

# The Eradication of Carcinogenic Viruses in Established Solid Cancers

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**Abstract:** Carcinogenic viruses (oncoviruses) can initiate cancer, but their impact on established cancer varies. Some of these viruses prolong survival while others shorten it. This study classifies oncoviruses into two categories: viruses which induce a strong CD8+ T cell reaction in non-cancerous tissues, and viruses which induce a weak CD8+ T cell reaction in non-cancerous tissues. The classification proves useful in predicting the effect of oncoviruses on the prognosis of solid cancers. Therefore, while eliminating carcinogenic viruses in healthy individuals (for example by immunization) may be important for cancer prevention, this study suggests that only viruses which induce a weak CD8+ T cell reaction should be eradicated in established solid tumors. The model correctly predicts the effect of oncoviruses on survival for six out of seven known oncoviruses, indicating that immune modulation by oncoviruses has a prominent effect on prognosis. It seems that CD8+ T cell response to oncoviruses observed in infected benign tissues is retained in infected tumors. Clinical significance: the effect of oncoviruses on solid cancer prognosis can be predicted with confidence based on immunological responses when clinical data are unavailable.

**Keywords:** carcinogenic viruses, oncoviruses, cancer prognosis, CD8+ T cell, Treg cells

## Introduction

Carcinogenic viruses drive the initiation of several types of cancer. Human papillomavirus (HPV) drives cervical cancer, head and neck cancer, and other less common cancer types such as vulva, vagina, penis, anus, and rectum cancers. Hepatitis B virus (HBV) and hepatitis C virus (HCV) drive hepatocellular carcinoma (HCC), human gamma herpesvirus 8 (HHV-8) triggers Kaposi's sarcoma, human T-cell lymphoma virus 1 (HTLV1) triggers adult T-cell lymphoma/leukemia (ATLL), Epstein-Barr virus (EBV) triggers Burkitt's lymphoma, nasopharyngeal carcinoma and Hodgkin's lymphoma (HL), Merkel cell polyomavirus (MCPyV) induces Merkel cell carcinoma (MCC).<sup>1</sup> HBV and HPV infections are responsible for 23–59% of HCC cases and for 100% of cervical cancer cases, respectively.<sup>1</sup> EBV is detected in the tumor tissue of almost 100% of the cases of endemic Burkitt lymphoma. Evidence of HTLV-1 infection was found in at least 90% of ATLL cases,<sup>2</sup> HHV-8 is present in 80–95% of Kaposi sarcoma lesions.<sup>3</sup> MCPyV was detected in 77% of all MCCs.<sup>4</sup> Although different carcinogenic agents use different mechanisms to induce their tumorigenic effects, they may broadly be divided into two classes: direct carcinogens which express viral oncogenes that directly contribute to cancer cell transformation (HPV, HTLV-1, EBV, MCPyV, and HHV-8), and indirect carcinogens that presumably cause cancer through chronic infection and inflammation, which eventually leads to carcinogenic mutations in host cells (HBV, HCV).<sup>1,5</sup> Oncoviruses hijack host cycle regulation machinery to promote their own genomic replication. Presumably, as part of this process, viruses target anti-cancer genes such as p53 and RB1 to delay host cell apoptosis, facilitating efficient virus production and export before cell death.<sup>5</sup>

Viruses elicit strong innate immune responses by activating diverse pathogen recognition receptors (PRRs), including toll-like receptors (TLR) on plasma or endosomal membranes, and cytoplasmic receptors such as cGAS for viral DNA, and RIG-I and MDA-5 for viral RNA. These receptors initiate separate signaling cascades that converge to activate transcription factors. This activation results in the expression of pro-inflammatory cytokines,

including IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-6, and TNF $\alpha$  through NF- $\kappa$ B activation. Additionally, type I and type III interferons are expressed through interferon response factors (IRFs), mainly IRF3 and IRF7.<sup>6</sup> Upon antigen-driven activation, IFN-I directs naive CD4<sup>+</sup> T cells to the Th1 phenotype, facilitates the activation, expansion, and IFN $\gamma$  secretion of cytotoxic CD8<sup>+</sup> T cells, and enhances NK cell activation and IFN $\gamma$  secretion.<sup>7</sup> IFN $\gamma$  plays a crucial role in coordinating immune responses by promoting IgG production, enhancing macrophage function, and improving dendritic cell antigen presentation.<sup>8</sup> Oncoviruses play a role in multistep tumorigenesis alongside chronic inflammation and immunosuppression. They enhance the expression of viral-encoded oncogenes in infected cells, including MCPyV-related T antigen, EBV-related LMP1, LMP2A, LMP2B, EBNA1, and EBNA2, as well as HTLV-1-related Tax and HPV-related E5, E6, and E7. Additionally, oncoviruses regulate the host epigenetic machinery, induce genomic instability through insertional mutagenesis,<sup>9</sup> and influence the mitochondrial function of infected cells.<sup>10</sup> They also impact tumor suppressor pathways (eg, p53 and pRB) and host signaling pathways (eg, PI3K–AKT–mTOR; MAPK; Notch; WNT/ $\beta$ -catenin; NF- $\kappa$ B).<sup>11</sup>

Eliminating several carcinogenic pathogens in healthy populations is recommended as a preventive measure to reduce the risk of cancer. It is unclear, however, whether a specific carcinogenic virus should be eradicated in populations of cancer patients, since some of these viruses have a beneficial effect on cancer prognosis while others have an adverse effect. This work proposes the use of CD8<sup>+</sup> T cell reaction to viral infection in healthy organisms, to determine whether or not an oncogenic virus should be eradicated in established solid tumors. It is demonstrated that viruses with impaired CD8<sup>+</sup> T cell reaction, in the context of a chronic infection of an otherwise healthy organism (henceforth: “chronic infection”), have a negative effect on solid cancer prognosis, and should be eradicated in established solid tumors, while an oncovirus that elicit a strong CD 8<sup>+</sup> T cell reaction in the context of chronic infection, improves prognosis, and therefore should remain untouched in solid cancers.

