anti-HCV direct-acting antivirals (DAAs)-based therapy [32,29]. The sudden inhibition of HCV production, and the consequent disruption of the inflammatory/immune phenotype, may be responsible of a decreased immune surveillance. This modification of the immune microenvironment may allow growth of clones of cancer cells originating the primary tumor. The abrupt reduction of liver natural killer (NK) cells and of their cytotoxic functions [149] have been claimed as a further risk factor for the development of HCC in HIV-positive patients [78], whose impaired immune system may have reduced NK cells even before anti-HCV therapies. This prompted a controversial debate due the unexpected high rate and pattern of HCC recurrence after ablative or surgical resection while on DAAAs-based therapies [138]. Though a direct influence of DAAAs on tumor cell growth cannot be entirely rejected, it is however highly improbable. For instance, HIV protease inhibitors have been shown to exert antitumoral properties in murine models [54], and growth inhibitory effects in vitro, on a number of malignant cancer cell
lines [40]. Nevertheless, growing evidence suggests that the increased risk of malignancy is not merely driven by patient’s immunological status, an issue of huge significance in the HAART era where reconstitution of quantitatively average CD4⁺ cell count is possible. Complex signaling pathways are involved in the pathogenesis and development of HCC with a major risk of developing HCC despite adequate HIV control, or HCV clearance [32].

Though HIV infection alone may not be sufficient to promote hepatocarcinogenesis [17], the complex interaction of HIV with hepatitis is a main aspect influencing HCC morbidity and mortality in HIV co-infected patients [60]. Persistent inflammation of the liver parenchyma almost always precedes HCV-induced HCC, with activated hepatic stellate cells (HSCs) and signals derived from inflammatory cells whose cross-talk is especially relevant to hepatic fibrogenesis, ultimately leading to an increased risk of HCC development [87]. Additional transcriptional events contributing to HSC activation include dysregulation of Wnt/β-catenin, hedgehog, and GATA4 signaling [184,39,107]. The multifaceted network of intracellular events during HSC activation includes regulatory pathways affecting, among others, the intracellular inflammasome activation, a recognized key transcription of signals derived from inflammatory cells that is critical to fatty liver disease [176]. HIV can directly infect parenchymal and non-parenchymal liver stromal cells, including Kupffer [67] and HSCs [163]; it induces collagen I expression, secretion of the proinflammatory cytokine monocyte chemotactrant protein 1 (MCP-1), and reactive-oxygen species overproduction [95]. The convergence of direct proinflammatory effects and of proinflammatory pathways upregulated by HCV and HIV on HSC provides evidence supporting the accelerated course of fibrosis observed in the context of co-infection.

Different host-related aspects have been shown to influence HCC predisposition, inducing a proliferation advantage and/or an altered immune response, factors ultimately altering the progression rate from cirrhosis towards tumor.

Immune activation is differently regulated as a consequence of underlying hepatotropic infection in HIV+ individuals [75]. Studies on HIV/HCV-coinfected patients have revealed changes in levels of soluble markers connected to immune activation (soluble CD14, CD163, autotaxin, and Mac2BP) during antiviral therapy for HCV, suggesting immune dysfunction as a key mechanism in HIV/HCV coinfection [83]. The host immune response to HBV-encoded antigens is responsible for necroinflammatory liver disease [30]; furthermore, HBV replication causes cyclical phases of hepatocellular necrosis, inflammation and subsequent regeneration, where a cytokines-enriched microenvironment, directed by IL-6 and IL-22 signaling and by activation of the nuclear factor-xB (NF-xB) and signal transducer and activator of transcription 3 (STAT3) pathways [55], confers a survival advantage to chronically damaged hepatocytes. Furthermore, chronic inflammation is associated with oxidative stress [50], which promotes DNA damage and modulates intracellular signaling, alters gene expression, and induces the expression of adhesion cell molecules (160). The protein X (HBx), one of the four proteins encoded by the HBV genome, exerts its oncogenic effects by dysregulating multiple pathways involved in cell cycle, apoptosis, and immunity [177]. In HIV-positive subjects, HBx has been shown to enable HIV-1 transcription by stimulating the binding of transcriptional regulatory proteins CCAAT/enhancer-binding protein beta (C/EBP), cAMP-response element-binding protein 1 (CREB1), and cAMP-response element-binding protein 2 (CREB2) to HIV long terminal repeats, providing evidence of potential synergy of HBV in HIV-1 replication during HBV/HIV co-infection [112]. Moreover, loss of CD4⁺ and CD8⁺ T cell responses and of the antigen presentation processes influences viral kinetics, favoring unrestrained viral replication and progression to fibrosis, cirrhosis, and HCC [73].

