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SWOG CANCER RESEARCH NETWORK

A PHASE III RANDOMIZED TRIAL OF PROPHYLACTIC ANTIVIRAL THERAPY IN PATIENTS WITH CURRENT OR PAST HEPATITIS B VIRUS (HBV) INFECTION RECEIVING ANTI-CANCER THERAPY FOR SOLID TUMORS

NCT# 03887702

STUDY CHAIRS:

Jessica Hwang, M.D., M.P.H.
(Study Chair, Internal Medicine)
MD Anderson Cancer Center
1400 Pressler St., Unit 1465
Houston, TX 77030
Phone: 713/745-4516
FAX: 713/563-4491
E-mail: jphwang@mdanderson.org

Anna S. Lok, M.D. (Study Co-Chair, Hepatology)
University of Michigan
1500 E Medical Center Drive
3912 Taubman Center, SPC 5362
Ann Arbor, MI 48109-5362
Phone: 734/936-7511
E-mail: aslok@med.umich.edu

Adam Gehring, Ph.D. (TM Co-Chair)
Toronto Centre for Liver Disease
Toronto General Hospital Research Institute
101 College St, Rm 10-356
Toronto, ON M5G 1L7
Phone: 416/634-7095
E-mail: Adam.Gehring@uhnresearch.ca

Jordan Feld M.D., M.P.H. (TM Co-Chair)
Toronto Centre for Liver Disease
Toronto General Hospital, University Health Network
Sandra Rotman Centre for Global Health
200 Elizabeth Street, 9EB-240
Toronto, ON M5G 2C4
Phone Clinical: 416/340-4584
Phone Lab: 416/581-8595
Fax: 416/340-4533
E-mail: Jordan.Feld@uhn.ca

AGENTS:

Commercially Available Agents
Tenofovir alafenamide (TAF)
Tenofovir disoproxil fumarate (TDF)
Entecavir (ETV)

BIOSTATISTICIANS:

Joseph M. Unger, Ph.D.
Edward Mayerson, M.S.
SWOG Statistics and Data Management Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N., M3-C102
P.O. Box 19024
Seattle, WA 98109
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: junger@fredhutch.org
E-mail: emayerso@fredhutch.org

NCTN-Group CHAMPION:

Edith Mitchell, M.D., ECOG-ACRIN

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG Cancer Research Network

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal: (Sign in at https://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org . Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

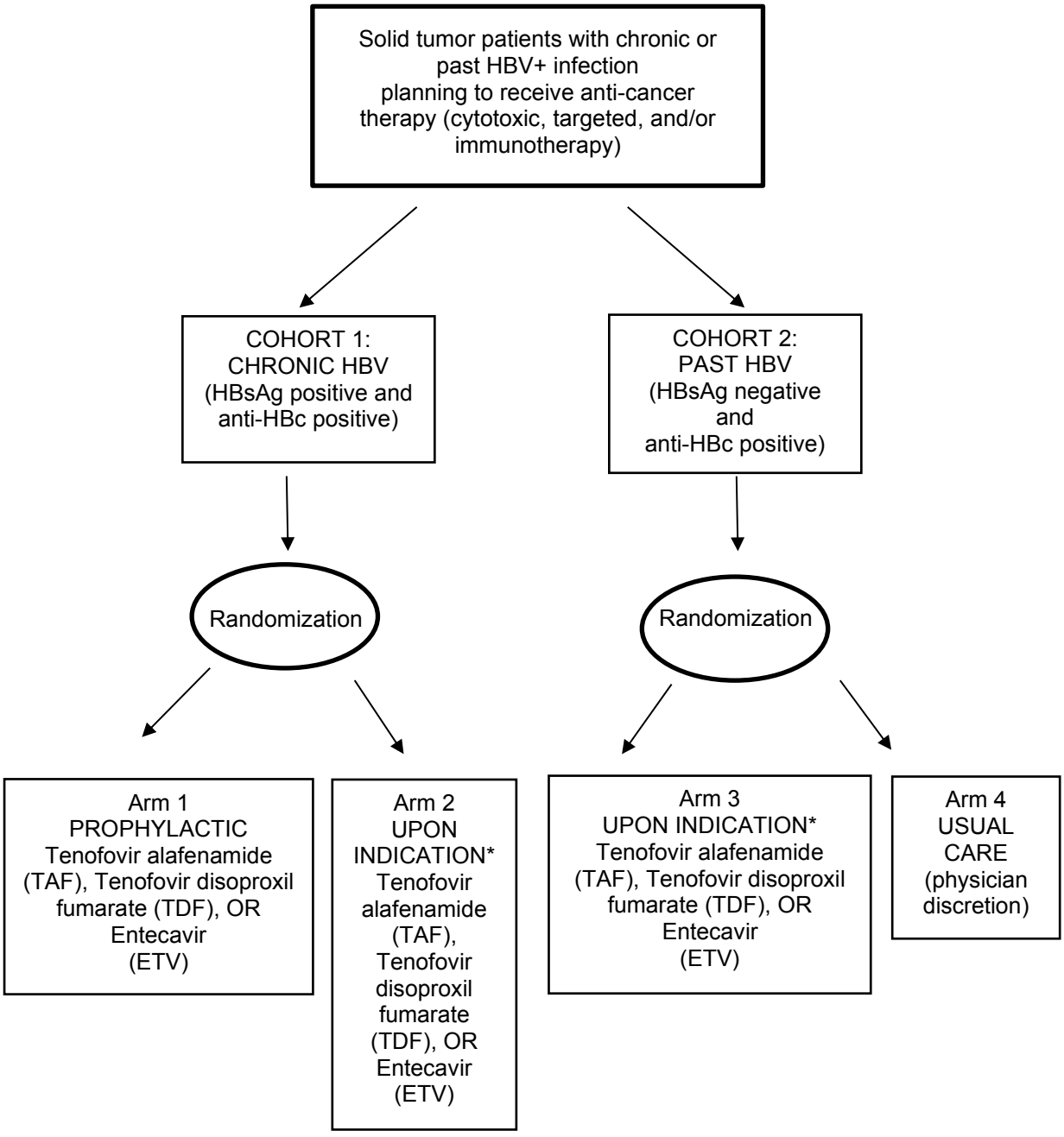
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log in with CTEP-IAM username and password.

For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email:
206/652-2267
cancercontrolquestion@crab.org

For treatment or toxicity related questions contact the Study Chair by phone or email: Jessica Hwang, M.D., M.P.H., Phone: 713/745-4516, e-mail: jphwang@mdanderson.org or Anna S. Lok, M.D., Phone: 734/936-7511, e-mail: aslok@med.umich.edu.

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

SCHEMA



* See Section 10.2c.

1.0 OBJECTIVES

1.1 Co-Primary Objectives

a. To compare the effect of prophylactic anti-HBV therapy versus upon indication anti-HBV therapy on time-to-adverse liver outcomes of liver failure or liver-related death in patients with chronic HBV infection (HBsAg+ and anti-HBc+) receiving anti-cancer therapy for solid tumors.

b. To compare the effect of upon indication anti-HBV therapy versus usual care on time-to-adverse liver outcomes of liver failure or liver-related death in patients with past HBV infection (HBsAg- and anti-HBc+) receiving anti-cancer therapy for solid tumors.

1.2 Secondary Objectives

a. Using time-to-event analysis, to compare the effect of anti-HBV therapy versus upon indication anti-HBV therapy on HBV reactivation, on the combined endpoint of adverse liver outcomes (liver failure or liver-related death) and HBV reactivation, and on HBV flare by arm in patients with chronic HBV infection receiving anti-cancer therapy for solid tumors.

b. Using time-to-event analysis, to compare the effect of upon indication anti-HBV therapy versus usual care on HBV reactivation, on the combined endpoint of adverse liver outcomes (liver failure or liver-related death) and HBV reactivation, and on HBV flare by arm in patients with past HBV infection receiving anti-cancer therapy for solid tumors.

1.3 Translational Objectives

a. To compare baseline and changes in overall immune status and HBV-specific immune response in patients with solid tumors and chronic or past HBV infection receiving anti-cancer therapy, and to compare the differences in these immune responses by HBV reactivation status.

b. To identify demographic and clinical predictors and correlative immunologic biomarkers of HBV reactivation after receipt of anti-cancer therapy in patients with solid tumors and chronic or past HBV infection.

2.0 BACKGROUND

2.1 General

Hepatitis B virus (HBV) reactivation is a potentially severe adverse sequela of anti-cancer therapy in patients with chronic HBV infection [hepatitis B surface antigen (HBsAg)+ and hepatitis B core antibody (anti-HBc) + or past HBV infection (HBsAg- and anti-HBc+). HBV reactivation can lead to hepatitis flare, liver failure, and death. Previous studies conducted in Asian countries, where HBV infection is endemic, showed that reactivation of HBV replication during chemotherapy occurred in approximately 40-50% of patients with chronic infection and 10-20% of patients with past infection. *(1,2,3,4,5)* Most of the studies on HBV reactivation were conducted in patients receiving chemotherapy for hematologic malignancies or hematopoietic stem cell transplantation. *(6,7,8,9,10,11)* These studies provide strong evidence in support of administering anti-HBV prophylaxis before certain therapies for hematologic malignancies or hematopoietic stem cell transplantation. *(12,13)* However, patients with hematologic malignancies represent a small proportion of patients with cancer. Small studies on HBV reactivation have been conducted in patients with solid tumors. *(14,15,16,17)*

Not all HBV patients receiving anti-cancer therapies experience HBV reactivation or hepatitis flare. Some clinical factors, such as HBV viral load and exposure to certain targeted therapies, are well-established risk factors for HBV reactivation, but most data were derived from studies in patients with hematologic malignancies. Due to the inefficiency of HBV risk-based screening, ASCO recommends that all patients with cancer be tested for HBV prior to the initiation of systemic anticancer therapy. (*18*)

HBV-associated immune responses in patients with cancer and HBV infection have not been well studied, but a growing body of evidence indicates that immune responses may have clinical relevance in mitigating the risk of reactivation and liver failure. Understanding the clinical predictors and immune mechanisms of HBV reactivation will be important in developing personalized strategies to mitigate the risk of adverse liver outcomes in HBV patients with solid tumors receiving anti-cancer therapy.

In the United States, the prevalence of chronic HBV infection is reported to be 0.3%, and the prevalence of past HBV infection is 4.6%, but these rates may underestimate the true prevalence since the National Health and Nutrition Examination Survey cohort on which they are based underrepresents populations with high HBV prevalence. *(19,20)*

In patients with HBV infection, the balance between liver injury and viral control is influenced by the host immune system, and immunosuppressive therapies that disrupt this immune balance can lead to reactivation of HBV replication and resultant adverse liver outcomes. *(21,22)* Reactivation can lead to elevated alanine aminotransferase (ALT) levels and in severe cases hepatitis flare, liver failure, and death. *(23)* Reactivation is manifested by elevation in serum HBV DNA levels, appearance of HBV DNA in patients with undetectable HBV DNA at baseline, or a positive HBsAg test in patients who were HBsAg-negative but anti-HBc-positive at baseline. *(24)* To date, the incidence and associated risk factors of HBV reactivation among patients with solid tumors with chronic or past HBV infection have not been defined. Many previous studies of HBV reactivation in patients with solid tumors were conducted in single institutions and are limited by referral and selection biases, and the total number of patients with solid tumors and HBV infection in these studies was inadequate to permit comprehensive analysis of the effect of cancer type, chemotherapy agents, and patient and viral characteristics on the risk of reactivation. *(25,26)*

Oral anti-HBV medication administered once daily can prevent reactivation, especially if administered before or at the onset of cytotoxic cancer therapy. *(27,28,29,30,)* Previous studies of anti-HBV therapy focused primarily on patients with hematologic malignancies; minimal data exist to guide anti-HBV therapy use during treatment for solid malignancies. Anti-HBV prophylaxis can be given concomitantly with cancer therapy. Currently, there are six approved anti-HBV medications: adefovir, entecavir, lamivudine, telbivudine, tenofovir disoproxil fumarate, and tenofovir alafenamide. The interventional arms of this trial will focus on antiviral therapy for HBV using the physicians choice of one of three commercially available agents that have high potency and low risk of drug resistance: tenofovir alafenamide (TAF), tenofovir disoproxil fumarate (TDF) or entecavir (ETV).

