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STUDY TITLE: An Open-Label, Phase I/II study of ME-401 and R-CHOP in Newly Diagnosed Diffuse Large B-Cell Lymphoma

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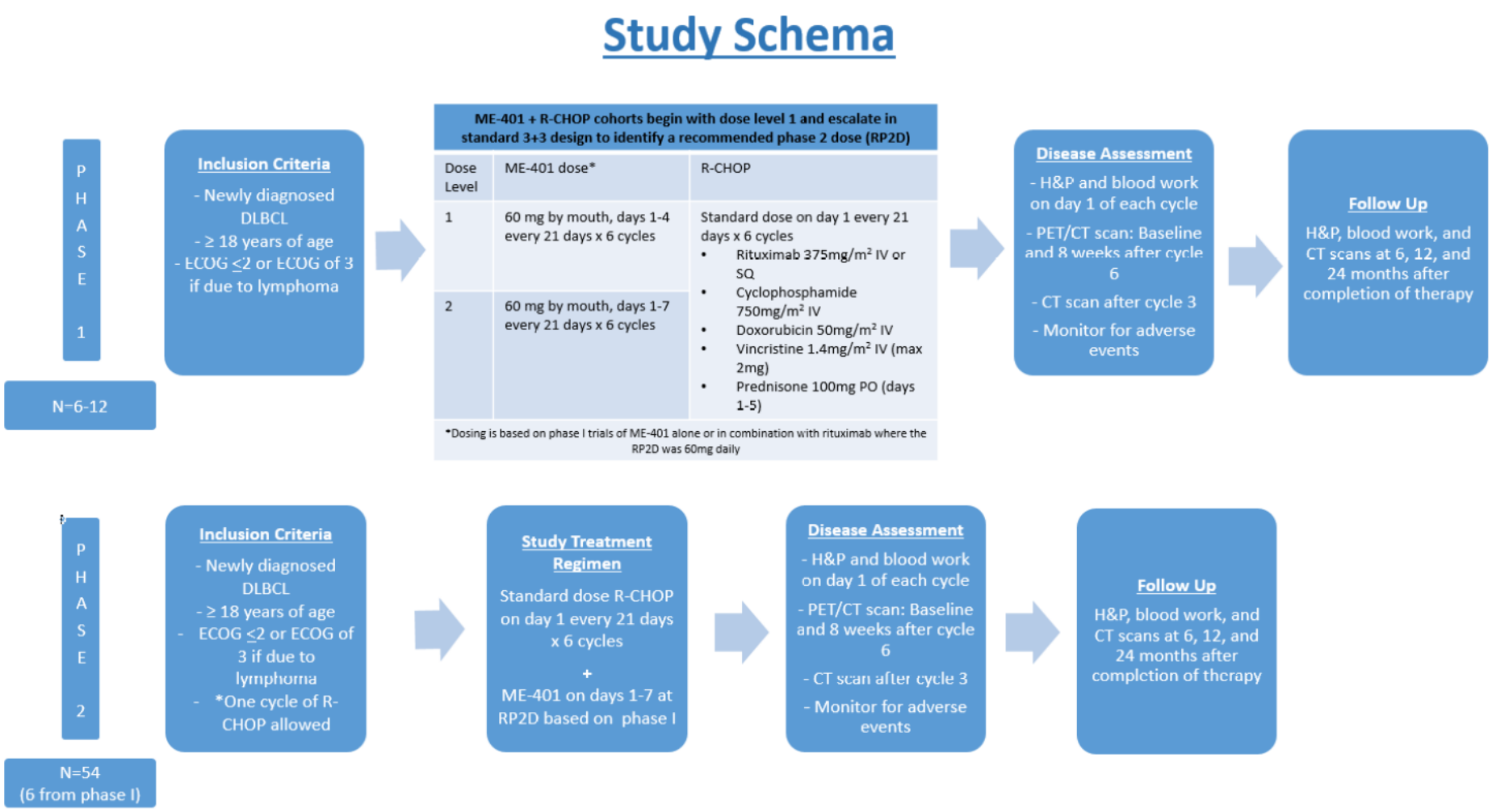
SUPPORT/FUNDING:	MEI Pharma
SUPPLIED AGENT*:*	ME-401, supplied by MEI Pharma
IND #:	[redacted]
OTHER AGENT*(S):*	R-CHOP: Rituximab, Doxorubicin,Vincristine, Cyclophosphamide, Prednisone

SUMMARY OF CHANGES

Protocol Date	Section	Change
08/20/2021	Cover Page	Cleveland Clinic Sub-I, Study Coordinator section updated, removed PI signature line as this is contained in a separate document
08/20/2021	6.0, 6.1.2, 9.7	Adding biosimilar use of Rituximab is permitted for this study per treating investigator discretion
08/20/2021	3.4.2; 11.1.2, 11.2	Allowing virtual visits for long-term follow up visits. Patients that start new treatment in follow up enter survival follow up.
08/20/2021	10.1.5	Change Cleveland Clinic Biorepository shipping ATTN to Genevieve Crane, MD
08/20/2021	3.2	Changed to "The phase 1 portion will enroll 6-12 participants" from 4-12
08/20/2021	10.1.3	Updated tissue requirements per the lab's preferences.
08/20/2021	13.1	Changed Forte to Advarra to be consistent with company name change.
04/22/2022	4.1.2	Changed study Inclusion Criteria to any tumor measuring at least 1.5 cm
04/22/2022	8.4	Removed definition of AESI; reference IB for latest definitions
04/22/2022	10.1.4	Additional correlative blood samples

