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A Phase II Study of the Combination of Pembrolizumab and All-Trans Retinoic Acid Combination Treatment of Relapsed Hodgkin Lymphoma (HL) and B-Non-Hodgkin-lymphoma (B-NHL)

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1. PROTOCOL/TRIAL SUMMARY

Protocol Title	A Phase II Study of the Combination of Pembrolizumab and All-Trans Retinoic Acid Combination Treatment of Relapsed Hodgkin Lymphoma (HL) and B-Non-Hodgkin-lymphoma (B-NHL)
Protocol Number	
Trial Objectives:	**Primary Objectives** • Describe the safety and toxicity of combined treatment with pembrolizumab and all-trans retinoic acid (ATRA) in relapsed lymphoma patients. **Secondary Objective** • To assess the anti-tumor activity of the combination of pembrolizumab and all-trans retinoic acid (ATRA) in relapsed lymphoma patients. • To investigate the impact of ATRA and pembrolizumab on myeloid-derived suppressor cells (MDSC) differentiation and function through in vitro experiments using patient-derived MDSCs **Exploratory Objectives** • To assess the influence of MDSC differentiation the immune cell subsets and their cytokines profile • To determine the clinical outcomes with tumor-specific T cell responses, immune cell subsets and ICP expression.
Trial Efficacy Endpoints:	1. Safety and Toxicity 2. Overall response rate 3. Progression-free survival 4. MDSC frequency and function 5. Immune cell subsets and cytokines profile
Trial Population:	• 24 subjects to be enrolled and treated • Male and female subjects • Ages 18-100
Trial Phase	II
Clinical Indication	Relapsed B-cell Lymphomas
Trial Type	Interventional
Description of Study Drug(s)	Pembrolizumab (Keytruda ®) will be administered Intravenous (IV) and All-Trans Retinoic Acid (ATRA) will be administered orally.

Trial Blinding	Open Label Clinical Trial
Treatment Groups	One
Number of Trial Subjects	24
Estimated Enrollment Period	1 year
Estimated Duration of Trial	5 years
Duration of Subject Participation	2 years
Estimated Average Length of Treatment Per Patient	ATRA will be administered over 12 weeks. Pembrolizumab will be administered every 3 weeks until progression of disease, intolerance of therapy, or for up to two years.

2. TRIAL SCHEMA

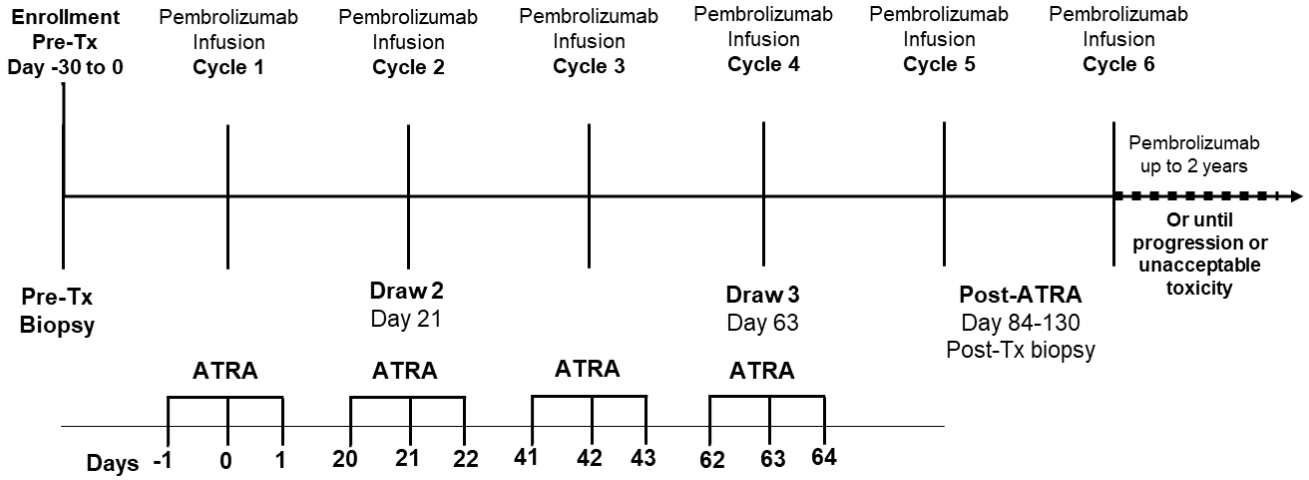


Figure 1. Diagram of the treatment and blood draw schedule for this study. Patients will receive pembrolizumab infusions every three weeks. Patients will also receive 3 days of ATRA treatment surrounding each of the first 4 infusions of pembrolizumab, beginning one day prior to the infusion (a total of 12 days of ATRA). Six tubes of peripheral blood (for a total of approximately 40 ml) will be drawn at enrollment, at the 2nd and 4th infusions, and within 60 days of the final ATRA dose for additional functional experiments.

3. BACKGROUND & RATIONALE

3.1 Overall Review of Relapsed lymphomas

In 2024, most patients with a new diagnosis of Hodgkin lymphoma (HL) can expect to be cured from their disease with frontline treatment [1]. Approximately 20% of patients will experience refractory disease or disease relapse, and for those who undergo salvage chemotherapy and autologous stem-cell transplantation (ASCT), approximately 50% can be cured [2, 3]. However, for patients who decline ASCT or who are ineligible for high-dose chemotherapy and/or ASCT because of age, comorbidity, or failure of salvage, treatment options are limited in efficacy and not well-defined by prospective data. In this setting, the emergence of novel targeted therapies such as the anti-CD30 antibody-drug conjugate brentuximab vedotin and immune checkpoint inhibitors (ICPI) have created promising opportunities to improve survival and potential cure in patients.

Compared with HL, NHL is more heterogenous with more than 60 subtypes and division into indolent or aggressive forms [4, 5]. The varied clinical features and histological appearances of lymphoma present specific challenges such as difficult diagnosis, various management strategies and assorted prognoses [4, 6]. The standard of care has evolved in the second-line treatment and includes traditional salvage chemotherapy followed by consolidation with autologous ASCT or chimeric antigen receptor (CAR)-T cell therapy in patients who are transplant ineligible or those with early disease relapse after front-line therapy [7-9] or additional immunochemotherapy.

Multiple challenges remain in delivering therapies with durable and curative potential in the R/R setting. For example, approximately half of patients with R/R diffuse large B-cell lymphoma (DLBCL) are unsuitable for ASCT, and, even after ASCT, only 50% attain a durable remission [10, 11]. For patients suitable for CAR-T cell therapy, there are multiple barriers, including manufacturing challenges, severe life-threatening toxicities and access to specialist treatment centers, which can increase health disparities [12, 13]. Furthermore, approximately 50% of patients with LBCL do not respond or relapse after CAR-T cell therapy [7, 8]. Although other treatments, including bispecific antibodies [14, 15], antibody–drug conjugates [16], monoclonal antibody combinations [17, 18], targeted therapies [19] and chemoimmunotherapy regimens [18, 20], are available, there remains a need to develop new regimens that balance safety, efficacy and patient access in R/R B-NHL, especially for non-tertiary and community practices where many patients receive treatments.

3.2 Role of Immune Checkpoint Inhibition in Lymphoma

Immune checkpoints have been shown to play a critical role in cancer immune evasion and the host antitumor response. Exploiting the susceptibility of these pathways to the antibody-mediated blockade constitutes an attractive target for therapeutic intervention. Alterations in chromosome 9p24.1 are commonly found in Hodgkin lymphoma and lead to overexpression of programmed death-ligand 1 (PD-L1) and PD-L2. Targeting of the programmed death-1 (PD-1) and PD-L1 pathway aims to restore disabled

immune checkpoints and thereby the antitumor activity of cytotoxic T cells. The anti-PD-1 monoclonal antibodies pembrolizumab and nivolumab are the two most commonly used immune checkpoint inhibitors in the setting of relapsed or refractory lymphoma, with comparable side effect profiles and efficacy in phase II clinical studies when used as monotherapy in R/R HL, although no head-to-head trials have been performed. With extended follow-up, both agents have shown to induce durable remissions and a median progression-free survival of approximately 17 months in heavily pretreated patients with R/R HL.
The use of ICPI in R/R lymphomas has yielded mixed results. In HL, the ORR ranged from 65% to 87% and CRR from 22% to 68%. In NHL, the response rates vary by subtype. In R/R primary mediastinal large B-cell lymphoma, pembrolizumab had an ORR of 45% with a CRR of 11% [21]. In R/R diffuse large B-cell lymphoma, the ORR is approximately 10% [22]. Nivolumab and pembrolizumab are both FDA approved as third-line therapy in R/R HL. Pembrolizumab is FDA approved for R/R PMBCL. There is increasing interest in the use of checkpoint inhibitors with combination chemotherapy or with other targeted agents in the second-line or even frontline setting of HL.