Hepatitis flare, or elevated ALT level, is common and can lead to interruptions in anti-cancer therapy in patients with solid tumors. *(31,32)* In a systematic review, the median incidence of hepatitis flare among patients with solid tumors and chronic HBV infection was reported to be 23%, but the incidences in individual studies ranged from 2% to 60%, likely because of the variability in definitions and reporting. *(33)* The risk of hepatitis flare among patients with solid tumors and past HBV infection has not been well studied. Further complicating analysis of hepatitis flare in HBV patients with solid tumors, such patients may experience hepatitis flare that is not related to HBV reactivation; hepatitis flare in such patients can also be caused by anti-cancer therapy–associated hepatotoxicity or withdrawal of anti-HBV therapy or even occur spontaneously. *(34,35,36,37)*

HBV-associated immune responses in patients with cancer and HBV infection have not been well studied but may have clinical relevance in mitigating the risk of reactivation and liver failure.

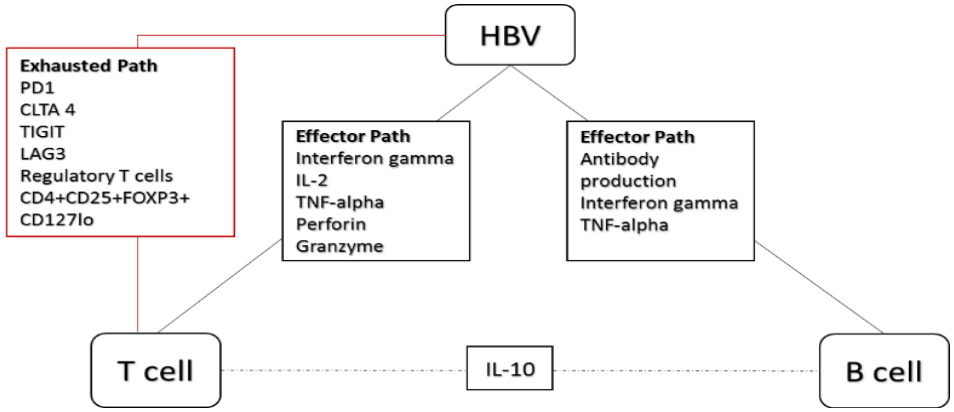


Figure 1. Conceptual model of immune mechanisms of reactivation

Chronic HBV infection impairs HBV-specific T cells, leading to T cell exhaustion and loss of T cell functions such as production of interleukin-2 (IL-2), tumor necrosis factor-alpha (TNFa), and interferon-gamma (IFNg). *(38,39)* B cell–depleting agents directly affect antibody production and also indirectly affect cellular immunity mediated through low levels of IL-10. *(40,41)* Subsequent dysregulation of the usual T cell exhaustive response to chronic viral antigen stimulation then occurs; therefore, HBV patients receiving anti-CD20 monoclonal antibody therapy such as rituximab have demonstrated high rates of HBV reactivation. *(42,43,44)* IFNg-induced chemokines increase during hepatitis flare and may lead to defects in NK cell functions, which may contribute to the HBV-associated immune response. *(45)*

In this protocol, the investigators will determine the optimal anti-HBV treatment strategy in a heterogeneous population of 444 patients with solid tumors and chronic or past HBV infection receiving anti-cancer therapy in the NCI's National Clinical Trials Network (NCTN), including NCI Community Oncology Research Program (NCORP) sites. The investigators will explore the mechanisms of HBV-specific immune responses by comparing cases with HBV reactivation (estimated number 44) with an equal number of matched controls without reactivation (Translational Aim 1), and identify the demographic and clinical predictors along with immune correlates of cancer therapy-induced severe adverse sequelae, including HBV reactivation and hepatitis flare, among all 444 patients in the study (Translational Aim 2).

This protocol is significant because it will permit the development of personalized approaches to prevent HBV reactivation, a potentially serious adverse sequela, in patients with solid tumors with chronic or past HBV infection treated with anti-cancer therapy. The data from this protocol will also permit development of evidence-based guidelines for monitoring of patients with HBV infection during anti-cancer therapy and use of anti-HBV therapy before and during anti-cancer therapy. The expected research contribution will also facilitate design of new anti-cancer strategies or anti-HBV management approaches that may decrease the risk of anti-cancer therapy-induced HBV reactivation. This study will create an important biorepository of plasma and peripheral blood mononuclear cell specimens from 444 patients with solid tumors and chronic or past HBV infection receiving anti-cancer therapy. These specimens will be available for future studies that will employ new technologies to investigate the contributions of HBV virologic markers and HBV-specific immune responses identified in this study to determine the mechanisms of HBV reactivation.

This protocol is novel because it will be the first to produce evidence-based data through a randomized clinical trial in HBV patients with solid tumors in a cooperative cancer network in the United States. The key collaborators have the requisite expertise in oncology, hepatology, immunology, and outcomes research. There is guidance available from the updated ASCO provisional clinical opinion (PCO) on HBV screening and management prior to cancer therapy (46). This PCO was intended to provide oncology teams with practical guidance for immediate use, but the recommendations were written with soft language regarding treatment details for chronic (as well as past) HBV patients with a solid tumor. This is because for both chronic and past HBV, the evidence about the treatment details is weak and thus recommendations could only be based on informal consensus. As noted in the Future Directions part of the PCO, large, randomized trials are needed to better understand the issue of HBV reactivation, especially for patients with a solid tumor. A key step forward is to conduct this trial and ultimately reveal the evidence-based best practice for these patients at risk for HBV reactivation.

This project will harness synergistic multidisciplinary collaborations to benefit patients with solid tumors and HBV infection. The results of this project can be used even beyond HBV to open new horizons of research on personalized prevention of severe sequelae from anti-cancer therapy for patients with cancer and other oncogenic viruses.

A priority of the NCORP is to "increase the knowledge base through the conduct of research as part of cancer control clinical trials focusing on identifying effective treatments for toxicities, side effects, and symptoms arising from cancer and its treatments and to discover mechanisms of action whereby interventions are effectively treating symptoms, toxicities, and side effects." *(47)* Although this protocol does not fit in one of the 9 priority areas identified by the NCI Symptom Control and Quality of Life (SXQOL) committee, this therapeutic trial is focused on preventing adverse liver outcomes as a toxicity of systemic cancer treatment, and it is important for patients across the United States and worldwide who are facing cancer in the context of chronic or past HBV infection. This trial is poised to define the evidence-based standard of cancer control care for patients with solid tumors and HBV infection receiving anti-cancer therapy, and it will also provide key mechanistic information through the conduct of complementary translational studies.

This trial is expected to determine whether patients with solid tumors and HBV infection should start prophylactic anti-HBV medication before anti-cancer therapy or be monitored and have anti-HBV therapy started only if necessary. The trial will also identify immune mechanisms of HBV reactivation and provide strong evidence regarding predictors of HBV reactivation. This will allow the development of personalized approaches to prevent HBV reactivation due to anti-cancer therapy.

2.2 Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1	1	1	4
Asian	8	5	3	2	18
Native Hawaiian or Other Pacific Islander	1	1	1	1	4
Black or African American	40	23	13	8	84
White	154	89	50	28	321
More Than One Race	6	4	2	1	13

Total	210	123	70	41	444

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, Tenofovir alafenamide (TAF), Tenofovir disoproxil Fumarate (TDF), and Entecavir (ETV), are commercially available; therefore, Investigator Brochures are not applicable to this drug. Information about commercial drugs is publicly available in the prescribing information and other resources.

Black Box Warnings: TAF, TDF, and ETV share a warning indicting severe acute exacerbations of HBV have been reported in HBV-infected patients who have discontinued anti-hepatitis B therapy. Hepatic function should be monitored closely in HBV-infected patients who discontinue therapy. Resumption of anti-hepatitis B therapy may be warranted, as clinically appropriate.

3.1 Entecavir (ETV)

a. PHARMACOLOGY

Mechanism of Action:

Entecavir is a guanosine nucleoside analogue. The phosphorylated active form inhibits the activity of hepatitis B virus (HBV) polymerase in base priming, reverse transcription of the negative strand pregenomic messenger RNA, and synthesis of the positive strand of HBV DNA.

b. PHARMACOKINETICS

1. Absorption:

The peak plasma concentration (C_{max}) of entecavir is achieved in 0.5 to 1.5 hours at doses ranging between 0.1 and 1 mg, and the steady state is achieved in 6 to 10 days. Both Cmax and area under the concentration-time curve (AUC) at steady state increases proportionally to increasing doses of entecavir. The oral tablet and the oral solution have a bioavailability ratio of 1:1 and may be used interchangeably.

Co-administration of entecavir with food has been shown to delay absorption, decrease Cmax by 44 to 46%, and decrease AUC by 18 to 20%. Entecavir should be administered at least 2 hours before or after a meal.

2. Distribution:

Pharmacokinetic studies have shown that entecavir distributes extensively into tissues and have an approximate protein binding of 13%.

3. Metabolism:

Entecavir is not metabolized by the cytochrome P450 enzymes, and it does not inhibit or induce the P450 enzymes.

4. Elimination:

Entecavir is mainly eliminated by the kidneys as 62 to 73% unchanged drug through glomerular filtration and net tubular secretion. The half-life of entecavir is approximately 128 to 149 hours, and the renal clearance ranges between 360 to 471 mL/min.

c. ADVERSE EFFECTS

1. Possible Side Effects of *Entecavir:*

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in > 10% of subjects treated with entecavir include elevated alanine aminotransferases.
Adverse effects reported in 1% to 10% of subjects include: headache, fatigue, skin rash, hematuria, glycosuria, hyperglycemia, abdominal pain, nausea, vomiting, diarrhea, unpleasant taste, elevated serum lipase, bilirubin, and creatinine.
Serious adverse effects reported in < 1% of subjects include: anaphylactoid shock, hepatomegaly with steatosis, lactic acidosis, macular edema, and thrombocytopenia.

2. Pregnancy and Lactation:

There is insufficient data from human studies to adequately assess the risk of using entecavir during pregnancy (including the risks of birth defects, miscarriage or adverse maternal or fetal outcomes). Animal studies in rats and rabbits have shown evidence of embryofetal toxicity and maternal toxicity at doses above the maximum recommended human dose. The use of entecavir should be avoided in pregnant women, as there are other agents available. For those who are pregnant and have been exposed to entecavir, a pregnancy registration is available to monitor fetal outcomes.

Entecavir has been found in the milk of rats, but its presence is unknown in human milk. Breast-feeding mothers should avoid taking entecavir.

3. Drug Interactions:

Coadministration of ETV with drugs that reduce renal function or compete for active tubular secretion may alter the pharmacokinetic or pharmacodynamics properties of ETV. **See Section 7.1 for details**.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Entecavir is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.2 Tenofovir alafenamide (TAF)

a. PHARMACOLOGY

Mechanism of Action: Tenofovir alafenamide (TAF) is an antiviral drug against the hepatitis B virus. It is a phosphonamidite prodrug that is converted intracellularly by hydrolysis to tenofovir, and then phosphorylated into active tenofovir diphosphate. The active moiety inhibits replication of hepatitis B virus (HBV) by incorporating into the viral DNA by HBV reverse transcriptase, thus resulting in DNA chain termination.

b. PHARMACOKINETICS

1. Absorption: There is an increased systemic exposure when taking with food. After administration of tenofovir alafenamide with a high-fat meal (800 kcal, 50% fat), mean AUC increased by 65% (range 51 to 81%).

2. Distribution: TAF is 80% bound to plasma proteins.

3. Metabolism: TAF is extensively metabolized in the liver, primarily by carboxyesterase 1 and minimally by CYP3A. TAF is metabolized by cathepsin A in peripheral blood mononuclear cells. Over 80% of TAF is metabolized to tenofovir, the active major metabolite.