Systemic therapy and real world data for the treatment of advanced HCC in patients with HIV

The Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP) trial, an international, multicenter, phase III randomized placebo-controlled study of 602 patients with advanced HCC, showed that the multitargeted tyrosine kinase inhibitor (TKI) sorafenib (endowed by both anti-angiogenic and anti-proliferative properties) significantly prolonged survival in patients with unresectable HCC, with an overall survival (OS) of 10.7 months compared to 7.9 months for placebo, with a 31% reduction of risk of death [96]. The favorable effect of sorafenib in improving survival and delaying tumor progression was also confirmed within the phase III Sorafenib Asia–Pacific trial, performed in China, South Korea, and Taiwan [28]. Jointly, these two trials proved the effectiveness and activity of sorafenib throughout different disease etiologies, leading to its approval as first-line systemic therapy for patients with advanced HCC [20,114,56,72] (Table 1).

Sorafenib is an oral multikinase inhibitor that, among the others, targets rapidly accelerated fibrosarcoma (Raf) kinases, vascular endothelial growth factor receptor (VEGFR), c-Kit and platelet-derived growth factor receptor (PDGFR), thus inhibiting both tumor-cell proliferation and angiogenesis [26,137]. The main molecular mechanisms by which sorafenib exerts its antitumor activity in different malignancies have not been completely clarified [131]; in HCC in particular, both Raf/MEK/ERK-dependent or -independent mechanisms have been reported [136,167,159]. At present, no validated biomarker of response to sorafenib has been identified [182].

Sorafenib is usually administered at a dose of 800 mg/day; however, dosage may vary based on physician decision, Child-Pugh class, performance status, and comorbidities [21,3].

Data about sorafenib effectiveness and safety in HIV-infected patients are limited, especially for patients who are on HAART, and could be at increased risk of developing drug–drug interactions [11,27,123,118,42,130,148]. Real life data [106] have suggested that sorafenib efficacy in HIV-infected patients may be inferior compared to registration trials, while the frequency and type of adverse events are similar to those described in other cohorts [100,154,79,129]. These findings are not unexpected when one considers the outcomes of a randomized controlled trial in which a toxic therapy is delivered to fit patients, as compared with the everyday treatment of patients with more advanced liver impairment. The Global Investigation of therapeutic DECisions in hepatocellular carcinoma and Of its treatment with sorafeNIB (GIDEON) trial, a non-interventional, international study undertaken to fulfill post approval commitments to the European Medicines Agency (EMA), showed that although median time to progression (TTP) was similar (4.7 vs. 4.4 months, respectively), median OS was longer for Child-Pugh A patients (13.6 months) compared to Child-Pugh B patients (5.2 months) [35,90,100].

Another concern is about potential overlapping toxicities and pharmacokinetic interactions between molecularly targeted agents as a whole, and sorafenib in particular, and HAART. Again, most studies of novel agents for the treatment of HCC (and not only) did not include patients with HIV, leading to the paucity of available data on the use of antineoplastic drugs for the treatment of this peculiar patient population. The potential drug interactions of HAART are well established [130,148]. Likewise, the risk of incremental toxicities and associated costs of new anticancer drugs approved for use by regulatory agencies are expected to be high with highly specific agents, and in less selected patients. The therapeutic index (defined as a ratio of a measure of therapeutic benefit to a measure of toxicity) for new drugs is likely to be lower for patients treated within routine clinical practice, compared with that reported in controlled clinical trials, highlighting the need for translational studies addressing potential interactions between anticancer agents and HAART [115]. Results from two meta-analyses didn’t show any improvement in OS for patients receiving sorafenib who were positive for HBV and negative for HCV, which is informative when using
a drug with a poor therapeutic index [105,71].

Currently, there are no published pharmacokinetic data about the combined usage of sorafenib or other multikinase inhibitors and HAART, as well as a guidance for dose adjustments when they are used concomitantly. However, sorafenib is not reported to modify the efficacy of HAART, as well as a guidance for dose adjustments when they are used concomitantly. However, sorafenib is not reported to modify the efficacy of HAART, as well as a guidance for dose adjustments when they are used concomitantly. However, sorafenib is not reported to modify.

Table 1
Targeted therapies evaluated in phase III – overall survival results.

| Trial | Clinical trial design | Arms | Schedule | Overall survival, months | HR (95% CI) |
|-------|-----------------------|------|----------|--------------------------|-------------|
| First-line | Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial | Sorafenib | Sorafenib 400 mg orally twice daily or matching placebo | 10.7 | 0.69 |
| Asia-Pacific [28] | Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial | Sorafenib | Sorafenib 400 mg orally twice daily or matching placebo in 6-week cycles | 6.5 | 0.68 |
| REFLECT [84] | Multicenter, randomized, open-label, phase 3, noninferiority trial | Lenvatinib | Lenvatinib 12 mg/day (for body weight >60 kg) or 8 mg/day (for body weight <60 kg) or sorafenib 400 mg orally twice daily | 13.6 | 0.92 |
| IMBRAVE150 [57] | Multicenter, randomized, open-label, phase 3, superiority trial | Atezolizumab | Atezolizumab 1200 mg plus bevacizumab 15 mg/kg body weight intravenously every 3 weeks or sorafenib 400 mg orally twice daily | NE | 0.58 |
| Second-line | Multicenter, randomized, double-blind, parallel-group, phase 3 trial | Regorafenib Placebo | Regorafenib orally 160 mg or placebo once daily during weeks 1-3 of each 4-week cycle | 10.6 | 0.63 |
| CELESTIAL [1] | Multicentre, randomized, double-blind, placebo-controlled, phase 3 trial | Cabozantinib Placebo | Cabozantinib orally 60 mg once daily or matching placebo | 10.2 | 0.76 |
| REACH-2 [183] | Multicentre, randomized, double-blind, placebo-controlled, phase 3 trial | Ramucirumab Placebo | Ramucirumab 8 mg/kg intravenous every 2 weeks or placebo | 8.5 | 0.71 |