Table 1: Cumulative data of immune checkpoint inhibitors in lymphoma

Disease	Phase	Drug Used	Checkpoint Target	No of pts	ORR	CR	PFS mo	OS mo	DOR mo	Comments
cHL	Phase 1	Nivolumab	Anti-PD-1	23	87%	17%	86% at 6 mos	NR	DOR not yet reached. 47% of patients with ongoing responses	Relapsed or refractory. 78% patients relapsed post HSCT. 78% patients relapsed post Brentuximab.
cHL	Phase 1	Nivolumab	Anti-PD-1	95	65%	7%	14.7	NR	8.7	Relapsed or refractory. serious adverse events were high. reported in 21% of patients in this study.
cHL	Phase 1	Nivolumab + BV	Anti-PD-1	18	89%	50%	N/A	5.5	NR	Relapsed or refractory
cHL	Phase 1/2	Nivolumab + BV	Anti-PD-1	62	82%	61%	89% at 6 mos	5.3	NR	Relapsed or refractory. peripheral blood biomarker analysis was done in this study.
cHL	Phase 1/Keynote 13	Pembrolizumab	Anti-PD-1	31	65%	17%	45% at 13 mos	100% at 6 mos	70% DOR >6 mos	Relapsed or refractory. Pembro dosage was every 2 weeks at 10 mg/kg until progression
cHL	Phase 2/Keynote 87	Pembrolizumab	Anti-PD-1	210	69%	22%	8.6	6	NR	Relapsed or refractory. large study with primary end point of ORR. PDL-1 positivity was not required for enrollment.
cHL	Phase 1	Nivolumab + ipilimumab	Anti-PD-1 & anti-CTLA-4	31	74%	19%	7.2	NR	NR	Relapsed or refractory. predominantly transplant naive group
DLBCL	Phase 2	Pidilizumab	PD-1	66	51%	68%	72% at 16 mos	16	N/A	treatment after auto-HSCT
DLBCL + FL	Phase 1b	5F9 + rituximab	CD47	22	50%	36%	7	NR	NR	Maximum tolerated dose not reached
DLBCL	Phase 2	Nivolumab	PD-1	34	3%	N/A	1.4	5.8	8	Relapsed/refractory; transplant ineligible
				87	10%		1.9	12.2	11	Transplant failed
FL	Phase 1b/2	Durvalumab + ibrutinib	Anti-PD-1	27	26%		10.2	NE	NE	No conclusive biomarker of response seen
GCB-DLBCL				16	13%		2.9	5.5	NE	Majority of pts had DLBCL
Non-GCB DLBCL				16	38%		4.1	7.3	NE	Highest ORR in non-GCB subset
DLBCL	Phase 1	Nivolumab	Anti-PD-1	11	36%	18%	0.3	NE	NE	Relapsed or refractory
DLBCL	Phase 1	Nivolumab + ipilimumab	Anti-PD-1 & anti-CTLA-4	10	20%	0%	2.9	1.5	NR	Relapsed or refractory
PMBCL	Phase 1	Pembrolizumab	Anti-PD-1	21	48%	33%	10.4	31.4	NR	Relapsed or refractory. failed or ineligible for transplant
PMBCL	Phase 1/2	Nivolumab + BV	Anti-PD-1	30	70%	37%	63.5% at 6 mos	86.3% at 6 mos	NR	Relapsed or refractory
CLL	Phase 1	Pembrolizumab	Anti-PD-1	16	0%	0	2.4 m	11.2 m	NR	Closed early
CLL	Phase 2	Nivolumab & ibrutinib	Anti-PD-1	5	60%	0	NR	NR	N/A	Very small study involving CLL only patients
FL	Phase 2	Pidilizumab + rituximab	PD-1	32	66%	52%	18.8	Not met	20.2	Allowed further optional infusions of Pidilizumab for stable disease patients
FL	Phase 1	Nivolumab	Anti-PD-1	10	40%	10%	NR	NR	6–81 weeks	n/a
FL	Phase 1	Nivolumab + ipilimumab	Anti-PD-1 & anti-CTLA-4	5	20%	0	1.5 m	2.9 m	NR	Small group of patients
FL	Phase 2	Pembrolizumab + rituximab	Anti-PD-1	30	80%	60%	NR	NR	NR	n/a
FL	Phase 2	Atezolizumab + obinatuzumab	Anti-PD-1	26	57%	N/A	N/A	N/A	N/A	PD-L1 and MHCI expression did not correlate with response in this study.
T-cell lymphoma	Phase 2	Pembrolizumab	Anti-PD-1	9	55%	0	12	NR	NR	MF
EBV Lymphoma	Phase 1	Pembrolizumab	PDL-1	30	24%	17%	NR	NR	NR	EBV
EBV NK/T-cell Lymphoma	Phase 1	Pembrolizumab	PDL-1	7	100%	29%	NR	NR	NR	EBV
NHL	Phase 1	Pembrolizumab	Anti-PD-1	5	40%	0	NR	NR	NR	HIV

ORR, overall response rate; CR, complete response; PFS mo, progression free survival in months; OS mo, overall survival in months; DOR mo, duration of response in months; cHL, classical Hodgkin lymphoma; DLBCL, diffuse large b-cell lymphoma; FL, follicular lymphoma; GCB, germinal center b-cell; PMBCL, primary mediastinal b-cell lymphoma; CLL, chronic lymp
ebstein barr virus; NHL, non Hodgkin lymphoma; r/r, relapsed refractory; SCT, stem cell transplant; BV, brentuximab vendotin; 5F9, Hu5F9-G4 macrophage immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PDL-1, programmed death ligand 1; CTLA 4, cytoxic T-lymphocyte associated protein 4.

Given their established single-agent activity, developmental trials of novel combinations with immune checkpoint inhibitors are needed to optimize patient care. It is also important to highlight the heterogeneity of the transplant-ineligible population in R/R Hl and B-NHL. Although patients of age ≥ 60

years represent a relatively small proportion of newly diagnosed cases, they have inferior disease control and higher rates of treatment-related toxicity [20] . The disease trajectory in these patients is often very different from younger patients whose disease is refractory to pretransplant salvage chemotherapy and who may be effectively rescued by the administration of an immune checkpoint inhibitor and proceed with ASCT at a later stage. Therefore, treatment goals with immune checkpoint inhibitor therapy may differ depending on the patient population in question.

Finally, monotherapy with immune checkpoint inhibitors can be relatively easily administered with a short intravenous infusion and is usually very well tolerated, with low discontinuation rates reported in clinical studies [23]. However, immune-related adverse events with checkpoint inhibitors are well recognized and constitute an important safety consideration.

3.3 Resistance to Immune Checkpoint Inhibition in Lymphoma Patients

Sustained responses and remissions are observed in a subset of patients treated with ICPIs [24]. One proven mechanism of action for these drugs is eliciting the frequency and function of tumor-specific T cells. However, tumor induced immunosuppression may limit the development of effective immune responses in some patients treated with ICPIs. Improving clinical responses to ICPIs by enhancing other immune-mediated mechanisms in a combinatorial approach is essential for the future evolution of immunotherapeutic strategies. The discrepancy in outcomes among patients responding to anti-PD-1 therapies versus not highlights the imperative to target resistance mechanisms.

3.4 Myeloid Derived Suppressor Cells (MDSCs) Influence the Tumor Microenvironment

MDSCs, a heterogeneous and plastic population of predominantly immature myeloid cells, play a crucial role in lymphoma progression [25]. MDSCs consist of three subpopulations: Monocytic MDSCs (MO-MDSCs, $CD14^{+}CD15^{-}$), polymorphonuclear-like MDSCs (PMN-MDSCs, $CD14^{-}CD15^{+}Lox1^{+}$), and early MDSCs (eMDSC, $CD14^{-}CD15^{-}$) [25]. MDSC myelopoiesis is thought to be triggered by pathologic stimuli to provide innate host defense; however, under conditions of chronic inflammatory stimuli, as with advanced cancers, MDSC production may be sustained as a protective mechanism against inflammation-mediated tissue damage [26]. For example, MDSCs levels correlate with tumor burden and response to therapy among patients with advanced cancer [27].

Unlike mature myeloid cells, MDSCs have low phagocytic potential, and instead exert broad suppression of effector T-cell functions. MDSCs suppress T, natural killer (NK) and dendritic cells, impairing the antitumor immune response. They inhibit T cell function through immunosuppressive molecules like arginase-1, inducible nitric oxide synthase, and reactive oxygen species (ROS), leading to T cell dysfunction and apoptosis [28]. MDSCs also disrupt NK cell-mediated cytotoxicity by downregulating activating receptors and promoting inhibitory receptors.

MDSCs contribute to therapy resistance and decreased response to chemotherapy, immunotherapy, and targeted therapies in lymphoma. MDSCs diminish the efficacy of ICPIs by inhibiting direct cell-cell interactions, the production of immunosuppressive cytokines (IL10, TGFβ, etc.) and ROS [29]. In addition, MDSCs secrete arginase-1 (ARG1) and indoleamine 2,3-dioxygenase 1 (IDO1), depleting nutrients necessary for T-cell functions [28]. By targeting CD8+ T cells, MDSCs diminish the effectiveness of ICPIs, which rely on CD8+ T cells as targets and effectors of activity.

The diversity of MDSC populations and their functions has generated multiple therapeutic strategies to overcome their tumorigenic effects. For example, MDSC recruitment and differentiation into M2-polarized macrophages can be targeted through inhibition of macrophage-specific colony-stimulating factors such as CSF1R [30]. In addition, the growth factor TGFβ, secreted by MDSCs, is a known mechanism of resistance to anti-PD-1 therapy. TGFβ can also be directly targeted to potentially overcome this MDSC-mediated resistance mechanism [31]. The therapeutic strategy with ATRA, however, is to alter the differentiation state of MDSCs, converting them to a less immunosuppressive and more mature myeloid cell.

3.5 Retinoic Acid: Pharmaceutical and Therapeutic Background

Retinoic acid (RA) is derived from Vitamin A (retinol) as a non-peptidic, lipophilic molecule. It is readily available in the precursor forms from diet (beta-carotene, retinol) but retinol cannot be synthesized de novo in the human body. The metabolism of RA is affected by synthesis using retinol (RDH5, 10) and retinaldehyde dehydrogenases (RALDH1,2,3) along with contribution from alcohol dehydrogenases (ADH1,5,7)) as well as degradation by cytochrome p450 (CYP26: various) [32-35].

ATRA belongs to the retinoid family and binds to nuclear retinoic acid receptors and retinoid X receptors to modulate transcription initiation and functions of various genes [36]. It also differentiates immature monocytes into more mature dendritic cells [36]. Its role in treating acute promyelocytic leukemia (APL) is well-known, as it induces degradation of the PML-RARα fusion protein and allows for normal maturation of APL cells, leading to complete remission in most patients.

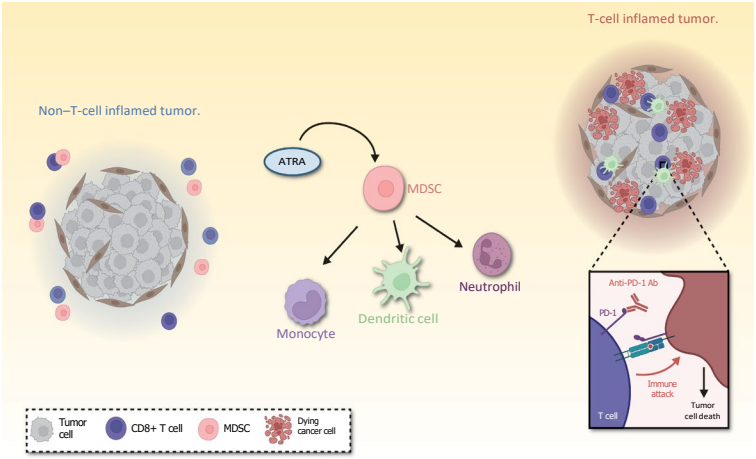
ATRA (tretinoin) is an FDA-approved commercially available retinoid. It is not approved in combination with pembrolizumab for the treatment of patients with cancer. It is available in a 10 mg soft gelatin capsule for oral administration. The recommended dose (for APL) is 45 mg/m^2/day administered as two evenly divided doses until complete remission is documented.