4. Elimination: Kidney (Less than 1%); Feces (31.7%); Elimination Half-life (0.51 hours).

c. ADVERSE EFFECTS

1. Possible Side Effects of tenofovir alafenamide (TAF):

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse effects reported in 1% to 10% of subjects treated with TAF include the following:
CNS: headache (9%), fatigue (6%)
Endocrine & metabolic: increased LDL cholesterol (4%), glycosuria, increased amylase
Gastrointestinal: abdominal pain (7%), nausea (5%)
Hepatic: increased serum ALT, increase serum AST
Neuromuscular & skeletal: decrease bone mineral density (3% to 6%), back pain (5%), increased serum creatine phosphokinase
Respiratory: cough (6%)

2. Pregnancy and Lactation: There are no human data on the use of tenofovir alafenamide (TAF) in pregnant women to inform drug-associated risks of adverse fetal developmental outcome. The background risk of major birth defects and miscarriage for the indicated population is unknown.

It is not known whether TAF and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAF and any potential adverse effects on the breastfed infant from TAF or from the underlying maternal condition.

Drug Interactions:
Concomitant administration of TAF with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's Wort, and inducers or inhibitors of P-gp may alter the pharmacokinetic or pharmacodynamics properties of TAF. Coadministration of TAF with drugs that reduce renal function or compete for active tubular secretion may also alter the pharmacokinetic or pharmacodynamics properties of TAF **See Section 7.1 for details**.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

TAF has oral route of administration, intended to be taken as a whole tablet.

e. HOW SUPPLIED

TAF is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

3.3 Tenofovir disoproxil fumarate (TDF)

a. PHARMACOLOGY

Mechanism of Action: tenofovir disoproxil fumarate (TDF) is a reverse transcriptase inhibitor and an analog of adenosine 5'-monophosphate. TDF first undergoes hydrolytic conversion to tenofovir and then subsequent phosphorylation to its active form, tenofovir diphosphate (TFV-DP). TFV-DP inhibits the activity of hepatitis B virus reverse transcriptase (HBV RT) by competing with the natural substrate deoxyadenosine 5'-triphosphate and acting as an obligate DNA chain terminator. HBV viral replication is thereby inhibited. TFV-DP also inhibits human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.

b. PHARMACOKINETICS

1. Absorption: In the fasted state, the bioavailability of TDF is approximately 25% and C_{max} occurs approximately 1 hour after administration. Addition of a high-fat meal increases AUC by approximately 40%, and food delays C_{max} by approximately 1 hour. However, these effects have not been deemed to be clinically significant and doses may be given with or without food.

2. Distribution: Tenofovir binds to less than 7.2% of serum proteins. Volume of distribution is 1.2 to 1.3 L/kg.

3. Metabolism: TDF is converted intracellularly by hydrolysis to tenofovir, which is then phosphorylated to active tenofovir diphosphate. Neither TDF nor tenofovir are substrates of CYP enzymes.

4. Elimination: TDF is eliminated by a combination of glomerular filtration and active tubular secretion, with 32% excreted as unchanged drug after oral administration. The terminal elimination half-life of tenofovir is approximately 17 hours.

c. ADVERSE EFFECTS

1. Possible side effects of tenofovir disoproxil fumarate:

   Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

   Adverse effects reported in > 20% of subjects treated with TDF include: hypercholesterolemia, abdominal pain, nausea, decreased bone mineral density

   Adverse effects reported in 4% to 20% of subjects include: insomnia, headache, pain, back pain, arthralgia, myalgia, dizziness, depression, anxiety, skin rash, pruritus, diarrhea, flatulence, vomiting, increased creatine phosphokinase, increased serum ALT/AST, increased serum amylase, increased serum creatinine, renal failure, fever, fatigue, peripheral neuropathy, sinusitis, upper respiratory tract infections

   Serious adverse effects reported in ≤ 3% of subjects include: bone loss and mineralization defects, lactic acidosis, immune reconstitution syndrome, new onset or worsening renal impairment, and severe hepatomegaly with steatosis

2. Pregnancy and Lactation:

   Tenofovir has a high level of transfer across the human placenta. However, data from the Antiretroviral Pregnancy Registry (APR) have not shown an increase in the incidence of birth defects in pregnancies exposed to TDF (across all trimesters) compared with the incidence in the general U.S. population; the APR does not report the rate of miscarriage. Published studies have not demonstrated an increased risk of adverse pregnancy related outcomes.

   Tenofovir has been shown to be present in human breast milk. In a study of 50 breastfeeding women taking tenofovir post-partum, tenofovir was undetectable in the plasma of most infants after 7 days of treatment in mothers. No serious adverse events were observed in mothers or infants.

   Use in these populations is not contradicted, but clinical risk versus benefit for mother and infant should be considered.

3. Drug Interactions:

   Coadministration of TDF with P-gp inhibitors or inducers may alter the pharmacokinetic or pharmacodynamics properties of TDF. Coadministration of TDF with drugs that reduce renal function or compete for active tubular secretion may also alter the pharmacokinetic or pharmacodynamics properties of TDF. **See Section 7.1 for details**.

d. DOSING & ADMINISTRATION

   See Section 7.0 Treatment Plan

e. HOW SUPPLIED

Tenofovir disoproxil fumarate is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

4.0 STAGING CRITERIA

Patients must have Stage I-III disease (AJCC 8TH EDITION, 2017).

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a participant to be considered eligible for registration in OPEN. Section 5 may be printed and used to by the site, but is not to be uploaded in RAVE (unless specially stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or cancercontrolquestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).**

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient participant scheduling without exceeding the guidelines. **If Day 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must be diagnosed with Stage I-III solid tumor malignancy. Patients with only carcinoma in situ or with Stage IV disease are excluded.

b. Patients must not have lymphoma, leukemia, or myeloma.

c. Patients must not have primary liver cancer, known cirrhosis, or evidence of any malignancy that involves the liver.

5.2 Prior/Concurrent Therapy Criteria

a. Patients must be planning to receive systemic anti-cancer therapy (either single agent or some combination of systemic cytotoxic therapy, systemic immunotherapy or systemic targeted therapy) for this solid tumor.

b. Patients must not have been previously treated with the same anti-cancer therapy regimen that is now anticipated. The anti-cancer therapy does not have to be first-line therapy. Prior and/or concurrent radiotherapy is allowed.

c. Patients must be registered ≤ 28 days prior to the planned start date of anti-cancer therapy. If the patient has started systemic anti-cancer therapy, patient must be registered ≤ 42 days after the initiation of first cycle of anti-cancer therapy.

d. Patients who have received prior anti-cancer therapy must have discontinued all previous therapies (excluding planned anti-cancer therapy to occur in conjunction with this study) ≥ 1 day prior to registration to this study.

e. Patients must not have had any cancer therapy regimen that includes anti-CD20.

f. Patients must not be receiving antiviral medications active against HBV, including: adefovir, entecavir, lamivudine, telbivudine, tenofovir disoproxil fumarate, tenofovir alafenamide (TAF), or any other FDA approved agents for the treatment of Hepatitis B. Patients who have previously received antiviral medication must not have required any antiviral medication active against HBV ≥ 90 days prior to registration to this study.

g. Patients must not have had hematopoietic stem cell transplantation therapy.

h. Patients must not be taking or planning to take warfarin.

i. Patients who will be treated with TAF must not be taking or planning to take oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's Wort.

NOTE: Patients taking or planning to take the above listed concomitant medications may be treated with ETV or TDF (instead of TAF).

j. Patients who will be treated with TAF and are concomitantly taking or plan to take carbamazepine must be given an increased dose of TAF (see Section 7.1) or alternatively be given ETV or TDF.

5.3 Clinical/Laboratory Criteria

a. Patients must have results for the following HBV tests done within 28 days prior to registration: HBsAg AND anti-HBc (total Ig or IgG, but not IgM only) AND anti-HBs. For the anti-HBs test, quantitative or qualitative (including "indeterminate") results are allowable. Refer to Appendix 18.2 for viral status information.

b. Patients must have tested positive for HBsAg or anti-HBc (total Ig, IgG, but not IgM) and must have baseline HBV DNA completed ≤ 42 days prior to registration. See Appendix 18.2 for viral status information.

c. Complete blood count (CBC) must be completed ≤ 28 days prior to registration. Results do not need to be in the institutional limits of normal.

d. International Normalized Ratio (INR) must be completed ≤ 28 days prior to registration. Results must ≤1.2x institutional limits of normal.

e. ALT and total bilirubin results must be obtained ≤ 28 days prior to registration. ALT and total bilirubin must be < 1.5x institutional ULN.

f. Patients must have a baseline calculated creatinine clearance within 28 days prior to registration.

NOTE: Patients with reduced creatinine clearance may need a reduced dose of an antiviral drug (see details in Dose Modifications, Section 8.2).

g. Patients must not have known current active hepatitis C infection (HCV). Active HCV is defined by a detectable HCV RNA level. Note: HCV testing is not required for eligibility.

h. Patients must not have a history of human immunodeficiency (HIV) infection. Patients with unknown HIV status must have HIV testing completed ≤ 365 days prior to registration.

i. Patients must have Zubrod performance status of 0-2.

j. Patients must be at least 18 years old.

k. Patients must not be pregnant or nursing, as the safety of the study drug in pregnant and nursing women has not been established. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

5.4 Specimen Submission Criteria

a. Patients must have specimens collected for submission as outlined in Section 15.1.

b. Patients must be offered the opportunity to participate in optional translational medicine studies as outlined in Section 15.2.

5.5 Regulatory Criteria

a. Patients with impaired decision-making capacity are eligible as long as their neurological or psychological condition does not preclude their safe participation in the study (e.g., tracking pill consumption and reporting adverse events to the investigator).

b. Patients may have concurrent participation in other clinical trials that entail cytotoxic, immunotherapy, targeted therapy; surgical treatment; radiotherapy treatment; or any combination thereof.

c. Patients ***must*** be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

d. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

6.1 Cohort 1: Chronic HBV cohort

Patients with chronic HBV will be randomized between Arm 1 (prophylactic anti-HBV therapy) or Arm 2 (upon indication anti-HBV therapy) using a dynamic allocation scheme. Patient randomization to the two treatment arms will be balanced on:

- Planned cancer therapy type: cytotoxic (with or without immunotherapy or targeted therapy) vs. immunotherapy alone vs. targeted therapy alone vs. immunotherapy and targeted therapy.

6.2 Cohort 2: Past HBV cohort

Patients with past HBV will be randomized between or Arm 3 (upon indication anti-HBV therapy) or Arm 4 (usual care) using a dynamic allocation scheme. Patient randomization to the two treatment arms will be balanced on:

- Planned cancer therapy type: cytotoxic (with or without immunotherapy or targeted therapy) vs. immunotherapy alone vs. targeted therapy alone vs. immunotherapy and targeted therapy.
- Anti-HBV status: positive vs. negative.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Jessica Hwang, M.D., M.P.H., Phone: 713/745-4516, E-mail: jphwang@mdanderson.org or Anna Lok, M.D., Phone: 734-936-7511 or E-mail: aslok@med.umich.edu. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies & Procedures " under the "About" menu and choose Policy 38).

7.1 General Treatment Information

a. Concomitant Medications

Concomitant medications must be assessed prior to initiation of antiviral therapy in Arm 1 (prophylaxis) or if initiated if HBV reactivation occurs (upon indication) in Arms 2 and 3.

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on concomitant medications.

TAF: Concomitant administration of oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, or St. John's Wort is not recommended. If co-administered with carbamazepine, TAF dose should be increased to two tablets once daily. Alternatively, if the above medications cannot be stopped, then study patients may take TDF or ETV.

TDF: none

ETV: none

If possible, avoid use of warfarin. If medically necessary, warfarin may be used during protocol participation after enrollment. For patients who need to take warfarin, monitor INR per Section 9. If the patient has an INR increase, the treating investigator should review to determine if the cause is due to warfarin, study treatment, or acute liver injury. If INR increase is due to acute liver injury, and the increased INR is accompanied by AST, ALT, and bilirubin increase, evaluate the cause per Section 9. Document this determination in the patient's chart.

b. Guidance for Offsite and Virtual Options during the Conduct of the Trial

1. **Laboratory assessments and specimen collections**: All laboratory assessments and specimen collections must be completed at protocol-specified timepoints (see Section 9.0).