STUDY SCHEMA



PROTOCOL SUMMARY

Protocol Number/Title	An Open-Label, Phase I/II study of ME-401 and R-CHOP in Newly Diagnosed Diffuse Large B-Cell Lymphoma
Study Phase	Phase I/II
Brief Background/Rationale	Rituximab-CHOP cures a high percentage of patients with diffuse large B-cell lymphoma (DLBCL)[1-3], however up to 40% of patients will relapse. After relapse treatment options are limited to intensive chemotherapy, transplant, or chimeric antigen receptor T therapy, all of which are potentially toxic and some patients are not eligible for such therapies[4-9]. Improving the cure rate in the upfront setting in order to limit the need for such therapies is a desirable goal. The activation of phosphatidylinositol 3-kinase inhibitors (PI3Kis) ultimately leads to cell survival, proliferation, and immune regulation. ME-401 is a highly selective inhibitor of the δ isoform of PI3K, and shows promising clinical activity alone and in combination with rituximab in the treatment of indolent lymphomas. The most common grade 3 or higher adverse events (AEs) seen in phase I trials are rash, diarrhea, neutropenia, transaminitis, colitis, and stomatitis [10-12]. The incidence and severity of these AEs is significantly lower than that seen with other PI3Kis. Based on preclinical rationale and clinical data of ME-401 in lymphoid malignancies, the relapse rate with R-CHOP, and shortcomings of second line therapies we propose a phase I/II study to evaluate ME-401 plus R-CHOP in newly diagnosed DLBCL.
Primary Objectives	**Phase I** <u>Primary Objective</u> To determine the recommend phase 2 dose (RP2D) of ME-401 in combination with R-CHOP for patients with newly diagnosed DLBCL. <u>Primary Endpoint</u> Dose limiting toxicity (DLT) as defined by non-hematologic clinically significant grade 3 or 4 treatment-related AEs or hematologic grade 3 or 4 treatment related AEs that are clinically significant (as defined in section 6.3) during the first cycle, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

	Phase II Primary Objective To estimate the clinical activity of ME-401 in combination with R-CHOP in patients with newly diagnosed DLBCL, as measured by 1 year PFS rate. Primary Endpoint Time from study treatment initiation to progression free survival, as defined as the time from first dose to documented disease progression, or death from any cause, whichever occurs first.
Secondary Objectives	**Phase I** Secondary Objective To describe tolerability of ME-401 in combination with R-CHOP for patients with newly diagnosed DLBCL. Secondary Endpoint Treatment related AEs, Treatment delays (# days treatment is delayed) **Phase II** Secondary Objectives • To estimate the overall response rates (complete and partial remission), duration of response (DOR), time to progression (TTP), and overall survival (OS) with ME-401 plus R-CHOP. • To characterize treatment-related AEs in patients treated with ME-401 plus R-CHOP. Secondary Endpoints • Response (overall, complete, and partial) as defined by Lugano criteria • Duration of Response defined as the time from documented response (CR or PR) to the time of confirmed disease progression or death due to any cause, whichever occurs first • Overall Survival defined as the time from first dose of study treatment to death from any cause • Time to Treatment Failure defined as the time from study entry to any treatment failure. • Treatment related AEs Please see section 12.1 for full definitions
Correlative Objective(s)	**Phase II** Correlative Objectives

	To explore the association between molecular subtyping (via next generation sequencing and RNA sequencing) and response to therapy (complete response or partial response). Correlative Endpoints Molecular subtype as defined by Schmitz et al. and Chapuy et al. [13,14]
Sample Size	Phase 1 N=6-12 patients Phase 2 N=54 total (6 from phase I)
Disease Conditions	Diffuse Large B-Cell Lymphoma
Interventions	Phase I • Standard dose R-CHOP PLUS ME-401 on days days 1-4 (dose level 1) and days 1-7 (dose level 2) of a 21 day cycle x 6 cycles • ME-401 will be dose escalated in 3+3 standard design with 2 dose levels • Pretreatment PET/CT, Interim CT scans after 3 cycles, Post treatment PET/CT 8 weeks after treatment completion. Phase 2 • Standard dose R-CHOP PLUS ME-401 at RP2D on a 21 day cycle x 6 cycles • Pretreatment PET/CT, Interim CT scans after 3 cycles, Post treatment PET/CT 8 weeks after treatment completion.

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1.0 INTRODUCTION

1.1 Background

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma. Rituximab-CHOP cures a high percentage of DLBCL,[1-3] but up to 40% relapse. The 1 year progression free survival (PFS) can range 55-85% depending on the patient population[1,2,6,15]. The standard of care for relapsed/refractory (r/r) DLBCL is second line chemotherapy followed by autologous stem cell transplantation (ASCT) [8]. However, a subset of transplant eligible patients does not qualify for the procedure due to lack of response to or disease progression during second line therapy. In some studies, only 50% of patients could proceed to transplant [5]. Additionally, the relapse rate after transplant is nearly 40-50% as seen in the long term analysis of the PRIMA trial [9]. Chimeric antigen receptor (CAR) T therapy was recently approved for r/r DLBCL after two or more lines of systemic therapy. Objective response rate are high at 72% and CR of 51% [4]. However, not all patients are eligible for CAR T therapy and we are awaiting long-term data. Patients who are ineligible for or relapse after ASCT or CAR T therapy have no long-term effective treatment options and this remains an unmet medical need with no approved or standard therapy. Management of patients with primary refractory disease is another challenge as the response rate to salvage chemotherapy in this population is low at <30% [8,16]. Improving the response and relapse rate to upfront treatment is much needed.