Virtually all patients with APL experience some drug-related toxicity, especially headache, fever, weakness, and fatigue. These adverse effects are seldom permanent or irreversible nor do they usually require interruption of therapy. Some of the adverse events noted in patients with APL are associated with rapid tumor response and include hemorrhage, infections, gastrointestinal hemorrhage, disseminated intravascular coagulation, pneumonia, septicemia, and cerebral hemorrhage. There are no reported adverse side effects in patients with solid tumors treated with a short course of 150 mg/m^2 ATRA combined with high dose IL-2 or a dendritic cell vaccine [37, 38].

3.6 Preclinical and Clinical Trial Data of ATRA Effects on MDSCs

Pre-clinical data suggest that ATRA abrogates the suppressive effects of MDSCs isolated from both human cancer patients and mouse cancer models in vitro [39-41]. Furthermore, mice treated with ATRA have decreased frequencies of MDSCs and increased frequencies of dendritic cells that improve T cell responses against tumors [42-44]. ATRA induces the differentiation of immature monocytes into more mature cells of the dendritic cell lineage [40, 41]. In agreement with these results, available data suggest that ATRA induces maturation of in vitro-derived MDSCs. Monocytes were cultured from healthy donors with GM-CSF/IL-4 or GM-CSF/IL-6 to generate mature monocytes of the dendritic cell lineage (a control population) or MDSCs, respectively [45]. In contrast to the control population, MDSCs express low levels of HLA-DR and maintain high expression of CD14, consistent with the phenotype of an immature monocyte. Furthermore, MDSCs express increased levels of molecules that inhibit T cell responses such as Arginase I, NOX1, iNOS, and PD-L1. Conversely, MDSCs cultured with ATRA are phenotypically more similar to the control dendritic cell population, expressing decreased levels of inhibitory molecules and CD14 and increased levels of HLA-DR. Most importantly, MDSCs derived in vitro with GM-CSF and IL-6 suppress T cell proliferation. However, treatment of these MDSCs with ATRA eliminates their suppressive effects and restores T cell proliferation. Finally, MDSCs express higher levels of retinoic acid receptors RAR and RXR, suggesting that ATRA treatment may selectively target these inhibitory cells.

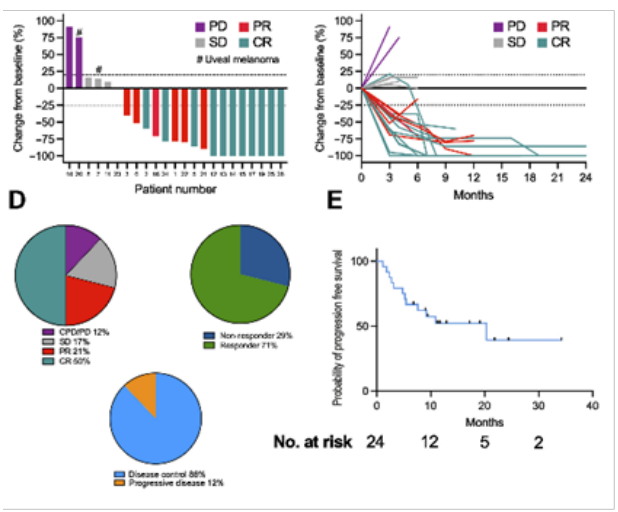
While ATRA is known to reduce MDSCs by inducing maturation, its additional mechanisms on MDSCs are not fully understood. ATRA has been specifically shown to decrease both the frequency and function of MDSCs through activation of ERK1/2, upregulation of glutathione synthase, and generation of glutathione [36]. Increased glutathione production decreases production of ROS and results in subsequent terminal differentiation of MDSCs to mature dendritic cells, macrophages, and granulocytes [28, 46, 47].

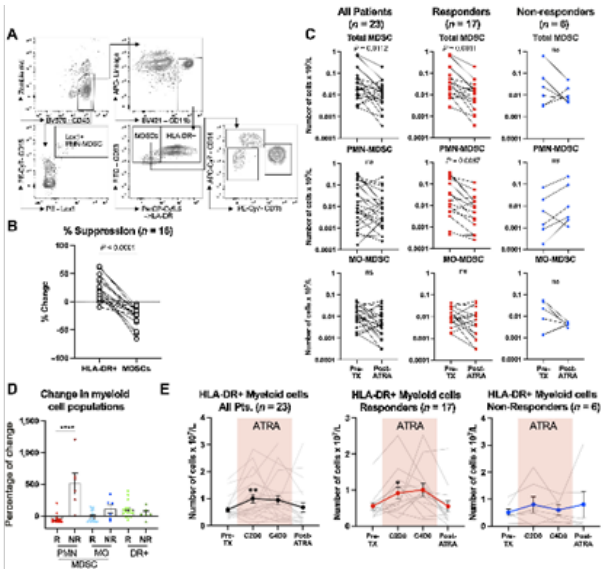


MDSCs are associated with primary resistance to anti-PD-1 therapy. The promise of ATRA is to enhance activity of anti-PD-1 therapy through alteration in the maturation state of MDSCs. Relatively immature and immune suppressive MDSCs can be induced by ATRA along the myeloid lineage toward differentiated mature myeloid phenotypes, such as monocytes, dendritic cells, and neutrophils. This change in turn decreases the immunosuppressive effects of MDSCs and may shift the tumor microenvironment toward a T-cell–inflamed tumor phenotype where anti-PD-1 therapy can provide effective antitumor immunity. (Adapted from an image created with BioRender.com.)

3.7 All Trans Retinoic Acid in Combination with Immune Checkpoint Inhibitors

While as a single agent, ATRA is unlikely to induce similar antitumor efficacy as seen with APL, prior studies suggest that it may synergize with more potent immunotherapy and chemotherapy partners. The specific combination of ATRA and ICPIs such as pembrolizumab was found to be beneficial in several studies of solid tumors [48]. I*n vitro* and *in vivo* lung cancer models showed that functional blockade of G-MDSCs with ATRA reversed immune suppression and sensitizes LKB1-deficient tumors to PD-1 blockade [49]. ATRA was recently reported to promote a tumor suppressive OTUD6B-β-TrCP-SNAIL axis in esophageal squamous cell carcinoma and enhance immunotherapy [50]. In another preclinical model of U14 cervical cancer, ATRA decreased MDSCs accumulation and increased the frequency of CD8+ T cells in BALB/C mice. Importantly, a combination treatment of ATRA and anti-PD-L1 antibody further delayed U14 tumor growth and did not increase the PD-L1 expression in HeLa cells in vitro [51]. Additionally, ATRA significantly reduced peripheral blood MDSCs when combined with pembrolizumab [52]. In a recent study conducted by Tobin et al in advanced melanoma patients, ATRA+pembrolizumab was found to be well-tolerated and produced positive responses. Among the 24 patients treated, the median PFS was 20.3 months, and the ORR was 71%, with 50% of patients experiencing a CCR, and the 1-year OS was 80%. The combination effectively lowered the frequency of circulating MDSCs in responders compared to non-responders. This pilot study demonstrated that ATRA plus pembrolizumab generates higher-than-expected responses that one would expect with pembrolizumab alone [53].





3.8 Rationale for the Trial and Selected Subject Population

Patients with R/R HL and B-NHL who fail or are not eligible for salvage chemotherapy, autologous stem cell transplant and/or CAR T-cell therapy have poor outcomes with no standard approaches, thus representing an unmet need. While some patients with advanced lymphomas enjoy a transformative

benefit from anti-PD-1 therapy, most patients do not respond, and combinations with additional ICPI leave most patients experiencing primary or acquired resistance. The discrepancy in outcomes among patients responding to anti-PD-1 therapies versus not highlights the imperative to target resistance mechanisms. Across multiple discrete pathways, MDSCs are implicated in impairing effective antitumor immunity [28].

Reducing immunosuppression by MDSCs during pembrolizumab treatment may maximize T cell activation and expansion, increasing the overall effectiveness and success of pembrolizumab treatment. This pilot clinical trial will demonstrate whether combinatorial immunotherapeutic approaches that target immunosuppressive MDSC's can augment tumor-specific T cells and benefit relapsed lymphoma patients. Stemming from the tissue-agnostic property of ICPIs, we sought to target MDSCs using the differentiating agent ATRA to enhance the efficacy of pembrolizumab in anti–PD-1 naïve patients with relapsed HL and B-NHL. We hypothesize that ATRA (Vesaoind) may overcome the negative immune effects of MDSCs in the tumor microenvironment, allowing patients to derive higher benefit from pembrolizumab. This IIT will actively include the vulnerable group of elderly and/or frail patients who are often excluded from trials, owing to its anticipated safety profile.

3.9 Rationale for Study Design/Dose Selection/Regimen/Modification

3.9.1 *Pembrolizumab Dose Selection*

Dosing of pembrolizumab has been evaluated in a variety of clinical settings. A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight-based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab. The exposure margins are based on the notion of similar efficacy and safety in lymphoma and solid tumors at 10 mg/kg Q3W vs. 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was found to be similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab is based on:

1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in solid tumor and lymphoma patients,
2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W,

3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and
4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that:

1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks,
2) will maintain individual patient exposures in the exposure range as associated with maximal efficacy response and
3) will maintain individual patients' exposure in the exposure range that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

All patients will receive 200mg Q3W pembrolizumab treatment plus the supplemental treatment of 150 mg/m2 ATRA orally for 3 days surrounding each of the first four infusions of pembrolizumab (day -1, day 0, day +1) for a total of 12 days of ATRA treatment. The total daily dose of ATRA may be taken anytime on the day before the pembrolizumab infusion (day -1) according to the patient's preferences, prior to the pembrolizumab infusion on the day of the infusion (day 0), and anytime on the day after the pembrolizumab infusion (day 1) according to the patient's preferences.

3.9.2 *ATRA Dose Selection*

Although ATRA is a standard treatment for patients with APL, it has also been used to treat patients with solid tumors. The dose of ATRA is based on several prior clinical trials that combined ATRA with other treatments. This same dose of ATRA is also based on the pharmacokinetics and effects on MDSCs observed in these trials (11, 12). Renal cell carcinoma patients treated with ATRA followed by high dose IL-2 had reduced frequencies of circulating MDSCs with reduced immunosuppressive function during the ATRA phase of the treatment regimen [37]. However, the subsequent high-dose IL-2 treatment abrogated these effects and resulted in a lack of clinical benefit overall. In another recent trial, ATRA was used in combination with a dendritic cell vaccine targeting p53 mutations in small cell lung cancer patients [38]. The survival outcomes have not yet been reported; however, the study demonstrated that the frequency and function of MDSCs was reduced following ATRA treatment and that p53-specific T cell responses were increased in more patients receiving the combinatorial therapy compared to patients receiving the dendritic cell vaccine alone [38]. These investigators performed a dose ranging pharmacokinetic analysis and correlated serum concentrations of ATRA with the desired target effect on MDSCs and determined that

the optimal oral dose of ATRA was 150mg/m^2/day. Lower doses of ATRA generally resulted in lower serum concentrations and less reliable effects on MDSCs. The authors also reported common side effects associated with the ATRA as dry skin, myalgia and headache that resolved when the ATRA was stopped. No specifics regarding the frequency or severity of these side effects were reported [37].
Prior studies combining ipilimumab with ATRA and pembrolizumab with ATRA, mostly in melanoma, found that the 150mg/m^2 dose of ATRA appeared to be safe and well-tolerated [52, 53] for a total of 12 days of ATRA treatment.