2. **Conducting labs at an offsite facility**: In order to provide participating sites flexibility in treating patients, it is the intent of the **S1614** protocol to

allow for laboratory assessments to be drawn and resulted by local healthcare providers (with appropriate oversight by the Responsible Investigator [local treating investigator]), where administration of the assessment at an off-site facility is in the best interest of the patient and provides for continuity of patient care. Utilization of offsite / local healthcare resources for conduct of patient's laboratory assessments must be documented including procedures for oversight (by the Responsible Investigator) of assessments performed offsite.

3. **Assessments via virtual methods**: The following assessments may be performed by a research RN, CRA, Advanced Practice Provider (APP), or physician. The assessments may be conducted virtually via phone or videoconferencing:
   - HBV Assessment
     - Obtain the HBV assessment in person, over the phone, or videoconference with the patient and document on the HBV Assessment Form (Section 14.4)
   - Toxicity Notation (AE Assessment)
     - Obtain the AE assessment in person, over the phone, or videoconference with the patient and document on the Anti-Viral Adverse Event Form (Section 14.4)
   - Review of Intake Calendar
     - Patient may be instructed to submit Intake Calendar electronically per site institutional standards.

7.2 Cohort 1 - Chronic HBV Anti-Viral Treatment

a. Arm 1: Prophylactic Anti-Viral Therapy

The treating investigator and patient will choose the appropriate anti-viral therapy from one of the three anti-viral therapies below. Patients may initiate anti-viral therapy with a reduced dose based on creatinine clearance (see Dose Modifications, Section 8.2)

Start anti-HBV treatment before anti-cancer therapy or up to 42 days after initial anti-cancer therapy. Continue anti-HBV treatment for 6 months after last dose of anti-cancer therapy or for up to 24 months after registration, whichever occurs first.

Agent	Dose	Route	Start Day	Schedule
Tenofovir alafenamide (TAF)	25 mg[A]	PO[B]	As soon as possible after registration; before or up to 42 days after initial dose of anti-cancer therapy	Daily for up to 6 months after the last dose of anti-cancer therapy or maximum of 24 months[C]
Tenofovir disoproxil fumarate (TDF)	300mg PO		As soon as possible after registration; before or up to 42 days after initial dose of anti-cancer therapy	Daily for up to 6 months after the last dose of anti-cancer therapy or Maximum of 24 months

Entecavir (ETV)	0.5mg	As soon as possible after registration; before or up to 42 days after initial dose of anti-cancer therapy.	Daily for up to 6 months after the last dose of anti-cancer therapy or Maximum of 24 months.

[A] In patients taking carbamazepine the TAF dose will be increased to 50 mg daily.
[B] See dosage administration details in Section 3.1d.
[C] Note: Chronic HBV patients should not abruptly stop antiviral therapy after 24 months. Please see Section 8.2 for details on cessation of anti-HBV therapy in chronic HBV patients.

b. Arm 2: Upon Indication Anti-Viral Therapy

The treating investigator and patient will choose the appropriate anti-viral therapy from one of the three anti-viral therapies below. Patients may initiate anti-viral therapy with a reduced dose based on creatinine clearance (see Dose Modifications, Section 8.2).

Monitor ALT at least every 4 weeks (+/- 2 weeks) as part of trial monitoring for the first 24 weeks, then every 8 weeks thereafter. If hepatitis flare occurs (see definition for hepatitis flare in Section 10.2b), then obtain an HBV DNA test per usual care. Start anti-HBV therapy if HBV reactivation occurs.

Agent	Dose	Route	Start Day	Schedule
Tenofovir alafenamide (TAF)	25 mg [A]	PO [B]	As soon as possible after HBV reactivation occurs (see criteria for HBV reactivation Section 10.2a).	Daily for up to 6 months after the last dose of anti-cancer therapy or a maximum of 24 months [C].
Tenofovir disoproxil fumarate (TDF)	300mg	PO	As soon as possible after HBV reactivation occurs (see criteria for HBV reactivation . Section 10.2a	Daily for up to 6 months after the last dose of anti-cancer therapy or Maximum of 24 months
Entecavir (ETV)	0.5mg	PO	As soon as possible after HBV reactivation occurs (see criteria for HBV reactivation . Section 10.2a	Daily for up to 6 months after the last dose of anti-cancer therapy or Maximum of 24 months.

[A] In patients taking carbamazepine the TAF dose will be increased to 50 mg daily.

[B] See dosage administration details in Section 3.1d.
[C] Note: Chronic HBV patients should not abruptly stop antiviral therapy after 24 months. Please see Section 8.2 for details on cessation of anti-HBV therapy in chronic HBV patients.

Anti-HBV therapy is initiated only when HBV reactivation. Once started, anti-HBV therapy continues for a minimum of 6 months after discontinuation of all anti-cancer therapy or for up to 24 months after registration, whichever comes first.

7.3 Cohort 2: Past HBV Anti-Viral Treatment

a. Arm 3: Upon Indication Anti-Viral Therapy

The treating investigator and patient will choose the appropriate anti-viral therapy from one of the three anti-viral therapies below. Patients may initiate anti-viral therapy with a reduced dose based on creatinine clearance (see Dose Modifications, Section 8.2).

Monitor ALT at least every 4 weeks (+/- 2 weeks) as part of trial monitoring for the first 24 weeks, then every 8 weeks thereafter. If hepatitis flare occurs (see definition for hepatitis flare in Section 10.2b), then obtain HBV DNA test per usual care. Start anti-HBV therapy if HBV reactivation occurs.

Agent	Dose	Route	Start Day	Schedule
Tenofovir alafenamide (TAF)	25 mg [A]	PO [B]	As soon as possible after HBV reactivation occurs (see criteria for HBV reactivation Section 10.2a).	Daily for up to 6 months after the last dose of anti-cancer therapy or a maximum of 24 months [C].
Tenofovir disoproxil fumarate (TDF)	300mg	PO	As soon as possible after HBV reactivation occurs (see criteria for HBV reactivation. Section 10.2a	Daily for up to 6 months after the last dose of anti-cancer therapy or Maximum of 24 months
Entecavir (ETV)	0.5mg	PO	As soon as possible after HBV reactivation occurs (see criteria for HBV reactivation. Section 10.2a	Daily for up to 6 months after the last dose of anti-cancer therapy or Maximum of 24 months.

[A] In patients taking carbamazepine the TAF dose will be increased to 50 mg daily.
[B] See dosage administration details in Section 3.1d.

Anti-HBV therapy is initiated only when HBV reactivation. Once started, anti-HBV therapy continues for a minimum of 6 months after discontinuation of all anti-cancer therapy or for up to 24 months after registration, whichever comes first.

b. Arm 4: Usual Care Anti-Viral Therapy

Initiate anti-HBV therapy at the discretion of the physician. Any FDA approved anti-viral medication for treatment of HBV may be utilized. See Section 18.5.

7.4 HBV Monitoring and Adverse Liver Outcomes

During anti-cancer therapy and for 24 months from initial registration, all patients will undergo monitoring for HBV reactivation and adverse liver outcomes (see Section 10.0). Patients will have ALT and total bilirubin assessed every 4 weeks (± 2 weeks) for the first 24 weeks, then every 8 weeks thereafter. Per usual care, if total bilirubin > 3 mg/dL or if ALT > 5x IULN or > 200 U/L then INR will be assessed.

As part of adverse liver outcome assessment, if a hepatitis flare occurs (defined as ALT > 3 x baseline and > 100 U/L) the following labs should be ordered on the same day as the flare or within 7 days of the flare:

- direct bilirubin,
- HBV DNA,
- IgM anti-HAV, and
- either anti-HCV or HCV RNA.

- Patients on Arms 1, and 2 must have HBeAg tested. HBV test results must be reported on the **S1614** Laboratory Values Form.
- If Patients on Arms 3 and 4 become HBsAg positive and have a hepatitis flare, HBeAg testing is required. HBV test results must be reported on the **S1614** Laboratory Values Form.

Additionally, for all HBsAg+ patients, it is recommended that the treating investigator contact Dr. Jessica Hwang, M.D., Dr. Anna Lok, M.D., or Dr. Jordan Feld at cancercontrolquestion@crab.org for evaluation during the study treatment and after discontinuation of study treatment to ensure continued monitoring and to determine whether antiviral therapy should be maintained after discontinuation of study treatment.

7.5 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment. Calendar should be kept in the patient's research chart. Sites utilizing the CIRB must use the Intake Calendar provided. Sites not utilizing the CIRB may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.6 Criteria for Removal from Protocol Treatment

a. Completion of 24 months on study.

b. If receiving anti-viral treatment, completion of anti-viral treatment 6 months after discontinuing all anti-cancer therapy or for up to 24 months after registration, whichever comes first.

c. Cumulative delay of anti-viral treatment > 30 days for any reason.

d. Unacceptable toxicity to anti-viral treatment. (See Section 8.2)

e. The patient may withdraw from the study at any time for any reason. If the patient allows for indirect follow-up or is refusing to complete any further patient forms but will allow the site to follow them indirectly, continue to submit the site-completed forms through Week 104.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Anti-Viral Protocol Treatment Notice.

7.8 Follow-Up Period

All patients will be followed until death or 24 months after registration, whichever occurs first. No further follow-up will be required once the patient completes 104 weeks (2 years) of protocol participation. Patients should continue to have their protocol-scheduled assessments until one of the outlined criteria for removal listed in Section 7.6 has been met.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Dose Modifications

General Considerations:

For a more comprehensive list of managing toxicities or management see package insert. Treatment and dose modifications are at the discretion of the treating investigator.

Unacceptable (Grade 3 or greater) and related toxicity necessitating removal from protocol treatment is expected to be rare. Cause of all ≥ Grade 3 toxicity should be investigated and changes to protocol treatment made only if toxicity deemed to be related (definite, probable or possible). Antiviral should not be stopped as withdrawal of antiviral may precipitate flare of hepatitis. Instead, patient should be switched to another antiviral that is not associated with that toxicity.

Acute kidney injury has only been reported for TDF. If deemed to be related to TDF, then stop TDF and switch to TAF or ETV.

Lactic acidosis is considered a class effect although data associating it with TDF or TAF are lacking. If deemed to be related, then stop the drug, monitor closely, and when resolved, switch to an alternate antiviral. *(48)*

Exacerbation of hepatitis associated with discontinuation of antiviral is not related to the antiviral drug itself. This is not applicable to this oncology population where antiviral therapy discontinuation is not expected during anticancer therapy.

TAF-treated patients:

No dosage adjustment of tenofovir alafenamide (TAF) is required in patients with renal impairment with a creatinine clearance ≥15 ml/min. Patients with a creatinine clearance <15 ml/min who are receiving hemodialysis may take the usual dose of TAF (25 mg) on days of dialysis after completion of hemodialysis treatment. TAF is not recommended for patients with creatinine clearance <15 ml/min who are not receiving hemodialysis.

If a study patient develops creatinine clearance below 15 mL/minute during study participation and is not receiving hemodialysis, then TAF will be discontinued with substitution with an appropriate alternative antiviral as described below at the discretion of the investigator.

TDF-treated patients:

The following guidelines should be used for dose modification of TDF based on creatinine clearance.

Creatinine clearance (mL/min)	Dose
≥50	300 mg daily
30-49	300 mg every 48 hours
10-29	300 mg every 72 to 96 hours
Hemodialysis	300 mg every 7 days

ETV-treated patients:

The following guidelines should be used for dose modification of ETV based on creatinine clearance.

Creatinine clearance(mL/min)	Dose
≥50	0.5 mg daily
30-50	0.25 mg daily or 0.5 mg every 48 hours
10-30	0.15 mg daily or 0.5 mg every 72 hours
<10 or hemodialysis or peritoneal dialysis	0.05 mg daily or 0.5 mg every 7 days

Dose Modification Contacts

For treatment or dose modification questions, please contact Jessica Hwang, M.D., M.P.H., Phone: 713/745-4516, E-mail: jphwang@mdanderson.org or Anna Lok, M.D., Phone: 734/936-7511 or E-mail: aslok@med.umich.edu.