## The Immune Reaction to Carcinogenic Viruses

Carcinogenic viruses are classified as strong or weak inducers of cytotoxic immune response. Various methods have been employed to assess the extent of this response. The evaluation of CD8<sup>+</sup> T cell reactivity may involve (a) measuring the capacity of CD8<sup>+</sup> T cells to proliferate after exposure to the virus or its epitope, in experimental animal models or infected human populations;<sup>12,13</sup> (b) assessing the ability of CD8<sup>+</sup> T cells to produce cytotoxic agents such as IL-2, IFN $\gamma$ , TNF $\alpha$ , perforins, and granzymes;<sup>14</sup> (c) examining the down- or up-regulation of CD8<sup>+</sup> T cell gene expression associated with anti-viral activity;<sup>15</sup> (d) detecting virus-specific CD8<sup>+</sup> T cells in a seronegative recipient of a graft infected with the virus.<sup>16</sup> While the patient remaining aviremic following graft implantation indicates strong anti-viral cytotoxicity, this method does not allow for the quantification of this anti-viral effect; (e) analyzing the down- or up-regulation of immune checkpoint gene expression (such as CD137, PD-1, TIM-3, CTLA -4, 2B4, ICOS, BTLA, LAG-3, KLRG-1, TIGIT) in CD8<sup>+</sup> T cells;<sup>17–23</sup> and (f) determining the killing rate of infected splenocytes by virus-specific CD8<sup>+</sup> T cells. This involves pulsing a population of mouse splenocytes with the viral epitope and transferring them into syngeneic hosts along with a population of unpulsed splenocytes. Loss of peptide-pulsed targets is measured in the mouse spleen, and the percent killing is estimated from the reduction in the ratio of pulsed target cells to unpulsed cells, corrected for the initial ratio.<sup>24</sup> It should be noted that this list of methods used to assess CD8<sup>+</sup> T cell response is not exhaustive.

Next, CD8<sup>+</sup> T cell response to oncoviruses, in the context of non-cancerous tissue infection, is reviewed:

## HPV

Human papillomavirus is a strong inducer of CD8<sup>+</sup> T cell reaction during both acute and chronic infections. The infiltration of cytotoxic CD8<sup>+</sup> T cells into HPV-infected human lesions is considered a crucial immunological characteristic in persistent papillomavirus infection and disease regression.<sup>25</sup> In female mice, intravaginal immunization with HPV followed by boosting with different HPV serotypes resulted in a 10-fold increase in cervicovaginal antigen-specific CD8<sup>+</sup> T cells compared to priming alone.<sup>12</sup> While “exhausted” CD1<sup>+</sup> HPV-specific CD8<sup>+</sup> T cell clusters have been observed in the context of HPV-positive head and neck squamous cell

carcinoma (HNSCC),<sup>26,27</sup> this cluster contributes to persistent anti-tumor immunity due to their extended cell survival and specialized cytotoxic capacity.<sup>26</sup> Moreover, it has been associated with longer survival in HPV-positive HNSCC.<sup>26</sup> Notably, no reports exist of exhausted anti-HPV CD8<sup>+</sup> T cells in the context of HPV infection in non-cancerous tissue.

## HBV

Hepatitis B virus triggers an exhausted CD8<sup>+</sup> T cell reaction in chronic infection. Most acute adult-onset HBV infections usually elicit strong, multifunctional CD8<sup>+</sup> T cell responses, while chronic hepatitis B is characterized by quantitatively and qualitatively weak HBV-specific CD8<sup>+</sup> T cell responses with markedly reduced capacity to proliferate or to produce IL-2, IFN $\gamma$ , TNF $\alpha$ , perforins and granzymes.<sup>14,28–31</sup>

## HCV

Hepatitis C virus triggers an exhausted CD8<sup>+</sup> T cell reaction in chronic infection. Similar to HBV, HCV acute infection results in a vigorous CD8<sup>+</sup> T cell response. Chronic HCV infection, on the other hand, may lead to a dysfunctional CD8<sup>+</sup> T cell response.<sup>32</sup> For example, Barili et al<sup>33</sup> have shown that during chronic infection, exhaustion of HCV-specific T cell responses is characterized by a broad gene downregulation associated with a wide metabolic and anti-viral function impairment. It was also demonstrated that a TCF1+CD127+PD-1<sup>hi</sup> HCV-specific CD8<sup>+</sup> T cell subset with phenotypic features of T-cell exhaustion and memory exists in chronically infected patients, both before and after treatment with direct acting antiviral agents (ie, after HCV eradication). This exhausted population expands after antigen re-challenge. Side-by-side with this expansion, terminally exhausted TCF1-CD127-PD-1<sup>hi</sup> HCV-specific CD8<sup>+</sup> T cells emerge.<sup>15</sup> The relationship between memory-like and terminally exhausted HCV-specific CD8<sup>+</sup> T cells can be regarded as progenitor–progeny relationship.<sup>34</sup>