4. OBJECTIVES

In this study, the authors propose ATRA as a possible therapy to enhance anti-PD-1 through targeting of immunosuppressive myeloid-derived suppressor cells (MDSC). We will monitor efficacy via two main endpoints (1) antitumor responses and (2) manipulation of MDSC subsets.

4.1 Primary Objectives

- Describe the safety and toxicity of the combination of pembrolizumab and ATRA in relapsed HL and B-NHL patients.

4.2 Secondary Objective

- To assess the anti-tumor activity of the combination of pembrolizumab and ATRA in relapsed HL and B-NHL.

- To assess the anti-tumor effect of the combination of pembrolizumab and ATRA in relapsed HL and B-NHL on the reduction in myeloid-derived suppressor cells (MDSC) frequency and suppressive function in peripheral blood of relapsed HL and B-NHL patients undergoing therapy, through in vitro experiments using patient-derived MDSCs.

4.3 Exploratory Objectives

- To assess the influence of MDSC differentiation the immune cell subsets and their cytokines profile
- To determine the clinical outcomes with tumor-specific T cell responses, immune cell subsets and ICP expression.

5. OUTCOME MEASURES

5.1 Primary Outcome Measures

- Safety will be assessed by NCI CTCAE v5.0 criteria.

5.2 Secondary Outcome Measures

a) Overall response rate (ORR)

b) Complete remission rate (CRR),

a) The reduction in myeloid-derived suppressor cells (MDSC) frequency and suppressive function in peripheral blood of relapsed HL and B-NHL patients undergoing pembrolizumab and ATRA combination therapy, through in vitro experiments using patient-derived MDSCs.

5.3 Exploratory Outcome Measures

a) Impact of MDSC differentiation on cytokine and chemokine panels, including immune functional groups Th1, Th2, Th9, Th17, regulatory, chemo-attractive, and cytotoxic T cells.

b) Impact of MDSC differentiation on the immune landscape of T cell subset will be specifically evaluated through the T-cell activation marker (CD69) and a T-cell exhaustion marker (TIM-3).

c) Impact of MDSC differentiation on circulating cytokines including IL1β, IL2, IL4, IL6, IL8, IL10, IL12p70, IL13, TNFα, and IFNγ.

d) Overall survival (OS),

e) Progression-free survival (PFS)

f) Time-to-events (TTE)

6. ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

1. ≥ 18 years old at the time of informed consent
2. Ability to provide written informed consent and HIPAA authorization
3. Willingness to comply with all study procedures and be available for the duration of the trial
4. Have a performance status of 0 to 2 on the ECOG Performance Scale.

5. Life expectancy ≥12 weeks as per investigator discretion
6. Patients with histologically proven, relapsed or refractory HL or B-NHL as follows:
    a. HL after failure of at least 1 prior line of systemic therapy
    b. Primary mediastinal large B-cell lymphoma (PMBCL) that is refractory to first-line therapy
    c. Other B-cell NHLs after failure of at least 2 prior lines of systemic therapy. The eligible types of B-cell NHLs are:
        i. Diffuse large B cell lymphoma
        ii. Follicular lymphoma
        iii. Marginal Zone lymphoma
        iv. Mantle Cell Lymphoma
    d. Indolent lymphoma are only eligible if they require systemic treatment
    e. Lymphocyte predominant HL are eligible

    Note: Formalin-fixed, paraffin embedded archival tumor sample from the primary cancer must be available for testing. If not available or sufficient, patients will be asked to undergo an US or CT guided biopsy prior to study entry to satisfy this eligibility criterion.
7. Adequate hematologic and end organ function, defined by the following laboratory results obtained within 10 days prior to the first study treatment:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
INR and aPTT	≤1.5 x ULN; this applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.
Renal	
calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	calculated creatinine clearance ≥ 60 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN **(patients with known Gilbert disease who have bilirubin levels ≤ 3 x ULN may be enrolled). Patients must be able to undergo biliary stenting if required before or, if required, during the trial**

AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	>2.5 mg/dL

8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: Female of childbearing potential definition: (ECOG definition) Any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

   a. Has not undergone a hysterectomy or bilateral oophorectomy; or

   b. Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

9. Female subjects of childbearing potential must be willing to use an adequate method of contraception for the course of the study through 120 days after the last dose of study medication. Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Refer to section 8.4.1 for more information.

10. Male subjects of childbearing potential must agree to use an adequate method of contraception of the protocol, starting with the first dose of study therapy through 120 days after the last dose of study therapy. Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. Refer to section 8.4.1 for more information.

11. Acceptable methods of contraception include IUD, oral contraceptive, subdermal implant, and double barrier (condom with a contraceptive sponge or contraceptive pessary). Micro-dosed progesterone preparations (“mini-pill”) are an inadequate method of contraception during treatment with ATRA. If patients are taking this pill they should be instructed to stop, and another form of contraceptive should be prescribed instead.

12. Patients with a history of CAR-T cell therapy are eligible if ≥ 3 months post treatment.

6.2 Exclusion Criteria

1. Patients currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Known brain metastases and/or leptomeningeal disease. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of

progression for at least 4 weeks by repeat imaging (repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

3. Significant reduction in ECOG performance status between the screening/ baseline visit and within 72 hours prior to commencement of treatment as per trial protocol, as per the Investigator's assessment, defined as a reduction in ECOG score to 3 or 4.

4. Patients with a diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs) within 7 days prior to the first dose of trial treatment.

   Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

5. Hypersensitivity to pembrolizumab or any of its excipients.

6. Contraindication to the use of ATRA including but not limited to: patients with a history of hypersensitivity reaction to tretinoin, vesanoid or related compounds (i.e. acitretin, isotretinoin, vitamin A); , Tetracyclines, Progesterone (low dose), drugs inducing P450 (rifampicin, glucocorticoids, phenobarbital, etc), ketoconazole and drugs inhibiting p450 (cimetidine, erythromycin, cyclosporine, etc); antifibrinolytic agents (e.g. tranexamic acid, aminocaproic acid, aprotinin) and hydroxyurea)

7. Prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day -1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

8. Prior chemotherapy targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day -1 or who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. Subjects with chronic conditions such as vision changes or prior hearing loss that is not reasonably expected to be exacerbated by the investigational product may be included.

   Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

   Note: Subjects with Grade 2 adrenal insufficiency or thyroid conditions who are not expected to resolve to baseline, are on a stable dose of medication may be included if it is not reasonably expected to be exacerbated by the investigational product, and asymptomatic whilst on treatment.

9. History of malignancy in the last 5 years with the exception of prior history of in situ cancer or basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer. Patients with other malignancies are

eligible if they were cured by surgery alone or surgery plus radiotherapy and have been continuously disease-free for at least 5 years.

10. Patient has undergone major surgery, other than diagnostic surgery (i.e., surgery done to obtain a biopsy for diagnosis without removal of an organ), within 4 weeks prior to Day -1 of treatment in this study.

    Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

11. Known history of, or any evidence of active, non-infectious pneumonitis.

12. Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.

13. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

14. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

15. Pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.

16. Patients on micro-dosed progesterone preparations (“mini-pill”) who are unwilling to receive an alternative form of contraception.

17. Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

18. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)

19. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

20. known history of active TB (Bacillus Tuberculosis).

21. Receipt of live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

22. Patients who receive a COVID shot and/or booster within 4 weeks of Cycle 1 Day -1.

23. Known sensitivity to retinoic acid derivatives.

24. Patient is taking any prohibited concurrent medication, including Vitamin A supplements, and CYP3A modulators (inducers and inhibitors) and is unwilling to stop use (washout period of 3 days for this protocol) prior to treatment start and during the trial.

25. History of allogenic stem cell transplant or received a solid organ transplant.

    Note: If history of transplant is ≥ 5 years, subjects may be deemed eligible at the discretion of the treating physician.

    Note: Patients with a history of autologous stem cell transplant performed for lymphoma are eligible.

7. PATIENT REGISTRATION

All patients will be registered with the Indiana University Simon Comprehensive Cancer Center (IUSCCC) Clinical Trials Office (CTO). Regulatory files will be maintained by the IUSCCC CTO. Applicable regulatory documents must be completed and on file prior to registration of any patients. Potential patients will be identified in the Oncology outpatient clinics or by referrals from outside physicians. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria. The original signed IRB approved Informed Consent Document and completed Eligibility Checklist will be forwarded to the CTO designee for eligibility verification and registration in the OnCore® database. Notification will be sent to the principal investigator, treating physician and research nurse when registration is complete to confirm registration and inform them of patient ID number.

8. STUDY DESIGN

This is a Phase II single-center open label trial of the combination of ATRA and pembrolizumab treatment to be conducted at the Indiana University Simon Comprehensive Cancer Center. A total of 24 evaluable patients will be recruited into the study. All the patients will receive 200mg Q3W pembrolizumab treatment plus the supplemental treatment of 150 mg/m^2 ATRA orally for 3 days surrounding each of the first four infusions of pembrolizumab (day -1, day 0, day +1) for a total of 12 days of ATRA treatment.

8.1 Study Drug Description

Trial treatment with Pembrolizumab should be administered on Day 0 of each cycle after all procedures/assessments have been completed as detailed on the *Trial Schedule of Events Chart (Section 10)*. All trial treatments will be administered on an outpatient basis. ATRA will be dispensed in advance for administration on day -1, 0 and 1 with each of the first four cycles of Pembrolizumab. ATRA will be administered twice a day (75mg/m^2 each dose for a total dose of 150mg/m^2), to be taken with food.

Pembrolizumab 200 mg will be administered as 30-minute IV infusion every 3 weeks. Given the variability of infusion pumps from site to site, a window of -10 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -10 min/+10 min). Pembrolizumab may continue until either progression, unacceptable toxicity, or 2 years of treatment has been completed.