CI, confidence interval; HR, hazard ratio; NE, could not be evaluated.

Immune checkpoint inhibitors (ICIs) in the challenging HIV population: T cell exhaustion and reversal of HIV latency

T-cell exhaustion, defined by poor effector function, sustained expression of inhibitory receptors (IRs) and a transcriptional state distinct from that of functional effector or memory T cells [174], is a main factor leading to flawed pathogen clearance in chronic viral infections [173,82] and reduced antitumor response.

Exhausted CD8+ T cells are a distinct cell lineage that develop during chronic infections and cancers in both murine models as well as in humans [104]. The degree of CD8+ T cells dysfunction varies according to viral burden, and the extent of infection. Additionally, during acute and chronic HIV-1 infection distinct phenotypes of the CD8+ T cell response have been reported also in relation to the number of specific CD4+ T cells [9,5].

Exhausted T cells are characterized by elevated expression of multiple IRs, an impaired response to homeostatic cytokines, altered transcriptional profiles, epigenetic features distinct from that of functional effector T cells and memory T cells [173,45,57,14,135,76,125,162,169,8,168] and are now the targets of immunotherapies in chronic infections and cancer [24,122]. In the last decade, various receptors have been recognized that can negatively regulate the activation and different properties of T lymphocytes and other leukocytes. The programmed death-1 (PD-1) molecule is one of the most relevant receptors for exhausted CD8+ T cells. PD-1 is a member of the B7:CD28 family that regulates the balance between T-cell activation and tolerance [144].

More recently, other drugs have shown clinical benefits in advanced HCC patients, and have been approved as first-line (i.e. lenvatinib and atezolizumab plus bevacizumab) [84,57], or second-line, therapies (i.e. regorafenib [22], cabozantinib in patients with baseline AFP >400 ng/mL [1], nivolumab [51] and ramucirumab [183]) (Table 1). Data about effectiveness and safety in HIV infected patients of these novel agents for HCC are even more sparse [98].

On HAART side, more recent therapeutic schemes include integrase inhibitors in combination with one or two nucleoside reverse transcriptase inhibitors (NRTIs); these schemes have demonstrated to be highly efficacious and an excellent safety profile. In particular, raltegravir can be administered to patients with decompensated liver disease. Moreover, the pharmacokinetics of TKI seems not to be affected by the concomitant raltegravir-based HAART [97]. This suggests no interaction with TKIs like sorafenib and lenvatinib even though field practice experiences are lacking so far.
exhausted HIV-specific CD8+ T cells showed reacquisition of effector molecules production and increase of HIV-specific CD8+ T cells following PD-1 blockade [37,125,162]. Low CD4+ T cells count in HIV infection may also foster T cells exhaustion [102]. Studies in animal models and humans suggested that CD4+ T cells are essential for immune regulation of HIV reproduction ([178,150,36,113]). PD-1 is up-regulated on HIV-specific CD4+ T cells and its expression is driven by viral replication [47]. In fact, inhibition of the PD-1 pathway with a PD-L1–blocking antibody enhanced HIV-specific CD4+ T cells proliferation [37,76,47]. Clinical trials to investigate PD-1 inhibitors in HIV patients have been conducted (NCT02028403), though results have yet to be established.

T cell exhaustion has a key function also in immune dysfunction in cancer [122,180]. In the tumor microenvironment, many factors can modulate the existing activated antitumor T cells immune response, acting as an immune rheostat or “immunostat.” PD-L1 is expressed on various cancer cells, as well as myeloid cells in the tumor microenvironment in response to inflammatory signals ([152];[46]). Also, tumor growth is usually sustained by aerobic glycolysis [104], and metabolic dysregulation promotes T cell exhaustion in the tumor microenvironment. Inhibition of the PD-1 pathway rises glucose availability in the tumor microenvironment thus enhancing tumor-infiltrating lymphocytes (TIL) function and tumor regression [81]. PD-1 pathway blockade has been shown to have antitumor effects both in vitro [69,66,77,34,157,15,70,161], and in vivo [179]. Notwithstanding the unique effectiveness of immune checkpoint inhibitors (ICIs), HCC patients embody a population with distinctive features. HCCs contain a combination of different cell types, involving cancer cells, immune cells, and endothelial cells within the extracellular matrix and stroma. This observation is consistent with prior evidence of the so-called “field effect” in the damaged liver secondary to chronic hepatitis and cirrhosis [63]. About one third of HCC patients with peritumoral immune profile displays immunosuppressive signals, for example TGF-β activation and T-cell exhaustion.