## HHV-8

Human herpes virus 8 infection triggers a strong CD8<sup>+</sup> T cell response. Cytotoxic T cell reaction to HHV-8, in patients that control the infection are frequent, diverse, and strongly differentiated toward a phenotype which expressed perforin (an effector phenotype). In addition, HHV-8-specific CD8<sup>+</sup> T cells were observed in a seronegative recipient of an HHV-8 infected graft who remained persistently aviremic and antibody negative, suggesting that specific CD8<sup>+</sup> T lymphocytes may provide protection from persistent HHV-8 infection.<sup>16</sup> HHV-8 epitopes activate monofunctional and polyfunctional CD8<sup>+</sup> T cells that produce various combinations of IFN $\gamma$ , IL-2, TNF $\alpha$ , the chemokine MIP-1 $\beta$ , and cytotoxic degranulation marker CD107a in healthy HHV-8-seropositive individuals.<sup>35</sup> However, there are also data describing HHV-8-induced immune evasion through the downregulation of MHC-I molecule expression<sup>36</sup> and by enhancing endocytosis of MHC I from the cell surface.<sup>37</sup> Another study notes the absence of HHV-8-specific T cells in Kaposi sarcoma.<sup>38</sup> This finding is supported by a more recent analysis of biopsies from Kaposi sarcoma patients. In this study, CD8<sup>+</sup> T cells were not detected in Kaposi sarcoma tissues with evidence of HHV-8 infected cells, but CD8<sup>+</sup> T cells were readily detectable in tumors without HHV-8 infected cells.<sup>39</sup> These results may suggest that a lack of specific CD8<sup>+</sup> T cells allows HHV-8 infection to progress. Overall, HHV-8 induces a robust specific CD8<sup>+</sup> T cell response, which persists despite the virus's evasion mechanisms.

## HTLV1

Human T cell leukemia virus type 1 induces dysfunctional CD8<sup>+</sup> T cells during HTLV1 infection. Kozako et al<sup>18</sup> examined PD-1/PD-L1 expression on cells from 27 asymptomatic HTLV-1 carriers (ACs) and 27 adult T-cell leukemia/lymphoma (ATLL) patients in comparison with cells from 18 healthy controls. PD-1 expression on HTLV-1-specific CD8<sup>+</sup> T cells from ACs and ATLL patients was substantially higher compared to healthy controls. Anti-PD-L1 antibody treatment upregulated HTLV1-specific CD8<sup>+</sup> T-cell response. Clements et al<sup>20</sup> compared the expression of negative-checkpoint-immune-receptors (T cell co-receptors that negatively regulate T cell activation), expressed by circulating CD8<sup>+</sup> T lymphocytes between three groups: a group of patients with

myelopathy/tropical spastic paraparesis (HAM/TSP) infected with HTLV1, a group of patients with asymptomatic HTLV-1 infection and a group of seronegative controls. Global CD8+T cells from HAM/TSP patients co-expressed multiple negative checkpoint receptors at much higher frequencies than asymptomatic carriers. In addition, TIM-3 expression in CD8+T cells from asymptomatic carriers was significantly higher compared to seronegative controls. In agreement, a model of immunodeficient NSG mice reconstituted with a functional human immune system demonstrated exhausted CD8+ T cells pattern following HTLV1 infection. These CD8+ T cells expressed reduced IFN $\gamma$  expression, even though granzyme B and perforin were fully expressed.<sup>40</sup> It was also reported that HTLV1 protein expression in naturally infected CD8+T lymphocytes renders them susceptible to killing mediated by autologous HTLV1-specific CD8+T lymphocytes.<sup>41</sup> Taken together, HTLV1 infection downregulates cytotoxic T cell activities.

## EBV

Epstein–Barr infection triggers a strong CD8+ T cell response that is retained following prolonged exposure to high antigen levels. Infectious mononucleosis is characterized by high viral loads and prolonged CD8+T cell stimulation.<sup>42</sup> In most cases, EBV enters latency and is under lifelong immune control. Using tetrameric MHC-peptide complexes to directly visualize antigen-specific CD8+T cells during the primary immune response to EBV infection in humans, Callan et al<sup>43</sup> demonstrated a massive expansion of activated, antigen-specific CD8+ T cells during the primary response to this virus. Responses to lytic cycle proteins account for most of the vigorous CD8+T cell expansion seen in acute infectious mononucleosis [Abbott]. Chatterjee et al<sup>19</sup> detected an expansion of PD-1 positive CD8+ T cells together with high frequencies of TIM-3, 2B4, and KLRG-1 expression in the plasma of patients with infectious mononucleosis and in the serum of a mouse model. These PD-1 positive CD8+ T cells, however, conserved cytokine production, proliferation, and cytotoxicity. PD-1 blocking resulted in virus-associated lymphomagenesis due to compromised EBV-specific immune control. Conflicting results were reported by Ma et al.<sup>21</sup> Using an EBV-infected cord blood-reconstituted huNSG mouse model, these authors demonstrated that blocking PD-1 and CTLA4 activity led to a reduced tumor burden. However, as noted by Chatterjee et al,<sup>19</sup> this model was deemed inappropriate as it does not induce efficient EBV-specific immune control of lymphoma. In summary, EBV induces a long-lasting high CD8+ T cell response.