The treatment to be used in this trial is outlined below in Table 3. The selected dose of ATRA is based on prior studies of ATRA combined with ipilimumab and pembrolizumab [52, 53].

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 0 of each 3-week cycle	Standard agent
ATRA	150 mg/m^2 per day	Q3W	Oral	Day -1, 0, and 1 of each 3-week cycle (first four cycles)	Experimental agent

8.2 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the Sponsor-Investigator and/or the subject's primary physician.

8.2.1 *Acceptable Concomitant Medications*

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 17.1.4.

8.2.2 *Prohibited Concomitant Medications*

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor-Investigator.
- Coadministration of ATRA with strong CYP3A inhibitors and inducers should be avoided. Withhold ATRA should a strong CYP3A inhibitor be required.
- Coadministration of ATRA with agents that can cause intracranial hypertension should be avoided.
- Concomitant use of ATRA with vitamin A should be avoided.
- Concomitant use of anti-fibrinolytic agents should be avoided.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.
Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

8.3 Rescue Medications & Supportive Care

8.3.1 *Supportive Care Guidelines*

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines

include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 9.2.1 - *Dose Modification Guidelines*.

8.4 Contraception and Reproductive Guidance

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Pembrolizumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 120 days after the last dose of pembrolizumab.

For this trial:

- ***Male subjects will be considered to be of non-reproductive potential if*** they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

- ***Female subjects will be considered of non-reproductive potential if they are either:***
  (1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

  OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

- ***Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner***, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

- ***Acceptable methods of contraception are‡:***

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines,

then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

9. TOXICITIES TO BE MONITORED/DOSAGE MODIFICATIONS

9.1 Dose Selection/Modification and Study Drug Risks

9.1.1 *Dose Modification*

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Principal Investigator. The reason for interruption should be documented in the patient's study record.

The toxicity profile of ATRA and Pembrolizumab may overlap causing difficulty in determining the causative agent. Our investigators have many years of prior experience treating patients with Pembrolizumab and their clinical judgement will be used to assess the toxicity and any potential relationship.

Subjects who discontinue ATRA treatment due to toxicity will be allowed to continue treatment with Pembrolizumab alone if the investigator feels the subject will continue to derive benefit from the treatment.

9.1.2 *Dose Modifications for ATRA*

For management of ATRA related toxicities, please refer to table 3 below. In the case where the grade 3 or 4 toxicity is believed to be related to Pembrolizumab, the dose modification guidelines in table 4 will be followed. If the toxicity appears to be related to a combination of Pembrolizumab and ATRA, ATRA will be held and the guidelines in table 4 will be followed. After the toxicity has resolved, ATRA will either be restarted at the next scheduled time at a reduced dose of 100mg/m^2

or will be discontinued for serious toxicities. The decision to discontinue treatment will be based on what the treating physician feels is in the subjects' best interest. If the grade 3 or 4 toxicity returns, ATRA will be held indefinitely.

The severity of the adverse events will be rated on a scale of Grade 1-5 and reported according to the Data and Safety Monitoring Plan using CTCAE version 5.0. Hematologists at the Indiana University Simon Comprehensive Cancer Center specialize in the treatment of lymphomas and have extensive experience treating patients with immune-based therapies that cause immune-related adverse events. The Principal Investigator will be notified of all adverse events that occur during this trial and will work with the treating oncology team to determine the likelihood of ATRA's contribution to the adverse event.

Table 3 Dose Modification Guidelines for ATRA-Related Adverse Events

Adverse Reaction	**Severity***	**Dosage Modification**
Non-hematologic toxicities	Grade 1 or 2	• Hold for grade 2 until grade 0 or 1 then restart at full dose. If toxicity occurs at Grade 2 again after restarting, hold then restart at dose level -1 • Grade 1: continue with current dose
	≥ Grade 3 or 4	Permanently discontinue
Hematologic toxicities	Grade 1, 2 or 3	• Grade 1 or 2 continue with current dose • Grade 3: hold until grade 2 or 1 • Restart at dose level -1[+]
	≥ Grade 4	Permanently discontinue
Other ATRA related AEs[#]	Grade 1 or 2	• Hold for grade 2 until grade 0 or 1 then restart at full dose. If toxicity occurs at Grade 2 again after restarting, hold then restart at dose level -1 Grade 1: continue with current dose
	≥ Grade 3 or 4	Permanently discontinue

***** Based on Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

[+] If Grade 3 toxicity occurs at dose level -1, permanently discontinue ATRA

[#] An exception is ATRA related headache not optimally managed with supportive care therapies [acetaminophen, non-steroidal anti-inflammatory medication, or Imitrex (sumatriptan)] or that does not resolve within 72 hours of stopping ATRA. A patient's choice to stop all ATRA, with or without a dose reduction, due to headache alone will not be considered a toxicity.

Table 4 Dose Modification Table:

Dose Level	ATRA	Pembrolizumab
1 (Starting Dose)	150 mg/m^2 PO on days -1, 0, and 1 every 3 weeks for the first 4 cycles	200 mg IV on Day 0 every 3 weeks
-1 (Dose adjustment)	100 mg/m^2 PO on days -1, 0, and 1 every 3 weeks for the first 4 cycles	200 mg IV on Day 0 every 3 weeks

9.2 Pembrolizumab

9.2.1 *Dose Modification Guidelines*

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune-related adverse events (irAEs) are of primary concern. An irAE is defined as a clinically significant AE of any organ that is associated with study drug exposure, is of unknown etiology, and is consistent with an immune-related mechanism. If an irAE is suspected, a thorough evaluation should be conducted in an effort to possibly rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes before diagnosing an irAE. Serological, immunological, and histological (biopsy) data should be considered to support the diagnosis of an immune-related toxicity.

Immune-related AEs, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-related AEs can occur after discontinuation of treatment.

Immune-related AEs affecting more than one body system can occur simultaneously. In clinical studies, most immune-mediated ARs were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids, and/or supportive care.

Consultation with the appropriate medical specialist should be considered when investigating a possible irAE. These events can occur at times ranging from after the first dose of treatment to several months after the last dose of treatment. Mild irAEs are usually treated symptomatically and

infrequently require dosing delays or discontinuation. Higher grade and persistent lower grade irAEs typically necessitate withholding or discontinuing treatment, and administration of systemic steroids or other immunosuppressive agents (such as tumor necrosis factor blockers) when systemic steroids are not effective. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of complications because the majority of irAEs are reversible with the use of steroids and other immune suppressants (please reference the clinical protocol for additional information regarding the management of irAEs). Therefore, early recognition and initiation of treatment is critical to reduce complications.

For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Suggested supportive care measures for the management of adverse events related to pembrolizumab, including use of corticosteroids, are also outlined in Section 8.3 - *Rescue Medications & Supportive Care.*

In addition to the immune-related risks noted below, infusion-related reactions are also an important identified risk for pembrolizumab; however, they are not considered immune-mediated.

Table 5 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Adverse Reaction	**Severity***	**Dosage Modification**
Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3	Withhold†

Hepatitis with tumor involvement of the liver‡	and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Pericarditis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
Recurrent toxicities that require Immunosuppression	Grade 3	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

‡ If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA based on recommendations for hepatitis with no liver involvement.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

9.2.2 *Management of Infusion Reactions:*

Pembrolizumab can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving Pembrolizumab. Monitor patient for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Interrupt or

slow the rate of infusion for Grade 1 or Grade 2 infusion-related reactions. For Grade 3 or Grade 4 infusion related reactions, stop infusion and permanently discontinue Pembrolizumab (see table 4).

9.3 Toxicity and Study Discontinuation Criteria

To closely monitor safety, subjects will be recruited into the study using a cohort size of 6. Toxicities will be assessed during the assessment window of 21 days following the first dose of ATRA and Pembrolizumab (Cycle 1 Day 0 to Cycle 2 Day 0). Patients who withdraw from the study prior to completing this assessment window for any reason other than a dose-stopping toxicity will be replaced.

After the first 6 subjects in cohort 1 complete the toxicity monitoring period, the Sponsor-Investigator will review data pertaining to the dose de-escalation decision in collaboration with the DSMC. Available adverse event data and laboratory assessments will be used to determine whether the ATRA dose should be continued at 150 mg/m^2 or whether the ATRA dose should be de-escalated to 100 mg/m^2 in the subsequent six subjects to be enrolled in cohort 2.

Toxicity will be evaluated according to NCI CTCAE Version 5.0. A dose-stopping toxicity will be defined as any of the following events that are considered by the investigator to be at least possibly related to treatment with ATRA and Pembrolizumab:

1. Any ≥ grade 3 non-hematologic toxicity related to ATRA, ≥ grade 4 hematologic toxicity related to ATRA or other grade ATRA related adverse events that lead to treatment discontinuation.

Note: An exception is ATRA related headache not optimally managed with supportive care therapies (acetaminophen or non-steroidal anti-inflammatory medication) or that does not resolve within 72 hours of stopping the VESANOID. A patient's choice to stop all ATRA, with or without a dose reduction, due to headache alone will not be considered a dose-stopping toxicity.

2. Any ≥ grade 3 toxicity related to Pembrolizumab.

The DSMC and Phase I Review Committee may recommend de-escalation or expansion of a cohort based on any clinically significant events or the totality of safety experience.

10. STUDY CALENDAR

Trial Period:	Screening Phase	Treatment Cycles					Post-Treatment			
Treatment Cycle/Title:	Screening	1	2	3	4	5+	EOT [i]	Safety Follow-up 1	Safety Follow-up 2[b]	Survival Follow-up
Scheduling Window (Days):	-28 to -2	Day -1	Day 0 ± 7	Day 0 ±7	Day 0 ± 7	Day 0 ± 7	± 7	30 days (±2 days) post last treatment or prior to starting new treatment	90 days (±7 days) post last treatment	Every 12 weeks (±14 days)[L]
Administrative Procedures										
Informed Consent	x									
Demographics and Medical History	x									
Prior and Concomitant Medication Review	x	x	x	x	x	x	x	x	x	x
ATRA Administration [a]		x	x	x	x					
Pembrolizumab Administration [a]		x	x	x	x	x				
Post-study anticancer therapy status							x	x	x	x
Survival Status								x	x	x
Clinical Procedures/Assessments										
Review Adverse Events		x	x	x	x	x	x	x	x	
Physical Examination	x	x	x	x	x	x		x		
Vital Signs	x	x	x	x	x	x		x		
ECOG Performance Status	x	x	x	x	x	x	x			
Laboratory Procedures/Assessments										
Pregnancy Test – Urine or Serum β-HCG [h]	x	x	x	x	x	x				

Trial Period:	**Screening Phase**	**Treatment Cycles**					**Post-Treatment**			
Treatment Cycle/Title:	Screening	1	2	3	4	5+	EOT[i]	Safety Follow-up 1	Safety Follow-up 2[b]	Survival Follow-up
Scheduling Window (Days):	-28 to -1	Day -1	Day 0 ± 7	Day 0 ±7	Day 0 ± 7	Day 0 ± 7	± 7	30 days (±2 days) post last treatment or prior to starting new treatment	90 days (±7 days) post last treatment	Every 12 weeks (±14 days)[L]
CBC with Differential [g]	x	x	x	x	x	x				
Comprehensive Serum Chemistry Panel [e & g]	x	x	x	x	x	x				
T3, FT4 and TSH [g]	x	x		x		x[f]				
Fasting Triglycerides	x						x			
Fasting Cholesterol	x						x			
Efficacy Measurements										
Tumor Imaging [c]	x					x	x			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood										
Archival or Newly Obtained Tissue Collection [d]	x							x	x	x
Correlative Studies Blood Collection	x		x		x	x[j]		x[j]	x	

Footnotes:

[a] Administered according to schedule outlined in table 2. ATRA drug supply will be dispensed in clinic as follows: Cycle 1 Day -1 for Cycle 1, Cycle 1 Day 0 for Cycle 2, Cycle 2 Day 0 for Cycle 3 and Cycle 3 Day 0 for Cycle 4. Pembrolizumab is administered on Day 0 of each Cycle.