Inhibitors of phosphatidylinositol 3 kinases (PI3K) have significant activity in lymphoma. Few trials have explored their use in aggressive lymphomas. We propose a phase I study of ME-401 and R CHOP to treat newly diagnosed DLBCL. Clinical data show the efficiency of PI3K inhibitors in relapsed/refractory (r/r) CLL and follicular lymphoma [17-19]. Preclinical data suggest PI3K inhibitors are effective at producing cell death in DLBCL [20,21]. Single agent PI3K inhibitors have been studied in r/r DLBCL with variable results [22-24].

1.1.1 PI3K pathway and importance in lymphoid malignancy

Phosphatidylinositol 3 kinases (PI3K) are heterodimeric ezymes that mediate signals from cell surface receptors to regulate the protein synthesis, gene transcription, cell growth and motility [25,26]. There are 4 classes of PI3K enzymes with class I isoforms α, -β, -γ and -δ being the most widely implicated in neoplasia [25,27]. PI3Ks are activated by tyrosine kinases or g protein coupled receptors. The pathway results in phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol (3,4,5) – triphosphate (PIP3) that leads to activation of AKT, mTOR, and nuclear factor kappa B (NF-kB) pathways. This in turn leads to cell survival, proliferation, and immune regulation [25,28]. The PI3K pathway is deregulated in many malignancies and can result in oncogenic transformation [25,27]. In particular, the PI3Kδ isoform is important in hematologic malignancies as it is highly expressed in lymphocytes and lymphoid tissue [27].

Another trigger for PI3K/AKT pathway activation is the loss of tumor suppression protein PTEN, which suppresses this pathway and its downstream targets [15].

In contrast to PI3K, PTEN helps to generate PIP2 by hydrolyzes of 3-phosphate and its absence leads to increased levels of PIP3 [11]. PTEN is often mutated or silenced in malignancy [28,29]. In DBLCL, aberrant PI3K signaling and PTEN deletions or mutations are often observed [21,25,30].

Recently, Schmidz et al. and Chapuy et al. used advanced molecular testing (via next generation sequencing and RNA sequencing) to sub classify DLBCL [13,14]. Chapuy et al. found five robust DLBCL subsets that predicted outcome independent of the clinical International Prognostic Index [13]. The subsets also suggested possible treatment strategies. For example, those with cluster 4 subtype often have alternations in PI3K and/or PTEN pathways. Thus, we hypothesize that these patients may have a better response to ME-401.

1.1.2 Studies to support the use of PI3K inhibitors

There are three FDA approved PI3K inhibitors (idelalisib, duvelisib, and copanlisib) to treat lymphoid malignancies including relapsed/refractory follicular B-cell non- Hodgkins lymphoma, SLL, and CLL. PI3K inhibitors have not been approved in the front line setting or for DLBCL.

Idelalisib is a potent, oral, selective small molecule inhibitor of PI3Kδ and is approved for indolent non-Hodgkin's lymphoma (iNHL) and CLL treatment [19,31]. In a phase II study of 125 patients with iNHL refractory to Rituximab or an alkylating agent, idelalisib 150 mg twice daily showed an overall response rate of 57%. The safety profile was acceptable with the most common grade 3 or higher adverse events being neutropenia (27% of patients), elevated aminotransferase levels (13%), diarrhea (13%), and pneumonia (7%)[19]. Idelalsib was studied in combination with Rituximab, bendamustine, or both in a phase I study if 79 patients with r/r iNHL. Overall response rates were 75%, 88%, and 79% respectively. The most common grade 3 or higher adverse events were neutropenia (41%), pneumonia (19%), transaminase elevation (16%), diarrhea/colitis (15%) and rash (9%) [32]. Phase III studies were pursued to investigate these combinations however terminated due to increased death rates and adverse events in the treatment arms.

Duvelisib (IPI-145), a highly selective and potent oral inhibitor of δ and γ PI3K isoforms, has activity in both B and T cell lymphoma. In a phase I study of duvelisib in advanced hematologic malignancies, 31 patients underwent the dose escalation phase receiving 8-100mg twice daily with a maximum tolerated dose (MTD) of 75mg BID. In the expansion phase, 31 patients with relapsed or refractory iNHL received duvelisib 25mg or 75mg with an ORR of 58% and 6 CRs [18]. Grade 3 or higher adverse events occurred in 84% of patients and included neutropenia (32%), alanine transaminase increase (20%), aspartate transaminase increase (15%), anemia and thrombocytopenia (each 14%), diarrhea (11%), and pneumonia (10%). Ultimately, duvelisib 25mg BID was selected for further clinical development [33,34]. A phase II study evaluating duvelisib as monotherapy for iNHL has closed and results have been submitted but not yet reported (NCT01882803). A phase Ib study of duvelisib in combination with rituximab or

rituximab plus bendamustine for r/r hematologic malignancies was completed but results have not been report (NCT01871675). Preclinical models have been used to study duvelisib in combination with other agents and have shown duvelisib with steroids is more effective than single agent treatment [35].

Copanlisib is a pan-class I PI3K inhibitor with greatest affinity for the α and δ isoforms. In a phase II study, 142 patients with relapsed or refractory iNHL received intravenous copanlisib. The ORR was 59% and 12% of patients achieved a CR. Grade 3 or higher toxicities included transient hyperglycemia (41%), transient hypertension (24%), neutropenia (24%), and lung infection (15%) [36].