8.3 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 ARM 1: Prophylactic anti-HBV therapy Arm (HBsAg+ Patients)

REQUIRED STUDIES	Week 0 (Registration)	Weeks from Registration (± 2 weeks unless otherwise specified)							Follow-Up after Off HBV Treatment (Every 8 Weeks Through Week 104)	at HBV Reactivation
		4	8	12	16	20	24	Every 8 Weeks from Week 32 through Week 104 (24 months)		
PHYSICAL										
History and Physical Exam	X									
HBV Assessment [F]	X	X	X	X	X	X	X	X	X	X
Toxicity Notation [F]		X	X	X	X	X	X	X		
Review Intake Calendar [F]		X	X	X	X	X	X	X		
LABORATORY										
Serum creatinine/Creatinine Clearance	X	X	X	X	X	X	X	X		
Total Bilirubin	X	X	X	X	X	X	X	X	X	
Direct Bilirubin [A] [E]	X	X	X	X	X	X	X	X	X	
ALT	X	X	X	X	X	X	X	X	X	
International Normalized Ratio (INR) [A]	X	X	X	X	X	X	X	X	X	
Complete Blood Count (CBC)	X									
HBV DNA [B]	X	X	X	X	X	X	X	X	X	
IgM anti-HAV [B] [E]	X	X	X	X	X	X	X	X	X	
anti-HCV [B] [E] or HCV RNA [B] [E]		X	X	X	X	X	X	X	X	
HBeAg [B]	X	X	X	X	X	X	X	X	X	

Calendar 9.1 continued on next page. Click here for Footnotes

REQUIRED STUDIES	Week 0 (Registration)	Weeks from Registration (± 2 weeks unless otherwise specified) 4	8	12	16	20	24	Every 8 Weeks from Week 32 through Week 104 (24 months)	Follow-Up after Off HBV Treatment (Every 8 Weeks Through Week 104)	at HBV Reactivation
SPECIMEN SUBMISSION [C]										
Serum (10 ml blood in red top tube)	X		X		X		X	X		X
Whole blood (50 ml in EDTA tubes)	X		X				X			X
TREATMENT										
Arm 1- Prophylactic Anti-HBV Therapy[D]	X	X	X	X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0. Click here for Footnotes.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in SWOG Best Practices, https://www.swog.org/clinical-trials/protocol-workbench.

FOOTNOTES:

(A) If total bilirubin > 3 mg/dL, or if ALT > 5 x IULN or > 200 U/L, per usual care (see Section 7.4).

(B) If hepatitis flare (defined as ALT > 3 x baseline and > 100 U/L).

(C) See Sections 15.0 and Appendix 18.1.

(D) See Section 7.2a.

(E) To be ordered the same day (or within 7 days) if hepatitis flare occurs.

(F) See Section 7.1b.

Allowable Windows

All visits and procedures must occur within ± 2 weeks of target date (based on date of registration), unless otherwise specified.

9.2 ARM 2 & ARM 3: Upon Indication Arms (HBsAg+ or HBsAg- Patients)

REQUIRED STUDIES	Week 0 (Registration)	Weeks from Registration (± 2 weeks unless otherwise specified)							Follow-Up after Off HBV Treatment (Every 8 Weeks Through Week 104)	at HBV Reactivation
		4	8	12	16	20	24	Every 8 Weeks from Week 32 through Week 104 (24 months)		
PHYSICAL										
History and Physical Exam	X									
HBV Assessment (H)	X	X	X	X	X	X	X	X	X	X
Toxicity Notation (G) (H)		X	X	X	X	X	X	X		
Review Intake Calendar (G) (H)		X	X	X	X	X	X	X		
LABORATORY										
Serum creatinine/Creatinine Clearance	X	X	X	X	X	X	X	X		
Total Bilirubin	X	X	X	X	X	X	X	X	X	
Direct Bilirubin (A) (F)										
ALT	X	X	X	X	X	X	X	X	X	
International Normalized Ratio(INR)(A)	X	X	X	X	X	X	X	X	X	
Complete Blood Count	X									
HBV DNA (B) (C) (F)	X	X	X	X	X	X	X	X	X	
HBsAg (C)	Not Indicated in Arm 2*									
IgM anti-HAV (B) (C) (F)	X	X	X	X	X	X	X	X	X	
anti-HCV (B) (C) (F) or HCV RNA (B) (C) (F)		X	X	X	X	X	X	X	X	
Anti-HBs (Arm 3) (B) (C)(F)	X	X	X	X	X	X	X	X	X	
HBeAg (if become HBsAg+) (B) (C) (F)	X	X	X	X	X	X	X	X	X	

REQUIRED STUDIES	Week 0 (Registration)	Weeks from Registration (± 2 weeks unless otherwise specified)							Follow-Up after Off HBV Treatment (Every 8 Weeks Through Week 104)	at HBV Reactivation
		4	8	12	16	20	24	Every 8 Weeks from Week 32 through Week 104 (24 months)		
SPECIMEN SUBMISSION [D]										
Serum (10 ml blood in red top tube)	X		X		X		X	X		X
Whole blood (50 ml in EDTA tubes)	X		X				X			X
TREATMENT										
Upon-Indication anti-HBV therapy [E]	X	X	X	X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in SWOG Best Practices, https://www.swog.org/clinical-trials/protocol-workbench.

FOOTNOTES for Calendar 9.2:

(A) If total bilirubin > 3 mg/dL, or if ALT > 5x IULN or > 200 U/L, per usual care (see Section 7.4).

(B) If hepatitis flare (defined as ALT > 3 x baseline and > 100 U/L) if patient is HBsAg-positive.

(C) If hepatitis flare (defined as ALT > 3 x baseline and > 100 U/L) in patient with baseline HBsAg-negative.

(D) See Sections 15.0 and Appendix 18.1.

(E) See Section 7.0

(F) To be ordered the same day (or within 7 days) if hepatitis flare occurs.

(G) If patient initiated anti-viral treatment per protocol.

(H) See Section 7.1b.

Allowable Windows

All visits and procedures must occur within ± 2 weeks of target date (based on date of registration), unless otherwise specified.

9.3 ARM 4: Usual Care Arm (HBsAg- Patients)

REQUIRED STUDIES	Week 0 (Registration)	Weeks from Registration (± 2 weeks unless otherwise specified)							Follow-Up after Off HBV Treatment (Every 8 Weeks Through Week 104)	at HBV Reactivation
		4	8	12	16	20	24	Every 8 Weeks from Week 32 through Week 104 (24 months)		
PHYSICAL										
History and Physical Exam	X									
HBV Assessment [H]	X	X	X	X	X	X	X	X	X	X
Toxicity Notation [G] [H]		X	X	X	X	X	X	X		
Review Intake Calendar [G] [H]		X	X	X	X	X	X	X		
LABORATORY										
Serum creatinine/Creatinine Clearance	X	X	X	X	X	X	X	X		
Total Bilirubin	X	X	X	X	X	X	X	X	X	
Direct Bilirubin [A] [F]	X	X	X	X	X	X	X	X	X	
ALT	X	X	X	X	X	X	X	X	X	
International Normalized Ratio (INR) [A]	X	X	X	X	X	X	X	X	X	
Complete Blood Count (CBC)	X									
HBV DNA [B] [C] [F]	X	X	X	X	X	X	X	X	X	
HBsAg [B] [C] [F]	X	X	X	X	X	X	X	X	X	
IgM anti-HAV [B] [C] [F]	X	X	X	X	X	X	X	X	X	
anti-HCV [B] [C] [F] or HCV RNA [B] [C] [F]		X	X	X	X	X	X	X	X	
Anti-HBs [B] [C] [F]	X	X	X	X	X	X	X	X	X	
HBeAg (if becomeHBsAg+) [B] [C] [F]	X	X	X	X	X	X	X	X	X	

SPECIMEN SUBMISSION (D)										
Serum (10 ml blood in red top tube)	X		X		X		X	X		X
Whole blood (50 ml in EDTA tubes)	X		X				X			X
TREATMENT										
Usual HBV Care (E)	X	X	X	X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0. Click here for Footnotes.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in SWOG Best Practices, https://www.swog.org/clinical-trials/protocol-workbench.

FOOTNOTES for Calendar 9.3:

(A) If total bilirubin > 3 mg/dL, or if ALT > 5x IULN or > 200 U/L, per usual care (see Section 7.4).

(B) If hepatitis flare (defined as ALT > 3 x baseline and > 100 U/L) if patient is HBsAg-positive.

(C) If hepatitis flare (defined as ALT > 3 x baseline and > 100 U/L) in patient with baseline HBsAg-negative

(D) See Sections 15.0 and Appendix 18.1

(E) Treat at discretion of physician. See Section 7.2ba.

(F) To be ordered the same day (or within 7 days) if hepatitis flare occurs

(G) If patient initiated anti-viral treatment per protocol.

(H) See Section 7.3b.

Allowable Windows

All visits & procedures must occur within ± 2 weeks of target date (based on date of registration), unless otherwise specified.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Primary Endpoint

a. Adverse liver outcome: Defined as liver-related death or liver failure (ascites, hepatic encephalopathy or impaired hepatic synthetic function defined as total bilirubin ≥ 5 mg/dL or INR ≥ 2.0) not due to disease progression in the liver. Assessment of the primary endpoint will be made by sites and subsequently adjudicated by the research oversight team by blinded review (see Appendix 18.4).

10.2 Other Endpoints

a. HBV reactivation is defined as one of the following:

- ≥ 2 log (100-fold) increase in HBV DNA compared to baseline in patients with detectable HBV DNA at baseline, or
- HBV DNA ≥ 3 log (1,000) IU/mL in a patient with previously undetectable HBV DNA, or
- HBV DNA ≥ 4 log (10,000) IU/mL if baseline HBV DNA not available, or
- HBsAg seroreversion (HBsAg- to HBsAg+) in a patient previously HBsAg-.

b. Hepatitis flare: Hepatitis flare is defined as ALT > 3 x baseline and >100 U/L.

c. Upon indication: On Arms 2 and 3, anti-HBV therapy is initiated only when HBV reactivation occurs (see Section 10.2a). Once started, anti-HBV therapy continues for a minimum of 6 months after discontinuation of all anti-cancer therapy or for up to 24 months after registration, whichever comes first (see Section 7.6).

d. Cancer therapy interruption is defined as dose reduction, treatment delay, or termination of anti-cancer therapy due to hepatic-related reasons other than disease progression in the liver.

e. Death due to any cause measured from date of randomization to date of death.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Endpoint

The following design pertains to each of the different study cohorts (chronic HBV [Cohort 1] and past HBV [Cohort 2]).

The primary endpoint for the clinical study is the time until adverse liver outcome. Patients will be assessed every 4 weeks (+/- 2 weeks) for the first 24 weeks, then every 8 weeks until 24 months. The study will recruit patients with multiple different cancer types, but predominantly lung, breast, colon, prostate, gynecological, and head and neck cancers. Since patient prognosis is sufficiently poor to be receiving anti-cancer therapy, dropout due to non-liver related death will be a significant factor in the design. One-year overall survival is anticipated to be 80% for the combined cohort. Therefore, non-liver related death represents a competing risk in the detection of adverse liver outcomes, which is accounted for in the study design. Both time to first evidence of adverse liver event and non-liver related death are assumed to exhibit exponential decline.

The rate of adverse liver outcomes in this population is not well characterized, as most studies in the literature only report on rates of HBV reactivation or hepatitis flares. For design purposes, the best estimate of the researchers is that 10% of both chronic (Cohort 1) and past (Cohort 2) HBV patients will experience an adverse liver outcome within one

year after registration with standard care. Based on a two-sample survival design accounting for the competing risk of death (~20% deaths at 1 year [hazard rate of 0.223]), and a one-sided alpha=0.05 test, then n=200 participants will give 80% power to detect a hazard ratio for adverse liver outcomes for experimental to standard arms of 0.30, representing a 70% reduction in the hazard risk of adverse liver events in the first year (from 10% down to 3.1%). Dropout for reasons other than death (e.g., transferring care to another institution, withdrawal of consent) following enrollment in the study is estimated to be around 10%. Non-death related dropouts will be censored. To account for non-death related dropouts, the sample size will need to be increased by a factor of N/(1-0.1) = 11%, giving a total required sample size of n=222 eligible patients (111 per arm) for each randomized experiment, or 444 total registered patients to the protocol. A single formal interim analysis for efficacy for each randomized trial will be conducted at the alpha=0.005 level when one half of patients have reached one year of follow-up. Therefore, the final analyses will be conducted at the alpha=0.045 level.