[b] To be completed only for subjects who have not initiated a new therapy. Can be collected at a regularly scheduled clinic visit or via patient contact by telephone.

[c] Tumor imaging generally performed every 12 weeks per standard of care for the clinic and evaluated by Lugano criteria (refer to Section 11.1 *Appendix*). Baseline tumor imaging should be completed within 28 days of starting treatment; however, exceptions may be approved after discussion with the principal investigator. Brain metastases that were radiated prior to starting the trial should be re-imaged at the standard 12-week frequency, or as deemed clinically appropriate, by the treating physician.

[d] **Screening tissue sample is required to confirm eligibility.** Optional additional tissue collection will be obtained from archival or future biopsies if available.

[e] To include lactate dehydrogenase at screening.

[f] To be collected every other cycle per standard of care for clinic.

[g] Screening labs should be performed within 10 days of Cycle 1 Day -1.

[h] Within 72 hours prior to receiving the first dose of study medication, and every cycle when applicable.

[i] To be completed when it is decided that the subject will discontinue study treatment. Tumor imaging is only required at investigator's discretion. This visit can be combined with the first safety follow-up visit if the subject is planning to start a new treatment.

[j] < 60 days after last ATRA treatment.

[k] vital signs will include: blood pressure, pulse ox, resp rate, temperature, weight, and height (screening only).

[L] Survival follow-up will continue until 2 years post last therapy or death, whichever comes first.

10.1 Trial Procedures

10.1.1 *Screening*

10.1.1.1 Within 28 days of Cycle 1 Day -1

- Informed consent
- Study eligibility per inclusion and exclusion criteria
- Medical history including concomitant medications and ECOG performance status
- Vital signs including height, weight, blood pressure, temperature, pulse, respiration rate
- Physical examination
- Complete blood count with differential (CBC)
- Comprehensive serum chemistry panel
- T3, FT4 and TSH
- Serum or urine pregnancy test in women of childbearing age
- Appropriate radiologic imaging for evaluating measurable disease at baseline
- Tissue Sample required at screening. Archival tissue is acceptable. If no archive sample is available, a fresh biopsy will be performed.
- Correlative blood sample collection

10.1.2 *On Treatment*

10.1.2.1 First 4 cycles

- Physical examination including ECOG performance status
- Vital signs including weight, blood pressure, temperature, pulse, respiration rate
- Complete blood counts with differential (CBC)
- Comprehensive serum chemistry panel
- T3, FT4 and TSH (Cycle 1,3,5 and every other cycle only)
- Serum or urine pregnancy test in women of childbearing age

- Concomitant medication use
- Adverse event assessment
- Radiologic imaging to monitor disease status: PET-CT every 12 weeks
- Correlative blood sample collection (Cycle 2, 4 and within 60 days of last ATRA dose)
- ATRA administration (Days -1,0 and Day1) for the first 4 cycles
- Pembrolizumab administration (Day 0)

10.1.2.2 Cycle 5 and beyond

- Physical examination including ECOG performance status
- Vital signs including weight, blood pressure, temperature, pulse, respiration rate
- Complete blood counts with differential (CBC)
- Comprehensive serum chemistry panel
- T3, FT4 and TSH (Cycle 1,3,5 and every other cycle only)
- Serum or urine pregnancy test in women of childbearing age
- Concomitant medication use
- Adverse event assessment
- Radiologic imaging to monitor disease status: PET-CT every 12 weeks
- Pembrolizumab administration (Day 0)

10.1.3 *Safety Follow-up Visit 1*

Subjects discontinued from the treatment phase of the study for any reason will be evaluated 30 days (± 2 days) after the last dose of study drug, or prior to starting new treatment. This visit should include the following:

- Physical examination
- Vital signs including weight, blood pressure, temperature, pulse, respiration rate
- Concomitant medication use
- Adverse Event Assessment
- Post-treatment anticancer therapy status
- Survival status
- Correlative blood sample collection

- Optional Tissue Sample collection

10.1.4 *Safety Follow-up Visit 2*

Subjects discontinued from the treatment phase of the study for any reason will be evaluated again 90 days (± 7 days) after the last dose of study drug, or prior to starting new treatment. This visit should include the following:

- Concomitant medication use
- Adverse Event Assessment
- Post-treatment anticancer therapy status
- Survival status
- Correlative blood sample collection
- Optional Tissue Sample collection

10.1.5 *Long term follow-up Evaluations*

Subjects will be followed every 12 weeks ± 14 days for up to 2 years from start of treatment until recurrence or death. This visit should include the following:

- Concomitant medication use
- Post-treatment anticancer therapy status
- Survival status
- Optional Tissue Sample collection

7.2.4 Tumor Tissue Collection and Correlative Studies Blood Sampling

Plasma will be banked from every patient for cytokine analysis, potential biomarker and other correlative studies. Plasma will also be collected for potential analysis of plasma ATRA levels in the event this could correlate with results from the immunologic analysis. Whenever possible, tumor samples will be cataloged and stored at the Lymphoma Biorepository. Additional correlative studies may include genomic analysis. Refer to the Study Procedure Manual for more details.

11. CRITERIA FOR EVALUATION/REMOVAL FROM STUDY

11.1 Definitions and Criteria for Response Associated with Lugano Criteria

The **Lugano classification** is a lymphoma staging system resulting from recommended changes in 2011 to the Ann Arbor staging with Cotswolds modifications [54-56]. It outlines the classification's response to treatment based on CT as following:

Non-progressive disease

- complete response
    - nodal site reduce ≤1.5 cm in longest transverse diameter (LDI) of a lesion
    - complete disappearance of radiologic evidence of disease
- partial response
    - ≥50% decrease in sum of the product of the perpendicular diameters (PPDs) of up to six representative nodes or extranodal lesions
- stable disease
    - <50% decrease from baseline in PPDs of up to six dominant, measurable nodes and extranodal sites
    - no criteria for progressive disease are met

Progressive disease

1. new or increased adenopathy; an individual node must be abnormal with:
    - (a) longest transverse diameter (LDi) >1.5 cm AND
    - (b) PPD increase by ≥50% from nadir AND
    - (c) longest transverse diameter (LDi) or shortest axis perpendicular to LDi (SDi) increase from nadir; the increase in LDi or SDi from nadir (the smallest recorded measurement) must be >0.5 cm for lesions ≤2 cm and >1.0 cm for lesions >2 cm
2. splenic volume increase:
    - (a) with prior splenomegaly: increase in length by >50% of its prior increase beyond baseline; for example, splenic length increases from 15 cm (2 cm above baseline splenomegaly of 13 cm) to >16 cm (>3 cm above baseline)
    - (b) without prior splenomegaly: length increase by at least 2 cm
    - (c) new or recurrent splenomegaly
3. new or larger non-measured lesions
4. recurrent previously resolved lesions

5. new extranodal lesion >1 cm in any axis (new lesions <1 cm in any axis are included if these are “unequivocally attributable” to lymphoma)
6. a new node >1.5 cm in any axis

The Lugano classification also recommends the Deauville five-point scale for reporting response by FDG PET-CT:

- no uptake or no residual uptake (when used interim)
- slight uptake, but below blood pool (mediastinum)
- uptake above mediastinal, but below or equal to uptake in the liver
- uptake slightly to moderately higher than liver
- markedly increased uptake or any new lesion (on response evaluation)

Non-progressive disease

- complete metabolic response (CMR)
- score of 1, 2 or 3 in nodal or extranodal sites with or without a residual mass
- partial metabolic response (PMR)
- score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size
- stable disease or no metabolic response
- score of 4 or 5 with no obvious change in FDG uptake

Progressive disease

score 4 or 5 in any lesion with an increase in intensity of FDG uptake from baseline (and/or new FDG-avid foci consistent with lymphoma)

11.2 Definitions for Response Evaluation

11.2.1 *First Documentation of Response*

The time between initiation of therapy and first documentation of PR or CR.

11.2.2 *Confirmation of Response*

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

11.2.3 *Duration of Overall Response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

11.2.4 *Duration of Overall Complete Response*

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

11.2.5 *Time to Progression*

A measurement from the start of the treatment until the criteria for disease progression is met (or death occurs), taking as reference the smallest measurements recorded since the treatment started. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 8 weeks).

11.2.6 *Progression Free Survival*

A measurement from the start of the treatment until the criteria for disease progression is met or death occurs, taking as reference the smallest measurements recorded since the treatment started.

Progression free survival will be measured from the date of initial treatment to the earliest date of disease progression, resection of measurable tumor or death for patients who fail; and to the date of disease evaluation for patients who remain at risk for failure.

11.2.7 *Overall Survival*

The overall survival time for each patient is the number of days from the day of first treatment to the earlier of (1) death (from any cause) and (2) the last date of patient contact. If the survival time does not correspond to the patient's death then it is treated as censored.