ME-401 (Zandelisib), a highly selective inhibitor or PI3Kδ that has not yet been FDA approved but shows promising clinical activity and a phase II study is ongoing to support accelerated approval (NCT03768505). It has been studied in a phase 1b dose escalation trial for patients with r/r follicular lymphoma or CLL/SLL. ME-401 was given daily on days 1-28 of a 28-day cycle. Of the 31 patients enrolled, 21 had follicular lymphoma with an ORR of 75% and 9 patients had CLL/SLL with an ORR of 100%. Five patients discontinued ME-401 due to adverse events. The most common grade 3 or higher adverse events were rash (26%), diarrhea (16%), neutropenia (10%), elevated transaminases (6%), colitis (6%), and stomatitis (3%) [10]. No DLTs were reported and based on PK data, the lowest dose, 60mg, was chosen as the recommend dose moving forward [10].

The phase 1b expanded to include two additional groups of patients who received combination Rituximab and ME-401 on either a continuous (CS) or intermittent (IS) dosing schedule. The intermittent dosing schedule of ME-401 (daily for 28 days for 2 cycles then changed to days 1-7 every 28 days with subsequent cycles) was associated with a lower rate of grade 3 AEs and while maintaining a similar response rate. All delayed grade 3 AEs of interest on IS occurred within 1-2 cycles of switching from CS to IS, suggesting that these might have represented a delayed effect of daily dosing [12]. An update of the follicular lymphoma cohort in the phase Ib trial was presented at ASCO 2019 and the Internal Conference on Malignant Lymphoma 2019. A total of 48 patients with FL were treated. Twenty discontinued therapy: 9 for progression of disease, 4 for AEs, 4 withdrew consent, and 3 for ASCT. Delayed (after cycle 2) grade 3 immune related AEs (irAEs) were seen in 9/30 (30%) patients on CS with the most common irAEs being diarrhea/colitis and rash. Six patients with AEs were able to resume ME-401 on IS without recurrence of AEs after a drug holiday and steroids. Response rates remained high with objective responses seen in 34/43 (79%) patients. The study also showed that progression of disease on IS could be salvaged by reverting to CS. Of 38 patients switched to IS, 33 (87%) remain on therapy (median: 14.5 months), 26 on IS and who switched back to CS due to POD [37-39].

1.1.3 Use of PI3K in DLBCL

While PI3K inhibitors have not be approved for use in patients with DLBCL, several studies have/are evaluating their role in the treatment of DLBCL. In a phase I

study evaluating the use of idelasib in r/r hematologic malignancies, 9 patients with DLBCL were enrolled and no response to single agent treatment was observed [22]. A phase II study evaluating copanlisib for treatment of r/r DLBCL has been completed but full results have not been published. Preliminary data shows ORR of 25% (10 of 40) and CR, PR, and stable disease in 5, 5, and 12 patients respectively. This study showed that response rates were higher in ABC subtype versus GCB subtype (ORR 37.5% versus 13.6%)[23]. Buparlisib is a pan-class I PI3K inhibitor that was evaluated in a phase II study for the treatment of r/r non-Hodgkin lymphoma. Of the 72 patients enrolled, 26 patients had DLBCL. The overall response rate for those with DLBCL was 11.5% [24].

1.2 ME-401

1.2.1 Preclinical Data

ME-401 (formerly referred to as PWT-143) is a novel, selective PI3Kδ inhibitor with an IC50 of 0.6 nM in cellular assays, and a molecular weight of 576.68. ME-401 has exhibited significant activity against several human cell lines and primary patient derived tumor cell samples of various hematological malignancies in preclinical studies. The activity was similar to or in many cases greater than the results obtained with either idelalisib or ibrutinib [40].

Preclinical safety studies demonstrated that the dog was the more sensitive species with a no observed adverse effect level (NOAEL) of 3 mg/kg/day in 28-day repeat dose studies. The combined-sex mean Cmax and AUC0-24hr values for ME-401 on Day 28 at this NOAEL were 175 ng/mL and 1740 hr*ng/mL, respectively. The toxicity observed at the highest dose (10 mg/kg/day) in the dog safety studies included increases in transaminases, QTc prolongation, and depletion of lymphocytes. QTc prolongation occurred on Day 28, but not at the Day 1 post-dose interval, which most likely reflects drug accumulation and higher plasma ME-401 concentrations. The combined-sex mean Cmax and AUC0-24hr values for ME-401 on Day 1 at 10 mg/kg were 498 ng/ml and 6,370 hr*ng/ml, respectively, while on Day 28 they were 1,830 ng/ml and 35,400 hr*ng/ml, respectively [40,41].

1.2.2 Clinical Data

Refer to section 1.1.3

1.2.3 Clinical Pharmacokinetics

A single dose study of ME-401 across a range of dose levels from 10 mg to 150 mg was conducted in the United Kingdom in normal healthy volunteers. The primary goals were to:1) establish bioavailability and preliminary pharmacokinetics (PK); 2) assess the impact of ME-401 on the standard biomarker assay for PI3Kδ inhibition, specifically inhibition of basophil activation (BAT) assessed by flow-cytometry for CD63 expression; and 3) assess clinical safety. No SAEs, severe AEs, AEs leading to death, or AEs leading to ME-401 withdrawal were noted in the study [41,42].

The PK results can be summarized as follows: both Cmax and AUC (0–last)

demonstrated linear increases over the dose range of 10 mg to 150 mg. The mean T1/2 for ME-401 was 28-29 hours from 30-150 mg, and appeared dose-independent. Plasma levels at later time points after the 10 mg dose were below the limit of quantitation, which may be responsible for the seemingly lower half-life at that dose level [41,42].
To assess the on-target pharmacodynamic effect of ME-401, inhibition of PI3K signaling in peripheral blood basophils was measured via a pharmacodynamic assay (basophil activation test MEI Pharma Inc. Protocol: ME-401-002 Amendment 8 [BAT]), which measured basophil activation via CD63 upregulation following ex-vivo stimulation with an anti-FCεR1 monoclonal antibody [41,42].