## MCPyV

Merkel cell polyomavirus specific CD8+ T cells demonstrate strong anti-viral activity during persistent infection. In immunocompetent individuals, polyomavirus (PyV) infection is asymptomatic and persists lifelong, primarily in the urogenital tract, in the central nervous system (CNS), and in hematopoietic cells.<sup>44</sup> Ganusov et al<sup>24</sup> have demonstrated a strong CD8+T cell anti-viral response to polyomavirus during persistent infection in a mouse model. Another study in a mouse model, by the same group, confirmed the functionality of virus-specific CD8+T cells recruited during persistent infection. In contrast, CD8+ T cells recruited early in MPyV infection express an exhausted functionality.<sup>45</sup> Long-lived antiviral CD8+ T cells are defective in self-renewal; however, newly generated T cells preserve antiviral CD8+ T cell populations during chronic PyV infection.<sup>46</sup>

## The Effect of Carcinogenic Viruses on Survival/Clinical Practice

### HPV

An analysis of 2845 patients with cervical cancer revealed 43% lower mortality of patients with high-risk HPV compared with patients without high-risk HPV.<sup>47</sup>

Among a group of 303 patients with stage IVC head and neck squamous cell carcinoma, HPV- positive patients had better head and neck cancer specific survival ( $P < 0.001$ ) and overall survival ( $P < 0.001$ ) compared to those with HPV-negative disease.<sup>48</sup>

## HBV

In a retrospective study with 175 hepatocellular carcinoma (HCC) patients, the overall survival (OS) rate of non-HBV non-HCV HCC patients was significantly better than that of HBV-HCC patients.<sup>49</sup> Another retrospective study with 562 HCC patients demonstrated a significantly better OS rate of non-HBV non-HCV patients with a history of HBV infection (self-resolved infection or HBV eradicated) compared to that of HCC patients with a current HBV infection.<sup>50</sup> A retrospective analysis of 756 HBV-associated HCC patients at the Beijing Ditan Hospital, China, demonstrated reduced mortality in HCC patients with low HBV-DNA levels after antiviral therapy.<sup>51</sup>

## HCV

A retrospective analysis of overall survival outcomes in 1389 HCV-related HCC patients revealed that HCV eradication after HCC development was associated with improved survival.<sup>52</sup> Another retrospective analysis of HCC patients concludes that HCV elimination substantially improved OS in HCC patients with active HCV infection, and patients who did not receive antiviral therapy had a poorer prognosis.<sup>53</sup> Studies addressing the relationship between DAA-induced eradication and risk of HCC recurrence have produced contradictory data.<sup>54</sup> However, a recent review by Muzica et al<sup>55</sup> concludes that most recent and relevant articles suggest a reduced incidence rate of both de novo and recurrent HCC in patients with chronic hepatitis C, HCV-related cirrhosis, and HCV-related HCC, after achieving sustained viral response with direct-acting antiviral therapy.

## HHV-8

Antiviral therapy is not included in the very recent S1 guidelines for the Kaposi sarcoma.<sup>56</sup>

## HTLV-I

A combination of two antiviral agents: zidovudine (AZT) and interferon-alpha (IFN $\alpha$ ) is a standard treatment in adult T-cell lymphoma/leukemia (ATL). It induces a high rate of response and significantly improves survival in the “leukemic-chronic” and “smoldering” subtypes of ATL.<sup>57,58</sup> The smoldering and the “favorable” chronic subtypes are regarded as indolent ATL subtypes.<sup>57</sup>

## EBV

In a meta-analysis of clinical studies investigating the effect of EBV status on the clinical outcome in patients with classical Hodgkin's lymphoma (cHL), almost all studies of older adults or elderly patients with cHL report a deleterious effect of an EBV- positive status on prognosis. In younger adults, there is either a moderate beneficial effect or no effect of EBV status on prognosis. The results of adolescents and children studies conflict. However, the largest study (N = 842) of children and adolescents reports a statistically significant shorter OS of EBV-positive patients compared to EBV- negative patients.<sup>59</sup> In this large study, LMP1 positivity was associated with poorer OS (RR = 3.08).<sup>60</sup> In a pooled analysis of 26 studies, EBV-positive nasopharyngeal carcinoma patients demonstrated worse OS and progression-free survival, compared to EBV-negative patients.<sup>61</sup>

## MCPyV

A recent meta-analysis of 14 studies reveals a significant correlation between MCPyV positivity and improved OS of Merkel cell carcinoma patients.<sup>62</sup>