Under the condition of constant effect size, if the 1-year event rate on the standard arm is 20% (15%), then a hazard ratio of 0.3 can be detected with 97% (92%) power, identifying a change from 20% (15%) down to 6.5% (4.9%). Alternatively, under the condition of constant power, if the 1-year event rate on the standard arm is 20% (15%), then 222 total patients allow detection from 20% (15%) down to 10.0% (6.5%) with 80% power and a hazard ratio of 0.48 (0.41).

Power will also vary as a function of the baseline event rate and the one-year overall survival, representing a competing risk, as shown in Table 2 below. Estimates of adverse liver outcomes at 1 year will be derived using cumulative incidence to account for the competing risk of death. The final analysis will rely on Cox regression, adjusting for the stratification factors.

Table 2. Main clinical study power calculations

	1-year death rate				
Hazard ratio	**70%**	**75%**	**80%**	**85%**	**90%**
0.20	84%	86%	89%	91%	92%
0.25	80%	82%	85%	87%	89%
0.30	75%	77%	80%	83%	85%
0.35	68%	71%	74%	77%	79%
0.40	62%	65%	67%	70%	73%

The primary analysis for each randomized experiment will be based on central, blinded review of adverse liver events among all randomized, eligible patients. A secondary examination in all randomized patients irrespective of their eligibility status will also be conducted under a fully intent-to-treat approach. To account for the potential for liver events to vary by cancer stage over and above what is reflected by the stratification variable (planned treatment type), in a secondary analysis, the investigators will adjust for cancer stage (adjuvant vs. advanced disease) as a covariate in the multivariable Cox regression model.

11.2 Secondary Endpoints

The main secondary objective for each randomized cohort is to determine the incidence of HBV reactivation among patients with solid malignancies and chronic or past HBV infection during or after completion of anti-cancer therapy. Based on preliminary data, it is anticipated that 20% of patients will experience HBV reactivation on the standard arm of each of the randomized trials. Estimates of HBV reactivation at one year will be derived using cumulative incidence to account for competing risks. Under this scenario, a sample size of n=222 patients for each randomized study will allow the investigators to estimate the confidence interval to within ± 6% (based on the upper bound of the 95% confidence

interval using an exact binomial in patients with complete follow-up), if the assumed incidence is at least 20%. Thus, this sample size will allow the confidence interval to be estimated to within ± 31.1% of the assumed incidence (the "relative accuracy", defined as: (95% CI upper bound – p)/p], where p is the assumed incidence). This estimate is conservative as it is based on the assumption of no information from the 10% of patients estimated to drop out.

The investigators will also compare HBV reactivation rates by arm within each randomized trial. Based on a two-sample survival design accounting for the competing risk of death (~20% deaths at 1 year [hazard rate of 0.223]), and a one-sided alpha=0.05 test, then n=222 patients (111 per arm) will give 81% power to detect a hazard ratio for HBV reactivation for experimental to standard arms of 0.47, representing a 53% reduction in the hazard risk of HBV reactivation in the first year (from a hazard=0.223 down to hazard=0.105), or an absolute reduction of 50% (from 20% down to 10%). Multivariable Cox regression will compare the effect of intervention assignment, adjusting for the stratification factors specified in the main clinical study.

The investigators will also determine the cumulative incidence of the combined endpoint of adverse liver events plus HBV reactivation, as well as the cumulative incidence of hepatitis flare, by arm within each randomized trial and compare it between the arms in similar fashion.

The accrual for this study is expected to come primarily from NCORP community sites. The estimated rate of past HBV infection in the cancer population is 4.6% based on studies by Ioannou and Roberts. *(49,50)* A slightly higher rate of 5% is assumed based on the expected enrollment distribution by race for this study using data from **S1204**. To enroll 222 eligible patients to the past HBV cohort, 222/0.05 = 4440 patients would need to be screened. Although it is typically estimated that one in 20 patients agree to enroll to a clinical trial, within SWOG sites this rate was found to be higher (14%) in a prospective SWOG barriers study. *(51)* Therefore, it is estimated that 1 in 7 patients identified as having past HBV infection will enroll to this trial, so 4440*7 = 31,080 patients in total will need to be screened. If 60 sites participate equally, each site would need to screen 18 patients/month to complete the study in 2.5 years.

The estimated rate of chronic HBV infection in the cancer population is 0.3% based on studies by Ioannou and Roberts. *(52,53)* Again, a higher rate, of 0.5% is assumed, based on the expected enrollment distribution by race for this study using data from **S1204**. To enroll 222 eligible patients to the chronic HBV cohort, using the same approach as above, it is estimated that 310,800 patients will need to be screened. Each participating site would need to screen 110 patients/month to complete this portion of the study in 4.0 years.

11.3 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistics and Data Management Center and will meet at the Group's bi-annual meetings as necessary.

The event rate on the standard arm will be monitored. If lower than anticipated, consideration will be given to extending accrual in order to achieve sufficient power to detect the design-specified effect size. Also, the treatment rate on Arm 4 (usual care) will be monitored. If deemed to be high enough to lead to meaningful loss of power, consideration will be given to extending accrual to Cohort 2. Additionally, the DSMC will monitor Grade 3-4 adverse events as part of routine monitoring.

Accrual will be monitored monthly. Accrual to the past and chronic HBV patient cohorts will be monitored on an ongoing basis to assess feasibility. NCI guidelines for accrual monitoring will be followed, including assessment of accrual at quarters 4 and 8 after activation, where activation is indexed according to the first patient enrolled. If quarter 4 accrual is <15% of total accrual or if quarter 8 accrual is <20% of total accrual for either the past or chronic HBV studies, changes to the study design – including eligibility modifications, recruitment procedures – will be considered. If study modifications fail to meaningfully impact accrual such that the studies can be conducted within a reasonable timeframe, closure of the study cohort (past or chronic) will be considered. The DSMC will be responsible for decisions regarding possible termination and/or early reporting of the study and they will have access to any available data needed to inform their decisions.

12.0 DISCIPLINE REVIEW

This study does not require a discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered ≤ 28 days prior to initial anti-cancer therapy. If the patient has already started systemic anti-cancer therapy, patient must be registered ≤ 42 days after the initiation of first cycle of anti-cancer therapy.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

13.3 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP’s web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	√	√			
Financial Disclosure Form	√	√	√		
NCI Biosketch (education, training, employment, license, and certification)	√	√	√		
GCP training	√	√	√		
Agent Shipment Form (if applicable)	√				
CV (optional)	√	√	√		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

13.4 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

a. **IRB Approval:**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org

to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol specific requirements (PSRs).

b. **Downloading Site Registration Documents:**

Download the site registration forms from the protocol specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *SWOG,* and protocol number ***S1614***
- Click on *Documents*, Protocol Related *Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU.)

c. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, on CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select *Regulatory Submission*.

Institutions with participants waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

d. **Checking Your Site's Registration Status:**

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the site 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.5 Oncology Participant Enrollment Network (OPEN) Registration Requirements

The Oncology Participant Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a participant transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Participant has met all eligibility criteria within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All participants have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander

- White
- Unknown

The OPEN system will provide a printable confirmation of the non-patient registration and additional instructions as needed. You may print this confirmation for your records.

13.6 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol page on the CTSU website (www.ctsu.org).

14.3 Data Submission Procedures

a. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent

a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidate via the CTSU membrs' website under *Data Management* > *Rave Home* and click to accept the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

d. Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

14.4 Data Submission Overview and Timepoints

a. WITHIN 15 DAYS OF REGISTRATION:

Submit the following:

S1614 Onstudy Form

*Source documentation for cancer diagnosis (Pathology Report preferred)

*Source documentation for pre-registration HIV, HBsAg, anti-HBc, anti-HBs, and HBV DNA test results

Specimens as outlined Section 15.0

*NOTE: Upload reports via the Source Documentation: Baseline form in Rave®

b. WITHIN 15 DAYS AFTER EVERY HBV MONITORING VISIT (per Section 7.4):

Submit the following:

S1614 HBV Assessment Form

S1614 Laboratory Values Form (if laboratory tests performed)

S1614 Anti-Cancer Treatment Form

S1614 Anti-Viral Treatment Form (if anti-viral treatment initiated per protocol)

S1614 Anti-Viral Adverse Event Form (if anti-viral treatment initiated per protocol)
Specimens as outlined Section 15.0

*Source documentation for HBV DNA test documenting HBV reactivation. NOTE: Upload report via the Source Documentation: Follow-up Form in Rave®. Select HBV DNA/HBsAg/Anti-HBs/Anti-HBC Test" as the "Type of scan."

c. WITHIN 15 DAYS OF HBV REACTIVATION:

Submit the following:

S1614 HBV Assessment Form

S1614 Laboratory Values Form (if laboratory tests performed)

S1614 Anti-Cancer Treatment Form

S1614 Anti-Viral Treatment Form (if anti-viral treatment initiated per protocol)

S1614 Anti-Viral Adverse Event Form (if anti-viral treatment initiated per protocol)

Specimens as outlined in Section 15.0

d. WITHIN 15 DAYS OF DISCONTINUATION OF HBV ANTI-VIRAL PROTOCOL TREATMENT:

Submit the following:

S1614 HBV Assessment Form

S1614 Off Anti-Viral Treatment Notice

S1614 Anti-Viral Treatment Form (if anti-viral treatment initiated per protocol)

S1614 Anti-Viral Adverse Event Form (if anti-viral treatment initiated per protocol)

e. WITHIN 15 DAYS OF DISCONTINUATION OF ANTI-CANCER TREATMENT:

S1614 HBV Assessment Form

S1614 Laboratory Values Form

S1614 Anti-Cancer Treatment Form

S1614 Anti-Viral Treatment Form (if anti-viral treatment initiated per protocol)

S1614 Anti-Viral Adverse Event Form (if anti-viral treatment initiated per protocol)

f. WITHIN 15 DAYS OF ADVERSE LIVER OUTCOME:

*Submit source documentation supporting diagnosis of adverse liver outcome per Section 10.1.

*NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®. Select "Adverse Liver Outcome" as the "Type of scan" and add a comment in the "Comments" field to specify the type of adverse liver outcome documentation as appropriate.

S1614 HBV Assessment Form

S1614 Laboratory Values Form (if laboratory tests performed)

S1614 Anti-Cancer Treatment Form

S1614 Anti-Viral Treatment Form (if anti-viral treatment initiated per protocol)

S1614 Anti-Viral Adverse Event Form (if anti-viral treatment initiated per protocol)

g. WITHIN 30 DAYS OF KNOWLEDGE OF DEATH:

Submit the following:

Notice of Death Form

S1614 Anti-Cancer Treatment Form

S1614 Anti-Viral Treatment Form (if anti-viral treatment initiated per protocol)

S1614 Anti-Viral Adverse Event Form (if anti-viral treatment initiated per protocol)

15.0 SPECIAL INSTRUCTIONS

15.1 Blood Serum Specimens (**REQUIRED)**

Specimens for translational medicine and banking (submitted to the Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) required for patient:

a. Blood serum for HBV DNA, HBsAg, ultrasensitive HBsAg, anti-HBs, HBV RNA, HBV core-related antigen (HBcrAg) testing and serum cytokine analysis must be submitted at the following time points (see Section 9.0):

1. At the time of registration (+/- 4 weeks)

2. Every 8 weeks (+/- 2 weeks) from date of registration

3. At time of HBV re-activation

b. At each time point, 10 mL of blood will be drawn into red top tube(s) using institutional supplies, spun down at 1500 G for 10 minutes at room temperature, and serum aliquoted into 1 mL aliquots. Serum should be stored in a -70 to -80ºC freezer (preferred, if available). Samples stored in a -70 to -80ºC freezer may be batch shipped. If batch shipped, samples must be shipped within 3 months of collection.