The BAT results for ME-401 clearly demonstrate the biologic potency of ME-401. From the fitted Emax model, the concentrations of ME-401 estimated to give 50% and 90% BAT inhibition (i.e., EC50 and EC90) of the maximum effect (Emax 91.6%) were 0.6 ng/ml and 5.2 ng/mL, respectively [41,42].

Based on the BAT inhibition results, the starting dose level (60 mg) should demonstrate clinical activity. The 60 mg dose has been identified as the Recommended Phase 2 Dose (RP2D) on the basis of a high response rate, acceptable toxicity, and plasma concentrations well above the EC90 of the BAT in healthy volunteers. After complete evaluation of the PK of the 60, 120, and 180 mg doses, and estimation of the PK parameters expected from a 45 mg dose, suggest sub-optimal plasma concentrations (i.e., C_{min} concentration of <5ng/ml). Given this and the addition of chemotherapy in this study, the starting dose will be 60 mg but a shorten time course (days 1-4) with goal dose of 60 mg on days 1-7 of a 21 day cycle [41,42].

1.3 R-CHOP Chemotherapy

Cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) have been the mainstay of treatment for patients with advanced stage DLBCL since its development in 1970s. A milestone phase III trial found that complex regimens adding other chemotherapy agents to CHOP, (i.e. m-BACOD; ProMACE- CytaBOM, and MACOP-B) did not demonstrate any significant benefit in overall survival (OS), disease-free survival (DFS), or remission rate over CHOP [43]. The development of rituximab – a monoclonal antibody targeting to CD20 led to combining this agent with chemotherapy (R-CHOP) [1,2].

1.3.1 Preclinical Data

Rituximab is a genetically engineered, chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant pre-B and mature B cells. The antibody is an IgG1 κ immunoglobulin containing murine light-and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular mass of 145 kD. Rituximab has a binding affinity for the CD20 antigen of ~8.0 nM. There are a number of preclinical studies which suggest that rituximab exerts its therapeutic effect by some combination of antibody-dependent cell-mediated cytotoxicity (ADCC), complement and/or direct cell lysis [44]. Determining the exact mechanism of rituximab is an active area of research.

1.3.2 Clinical Data

Several seminal studies demonstrated that the overall survival of patients with DLBCL is improved when rituximab is added to CHOP [1,2,45]. Standard dosing or R-CHOP is 375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide, 50 mg/m^2 doxorubicin, and 1.4 mg/m2 (capped at 2 mg) vincristine all given intravenously on days 1 and 100 mg prednisone given orally on days 1–5 every 21 days for 6 cycles.

1.3.3 Clinical Pharmacokinetics

Rituximab likely acts synergistically with chemotherapy, in which case having therapeutic levels of rituximab throughout all cycles of therapy should be beneficial. Pharmacokinetic studies of rituximab used in R-CHOP-14 schedule showed that rituximab levels rise slowly and a plateau is attained only after 5 cycles [46]. Based on this observation, the German High Grade NHL Study Group (DSHNHL) evaluated the benefit of intensifying the rituximab dosing. This concept was combined with dose intensification of chemotherapy (R-CHOP-14). In the early phase of this DENSER-CHOP trial, increased infectious events occurred, but with increased supportive care in terms of prophylactic antimicrobials and PEG- filgrastim the regimen was felt to be safe and effective [47]. Nonetheless, this approach has not been generally adopted. This likely reflects the absence of data on its benefit, as well as the need for extensive antimicrobial prophylaxis and growth factor support, as well as observed and potential excess toxicity of the 14 day schedule.

1.5 Rationale

As discussed above, newly diagnosed DLBCL is treated with R-CHOP but up to 40% relapse [1-3]. After relapse treatment options are limited to intensive chemotherapy, transplant, or chimeric antigen receptor T therapy, all of which are potentially toxic and some patients are not eligible for such therapies[4-9]. Improving the cure rate in the upfront setting in order to limit the need for such therapies is a desirable goal.

The activation of phosphatidylinositol 3-kinase inhibitors (PI3Kis) ultimately leads to cell survival, proliferation, and immune regulation. ME-401 is a highly selective inhibitor of the δ isoform of PI3K, and shows promising clinical activity alone and in combination with rituximab in the treatment of indolent lymphomas. The most common grade 3 or higher adverse events (AEs) seen in phase I trials are rash, diarrhea, neutropenia, transaminitis, colitis, and stomatitis [10-12]. The incidence and severity of these AEs is significantly lower than that seen with other PI3Kis. As discussed above, this is particularly true with intermittent dosing [37-39].

Based on preclinical rationale and clinical data of ME-401 in lymphoid malignancies, the relapse rate with R-CHOP, and shortcomings of second line therapies we propose a phase I/II study to evaluate ME-401 plus R-CHOP in newly diagnosed DLBCL. Dosing and schedule are derived from phase I and PK studies. The RP2D for single agent is 60 mg [10-12,40] and PK data suggest sub-optimal dosing even at the 45mg dose [40]. Therefore we will start with 60 mg dose but given for a shorter duration (days 1-4 of 21 day cycle) with the goal of reaching full intermittent dosing of days 1-7 of 21 day cycle. ME-401 on days 1-7

as intermittent dosing (days 1-7 of 28 day cycles) has shown to decrease toxicity and retain efficacy compared to continuous dosing [11,12,40].