Early data on the PD-1 inhibitor nivolumab in patients with advanced HCC (with a Child-Pugh score ≤B7) involved patients with chronic HBV or HCV infection. In patients with HCC who had disease progression or unacceptable adverse effects under sorafenib treatment, nivolumab showed a 10% rate of grade ≥3 liver enzyme elevation, but an overall manageable safety profile. Nivolumab achieved a median OS of 15.6 months [51], while the overall response rate was 14.3% according to Response Evaluation Criteria in Solid Tumors (RECIST); furthermore, in 55% of the treated patients the duration of the response was of more than 12 months [51] and responses to treatment were observed in both patients with HBV or HCV. The response data achieved in this single-phase 2 trial prompted Food and Drug Administration (FDA) approval under accelerated program [117] (https://www.accessdata.fda.gov/drugsatfda_docs/label/). In patients with unresectable HCC, anti-PD-L1 atezolizumab combined with bevacizumab significantly improved survival outcomes compared with sorafenib in previously untreated patients [57].

Treatment with ICIs might potentially play a double action in HIV infected patients, acting on one side on cancer cells and on the other improving the eradication of HIV reservoirs that persist during HAART by enhancing the HIV-specific CD8 T-cell response. A likely assumption is that ICIs may induce a transient reactivation of HIV transcription within latently infected CD4+ T cells and simultaneously decrease the expression of PD-L1+ and CD4+ T cells displaying high PD-1 levels [38]. This hypothesis has not been proven yet. Nevertheless, a recent report showed for the first time a case of a drastic and sustained decrease of the HIV reservoir, together with the restoration of HIV-specific CD8+ T cells function under anti-PD1 therapy in a patient affected with lung cancer [64]. Whether this promising effect is reproducible is presently the object of the French cohort study of HIV-infected patients treated with ICIs (ANRS-CO24, OncoVHAC cohort; NCT03354936) and might open new treatment strategies on HIV cure. Moreover, preliminary data on safety profile in real-life case series of HIV patients treated with an anti-Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4) monoclonal antibody ipilimumab [175], or with nivolumab [88] (mainly for melanoma or lung cancer), indicated a tolerability and safety profile comparable with those observed in non-HIV patients [65,146]. The PD-1 inhibitor pembrolizumab has been also evaluated in patients with HIV and advanced cancers; this study allowed a variety of cancers and required a CD4+ T cells count of ≥100 cells/mm [166]. Pembrolizumab showed clinical benefit and an acceptable safety profile in cancer patients with HIV on HAART and >100 CD4+ cells/μL [166], comparable to patients without HIV infection. Therefore, anti-PD1 inhibitors are proper for FDA-approved indications in this setting and HCC—HIV patients with appropriate eligibility criteria should be involved in immunotherapy-based clinical trials. Awaiting more mature data, HIV infection should not be considered a contraindication to treatment with anti-PD-1.

HIV and inclusion in clinical trials

Notwithstanding the dramatic outcome improvement as a result of advances in the treatment of HIV over the past 20 years, and the increasing public health need to treat cancer in people with HIV, most oncology clinical trials still exclude people with HIV [165]. Lack of prospective data on therapies in HIV-infected patients limits evidence-based treatment decision and contributes to huge treatment disparities for this patient population [80]. Nevertheless, management of cancer in HIV-positive patients should converge on appropriate approaches for the malignancy. This normally comprises standard regimens combined with treatment of HIV and supportive care when required. In properly selected patients' treatment outcomes are comparable to those of HIV-uninfected individuals [164]. This has been confirmed for Burkitt’s lymphoma [49], diffuse large B-cell lymphoma [48], classic Hodgkin lymphoma [110], as well as lung cancer [44].

In 2016, the HIV Working Group of the ASCO–Friends of Cancer Research engaged in several summits to revise the eligibility criteria related to HIV within oncology trials [165]. The Working Group established consensus recommendations based on an analysis of New Drug Applications from registration trials of single agents that conducted to FDA approval. HIV-related eligibility criteria from National Cancer Institute-sponsored studies were also examined. An FDA analysis of 2015 Investigational New Drug applications revealed that just five (1.7%) of 250 protocols allowed enrollment of HIV-infected patients with stable disease and adequate CD4+ T cell count. Likewise, the working group noted that none of 46 studies examined inclusion criteria for patients with HIV, 30 studies contained specific HIV exclusion criteria, and nine studies considered exclusion of patients with active infection and likely HIV infection [165].