If -70 to -80°C freezer is not available, then ship immediately on dry ice (ship overnight Monday – Thursday), or store in a -20°C to -80°C freezer and ship within 2 weeks, noting the storage temperature in the Specimen Tracking System.

Samples must be shipped (Monday – Thursday) on dry ice by overnight shipping for receipt Tuesday - Friday. Samples should not be shipped prior to a holiday. The SWOG Biospecimen bank is not able to receive frozen samples on Saturdays, Sundays, or holidays. See Section 15.3 for specimen shipment instructions.

15.2 Whole Blood Specimens (**OPTIONAL for Patient**)

a. With patient's consent whole blood specimens for intracellular cytokine staining (ICC), ELISA, IFN-gamma elispot testing (submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma, and Lymphoma Division, Lab #201) must be submitted at the following time points (see Section 9.0).

1. At time of registration (+/- 4 weeks)

2. 8-12 weeks from registration

3. 24 weeks (+/- 4 weeks) from date of registration

4. At time of HBV-re-activation

b. At each time point, a total 50 mL of blood will be drawn into five to eight purple top (EDTA) tubes using institutional supplies. Blood should be shipped the day of collection, overnight at ambient temperature. Blood may be shipped on Monday through Friday for Tuesday through Saturday delivery. If shipping for Saturday delivery, please mark Saturday delivery and notify the Bank. See Section 15.3 for specimen shipment instructions.

15.3 SHIPPING SAMPLES

All specimens for this protocol should be shipped as Category B Infectious Substances.

a. Specimen Labeling

Liquid specimens must be labeled with the following:

- SWOG patient number
- Patient initials
- Collection date (date the specimen was collected from the patient)
- Specimen type (e.g., blood, serum, etc.)

b. For additional information about labeling and shipping instructions (including address) refer to the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures**).**

c. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org). Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU". SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

(NOTE: If a specimen had an incomplete submission, this must be documented in the Specimen Tracking System under "Special Instructions" at time of specimen submission. If no specimen was available, this must be documented in the Specimen Tracking System by choosing "Notify that Specimen Cannot be Submitted").

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the SWOG Statistics and Data Management Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue and blood samples for SWOG Biospecimen Bank Submission is identified as follows:

Lab #201: SWOG Biospecimen Bank
Solid Tissue, Myeloma, and Lymphoma Division
Phone: 614-722-2865
FAX: 614-722-2897
E-mail: bpcbank@nationwidechildrens.org

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients on all study arms within 30 days of the last administration of the commercial agent.

Attribution	Grade 3		Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 15 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210/614-0006.

17.0 BIBLIOGRAPHY

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18.0 APPENDIX

18.1 Translational Medicine

18.2 Instructions for the SWOG Biospecimen Bank

18.3 Viral Status Information

18.4 Intake Calendar

18.5 Blinded Central Review of Primary Endpoint

18.6 Approved Antiviral Therapies in Adults

18.1 Translational Medicine

HBV DNA, HBsAg, ultrasensitive HBsAg, anti-HBs, HBV RNA, HBV core-related antigen (HBcrAg)

Blood specimens for 444 study participants enrolled in the main clinical study will be collected at baseline and at regular intervals after registration as outlined above in Section 9.0 Study Calendar and Section 15.0. Sixty sites will enroll 222 chronic HBV and 222 past HBV patients, collect blood specimens at study time points, and send specimens to the SWOG Biospecimen Bank. The SWOG Biospecimen Bank will prepare and batch-ship specimens to Toronto Centre for Liver Disease Laboratories during the main clinical study for research tests (HBV DNA, HBsAg, ultrasensitive HBsAg, HBV RNA, HBcAg, anti-HBs, and HBeAg tests) to retrospectively identify patients with HBV reactivation. The results from labs at Toronto Centre for Liver Disease will be used to determine cases of HBV reactivation and matched controls.

a. Specimen Collection and Processing:

Specimens for the TM studies will be collected in red top tubes at 5 time points (+/- 4 weeks) and processed at the site as detailed in Section 15.0.
See Section 18.1d for SWOG Biospecimen Banking Instructions

At the end of the study, the bank will ship specimens to The Toronto Centre for Liver Disease labs where the following HBV tests will be performed: HBV DNA, HBsAg, ultrasensitive HBsAg, HBV RNA, HBcAg, anti-HBs, and HBeAg tests. ALT, total bilirubin, and INR will be performed as part of routine monitoring in the main clinical study SWOG **S1614**.

b. **Translational Aim 1. To determine baseline and changes in overall immune status and HBV-specific immune response in solid tumor patients with chronic or past HBV infection receiving anti-cancer therapy, and to compare the differences in these immune responses by HBV reactivation status.**

HBV-specific T cell and B cell responses are weak in patients with chronic HBV infection. However, evidence from patients receiving immunosuppressive therapy confirms that there is ongoing immune control in chronic HBV infection. Multiple agents with different immunosuppressive and/or immunomodulatory properties have been associated with HBV-reactivation. Reactivation occurs with non-specific therapy like corticosteroids, as well as with targeted treatments like B cell-depleting agents and anti-TNF therapies. Therefore, perturbation of immune composition and/or specific antiviral pathways can result in reactivation. However, HBV reactivation does not occur in all patients who receive immunomodulatory therapies. We hypothesize that the composition, phenotype and function of immune cells at baseline will predict HBV reactivation after starting anti-cancer chemotherapy.

Aim 2 will conduct a case-control study comparing immune status in patients who develop HBV reactivation during chemotherapy with a 1:1 matched set of controls who were not on anti-HBV therapy and did not develop HBV reactivation. Specimens will be collected at the time points detailed in Section 9.0 Study Calendar and Section 15.0. Participants who are clinically diagnosed to have HBV reactivation will have an additional blood draw for future immune studies. All blood specimens will be collected from 444 study participants then shipped overnight to SWOG Biospecimen Bank for processing and storage in a -80°C freezer. Specimens will be sent from SWOG Biospecimen Bank to Drs. Jordan Feld and Adam Gehring's laboratory at the Toronto Centre for Liver Disease for immune

studies detailed below. Dr. Hwang and her immunology collaborators will have priority access to the specimens at SWOG Biospecimen Bank at all times.

The samples are the key novel aspect of the study. Using data from Translational Aim 1, we will identify patients with reactivation defined by increasing HBV viral load with an equal number of patients not experiencing HBV reactivation after treatment. The primary analysis will be performed on longitudinal samples comparing change from baseline upon starting chemotherapy in HBV reactivation patients and those without reactivation. Patients will be matched by age (5-year strata), sex, type of anti-cancer therapy (cytotoxic, immune or targeted) and chronic vs. past HBV.

Chemotherapeutic disruption of the immunological profile maintaining HBV control (500,000 cells). To identify population-based changes in patients experiencing HBV reactivation after chemotherapy, we will use an extensive (30+) parameter CyTOF analysis to quantify CD4, CD8, γδ, MAIT, Treg, NK CD56br, NK CD56dim, memory B cells, plasma blasts, CD14, CD14/16, CD16 monocytes, CD1c, CD141, and plasmacytoid dendritic cells. Comparison between patients that do and do not experience reactivation will identify key biomarkers to stratify patient risk of reactivation and antiviral prophylaxis decisions.

Chemotherapeutic disruption of immunological functions responsible for HBV control (1 – 2 mil cells). To measure how chemotherapeutic agents alter the functional profile of leukocytes we will stimulate lymphocytes and myeloid cells with non-specific agonists such as anti-CD3, IL-12 + IL-18, and TLR agonists. To evaluate the cytokine profile we will use conventional 13 color flow cytometry panels to measure the frequency of single/multiple cytokine positive cells. We will compare samples longitudinally within patients and between patients with and without HBV reactivation. These data have the potential to identify a functional biomarker associated with HBV reactivation and an immunological pathway responsible for HBV control.

Longitudinal analysis of HBV-specific T & B cell immunity (3 – 5 mil cells). To determine whether reactivation is the result of suppression of HBV-specific immunity vs. frequency/functional alterations we will perform HBV-specific T and B cell ELISpot. We will use a pool of overlapping peptides covering the entire HBV genome.[37] Because of the low frequency of HBV-specific T cells, even in patients with previous HBV infection (anti-HBc+), we will use in vitro expansion to increase the rate of HBV-specific T cell detection. To investigate the HBV-specific B cell frequency, we will isolate B cells by magnetic selection and perform HBsAg-specific B cell ELISpot. B cell frequency will be compared longitudinally in patients with and without reactivation and correlated with detection of anti-HBs antibodies in the serum of patients with both chronic and resolved HBV infection. This will allow us to evaluate how the decay of anti-HBs antibodies in the serum correlates with HBV reactivation and quantify the extent to which anti-HBV antibodies are maintaining control of HBV replication in both chronic and resolved HBV infection.

Serum analysis to identify serum biomarkers predicting HBV reactivation. We will use clinical assays to quantify HBV-specific antibodies in the serum and a comprehensive CBA or luminex assay to analyze immunological cytokines/chemokines in longitudinal serum samples. Arginase will be measured by ELISA. HBV RNA, HBcrAg and ultrasensitive HBsAg will be measured in the serum by qPCR (RNA) and ELISA (HBcrAg and ultrasensitive HBsAg) in patients who do and do not experience HBV reactivation to determine if the levels of these markers that indicated active transcription of HBV DNA in the liver increase prior to clinical reactivation and could be used as biomarkers of impending reactivation.

Understanding the serum profile of key molecules associated with HBV reactivation may provide a baseline predictor of HBV control during chemotherapy.

c. **Translational Aim 2. To identify demographic and clinical predictors and correlative immunologic biomarkers of HBV reactivation after receipt of anti-cancer therapy in patients with solid tumors and chronic or past HBV infection.**

The determinants of HBV reactivation in patients with solid tumors are not known. In this aim, we will identify the demographic and clinical predictors as well as immune correlates of HBV reactivation and hepatitis flare among all 444 study patients. For Aim 2, all immune studies will be performed on stored plasma and PBMCs that would have already been prospectively collected at predetermined time points as noted in Section 9.0 Study Calendar and Section 15.0 above. Immune tests will include ELISA, ICC assay, IFN-gamma elispot. If any immune test listed for Aim 2 has already been performed as part of the case control study in Aim 1, it will not be repeated in this aim. In the main clinical study, SWOG sites will collect clinical information for use in Aim 2. The following tests will be considered usual care monitoring for HBV patients receiving anti-cancer therapy and will be recorded at the study follow up time points listed in Section 9.0 Study Calendar: ALT, total bilirubin, and INR. The primary outcome for Aim 2 is time to first evidence of HBV reactivation.

Statistical Analyses plan

Only the patients randomized to the standard arm of each randomized study (chronic vs. past HBV infection) will be the potential participants for this aim. A case-control analysis, using a ratio of cases to controls of 1:1, will be conducted to explore baseline and changes of overall immune status and HBV-specific immune response factors that differ between patients with vs. without HBV reactivation. Based on expected rates of HBV reactivation for patients with chronic and past HBV infection (20%), we estimate that 22 patients with chronic and 22 patients with past HBV infection (n=44 total cases) will develop HBV reactivation. Under this scenario, we will also examine a matched set of 44 control patients. Matching will occur based on age and randomized study type (chronic vs. past HBV infection). Power is low in this setting and therefore this aim is considered exploratory, with any positive findings requiring validation in future studies. For a given binary predictor (i.e. immune status, group 1 = high vs. group 2 = low), 88 total patients (44 cases and 44 controls) is sufficient to detect an absolute difference of 26% in HBV reactivation rates (i.e. 7% for group 1 and 33% for group 2), assuming the overall rate of HBV reactivation is 20%, using a 2-arm binomial alpha=.05 test with 80% power. In addition, changes in overall immune status and HBV-specific immune responses after onset of cytotoxic chemotherapy or immunotherapy will be described for the cases and controls using descriptive statistics (means, standard deviations). To avoid incorrect inference induced by the potentially endogenous relationship between HBV reactivation and immune response, landmark analyses will be used, conditioning on patients surviving to a given assessment time without developing HBV reactivation.