1.6 Background and rationale of correlative studies

Currently, DLBCL is grouped into two groups by cell of origin – activated B cell (ABC) and germinal center B cell [48]. It has been shown that those with ABC subtype have worse outcomes. Recently, Schmidz et al. and Chapuy et al. used advanced molecular testing (via next generation sequencing and RNA sequencing) to further sub classify DLBCL [13,14]. Chapuy et al. found five robust DLBCL subsets that predicted outcome independent of the clinical International Prognostic Index [13]. The subsets also suggested possible treatment strategies. For example, those with cluster 4 subtype often have alternations in PI3K and/or PTEN pathways. Thus, we hypothesize that these patients may have a better response to ME-401.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Phase I

2.1.1 Primary Objective

- To determine the recommended phase 2 dose (RP2D) of ME-401 in combination with R-CHOP for participants with newly diagnosed DLBCL.

2.1.2 Primary Endpoint

- Dose limiting toxicity (DLT) as defined by significant grade 3 or 4 treatment-related AEs that are not amendable to optimal supportive care or hematologic grade 3 or 4 treatment related AEs that are clinically significant (as defined in section 6.3) during the first cycle, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

2.1.3 Secondary Objective

- To describe tolerability of ME-401 in combination with R-CHOP for participants with newly diagnosed DLBCL.

2.1.4 Secondary Endpoints

- Treatment related AEs, Treatment delays (#days treatment is delayed)

2.2 Phase II

2.2.1 Primary Objective

- To estimate the clinical activity of ME-401 in combination with R-CHOP in participants with newly diagnosed DLBCL, as measured by 1 year PFS rate

2.2.2 Primary Endpoint

- Time from study treatment initiation to progression free survival, as defined as the time from first dose to documented disease progression, or death from any cause, whichever occurs first

2.2.3 Secondary Objective

- To estimate the response rates (complete and partial remission), duration of response (DOR), time to progression (TTP), and overall survival (OS) with ME-401 plus R-CHOP.
- To characterize treatment-related AEs in participants treated with ME-401 plus R-CHOP.

2.2.4 Secondary Endpoints

- Response (overall, complete, and partial) as defined by Lugano criteria.
- Duration of Response defined as the time from documented response (CR or PR) to the time of confirmed disease progression or death due to any cause, whichever occurs first
- Overall Survival defined as the time from first dose of study treatment to death from any cause
- Time to Treatment Failure defined as the time from study entry to any treatment failure.
- Treatment related AEs

Please see section 12.1 for full definitions

2.3 Correlatives

2.3.1 Correlative Objective

- To explore if there is an association between molecular subtyping (via next generation sequencing and RNA sequencing) of tumor tissue and treatment response.

2.3.2 Correlative Endpoint

- Molecular subtype as defined by Schmitz et al. and Chapuy et al. [13,14]. See section 10.0.

3.0 Study Design

The proposed study is a multi-institution, open-label, phase I/II study designed to evaluate the safety and efficacy of R-CHOP + ME-401 for participants newly diagnosed DLBCL.

3.1 Study design including dose escalation

Phase I

- ME-401 60 mg will be given on days 1-4 (dose level 1) OR days 1-7 (dose level 2) of a 21 day cycle with standard dose R-CHOP x 6 cycles.
- Dose escalation will be performed in a standard 3+3 design. See study schema on page 7 and section 6.0 for treatment plan, including dose escalation.

Phase II

- ME-401 at RP2D will be given with standard dose R-CHOP every 21 days x 6 cycles.

3.2 Number of Participants

Phase I

- The phase 1 portion will enroll 6-12 participants

Phase II

- The phase II portion will enroll an additional 47 participants, for a total of 54 participants in the phase II portion of the study (6 from the phase I portion). Assuming 49 of the 54 are not lost to follow up by 1 year, the study will have 80% power to detect an improvement in 1-year PFS from 65% to 80% using a one sample log-rank test using a one-sided type 1 error of 5%.

3.3 Replacement of Participants

- If a participant is withdrawn from the Phase I dose escalation cohort for any reason other than toxicity prior to completing the first 21 days of treatment, a replacement participant will be enrolled and will be assigned to the same dose level. No subjects will be replaced after receiving the first 21 days of treatment. Participants removed from study due to toxicity during phase I cycle 1 will be considered as a DLT regardless of whether the toxicity fulfills the DLT criteria.

- For the phase II study, any participant who receives a dose of the study drug will be included in the progression-free survival analysis. No subjects will be replaced after receiving the first dose of study treatment.

3.4 Expected Duration of Treatment and Participation

3.4.1 Duration of Treatment

In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles of 21 days in length or until one of the following criteria applies:

- Disease progression,
- Illness that prevents further administration of treatment,
- The investigator considers it, for safety reasons, to be in the best interest of the participants,
- Any toxicity or other issue that causes delay of study drug administration by more that 4 weeks,
- General or specific changes in the participants' condition rend the patient unacceptable for further treatment in the judgment of the investigator,
- Participant decision to withdraw from the treatment (partial consent) or from the study (full consent),
- Pregnancy during the course of the study for a child-bearing participant,
- Death, or
- Sponsor temporarily suspects or prematurely discontinues the study

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

3.4.2 Duration of Follow Up

- Participants will be followed for a total of 24 months after completion of therapy or until death, whichever comes first. If the patient is unable to follow up in person, virtual visits may be used to capture applicable procedures during long-term follow up only. If a virtual visit is completed, every attempt should be made to complete the required assessments though if they are not completed it will not be considered a protocol deviation. For patients that progress or start a new treatment, they will be followed via phone calls rather than clinic visits if desired.
- Participants will be followed for toxicity for 30 days after the final dose of study drug, and 90 days for evaluation and capture of pre-specified AESIs after their final dose of MEI-401, or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause with a cut off of 24 months after completion of therapy. Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

4.0 PARTICIPANT SELECTION

Each of the criteria in the sections that follow must be met in order for a participant to be considered eligible for this study. Use the eligibility criteria to confirm a participants' eligibility.