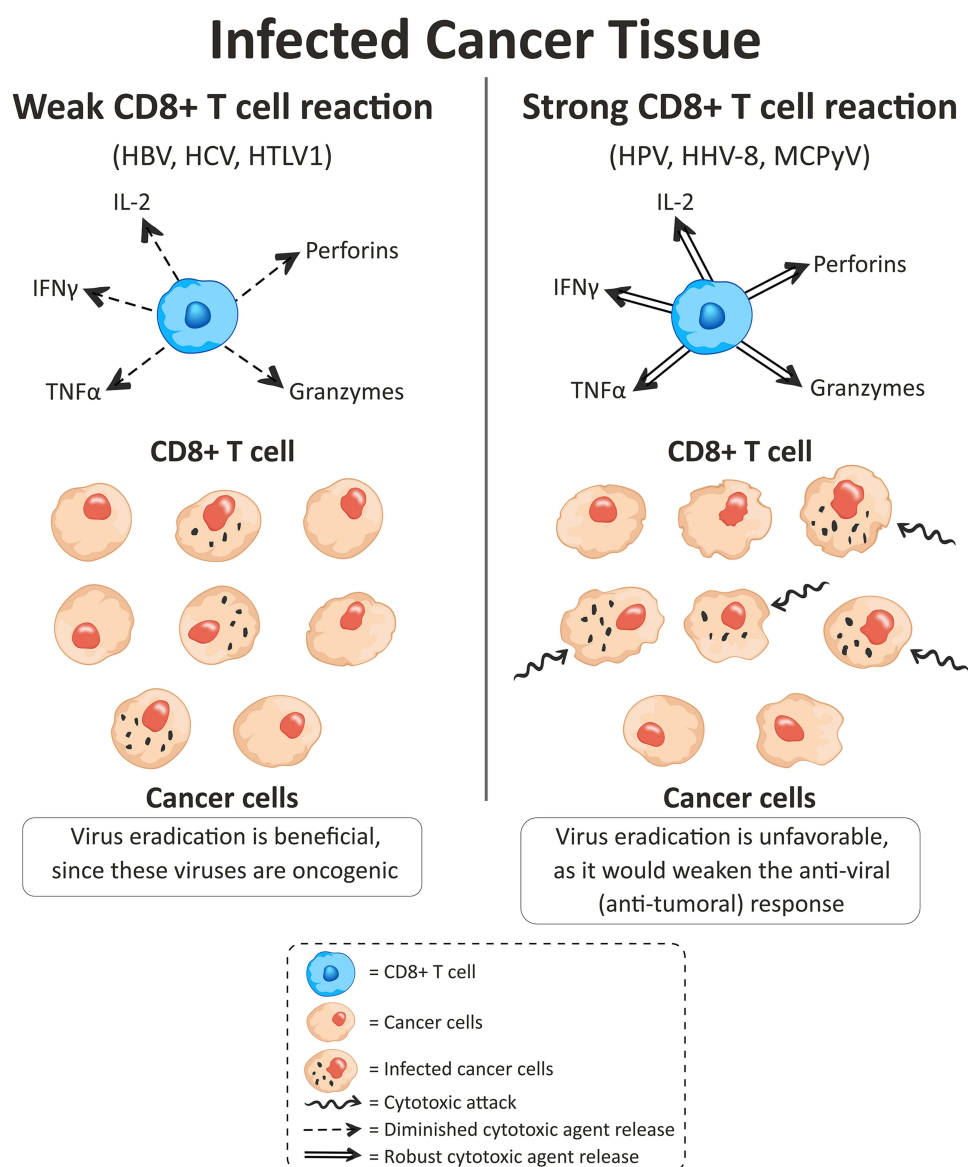
## Which Viruses Should Be Eradicated and Which Should Be Left Untouched?

Two mechanisms are utilized by viruses to exert their direct tumorigenic effect: (a) an infliction of DNA damage and carcinogenic mutations in the host cell genome following the induction of chronic inflammation (b) an upregulation of pro-cancer genes or downregulation of anti-cancer genes following integration of the viral genome into the host cell chromosomes or following persistency of a latent form of the viral genome in an

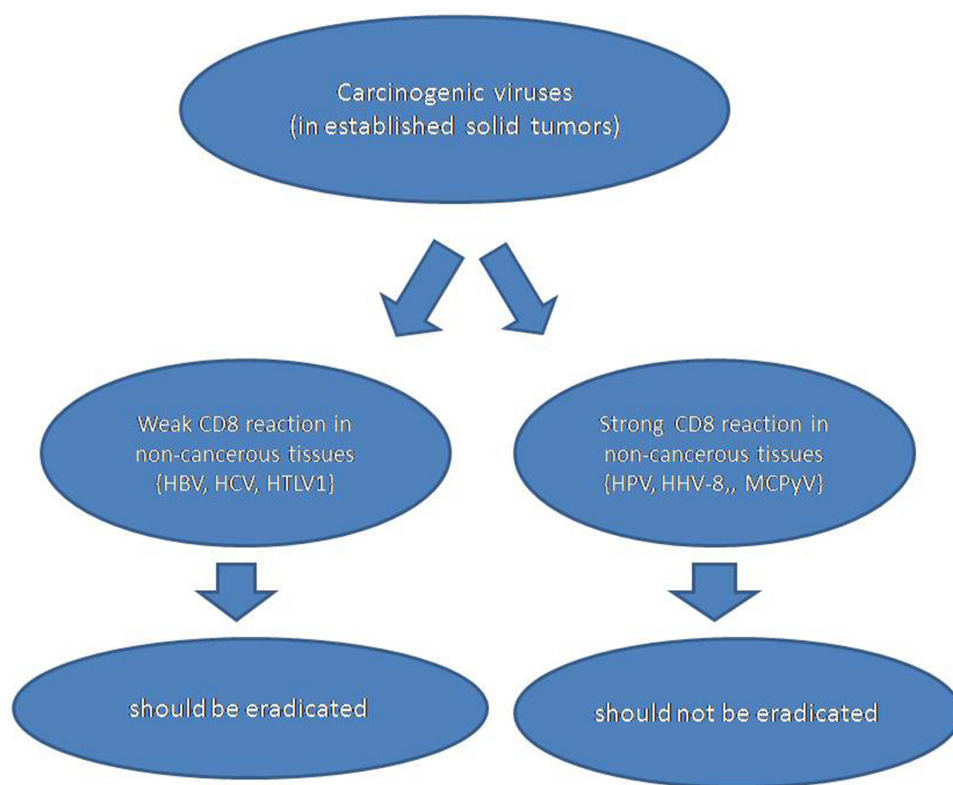


infected cell.<sup>63</sup> As a counter-reaction, an anti-viral immunity is triggered. Viruses (and intracellular bacteria) induce an MHC-I-mediated CD8+T activation. By releasing perforin, granzyme, granulysin and supramolecular attack particles, these activated CD8 cells destroy the host cells as a means of virus elimination.<sup>64,65</sup> Since the host is a cancer cell, the result is an anti-cancer effect. When this anti-cancer response is intensive enough, it may overcome the direct pro-tumor effects of the virus and improve prognosis. However, if this response is weak, the pro-tumor effects of the pathogen will prevail and exacerbate prognosis. Based on these arguments, the present work proposes a division of oncoviruses into two classes: viruses that induce strong anti-viral CD8+ T cell reaction and viruses that induce weak anti-viral CD8+ T cell reaction. In established solid tumors, viruses that induce strong cytotoxic reaction will prolong survival and should therefore be left untouched, while viruses that induce weak cytotoxic reaction will shorten survival and should better be eradicated. Figure 1 depicts a schematic representation of the model. Figure 2 presents a decision tree with respect to the eradication of viruses (and intracellular bacteria) in established solid tumors.