11.3 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease. All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

11.3.1 *PET-CT and MRI*

PET-CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on PET-CT scan based on the assumption that CT slice thickness is 3mm or less. When PET-CT scans have slice thickness greater than 3 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

11.3.2 *Clinical Examination*

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

11.3.3 *Cytology and Histology*

Cytologic and histologic techniques can be used to differentiate between complete and partial responses in rare cases (e.g. after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

11.3.4 *Endoscopy, Laparoscopy*

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained

or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

11.3.5 *Tumor Markers*

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

11.4 Criteria for Removal from Study

11.4.1 *Subject Withdrawal*

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

11.4.2 *Subject Discontinuation*

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- Confirmed radiographic disease progression (i.e. progressive disease per Lugano Criteria as documented by tumor imaging at any time point). Subjects with disease progression indicated on imaging should discontinue all study treatment but may continue pembrolizumab outside of the study at investigator discretion. Subjects with suspected clinical progression may continue study treatment at investigator discretion until there is radiographic confirmation of disease progression.
- Unacceptable adverse experiences as described in Section 9 (*Toxicities to be Monitored/Dosage Modifications)*
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up (3 attempts, including but not limited to phone calls, email, certified letter, etc. to be made in 9 months, with no more than 1 attempt in a month)

- Administrative reasons

11.4.3 *Discontinuation of Study Therapy after CR*

Discontinuation of treatment may be considered for subjects who have attained a confirmed Complete Response (CR) that have had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

11.4.4 *Discontinuation of Study Therapy after Disease Stability*

Patients who achieve a partial response and prolonged disease stability may stay on Pembrolizumab (200mg Q3 weeks) for up to two years on study. In the absence of significant toxicity, the study drug may be discontinued at the discretion of the treating medical oncologist or Sponsor-Investigator after a prolonged period of disease stability. Subjects who then experience radiographic disease progression may be eligible for retreatment (200mg Q 3 weeks) for up to one additional year.

11.4.5 *Clinical Criteria for Early Trial Termination*

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete.
2. Poor adherence to protocol and regulatory requirements.
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects.
4. Any Grade 5 toxicities

12. DRUG INFORMATION

12.1 All-Trans Retinoic Acid

12.1.1 *Other Names*

Vesanoid®; Tretinoin

12.1.2 *Classification*

Tretinoin is a retinoid. The chemical name is all-trans retinoic acid. The molecular formula is $C_{20}H_{28}O_2$ and the molecular weight is 300.44 g/mol.

12.1.3 *Mode of Action*

Tretinoin induces cytodifferentiation and decreased proliferation of APL cells in culture and in vivo. In APL patients, tretinoin treatment produces an initial maturation of the primitive promyelocytes derived from the leukemic clone, followed by a repopulation of the bone marrow and peripheral blood by normal, polyclonal hematopoietic cells in patients achieving complete remission (CR). The exact mechanism of action of tretinoin in APL is unknown.

12.1.4 *Storage and Stability*

Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to 15°C to 30°C (59°F to 86°F).

Keep bottle tightly closed. Protect from light.

12.1.5 *Metabolism*

Tretinoin induced its own metabolism with plasma concentrations after 1 week of continuous therapy decreased to one-third of their day 1 values. Tretinoin is metabolized by cytochrome P450 enzymes, CYP3A4, 2C8, and 2E and undergoes glucuronidation by UGT2B7. Metabolites include 9-*cis* retinoic acid, 13-*cis* retinoic acid, 4-oxo *trans* retinoic acid, 4-oxo *cis* retinoic acid, and 4-oxo *trans* retinoic acid glucuronide. The metabolites 4-oxo retinoic acid and 4-oxo *trans* retinoic acid glucuronide have one-third of the pharmacological activity of the parent compound.

12.1.6 *Preparation*

ATRA is supplied as 10 mg, two-tone (lengthwise) orange-yellow and reddish-brown capsules with black print “10 mg” available in:

• 100 count bottles with child-resistant closure

Capsules: 10 mg, two-tone (lengthwise) with orange-yellow and reddish-brown, imprinted with “10 mg” in black ink.

12.1.7 *Administration*

Take with food.

12.1.8 *Incompatibilities*

Strong CYP3A Inhibitors

The coadministration of ATRA with ketoconazole, a strong CYP3A4 inhibitor, increased tretinoin plasma concentration, which may increase the risk of adverse reactions. Avoid

coadministration of ATRA with strong CYP3A inhibitors if possible. Monitor subjects taking a strong CYP3A inhibitor with ATRA more frequently for adverse reactions.

Strong CYP3A Inducers

The coadministration of ATRA with strong CYP3A4 inducers may decrease tretinoin plasma concentrations, which may reduce its efficacy. Avoid coadministration with strong CYP3A inducers if possible.

Concomitant Use of Products Known to Cause Intracranial Hypertension

Intracranial hypertension has been reported in patients who received ATRA and concomitant use of other products that can cause intracranial hypertension, such as tetracyclines, may increase the risk. Avoid concomitant use of ATRA with other products agents that can cause intracranial hypertension.

Vitamin A

The concomitant use of vitamin A with ATRA may lead to vitamin A related adverse reactions. Avoid concomitant use of ATRA with vitamin A.

Anti-fibrinolytic Agents

Fatal thrombotic complications have been reported in patients who have received ATRA and concomitant use of anti-fibrinolytic agents may increase the risk. Avoid concomitant use of ATRA with anti-fibrinolytic agents.

12.1.9 *Availability*

ATRA will be supplied through the IUSCCC Investigational Pharmacy. This study will be conducted in compliance with 21 CFR 312.8 (promotion and charging for investigational drugs).

12.1.10 *Side Effects*

The most common adverse reactions (≥30%) are headache, fever, skin/mucous membrane dryness, bone pain, malaise, shivering, upper respiratory tract disorders, dyspnea, hemorrhage, infections, nausea/vomiting, rash, peripheral edema, leukocytosis, pain, gastrointestinal hemorrhage, chest discomfort, abdominal pain

12.1.11 *Nursing Implications*

There are no data on the presence of tretinoin in human milk, the effects on the breastfeed child or the effects on milk production. Because of the potential for serious adverse reactions from ATRA in breastfed infants, advise women not to breastfed during treatment with ATRA and for 1 week after the last dose.

12.2 Pembrolizumab

12.2.1 *Other Names*

KEYTRUDA®

12.2.2 *Classification*

Please refer to the Package Insert for further information.

12.2.3 *Mode of Action*

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.2.4 *Storage and Stability*

The product does not contain a preservative. Store the diluted solution from the Pembrolizumab 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after 96 hours under refrigeration.

Do not freeze.

12.2.5 *Metabolism*

Pembrolizumab is catabolized through nonspecific pathways; metabolism does not contribute to its CL.

12.2.6 *Preparation*

Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

Dilute Pembrolizumab injection (solution) prior to intravenous administration.
Withdraw the required volume from the vial(s) of Pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. **Mix diluted solution by gentle inversion.** Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.

12.2.7 *Administration*

- IV infusion: 200 mg every 3 weeks
- Administer diluted solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

12.2.8 *Availability*

Pembrolizumab will be supplied as Standard of Care therapy via commercial means. This study will be conducted in compliance with 21 CFR 312.8 (promotion and charging for investigational drugs).

12.2.9 *Side Effects*

Most common adverse reactions (reported in ≥20% of patients) were: fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism.

Based on its mechanism of action, Pembrolizumab can cause fetal harm when administered to a pregnant woman. There are no available human data informing the risk of embryo-fetal toxicity. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue (see Data). Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

12.2.10 *Nursing Implications*

There are no data on the presence of pembrolizumab in either animal or human milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Pembrolizumab and for 4 months after the final dose.

13. STATISTICAL ANALYSIS PLAN

The study involves several subtypes of lymphomas: HL, and B-NHL. B-NHL are further subgrouped in two categories: aggressive B-NHL (DLBCL, PMBCL and High-grade B-cell lymphomas) and indolent B-NHL (FL, MZL, MCL). For this trial, we will use a Simon's optimal two-stage design. The null hypothesis is that the true response rate is 0.05, and the alternative hypothesis is that the true overall response rate (ORR) is 0.4 in each subgroup (HL vs B-NHL). Based on a desired ORR of 40%, a type I error (α) of 5% and power of 80%, we determined a total sample size of 24 patients including HL (n=8), aggressive B-NHL (n=8) and indolent B-NHL (n=8). The trial is carried out in two stages for each subgroup. In the first stage of each subgroup, 4 patients will be enrolled followed by an interim analysis. If there are 0 response among these 4 patients, the study will be early stopped for this subgroup. If the observed ORR meets or exceeds the threshold rate, the remaining 4 patients will be enrolled in the second stage for each subgroup. If there are 2 or more responses among these 8 patients, we reject the null hypothesis and claim that the treatment is promising in every corresponding subgroup.

We will next analyze the CRR, adverse events (AEs) per CTCAE v5 guidelines, and other relevant outcomes. We will calculate confidence intervals and p-values to assess the efficacy of the treatment combinations. If relevant, we will conduct subgroup analysis considering factors like patient characteristics, disease stage, or treatment duration. Survival data such as PFS, OS and TTE outcomes will be measured using Kaplan-Meier estimates.

13.1 Safety Analyses

All patients who received any protocol therapy will be employed for safety analyses.
Patient incidence of all treatment-emergent AEs will be tabulated by dose and system organ class and preferred term. Tables of fatal adverse events, serious adverse events, treatment-related AEs, and adverse events leading to withdrawal from investigation product will also be provided. The NCI CTCAE version 5.0 will be used to grade severity of adverse events and laboratory toxicities.

Summary statistics will be provided for total number of subjects treated under each dose, average dose administered, and duration of treatment.

For select laboratory parameters, changes of laboratory values over time (eg, change from baseline summary statistics), grade shifts in laboratory values from baseline to worst on-study value, and grade 3 or higher laboratory toxicities will be summarized. The ECG measurements from this study will be performed as per standard of care for routine safety monitoring.

13.2 Efficacy analysis

The efficacy analysis population consists of all subjects who receive at least one cycle treatment (3-day doses of study treatment).

T-cell subsets (CD4, CD8, Treg) and MDSC subsets (CD14+, CD15+) will be analyzed by flow cytometry at each of the blood draws time points and compared to whole blood cells, total lymphocytes and monocytes populations between time points and compared between pretreatment, on treatment and post treatment. T cell activation will be assessed by CD107 and IFNg production in response to PMA and ionomycin and compared between pretreatment, on treatment and post treatment. MDSC functional assays will assess the ability of MDSC's to suppress stimulated T cell proliferation as a percent of positive control and will be compared between time points and compared between pretreatment, on treatment and post treatment.

Linear mixed effects models will be used to assess the frequency of MDSC subsets over times. Contrast statements will be used to estimate changes in the frequency of MDSC subsets and its suppressive function from baseline after treatment at different time points. For PFS endpoint, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. The change in frequency of T-cell subsets, the expression of activation markers, and the CTL response will be evaluated using paired t-test. Correlations between the frequencies of MDSCs and T cell subsets or expression of activation markers will be evaluated using Pearson or Spearman Correlation Coefficients at a specified timepoints. Alternatively, Intraclass correlation coefficients will be used to assess the potential correlations among those measurements over time.