Participant's Name

_____

Medical Record #

_____

Research Nurse / Study Coordinator Signature:

_____

Date _____

Treating Physician [Print]

_____

Treating Physician Signature:

_____

Date _____

4.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for enrollment:

___ 4.1.1 Participants must have histologically confirmed diffuse large B-cell lymphoma (DLBCL) and high grade B cell lymphoma NOS (not otherwise specified). Participants with previously diagnosed indolent lymphoma (follicular and marginal zone lymphoma but not small lymphocytic lymphoma) who have transformed to DLBCL are eligible only if they have not previously been treated for indolent lymphoma.

- If patients received single rituximab (maximum 4-8 doses with no maintenance) for their low grade lymphoma ≥12 months prior to starting study drug are eligible to participate

___ 4.1.2 Participants must have radiographically measurable disease. At least one bi-dimensionally measurable lesion ≥ 1.5 cm in its longest diameter must be identified.

a. Previously irradiated lesions should not be counted as target lesion.
b. Lesions that are intended to be used to collect tissue samples for biopsy should not be counted as target lesions.
c. Bone lesions should not be counted as target lesions

___ 4.1.3 Patients participating in the phase II part are allowed to receive brief (<15 days) treatment with glucocorticoids (max dose of prednisone 40 mg) and/or 1 cycle of chemotherapy such as R-CHOP [or some component(s) thereof] for the diagnosis of B-cell lymphoma provided they had all necessary staging tests performed prior to R- CHOP or steroids including CT and/or PET/CT scans, and bone marrow biopsy. Treatment must occur within 30 days prior to enrollment.

Previous treatment ___YES _____ No
If Yes, Please List Treatment agents and dates:
_____

___ 4.1.4 No prior therapy with PI3K inhibitors or Bruton tyrosine kinase (BTK) inhibitors

___ 4.1.5 Age ≥18 years. Dosing or adverse event data are limited on the use of ME-401 in patients <18 years of age, therefore children are excluded from this study.

___ 4.1.6 ECOG Performance status ≤ 2. Performance Status of 3 will be accepted if impairment is caused by DLBCL complications and improvement is expected once therapy is initiated. [See Appendix A]

___ 4.1.7 Participants must have adequate hematologic, hepatic, and renal function as defined below:
_____ 4.1.7.1 Hemoglobin ≥ 9.0g/dl unless the anemia is clearly due to DLBCL.

If there is BM involvement, this criteria can be waived after discussion with the Sponsor Investigator (per investigators discretion).

Hemoglobin: _____
Date of Test: _____

_____ 4.1.7.2 Absolute neutrophil count ≥ 1,000/mcL, unless the neutropenia is clearly due to DLBCL. If there is BM involvement, this criteria can be waived after discussion with the Sponsor Investigator (per investigator discretion)

Absolute neutrophil count: _____
Date of Test: _____

_____ 4.1.7.3 Platelet count ≥ 75,000/mcl unless thrombocytopenia is clearly due to DLBCL. If there is BM involvement, this criteria can be waived after discussion with the Sponsor Investigator (per investigator discretion)

Platelet count: _____
Date of Test: _____

. _____ 4.1.7.4 Bilirubin ≤ 2.0 x ULN unless considered secondary to Gilbert's syndrome, in which case ≤ 3 x ULN

Total bilirubin: _____
Date of Test: _____

_____ 4.1.7.5 AST (SGOT) ≤ 2.0 x institutional upper limit of normal

AST (SGOT): _____
Date of Test: _____

_____ 4.1.7.6 ALT (SGPT) ≤ 2.0 x institutional upper limit of normal

ALT (SGPT): _____
Date of Test: _____

_____ 4.1.7.7 Creatinine clearance ≥45 mL/min calculated by Cockcroft-Gault or 24 hour collection

Creatinine Clearance: _____
Date of Test: _____

___ 4.1.8 Adequate cardiac function left ventricular ejection fraction (LVEF) ≥ 50% as assessed by echocardiogram or MUGA (Multi Gated Acquisition Scan).

___ 4.1.9 QT-interval corrected according to Fridericia's formula (QTcF) ≤ 450 milliseconds (ms); participants with QTc < 480 msec may be enrolled provided the QTc prolongation is due to a right bundle branch block and stable .

___ 4.1.10 Negative pregnancy test in women of child-bearing age. The effects of ME-401 on the developing human fetus are unknown. For this reason and because chemotherapeutic agents used in this study are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (double barrier method of birth control or abstinence) 2 weeks

prior to initiation of treatment, for the duration of study participation and for 3 months after completing treatment. Should a woman become pregnant or suspect that she is pregnant while she or her partner is participating in this study, she should inform the treating physician immediately. Men must agree to refrain from sperm donation for at least 90 days after the last dose of ME-401.

___ 4.1.11 Participants must have the ability to understand and the willingness to sign a written informed consent document.

___ 4.1.12 International Prognostic Index must be documented:

ECOG performance status ≥2 _____ (1 point)

Age ≥60 years _____ (1 point)

≥2 extranodal sites _____ (1 point)

LDH > upper limit of normal _____ (1 point)

Ann Arbor Stage III or IV _____ (1 point)

Is there evidence of transformation from indolent lymphoma?__yes_ no

4.2 Exclusion Criteria

The presence of any of the following will exclude a participant from study enrollment.