Modernization of eligibility criteria to comprise HIV-infected patients in cancer clinical studies is crucial to extend the generalizability of trial results to this patient population. Exclusion to clinical trial participation based on HIV infection alone is not validated, and eligibility criteria linked to HIV infection in adult patients with cancer ought to be established based on existing medical knowledge and scientific basis [124]. The HIV Working Group identified criteria to define patients with HIV as sufficiently healthy from the HIV perspective to be enrolled in oncology clinical trials [165]. For example, the HIV Working Group underlined that eligibility should be established through assessment of present and historic CD4+ T cell counts, evaluation of any history of likely AIDS complications, and estimation of use of active HAART [165].

Personal perspectives

Still there is much concern about HCC patients co-infected with HIV and all issues related to HCC are even more amplified in this subgroup of patients. The main point for HCC—HIV patients is not only to select which drug to use but rather how to manage these patients and how to make all available drugs accessible. The main causes which could
negatively influence the number of HCC patients treated with targeted drugs are connected to difficult patient profiling in particular for possible drug-drug interactions and the lack of solid data on best treatment to offer. Therefore, a multidisciplinary approach is really necessary and require a constant cooperation between HIV and HCC experts. The ongoing phase IIIb AMETHYSTA study (NCT04487067), designed to evaluate the safety and efficacy of atezolizumab in combination with bevacizumab in patients with unresectable HCC who have received no prior systemic treatment, includes HIV positive patients who are considered to be good candidates for clinical trials and can potentially benefit from immunotherapy.

Conclusions

In addition to its role in triggering the pathogenesis of HCC, HIV infection augments complexity to the various process of treatment provision that differentiates the management of HCC. With the improving of novel therapeutic options for both viral hepatitis and cancer therapy, including novel target-based drugs and ICIs for HCC, there is yet the necessity to gather further knowledge about the clinical outcome of patients with HIV-HCC after viral cure and intensive efforts to combine expertise across HIV treatment, hepatology and oncology. This is especially relevant in the niche of patients that has not been included in pivotal trials. HIV patients with cancer should not be treated differently with regards to clinical trials enrolment; consequently, we need to ensure their participation in clinical trials when appropriate.

Author contributions

FN, CP, and GM: conceptualization and writing original draft. FN, GM, ADA and CP: review and editing. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

All authors had nothing to disclose.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] G.K. Abou-Alfa, T. Meyer, A.L. Cheng, et al., Cabozantinib in patients with advanced and progressing hepatocellular carcinoma, N. Engl. J. Med. 379 (2018) 54-63.
[2] A. Albini, G. Barilari, R. Benelli, et al., Tat, the human immunodeficiency virus type regulatory protein, has angionic properties, Proc. Natl. Acad. Sci. USA. 92 (1995) 4388–4426.
[3] R. Al-Rajabi, S. Patel, N.S. Ketchum, et al., Comparative dosing and efficacy of sorafenib in hepatocellular cancer patients with varying liver dysfunction, J. Gastrointest. Oncol. 6 (2015) 259-267.
[4] G. Altavilla, A. Caputo, M. Lanfredi, et al., Enhancement of chemical hepatocarcinogenesis by the HIV-1 tat gene, Am. J. Pathol. 157 (2000) 1081–1089.
[5] V. Appay, L. Papagno, C.A. Spina, et al., Dynamics of T cell responses in HIV infection, J. Immunol. 168 (2002) 3660-3666.