13.3 Interim Analysis

To closely monitor safety, subjects will be recruited into the study using a cohort size of 6. Toxicities will be assessed during the assessment window of 21 days following the first dose of ATRA and Pembrolizumab (Cycle 1 Day 0 to Cycle 2 Day 0). Patients who withdraw from the study prior to completing this assessment window for any reason other than a dose-stopping toxicity will be replaced.

After the first 6 subjects in cohort 1 complete the toxicity monitoring period, the Sponsor-Investigator will review data pertaining to the dose de-escalation decision. Available adverse event data and laboratory assessments will be used to determine whether the ATRA dose should be continued at 150 mg/m$_2$ or whether the ATRA

dose should be de-escalated to 100 mg/m2 in the subsequent six subjects to be enrolled in cohort 2.

14. PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board as required by the board, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

15. DATA AND SAFETY MONITORING PLAN

This study will be conducted in accordance with the IU Simon Comprehensive Cancer Center Institutional DSMP for **High Risk Trials**.

Investigators will conduct continuous review of data and subject safety. **Monthly review meetings** for high risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). Meeting summaries should include review of data and subject safety by including for each dose level: the number of subjects, significant toxicities as described in the protocol, dose adjustments and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

15.1 Data and Safety Monitoring Committee

The IUSCCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study semi-annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.
Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.
For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and

attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.
At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

15.2 DSMC DLT Review

The study principal investigator and study team are responsible for conducting continuous review of data and subject safety at their weekly meetings for first six subjects; and monthly meetings after interim analysis. Prior to making dose expansion/de-escalation decisions, the PI and the study team will officially review all toxicity events for each subject for confirming treatment-related DLT after the first 6 subjects are enrolled. Formal Dose Decision meetings will be held to discuss decisions with the Phase I Program Leader and DSMC Chair, or appropriate designees. The study statistician will assist the determination of DLT and the interpretation of the dosing for next subjects. Once a decision has been reached by the investigator, the official decision and toxicity data will be submitted to the DSMC via email (IUSCC-DLT-Review-L@list.iupui.edu) and copy the DSMC Chair and Compliance Officer. Treating additional subjects may not proceed until official DSMC correspondence confirms approval of dosing decisions for the next stage.

15.3 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

15.4 Study Auditing and Monitoring

All trials conducted at the IUSCCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

15.5 Data Management/ Oncore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than 15 business days from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

15.6 Study Accrual Oversight

Accrual data will be entered into the IU Simon Comprehensive Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

15.7 Oncore Safety Reporting

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

15.8 Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

16. DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize electronic Case Report Form completion in the OnCore® database. A calendar of events and required forms are available in OnCore®. The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCCC Clinical Trials Office and supported by the Indiana Clinical and Translational Sciences Institute (CTSI). OnCore® properly used is compliant with Title 21 CFR Part 11. The system is supported and managed by Advarra, Inc. who have developed a security program that is compliant with HIPAA and HITECH requirements. Applications and databases are housed off-site at Rackspace, Inc. which is SSAE16 SOC2, ISO 27001, PCI, and HITRUST certified.

OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IUSCCC Data Safety Monitoring Committee.

17. REPORTING ADVERSE EVENTS

17.1 Definitions of Adverse Events

17.1.1 *Adverse Event (AE)*

An **adverse event** is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 5.0 (Appendix I).

17.1.2 *Suspected Adverse Reaction (SAR)*

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event.

Examples of types of evidence that would suggest a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

17.1.3 *Adverse Reaction (AR)*

An adverse reaction is any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

17.1.4 *Serious Adverse Event (SAE)*

An adverse event or suspected adverse reaction is considered "serious" if it results in any of the following outcomes:

- Results in death
- Is life-threatening. Life-threatening is defined as an adverse event or suspected adverse reaction that places the subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization > 24 hours or prolongation of existing hospitalization

  NOTE: Hospitalizations that are not considered SAEs are:

  - Hospitalization planned prior to first study intervention
  - Hospitalization for elective treatment of a pre-existing condition unrelated to the study intervention
  - Hospitalization lasting ≤ 24 hours
- Pregnancy

  Pregnancy of a patient or of the female partner of a male patient during the study or within 30 days after the last dose of study drug should be reported via an SAE report. Should pregnancy occur in a female participant during the treatment period, study drug should be discontinued and the Principal Investigator notified immediately. Should a pregnancy occur in a female companion of a male participant during the treatment period, the male participant can continue treatment and the Principal Investigator notified immediately. Any such pregnancy is to be followed until final outcome.

17.1.5 *Unexpected Adverse Event*

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or

elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

This definition relies entirely on the adverse events or suspected adverse reactions listed in the investigator brochure for the particular drug under investigation (or elsewhere in the general investigational plan if an investigator brochure is not required or available) as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is *unexpected*. This means that events not listed for the particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is "unexpected" for IND safety reporting purposes. In the clinical trial setting, there has been some confusion with the term "expected" as it has been used to mean "anticipated" for the disease being treated or population being studied rather than "listed in the investigator brochure." For example, some adverse events can be anticipated to occur as a result of a disease or in an older population (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not "expected" because they are not listed in the investigator brochure (i.e., the test drug is not suspected or known to cause them).

Adverse events listed in the investigator brochure as occurring with members of the same class of drugs, or as anticipated from the pharmacological properties of the drug, would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the investigator brochure as a class effect, a case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes until it is included in the investigator brochure as occurring with the drug under investigation.

17.1.6 *Adverse Events of Special Interest (AESI)*

Selected non-serious and serious adverse events are also known as Adverse Events of Special Interest and must be reported be within 24 hours to the Sponsor-Investigator and within 5 business days to the DSMC, and in accordance with IRB reporting requirements (within 5 business days or during continuing review).

For the time period beginning when the consent form is signed until treatment allocation, any AESI, or follow up to an AESI, that occurs to any subject must be reported within 24 hours to the investigator if it causes the subject to be excluded from the trial, or is the result of a protocol specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any AESI, or follow up to an AESI, must be reported within 24 hours to the Sponsor-Investigator, within 5 business days to the DSMC, and in accordance with IRB reporting requirements (within 5 business days or during continuing review).

Events of clinical interest for this trial include:

1. An elevated AST or ALT lab value that is ≥ to 3X the upper limit of normal and an elevated total bilirubin lab value that is ≥ to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that < 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

17.1.7 *Determining Attribution to the Investigational Agent(s)*

Attribution: An assessment of the relationship between the AE and the medical intervention. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE is clearly NOT related
	Unlikely	The AE is doubtfully related
Related to investigational agent/intervention	Possible	The AE may be related
	Probable	The AE is likely related
	Definite	The AE is clearly related

17.2 Adverse Event (AE) Reporting Requirements:

Adverse events (AEs) will be recorded from the time of first study drug administration and for at least 90 days after treatment discontinuation, regardless of whether or not the event(s)

are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

17.2.1 *Reporting to the FDA:*

Per CFR 312.32 (c), the investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any adverse experience. There are two types of reports to the FDA: 7-day and 15-day reports.

17.2.1.1 15-Day IND Reports

The investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any:

- **suspected adverse reaction** that is ***both***
- **serious *and***
- **unexpected**

Each written notification shall be made as soon as possible, and no later than **15 calendar** days after the investigator-sponsor's initial receipt of the information.

17.2.1.2 7-Day Reports

The investigator-sponsor must notify FDA and all participating investigators in a written IND safety report of any adverse experience:

- **fatal or life-threatening experience** that is ***both***
- **associated with use of the drug *and***
- **unexpected**

The FDA will be notified as soon as possible but no later than **7 calendar** days after initial receipt of the information.

17.2.1.3 Report Content

Each written notification may be submitted on FDA Form 3500A or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". For purposes of this protocol, the **MedWatch Report Form (FDA 3500A mandatory reporting), along with FDA Form 1571, and a cover letter** submitted

to the appropriate FDA division, will serve as the written IND safety report. Follow-up information to a safety report should be submitted as soon as the relevant information is available.

17.2.1.4 Submit

- MedWatch Report Form (FDA 3500A)
- FDA Form 1571
- Cover Letter

The IUSCCC Protocol Development Coordinator should be contacted to assist with all FDA submissions and will be provided with a copy of all events that are reported to the FDA. All IND submissions will be maintained in a master file in the Clinical Trials Office of the IU Simon Comprehensive Cancer Center.

17.2.2 *Reporting to the IRB*

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- are unexpected;
- are related or possibly related to participation in the research; and
- suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

Prompt reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

17.2.3 *Reporting to the IUSCCC DSMC*

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms, AdEERS reports, MedWatch, and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is in addition to any other regulatory bodies to be notified (i.e., IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly.

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19. APPENDICES

19.1 Appendix I. NCI CTCAE Version 5.0

Due to the size of the latest version of the Common Toxicity Criteria, copies of this appendix are not included with this protocol document.

An electronic copy is available on the CTEP web site,

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

19.2 Appendix II. Performance Scales/Scores

ECOG or Zubrod		Karnofsky		Lansky	
Score	Activity	Score	Activity	Score	Activity
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

19.3 Appendix III. Subject Dosing Instructions and Diary

PATIENT DOSING INSTRUCTIONS AND DIARY

Subject ID: _____ Cycle: _____

Date Medication Dispensed _____/_____/_____

Dosing Instructions

ATRA

- Take your ATRA dose orally once daily and should not be cut, chewed, or crushed for dissolving in liquid.
- You should store your ATRA at room temperature.
- You should take your ATRA with a glass (about 8oz) of water.
- You should take your ATRA with food.
- Take ATRA at about the same time each morning (for example, 8 am). The time you take your dose can vary by 1 hour. If you forget to take your dose in the morning, you should not take it less than 12 hours before your next dose.
- If you completely miss a dose, do not replace that dose or take a second dose the next day.

Dosing Diary

Subject ID: _____ Cycle: _____

Use the table below to record each dose of ATRA you take. Record the date and the time of each dose in the space provided. Return your diary to the study team at the end of each cycle.

Day	ATRA	Dose	ATRA	Dose
Example Day 1 ***01/01/2001***	8:00 am			8:00 pm
Day -1: ___/___/____	_____:_____			_____:_____
Day 0: ___/___/____	_____:_____			_____:_____
Day 1: ___/___/____	_____:_____			_____:_____

Return Section:

Subject Signature: _____ Date:_____

MD/CRN/CRC Signature:_____ Date:_____