Table 1 presents, side by side, the binary classification of known oncoviruses, the eradication recommendations based on the binary model, and the effect of each virus on patients' prognosis, as reported in the literature.



**Figure 1** A schematic presentation of the binary model for CD8+ T cell response to oncoviruses (and intracellular carcinogenic bacteria).



**Figure 2** A decision tree regarding the eradication of oncoviruses (and intracellular carcinogenic bacteria) in established tumors.

**Note:** The model cannot be applied to certain lymphomas, to extracellular pathogens, and to pathogens which elicit host-sensitive immune response.

## Discussion

Cytotoxic CD8<sup>+</sup> T cells employ multiple mechanisms to eliminate viruses and other intracellular pathogens. These mechanisms include the secretion of IFN $\gamma$  and TNF $\alpha$ , as well as the utilization of pathways mediated by perforin, FasL, and the TNF-related apoptosis-inducing ligand (TRAIL).<sup>66</sup> Ultimately, these modalities lead to the elimination of the host

**Table 1** Binary Classification of CD8<sup>+</sup>T Cell Reaction to Viral Infection of Benign Tissues, Eradication Recommendations, and Clinical Evidence Regarding the Effect of the Virus on Patients' Prognosis

Oncovirus	Related Cancer(s)	CD8 <sup>+</sup> T Cell Reaction	References	Pathogen Eradication (the Binary Model)	Pathogen Eradication (Clinical Evidence or Practice)	References
HPV	Cervical cancer and head and neck cancer (mainly)	Strong	[12,25]	No	No	[47,48]
HBV	Hepatocellular carcinoma	Weak	[14,28–31]	Yes	Yes	[49–51]
HCV	Hepatocellular carcinoma	Weak	[15,32–34]	Yes	Yes	[52,53,55]
HHV-8	Kaposi's sarcoma	Strong	[16,35]	No	No	[56]
HTLV1	Adult T-cell lymphoma/leukemia	Weak	[18,20,40,41]	Yes	Yes	[57,58]
EBV	Hodgkin lymphoma,	Strong	[13,19,42,43]	No	Yes (in elderly patients and in the largest study in children)	[59] (a review), [60]
EBV	Nasopharyngeal carcinoma	Strong	[13,19,42,43]	No	Yes	[61] (a pooled analysis)
MCPyV	Merkel cell carcinoma	Strong	[24,45,46]	No	No	[62]

**Abbreviations:** HPV, human papillomavirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human gamma herpesvirus 8; HTLV1, human T-cell lymphoma virus 1; EBV, Epstein-Barr virus; MCPyV, Merkel cell polyomavirus.

cell. If the host cell is a cancer cell, this results in an anti-tumor effect. However, in the case of dysfunctional CD8<sup>+</sup> T cells, this anti-tumor effect is impaired.

An earlier publication introduced a binary criterion for selecting drugs for the treatment of severe COVID-19 infection.<sup>67</sup> The study demonstrated that drugs suppressing CD8<sup>+</sup> T cell activity are ineffective in treating the severe state of the disease. Additionally, Kumagai et al<sup>68</sup> proposed a binary classification of CD8<sup>+</sup> T cell responses in the tumor microenvironment (TME) of non-small cell lung cancer (NSCLC) and gastric cancer to assess survival outcomes following immunotherapy. These authors illustrated that in patients treated with a monoclonal antibody to PD-1, a high frequency (>57%) of PD-1<sup>+</sup> CD8<sup>+</sup> T cells in the TME is linked to improved survival compared to a low frequency (<57%). Several studies suggest that elevated expression of inhibitory checkpoint molecules in CD8<sup>+</sup> T cells is associated with their exhaustion.<sup>15,69–71</sup> The cytotoxic activity in the TME is evidently associated with the frequency of non-exhausted CD8<sup>+</sup> T cells. Therefore, Kumagai et al's study proposes classifying cancer patients into two groups based on CD8<sup>+</sup> T cell activity: those with robust activity and those with diminished activity. Patients with diminished activity, characterized by a high frequency of exhausted CD8<sup>+</sup> T cells in the TME, exhibit a more favorable prognosis following immunotherapy. This result is likely attributed to the reactivation of these exhausted cells by PD-1 antibodies.

The current study suggests a binary classification of CD8<sup>+</sup> T cell response to an oncovirus as either high or low. This classification aims to evaluate whether the virus should be eradicated in established solid tumors. This study assumes that, in most cases, viruses elicit a similar CD8<sup>+</sup> T cell reaction regardless of whether the infected cell is benign or malignant. Based on this presumption, it becomes possible to classify viruses as “cytotoxic” or “non-cytotoxic” when infecting healthy tissues, allowing for the prediction of their effect on cancer cells. As shown in Table 1, the prediction is accurate for six out of the seven known oncoviruses. Epstein–Barr virus is an exception. The immune response to EBV may vary, depending on the host's pathological state.<sup>72</sup> While EBV elicits a strong CD8<sup>+</sup> T cell reaction in patients with mononucleosis,<sup>19,42,43</sup> a reduced frequency and impaired CD8<sup>+</sup> T cell response is reported in diffuse large B cell lymphoma (DLBCL).<sup>73</sup> In nasopharyngeal cancer, CD8<sup>+</sup> T cell activities are suppressed by cancer-derived miR-21 and the generation of suppressive B cells.<sup>74</sup> A recent review by Zheng et al<sup>75</sup> explores CD8<sup>+</sup> T cell exhaustion in various EBV-associated malignancies. The binary model fails to predict the effect of EBV on cancer prognosis due to the plasticity of the immune response against EBV. In addition, as will be discussed later in this chapter, Tregs rather than CD8<sup>+</sup> T cells display anti-cancer activity in HL. This renders Hodgkin lymphoma an inappropriate candidate for the application of the present binary model.