[6] D.L. Barber, E.J. Wherry, D. Masopust, et al., Restoring function in exhausted CD8+ T cell subsets is associated with duration of viral infection, J. Immunol. 168 (2002) 3660–3666.
[7] B. Bengsch, B. Seigel, M. Ruhl, et al., Correlation of CD4+ T cell enumeration with viral load in chronic HIV infection, J. Immunol. 168 (2002) 3660-3666.
[9] D. Blackburn, H. Shin, W.N. Haining, et al., Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection, Nat. Immunol. 10 (2009) 29-37.
[10] C. Blank, I. Brown, A.C. Peterson, et al., PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells, Cancer Res 64 (2004) 1140–1145.
[11] A.L. Cheng, Y.K. Kang, Z. Chen, et al., Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial, J. Hepatol. 57 (2012) 821–829.
[12] J. Bruix, S. Qin, P. Merle, et al., Sorafenib in patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESONARE): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet 389 (2017) 56-66.
[13] M. Bruyand, R. Thiébaut, S. Lawson-Ayayi, et al., Role of controlled HIV RNA level and immunodeficiency in the occurrence of malignancy in HIV-infected patients during the combination antiretroviral therapy era: agence Nationale de Recherche sur le Sida (ANRS) CO3 Aquitaine Cohort, Clin. Infect. Dis. 49 (2009) 1109–1116.
[14] M.K. Callahan, M.A. Postow, J.D. Wolchok, Immunity 44 (2016) 1069-1078.
[15] D. Campioni, A. Corallini, G. Zauli, et al., HIV type 1 extracellular Tat protein stimulates growth and protects cells of BK virus/tat transgenic mice from apoptosis, AIDS. Res. Hum. Retroviruses. 11 (1995) 1039–1048.
[16] Y.S. Chang, J. Adnane, P.A. Trail, et al., Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models, Cancer Chemother. Pharmacol. 59 (2007) 561–574.
[17] L. Chelis, N. Nittos, V. Soufias, et al., Complete response after sorafenib therapy for hepatocellular carcinoma in an HBV-HIV co-infected patient: possible synergy with HAART? A case report. Med. Oncol. 28 (Suppl 11) (2011) S165-S168.
[18] A.L. Cheng, Y.K. Kang, Z. Chen, et al., Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial, Lancet Oncol. 10 (2009) 25–34.
[19] M.C.M. Cheung, A.J. Walker, B.E. Hudson, et al., Outcomes after successful antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis, J. Hepatol. 65 (2016) 741-747.
[20] F.V. Chisari, C. Ferrari, Hepatitis B virus immunopathogenesis, Annu. Rev. Immunol. 13 (1995) 29-60.
[21] G.M. Clifford, M. Rickenbach, J. Bosch, et al., Influence of HIV-related immunodeficiency on the risk of hepatocellular carcinoma, AIDS 22 (2008) 2135–2141.
[22] F. Conti, F. Buonfiglioli, A. Scuteri, et al., Early occurrence and recurrence of hepatocellular carcinoma in HIV-related cirrhosis treated with direct-acting antivirals, J. Hepatol. 65 (2016) 727-735.
[23] A. Corallini, G. Altavilla, L. Pozzi, et al., Systemic expression of HIV-1 tat gene in transgenic mice induces endothelial proliferation and tumors of different histotypes. Cancer Res. 53 (1993) 5569-5575.
[24] T. Curiel, S. Wei, H. Dong, X. Alvarez, P. Cheng, et al., Blockade of B7-H1 improves myeloid dendritic cell-mediated antitumor immunity, Nat. Med. 9 (2003) 562-567.
[25] B. Daniele, A. Cruzor, C. Papandreu, et al., Impact of sorafenib dosing on outcome from the European patient subset of the GIDEON study, Future Oncol 11 (2015) 2553-2562.
[26] C.L. Day, B.D. Walker, Progress in defining CD4 helper cell responses in chronic viral infections, J. Exp. Med. 199 (2003) 1773-1777.
[27] C.L. Day, D.E. Kaufmann, P. Kiepiela, et al., PD-1 expression on HIV specific T cells is associated with T-cell exhaustion and disease progression, Nature 443 (2006) 350–354.
[28] F. Benneks, S.R. Lewin, A.L. Ross, et al., International AIDS society towards a cure working group. International AIDS Society global scientific strategy: towards an HIV cure 2016, Nat. Med. 22 (2016) 839-850.