The study will also assess the association of potential risk factors (including demographic, clinical, and immunologic markers) for HBV reactivation. For any potential demographic, clinical, or immunologic factor, time-to-HBV reactivation will be examined using Cox regression, adjusting for the stratification factors specified in the main clinical study. Analyses will be conducted for each randomized study (chronic vs. past HBV), each with a total sample size of n=222 patients. For instance, to identify a hazard ratio of 2.5 between patients with or without a given condition (say, status for a specified candidate marker or

composite, yes vs. no), 222 patients will give 87% power using alpha=.05 two sided tests with 80% survival at 1 year of follow-up data. Power will vary as a function of the proportion in subgroups (i.e. 40% have risk factor vs. 60% do not) and the hazard ratio as indicated in Table 18.1 below, and it will generally be adequate to identify hazard ratios of ≥ 2.5.

Table 18.1. Power to detect a specified difference in risk of HBV reactivation or hepatitis flare

Power	**% of Patients with vs. without a Risk Factor**			
Hazard Ratio	**50 vs. 50**	**40 vs. 60**	**30 vs. 70**	**20 vs. 80**
2.0	77%	73%	66%	54%
2.5	90%	87%	81%	68%
3.0	95%	93%	88%	76%
3.5	97%	96%	91%	81%

TM Endpoints

Hepatitis B-associated hepatitis defined as ALT>3xULN and one of the following: ≥ 2 log (100-fold) increase in HBV DNA compared to baseline in patients with detectable HBV DNA at baseline, or HBV DNA ≥3 log (1,000) IU/mL in a patient with previously undetectable HBV DNA, or HBV DNA ≥4 log (10,000) IU/mL if baseline HBV DNA not available, or HBsAg seroreversion (HBsAg- to HBsAg+) in a patient previously HBsAg-.

Hepatitis B reactivation defined as one of the following: ≥2 log (100-fold) increase in HBV DNA compared to baseline in patients with detectable HBV DNA at baseline, or HBV DNA ≥3 log (1,000) IU/mL in a patient with previously undetectable HBV DNA, or HBV DNA ≥4 log (10,000) IU/mL if baseline HBV DNA not available, or HBsAg seroreversion (HBsAg- to HBsAg+) in a patient previously HBsAg-.

18.2 Instructions for the SWOG Biospecimen Bank

NOTE: The SWOG Biospecimen Bank will prepare specimens for immune studies by separating the plasma, isolating the peripheral blood mononuclear cells (PBMCs), and then cryopreserving

1. Frozen serum
   Processed, frozen serum aliquots will be received at up to 7 time points. Upon receipt, the Bank will accession and barcode before banking in a -80°C freezer until distribution for testing.

   At the end of the study, the Bank will receive notification from the SWOG Statistics and Data Management Center with the cases to distribute for HBV DNA, HBsAg, anti-HBs, HBV RNA, HBV core-related antigen testing, and serum cytokine analysis.

2. Blood in EDTA tubes
   Fresh whole blood collected in EDTA tubes will arrive at ambient temperature from up to 7 time points per patient. At each time point, the Bank will accession and process all specimens for white blood cells (WBC) using a red blood cell lysing technique. WBCs will be aliquoted with freezing media in vials with 1 x 10^7 cells per vial. WBCs will be stored in a liquid nitrogen vapor phase freezer until distribution for future testing.

   At the end of the study, the Bank will receive notification from the SWOG Statistics and Data Management Center with the cases to distribute for ICC, ELISA, IFNg, and ELIspot testing.

18.3 Viral Status Information

HBV STATUS BASED ON HBV TEST RESULTS

Results of Standard Tests			HBV
HBsAg	**anti-HBc**	**anti-HBs**	**Status**
Positive	Positive	Negative	Positive (chronic infection)*
Positive	Negative	Negative	Positive (chronic infection)
Negative	Positive	Positive	Positive (past HBV exposure, now immune)**
Negative	Positive	Negative	Positive (chronic infection or past HBV exposure)**
Negative	Negative	Positive	Negative (prior vaccination, now immune)
Negative	Negative	Negative	Negative

* At high risk for HBV reactivation due to chemotherapy. Consider ordering confirmatory HBV DNA.

** At risk for reactivation due to chemotherapy, although risk is lower than those who are HBsAg-positive. Consider ordering confirmatory HBV DNA.

Three HBV screening tests should be done to determine HBV status: **HBsAg:** hepatitis B surface antigen; **anti-HBc:** antibody to hepatitis B core antigen (total Ig or IgG, but not IgM only); **anti-HBs:** antibody to hepatitis B surface antibody.

Refer to protocol Section 10.2a for the definition for HBV reactivation.

HCV STATUS BASED ON HCV TEST RESULTS

Results of Standard Tests		
anti-HCV Screening Test (CIA or EIA)	**anti-HCV Confirmatory Test (HCV RNA)**	**HCV Status**
Positive	Detectable	Positive (active infection)
Positive	Not detectable	Negative (prior infection)
Negative	Not needed	Negative

CIA: chemiluminescence immunoassay; **EIA:** enzyme immunoassay.

HIV STATUS BASED ON HIV TEST RESULTS

Results of Standard Tests		
Antibody OR combination Antigen and Antibody Test (Rapid HIV Antibody, EIA or ELISA)	**Western Blot Confirmatory Test**	**HIV Status**
Positive	Positive	Positive
Positive	Negative	Negative*
Negative	Not needed	Negative*

Rapid HIV antibody test: dot blot or immunoblot; **EIA:** enzyme immunoassay; **ELISA:** enzyme-linked immunosorbent assay; **PCR:** *Polymerase Chain Reaction*.

* If the patient is suspected to have acute retroviral infection, viral load (by PCR) should be obtained to confirm HIV status.

CONFIRMATORY TESTING

Tests for viral load (viral DNA or RNA) are typically done as confirmation of a positive screening test or to monitor patients who are known to have positive viral test results. Viral load tests should not be ordered as primary screening tests. Upload source documentation for both the initial and the confirmatory testing results in Rave.

FEDERAL GUIDANCE: GUIDELINES AND RECOMMENDATIONS

Please refer to the following links for more information on federal guidelines and recommendations for testing.

HBV: http://www.cdc.gov/hepatitis/HBV/TestingChronic.htm
HCV: http://www.cdc.gov/hepatitis/hcv/guidelinesc.htm
HIV: http://www.cdc.gov/hiv/guidelines/testing.html

18.4 Intake Calendar

Site Staff Instructions: There is the option for site staff to instruct patients to submit the Intake Calendar electronically (See Section 7.1b).

(Intake Calendar Page 1)

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #**_____

Institution/Affiliate _____ Physician _____

Instructions for the participant:
This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your study drug is: _____

Your next appointment is: _____

Special instructions: Please note the following instructions when taking your an antiviral study drug:

- Take all of your doses as scheduled; do not miss a dose. If you forget a dose, take it as soon as possible, as long as it is at least 12 hours before your next dose is due. If your next dose is due within the next 12 hours, skip the missed dose.
- The antiviral drug is an oral administration, to be taken as a whole tablet. However, the tablet can be crushed, split or administered via feeding tube with guidance from the treating physician is permitted.
- Take the antiviral drug with food.
- The antiviral drug has interactions with other drugs. Tell your doctor you are taking an antiviral drug before starting any new medications.
- The antiviral drug can cause damage to your liver (called hepatotoxicity). This can cause stomach pain, nausea, unusual tiredness, dark-colored urine, light-colored stools, yellowing of the skin and eyes, loss of appetite, and fever. If you experience these symptoms, contact your doctor immediately.
- The antiviral drug can cause a build-up of lactic acid in your body. This can cause stomach pain, loss of appetite, diarrhea, fast and shallow breathing, general feeling of discomfort, muscle pain or cramping, unusual sleepiness, or tiredness. If you experience these symptoms, contact your doctor immediately.
- Talk to your doctor before you stop taking the antiviral drug.

(Intake Calendar Page 2)

SWOG Study #_____ **Your Study Drug is: _____**
Month: _____ **Year: _____**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

18.5 Blinded Central Review of Primary Endpoint

The blinded review will be conducted by the Study Chairs, and representatives from the SWOG Statistics and Data Management Center, Oncology Nursing Professionals Committee, and Committee Leadership. The blinded review will be facilitated by provision to the review team of all patient chart information pertaining to the primary endpoint. Identifying information about patient identifiers and treatment assignment will be abstracted, the information will be compiled into a single PDF for each patient, and transmitted to the reviewers in encrypted, password protected electronic files. The blinded review will occur at the completion of study follow-up.

18.6 Approved Antiviral Therapies in Adults

Drug	Dose in Adults*	Use in Children*	Pregnancy Category†	Potential Side Effects†	Monitoring on Treatment‡
Preferred					
Peg-IFN-α-2a (adult) IFN-α-2b (children)	180 mcg weekly	;::1 year dose: 6 million IU/m^2 three times weekly§	C	Flu-like symptoms, fatigue, mood disturbances, cytopenia, autoimmune disorders in adults, anorexia and weight loss in children	Complete blood count (monthly to every 3 months) TSH (every 3 months) Clinical monitoring for autoimmune, ischemic, neuropsychiatric, and infectious complications
Entecavir	0.5 mg daily[k]	;::2 years dose: weight-based to 10-30 kg; above 30 kg: 0.5 mg daily[k]	C	Lactic acidosis (decompensated cirrhosis only)	Lactic acid levels if there is clinical concern Test for HIV before treatment initiation
Tenofovir dipovoxil fumarate	300 mg daily	;::12 years	B	Nephropathy, Fanconi syndrome, osteomalacia, lactic acidosis	Creatinine clearance at baseline If at risk for renal impairment, creatinine clearance, serum phosphate, urine glucose, and protein at least annually Consider bone density study at baseline and during treatment in patients with history of fracture or risks for osteopenia Lactic acid levels if there is clinical concern Test for HIV before treatment initiation
Tenofovir alafenamide	25 mg daily	—	There are insufficient human data on use during pregnancy to inform a drug-associated risk of birth defects and miscarriage.	Lactic acidosis	Lactic acid levels if clinical concern Assess serum creatinine, serum phosphorus, creatinine clearance, urine glucose, and urine protein before initiating and during therapy in all patients as clinically appropriate Test for HIV before treatment initiation
Nonpreferred					
Lamivudine	100 mg daily	;::2 years dose: 3 mg/kg daily to max 100 mg	C	Pancreatitis Lactic acidosis	Amylase if symptoms are present Lactic acid levels if there is clinical concern Test for HIV before treatment initiation
Adefovir	10 mg daily	;::12 years	C	Acute renal failure Fanconi syndrome Lactic acidosis	Creatinine clearance at baseline If at risk for renal impairment, creatinine clearance, serum phosphate, urine glucose, and urine protein at least annually Consider bone density study at baseline and during treatment in patients with history of fracture or risks for osteopenia Lactic acid levels if clinical concern
Telbivudine	600 mg daily	—	B	Creatine kinase elevation and myopathy Peripheral neuropathy Lactic acidosis	Creatine kinase if symptoms are present Clinical evaluation if symptoms are present Lactic acid levels if there is clinical concern

* Dose adjustments are needed in patients with renal dysfunction.
†In 2015, the U.S. Food and Drug Administration replaced the pregnancy risk designation by letters A, B, C, D, and X with more specific language on pregnancy and lactation. This new labeling is being phased in gradually, and to date only TAF includes these additional data.
‡Per package insert.
§Peg-IFN-a-2a is not approved for children with chronic hepatitis B, but is approved for treatment of chronic hepatitis C. Providers may consider using this drug for children with chronic HBV. The duration of treatment indicated in adults is 48 weeks.
kEntecavir dose is 1 mg daily if the patient is lamivudine experienced or if they have decompensated cirrhosis.
Abbreviation: TSH, thyroid stimulating hormone.
https://aasldpubs.onlinelibrary.wiley.com/doi/pdfdirect/10.1002/hep.29800