The probability of correct predictions for all 6 out of 6 pairs by arbitrary chance (assuming events are independent) is very small ( $P\text{-value} = 0.5^6 = 0.0156$ ), indicating a strong predictive power of 0.984 when the immune response is robust (ie, when the immune response is insensitive to the pathological condition of the patient). The strong correlation observed between the model's prediction and clinical practice suggests that the impact of immune modulation by oncoviruses on prognosis outweighs the direct (pro-tumor) effects of the virus on host cells (for most viruses). Moreover, it seems that highly activated CD8<sup>+</sup> T cells, observed during a persistent infection of non-cancerous tissue, retain their anti-cancer (and anti-viral) activity within the TME of infected cancer cells, although the TME is considered a highly suppressive environment in advanced cancers.

Indeed, the binary classification approach could potentially be extended to encompass any intracellular pathogen, regardless of its oncogenic nature. The current study puts forth the hypothesis that any intracellular pathogen capable of eliciting a robust CD8<sup>+</sup> T cell response might induce an anti-cancer effect in solid tumors. For instance, the BCG vaccine, derived from a strain of attenuated live bovine tuberculosis bacillus called *Mycobacterium bovis*, has been widely utilized as the standard treatment for patients diagnosed with non-muscle-invasive bladder cancer since 1977.<sup>76,77</sup> Notably, BCG vaccination stimulates an augmented CD8<sup>+</sup> T cell response,<sup>76,78</sup> and both *M. tuberculosis* and *M. bovis* are intracellular bacteria.<sup>79,80</sup>

It is not advisable to apply the binary model to extracellular pathogens, since CD8<sup>+</sup> T cells are specifically designed to eliminate intracellular pathogens.<sup>81</sup> A direct assault of CD8<sup>+</sup> T cells on an extracellular pathogen will not necessarily lead to the destruction of host cells, as they do not harbor the pathogen. In fact, the main immune reaction against extracellular pathogens is antibacterial antibodies, which usually do not penetrate into the cytoplasm.<sup>82</sup> The immune response to *Helicobacter pylori* (*H. pylori*) is an example.



Ninety percent of noncardia gastric cancer and 86% of non-Hodgkin lymphoma (NHL) of gastric location are attributable to *H. pylori* infection.<sup>1</sup> *H. pylori*, can primarily be considered an extracellular bacterium, although in *H. pylori* infection, 1–5% of epithelial cells appear to harbor an intracellular population of the bacterium.<sup>83</sup> As other extracellular oncopathogens, *H. pylori* is an indirect carcinogenic pathogen.<sup>1</sup> The effector protein CagA, which is part of the *cag* (cytotoxin-associated gene) pathogenicity island (PAI), the secreted toxin vacuolating cytotoxin A (VacA), the blood-group antigen-binding adhesin (BabA), and *H. pylori* neutrophil-activating protein (HP-NAP) are four of the most important pathogenicity factors of *H. pylori*.<sup>84</sup> *H. pylori* DNA vaccines encoding fragments of CagA, VacA, and BabA can induce Th1 shift to Th2 response in immunized BALB/c mice.<sup>85</sup> On the other hand, HP-NAP-activated dendritic cells present a Th1 cytokine secretion profile, with high IL-12 and relatively low IL-10 secretion.<sup>86</sup> Cytotoxic T cell reaction is attenuated in *H. pylori* persistent infection: In rodents, CD4 T cells are the main cellular infiltrate in chronic gastritis. Cytotoxic CD8+ T cell response to *H. pylori* infection is scarcely detected in rodents due to the suppression of CD8+ T cell proliferation by CD4 T cells.<sup>87</sup> A recent report suggests that CagA-specific gastric CD8+ tissue-resident T cells restrict *H. pylori* activity during the early phase of infection in mice and humans, however, this phenotype is lost following prolonged gastritis, and is replaced by CD4 T cells.<sup>88</sup> In line with this observation, it was found that persistent *H. pylori* infection suppresses virus-specific CD8+ T cell response.<sup>89</sup> Therefore, the anti-cancer response of the adaptive system observed in *H. pylori* infected cancer cells, is probably related to Th1 cytokines. As will be explained later, the TME of indolent lymphoma is characterized by low Treg levels, which allow an effective Th1 anti-cancer response by *H. pylori*. In contrast, the immune response within TME of most solid cancers is suppressed by high Treg levels, which inhibit the Th1 related anti-cancer effect of this bacterium. In agreement, a meta-analysis of 59 published studies concludes that non-cardia gastric cancer patients with *H. pylori* have a better OS and a better disease-free survival than patients that do not harbor *H. pylori*.<sup>90</sup> On the other hand, *H. pylori* eradication therapy is recommended as a first-line treatment in all gastric MALT lymphomas regardless of their clinical stage.<sup>91</sup> Taken together: (a) the anti-tumor reaction associated with *H. pylori* is not driven by CD8+ T cell immunity (b) in contrast to (most) oncoviruses, this antitumor activity is sensitive to the tumor microenvironment. It may be speculated that a robust immune response to an extracellular pathogen during a persistent infection of a benign tissue will not necessarily result in an anti-tumor effect in cancerous tissue infected by the same pathogen. On the other hand, as demonstrated above, a strong CD8+ T cell response to an intracellular pathogen during a persistent infection of a benign tissue evidently persists in infected cancerous tissue, and favors prognosis.