F. Negrí et al.

Translational Oncology 14 (2021) 101153
[30] I. Delgado, M. Carrasco, E. Cano, et al., GATA4 loss in the septum transversum mesenchyme promotes liver fibrosis in mice, Hepatology 59 (2014) 2358–2370.
[31] E. De la Cruz-Hernandez, J.L. Medina-Franco, J. Trujillo, et al., Ribavirin as a tri-targeted antitumor repositioned drug, Oncol. Rep. 33 (2015) 2384–2392.
[32] F. De Marchi, P. D’adda Di Fagagna, A. Falaschi, et al., Activation of transcription factor NF-κB by the tat protein of human immunodeficiency virus type-1, J. Virol. 70 (1996) 4472–4481.
[33] P. De Nardo, M. Viscone, A. Corpolongo, et al., Treatment of recurrent hepatocellular carcinoma with sarefinitab in a HIV/HC-co-infected patient in HAART: a case report, Infect. Agent. Cancer 7 (2012) 15.
[34] I.E. Dika, J.J. Harding, G.K. Abou-Alla, Hepatocellular carcinoma in patients with HIV, Curr. Opin. HIV. AIDS. 12 (2017) 20–25.
[35] G.A. Djaen, L. Pantanowitz, M. Bower, et al., Human immunodeficiency virus-associated primary lung cancer in the era of highly active antiretroviral therapy: a multi-institutional collaboration, Clin. Lung Cancer 11 (2010) 396–404.
[36] T.A. Doering, A. Crawford, J.M. Angelosanto, et al., Network analysis reveals centrally connected genes and pathways involved in CD8+ T cell exhaustion versus memory, Immunity 37 (2012) 1130–1144.
[37] H. Dong, S.E. Strome, D.R. Salomon, et al., Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion, Nat. Med. 8 (2002) 793–800.
[38] M. D’Souza, A.P. Fontenot, D.G. Mack, et al., Programmed death 1 expression on HIV-specific CD4+ T cells is driven by viral replication and associated with T cell dysfunction, J. Immunol. 179 (2007) 1979–1987.
[39] K. Dunleavy, R.F. Little, S. Pittaluga, et al., The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma, Blood 115 (2010) 3017–3024.
[40] K. Dunleavy, S. Pittaluga, M. Shovlin, et al., Low-intensity therapy in adults with Burkitt’s lymphoma, N. Engl. J. Med. 369 (2013) 1915–1925.
[41] F. Duygu, H. Kasevich, Y. Watanabe, et al., Relationship of oxidative stress in hepatitis B infection activity with HBV DNA and Fibrosis, Ann. Lab. Med. 32 (2012) 113–118.
[42] A.B. El-Khoueiry, B. Sangro, T. Yau, et al., Nivolumab in patients with advanced hepatocellular carcinoma, N. Engl. J. Med. 375 (2016) 1250–1259.
[43] J. Esposito, E. Palescandolo, E.P. Spugnini, et al., Evaluation of antitumoral properties of the protease inhibitor indinavir in a murine model of hepatocarcinoma, Clin Cancer. Res. 12 (2006) 2634–2643.
[44] M. D’Souza, B. Ensoli, G. Barillari, Z.S. Salahaudin, et al., Tat protein of HIV-1 stimulates the immunoinhibitory receptor by a novel B7 family member leads to negative dysfunction, J. Immunol. 179 (2007) 1979–1987.
[45] V. Esposito, E. Palescandolo, E.P. Spugnini, et al., Activation of transcription factor NF-Kb by the tat protein of human immunodeficiency virus type-1, J. Virol. 70 (1996) 4472–4481.
[46] P. Ferenci, M. Fried, D. Labrecque, et al., world gastroenterology organisation guidelines for the management of patients with HCV co-infected patients with hepatocellular carcinoma: the CARCINOVIC multi-institutional collaboration, Clin. Lung Cancer 11 (2010) 396–404.
[47] K. Dunleavy, S. Pittaluga, M. Shovlin, et al., Low-intensity therapy in adults with Burkitt’s lymphoma, N. Engl. J. Med. 369 (2013) 1915–1925.
[48] K. Dunleavy, R.F. Little, S. Pittaluga, et al., The role of tumor histogenesis, FDG-PET, and short-course EPOCH with dose-dense rituximab (SC-EPOCH-RR) in HIV-associated diffuse large B-cell lymphoma, Blood 115 (2010) 3017–3024.
[49] E.P. Spugnini, et al., Evaluation of antitumoral properties of the protease inhibitor indinavir in a murine model of hepatocarcinoma, Clin Cancer. Res. 12 (2006) 2634–2643.
[50] B. Ensoli, G. Barillari, Z.S. Salahaudin, et al., Tat protein of HIV-1 stimulates growth of cells derived from Kaposis’s sarcoma lesions of AIDS patients, Nature 345 (1990) 84–86.
[51] F. Hirano, K. Kaneko, H. Tamura, H. Dong, S. Wang, et al., Blockade of B7-H1 and PD-1/PD-L1 improves survival of human CD8+ T cells and reverses immune dysfunction, J. Immunol. 179 (2007) 1979–1987.
[52] B. Ensoli, R. Gendelman, P. Markham, et al., Synergy between basic fibroblast growth factor and HIV Tat protein in induction of Kaposis’s sarcoma, Nature 371 (1994) 674–680.
[53] V. Esposito, E. Palescandolo, E.P. Spugnini, et al., Evaluation of antitumoral properties of the protease inhibitor indinavir in a murine model of hepatocarcinoma, Clin Cancer. Res. 12 (2006) 2634–2639.
[54] Y. Fan, R. Mao, J. Yang, NF-kappab and STAT3 signaling pathways collaboratively link inflammation to cancer, Protein Cell 4 (2013) 176–185.
[55] P. Ferenci, M. Fried, D. Labrecque, et al., world gastroenterology organisation guidelines and publication committee. World gastroenterology organisation guideline (HCC): a global perspective, J. Gastrointestinal. Liver. Dis. 19 (2010) 311–317.
[56] P. Marcellin, F. Pequignot, E. Delarocque-Astagneau, et al., Mortality related to cirrhosis and hepatocellular carcinoma in patients with HIV infection, Lancet 377 (2011) 1198–1209.
[57] S.M. Kahan, E.J. Wherry, A.J. Zajac, T cell exhaustion during persistent viral infections, Virology 479–480 (2015) 180–193.
[58] A. Guihot, A.G. Marcelin, M.A. Massiani, et al., Drastic decrease of the HIV-1 Tat protein in patients with HIV infection, J. Clin. Oncol. 35 (2017) 622–628.
[59] S. Jelic, G.C. Sotopoulos, et al., Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 21 (2010) v59–v64.
[60] D. Josh, J. O’Grady, D. Dieterich, et al., Increasing burden of liver disease in patients with HIV infection, Lancet 377 (2011) 1198–1209.
[61] F. Negri et al. Translational Oncology 14 (2021) 101153
I. Vujkovic-Cvijin, R.M. Dunham, S. Iwai, et al., Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. Sci. Transl. Med. 5 (2013), 193ra91.

[159] W.T. Tai, A.L. Cheng, C.W. Shiu, et al., Signal transducer and activator of transcription 3 is a major kinase-independent target of sorafenib in hepatocellular carcinoma, J. Hepatol. 55 (2011) 1041–1048.