The growth of solid tumors is regulated by the cytotoxic activity of CD8+ T cells.<sup>92</sup> In contrast, the proliferation of various lymphomas (DLBCL for example) is controlled by a specific subset of regulatory T cells (Tregs).<sup>93</sup> Correspondingly, a meta-analysis involving 14 studies on patients with DLBCL demonstrated a correlation between increased expression of FOXP3 +Tregs and an improved survival (when assessed by the number or percentage of FOXP3 positive T cells).<sup>94</sup>

Additionally, it has been proposed that low levels of Tregs promote indolent lymphoma growth, whereas high Tregs levels exert control over it. Certain lymphomas such as follicular lymphoma (FL) and Hodgkin's lymphoma (HL) are characterized by a prolonged indolent period lasting several years. During this period, the tumor is sensitive to the suppressive effect of TGF $\beta$  secreted by Tregs.<sup>95</sup> Indeed, higher infiltration of Tregs was associated with more favorable prognosis in FL,<sup>96</sup> and in most studies on HL, Tregs' infiltration into the TME correlates with prolong survival,<sup>97</sup> while a greater abundance of activated (GrB+ TIA1+) CD8+ T cells was linked to poorer survival.<sup>98</sup> These findings support the notion that Tregs play a suppressive role in the progression of these lymphomas. A word of caution is warranted: a positive impact of tumor-infiltrating Tregs on prognosis does not necessarily indicate a beneficial effect solely attributable of Treg cells. In certain types of cancer, the infiltration of Tregs into the TME coincides with the infiltration of CD8+ T cells, which are responsible for inducing the observed anti-cancer effect.<sup>99</sup> However, this scenario is unlikely in the case of lymphoma: in several types of lymphoma, CD8+ T cells are dysfunctional. For example, in B-cell non-Hodgkin's lymphoma, Tregs suppress the activity of CD8+ T cells.<sup>100</sup> This suppressive effect is mediated by soluble and membrane-bound TGF $\beta$ <sup>101</sup> and upregulated TIM-3 expression.<sup>69</sup> In follicular lymphoma study, the majority of CD8+ T effector memory cells were found to express TIGIT (T-cell immunoglobulin and ITIM domain), a co-inhibitory receptor, resulting in dysfunctional TCR signaling in these CD8+ T cells.<sup>70</sup> Additionally, the expression of LAG-3 by PD-1+ CD8 T cells has been identified as another mechanism leading to CD8 cell exhaustion in follicular lymphoma.<sup>71</sup>

In contrast, a recent publication showed the absence of many hallmarks of exhaustion in PD-1+, TIM-3+, and CTLA-4+ CD8+ T cells in DLBCL.<sup>102</sup> However, it is important to note that PD-1+ and TIM3+ CD8 T cells constitute less than 10% of CD8+ T cell population in the TME of DLBCL.<sup>103</sup> Thus in DLBCL, FL and HL, Tregs exert an anti-tumor effect that leads to an improved survival, while CD8+ T cells experience exhaustion within the TME of these lymphomas. Consequently, the binary classification of CD8 cytotoxic response cannot be applied to these lymphomas.

Contrary to DLBCL, FL and HL, adult T cell leukemia/lymphoma (ATLL) is not controlled by Tregs. In fact, this cancer originates from CD4+T cells with Treg phenotypes.<sup>104</sup> For this reason, the binary model may apply to HTLV1-associated ATLL.

Clinical implications of these results: relying on the host's immunological response to an intracellular oncopathogen (evaluated in animals or humans), the binary model can accurately forecast the pathogen's impact on survival, particularly when data are scarce. This is applicable, for instance, in the case of a rare pathogen linked to cancer or a newly discovered pathogen associated with indolent cancer. In the first scenario, the limited population size may hinder statistical assessment of survival, while in the second scenario, survival studies may extend over many years.

## Summary

This study introduces a binary classification of CD8+ T cell cytotoxic reactions to intracellular oncopathogens in non-cancerous tissue as either weak or strong. The objective is to evaluate the impact of these pathogens on the prognosis of solid cancers. The model accurately predicts the effect of six out of seven known oncoviruses on prognosis. However, it is not applicable to extracellular pathogens, certain lymphomas, and pathogens that elicit a host-sensitive immune response. The strong correlation between the model's predictions and clinical outcomes suggests that immune modulation by oncoviruses has a more significant impact on prognosis than the direct effects of the virus on host cells. Moreover, the observed CD8+ T cell response to oncoviruses in infected benign tissues is retained in the infected TME, indicating that a strong response is not suppressed in the TME. These findings hold clinical significance: based on the host's immunological response to an intracellular pathogen (evaluated in animals or humans), the binary model can reliably predict the effect of the pathogen on survival when such data are unavailable.

## Acknowledgment

The views and opinions expressed, and/or conclusions drawn, in this article are those of the author and do not necessarily reflect those of Taro Pharmaceutical Industries Ltd., its affiliates, directors or employees.

## Disclosure

Zeev Elkoshi is employed by Taro Pharmaceutical Industries Ltd.

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