[160] M. Tien Kuo, N. Savaraj, Roles of reactive oxygen species in hepatocarcinogenesis and drug resistance gene expression in liver cancers, Mol. Carcinog. 45 (2006) 707–709.

[161] S.L. Topalian, C.G. Drake, D.M. Pardoll, Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity, Curr. Opin. Immunol. 24 (2012) 207–212.

[162] L. Trautmann, L. Janbazian, N. Chomont, et al., Upregulation of PD-1 expression in acute hepatitis C virus (HCV) infection is associated with HCV-specific CD8+ T cell exhaustion during chronic viral infection, Immunity 27 (2007) 670–684.

[163] A.C. Tuyama, F. Hong, Y. Saiman, et al., Human immunodeficiency virus (HIV)-1 infects human hepatic stellate cells and promotes collagen I and monocyte chemoattractant protein-1 expression: implications for the pathogenesis of HIV/hepatitis C virus-induced liver fibrosis, Hepatology 52 (2010) 612–622.

[164] T.S. Uldrick, R.F. Little, How I treat classical Hodgkin lymphoma in patients infected with human immunodeficiency virus, Blood 125 (2015) 1226–1235.

[165] T.S. Uldrick, G. Ison, M.A. Rudek, et al., Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology-Friends of Cancer Research HIV Working Group. J. Clin. Oncol. 35 (2017) 3774–3780.

[166] T.S. Uldrick, P.H. Gonçalves, M. Abdul-Hay, et al., Assessment of the safety of pembrolizumab in patients with HIV and advanced cancer-A phase 1 study, JAMA Oncol 5 (2019) 1332–1339.

[167] P. Ulivi, C. Arienti, D. Amadori, et al., Role of RAF/MEK/ERK pathway, p-STAT-3 and Mcl-1 in sorafenib activity in human pancreatic cancer cell lines, J. Cell. Physiol. 220 (2009) 214–221.

[168] V. Velu, K. Titanji, B. Zhu, et al., Enhancing SIV-specific immunity in vivo by PD-1 blockade, Nature 458 (2009) 206–210.

[169] S. Urbani, B. Amadei, D. Tola, et al., PD-1 expression in acute hepatitis C virus (HCV) infection is associated with HCV-specific CD8+ exhaustion, J. Virol. 80 (2006) 11398–11403.

[170] I. Vujkovic-Cvijin, R.M. Dunham, S. Iwai, et al., Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. Sci. Transl. Med. 5 (2013), 193ra91.

[171] R. Weber, M. Ruppin, M. Rickenbach, et al., Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study, HIV. Med. 14 (2013) 195–207.

[172] M.O. Westendorp, M. Li-Weber, Frank, et al., Human immunodeficiency virus type 1 upregulates interleukin secretion in activated T cells, J. Virol. 68 (1994) 4177–4185.

[173] E.J. Wherry, S.J. Ha, S.M. Kaech, et al., Molecular signature of CD8+ T cell exhaustion during chronic viral infection, Immunity 27 (2007) 670–684.

[174] E. Wherry, T cell exhaustion, Nat. Immunol. 12 (2011) 492–499.

[175] F. Wightman, A. Solomon, S.S. Kumar, et al., Effect of ipilimumab on the HIV reservoir in an HIV-infected individual with metastatic melanoma, AIDS 29 (2015) 504–506.

[176] A. Wree, L. Broderick, A. Canbay, et al., From NAFLD to NASH to cirrhosis: new insights into disease mechanisms, Nat. Rev. Gastroenterol. Hepatol. 10 (2013) 627–636.

[177] C. Xu, W. Zhou, Y. Wang, et al., Hepatitis B virus-induced hepatocellular carcinoma. Cancer. Lett. 345 (2014) 216–222.

[178] A.J. Zajac, J.N. Blattman, K. Murali-Krishna, et al., Viral immune evasion due to persistence of activated T cells without effector function, J. Exp. Med. 188 (1998) 2205–2213.

[179] J.Y. Zhang, Y.Y. Yan, J.J. Li, et al., PD-1/PD-L1 Based Combinational Cancer Therapy: icing on the Cake, Front. Pharmacol. 11 (2020) 722.

[180] H.M. Zanour, Reversing T-cell dysfunction and exhaustion in cancer, Clin. Cancer Res. 22 (2016) 1856–1864.

[181] G. Zauli, D. Gibellini, D. Milani, et al., Human immunodeficiency virus type 1 Tat protein protects lymphoid, epithelial, and neuronal cell lines from death by apoptosis, Cancer Res 53 (1993) 4481–4485.

[182] A. Zehir, R. Benayed, R.H. Shah, et al., Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients, Nat. Med. 23 (2017) 703–713.

[183] A. Zhu, Y.K. Kang, C.J. Yen, et al., Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Oncol 20 (2019) 282–296.

[184] N.L. Zhu, K. Asahina, J. Wang, et al., Hepatic stellate cell-derived delta-like homolog 1 (DLK1) protein in liver regeneration. J. Biol. Chem. 287 (2012) 10355–10367.