___ 4.2.1 Participants receiving any other investigational agents.

___ 4.2.2 Known CNS involvement by lymphoma. Participants at high risk for secondary CNS involvement but without neurologic symptoms suspected to be due to lymphoma are allowed to be enrolled and receive prophylactic intrathecal chemotherapy including but not limited to methotrexate, cytarabine and glucocorticoids. Participants who are enrolled and subsequently identified to have pathologic confirmation of CNS involvement by lymphoma may be continued on study at the discretion of the principal investigator.

___ 4.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to R-CHOP.

___ 4.2.4 Participants with ongoing uncontrolled illness including, but not limited to ongoing significantly active infections requiring intravenous antibiotics, hypertension, angina, arrhythmias, pulmonary disease, or autoimmune dysfunction.

___ 4.2.6 Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia.

___ 4.2.7 Ongoing drug-induced pneumonitis.

___ 4.2.8 History of clinically significant gastrointestinal (GI) conditions, particularly:

- Known GI condition that would interfere with swallowing or the oral absorption or tolerance of study drug
- Pre-existing malabsorption syndrome or other clinical situation that would affect oral absorption

___ 4.2.9 Active congestive heart failure (New York Heart Association [NYHA] Class ≥2), symptomatic ischemia, or conduction abnormalities uncontrolled by conventional intervention or myocardial infarction within six months prior to enrollment.

___ 4.2.10 Participants who have tested positive for hepatitis B surface antigen and/or hepatitis B core antibody PLUS have detectable viral load on hepatitis B polymerase chain reaction (PCR) assay (participants with a negative PCR assay are permitted with appropriate anti-viral prophylaxis)

___ 4.2.11 Positive hepatitis C virus antibody (HCV Ab) participants with positive hepatitis C antibody are eligible if they are negative for hepatitis C virus by PCR

___ 4.2.12 HIV-positive participants on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ME-401.

___ 4.2.13 Pregnant or breastfeeding women are excluded from this study because there are no studies assessing the reproductive and developmental toxicity or excretion into breast milk of ME-401. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with ME-401, breastfeeding should be discontinued if the mother is treated with ME-401. These potential risks may also apply to other drugs used in this study.

___ 4.2.14 Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin, or low-risk prostate cancer after curative therapy.

___ 4.2.15 Participants who have had major surgical procedures or significant traumatic injury within 28 days prior to study treatment.

Date of Last Major Surgery: _____

Scheduled Day 1 of Protocol Treatment: _____

___ 4.2.16 Psychiatric illness/social situations that would interfere with study compliance

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION

All participants who have been consented are to be registered in the OnCore™ Database. For those participants who are consented, but not enrolled, the reason for exclusion must be recorded.

All participants will be registered through Cleveland Clinic and will be provided a study number by contacting the study coordinator (contact information on page 2).

6.0 TREATMENT PLAN

Treatment Regimen					
Agent	**Premedication**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Rituximab (give first)	Acetaminophen (650 mg) PO and diphenhydramine (50 mg) PO or IV, 30 -60 minutes prior to each infusion[1].	375 mg/m^2	IV/SQ[2]	Day 1	21 days
Cyclophosphamide	NA	750 mg/m^2	IV	Day 1	
Doxorubicin	NA	50 mg/m^2	IV	Day 1	
Vincristine	-NA-	1.4 mg/m^2 (max 2 mg)	IV	Day 1	
Prednisone	-NA-	100mg	PO	Days 1-5	
Pegfilgastim4[,5]	-NA-	6mg	SC	Day 2	
ME-401	-NA-	60 mg	PO	Days 1-7 (or 1-4 for dose level 1)	
PJP prophylaxis (pick ONE)[6]					
TMP-SMX	-NA-	160mg/800 mg (double strength)	PO	Three days weekly (M,W,F)	
Pentamidine	-NA-	300 mg	aerosolized	Every 4 weeks	
VZV prophylaxis					
Acyclovir[7]	-NA-	400 mg	PO	Twice daily	

1. Hydroxyzine may be substituted in participants intolerant of diphenhydramine
2. First dose of rituximab will be given IV and subsequent doses can be either IV or SQ based on institutional guidelines. Rituximab infusion as per institutional standard. Rituximab biosimilars are allowed per institutional protocol.
3. See ME-401 dosing Study Schema and Section 6.1.1.
4. Administration of growth factors as per institutional standards. Filgrastim 300 or 480 mcg IV/SC daily x 5-10 days (beginning on day 2) per institutional standard may be substituted if pegfilgrastim is unavailable. Biosimilars are allowed per institutional protocol.
5. ONPRO™ (On Body Injection) is acceptable mode of administration of pegfilgrastim on day 1. Biosimilars are allowed per institutional protocol.

6. PJP prophylaxis will continue for 2-6 months after discontinuation of ME-401
7. Acyclovir will be given from 6 months after completion of cycle 6

6.1 Treatment Administration

- Treatment Regimen is noted above.
- Treatment may be administered either inpatient or outpatient at the discretion of treating physician or institutional standard.
- Appropriate dose modifications for ME-401 and R-CHOP are described in Section 7.0.
- Intra-participant dose escalation is allowed for participants treated with ME-401 at 60 mg days 1-4 ONLY after ME-401 60 mg days 1-7 has been given to 6 participants and is determined to be the RP2D. This will need discussion with and approval by study PI.
- Antiemetic premedication as per institutional standard
- Reported adverse events and potential risks of ME-401 and R-CHOP are described in Section 8.0.
- No investigational or commercial agents or therapies other than those described above may be administered with the intent to treat the participant's DLBCL.
- In the case of patients who received 1 treatment of R-CHOP [or some component(s) thereof] prior to study enrollment, will begin the study with Cycle 2 study treatment (R-CHOP round 2). Patients should receive at least 6 full rounds of R-CHOP (between SOC and study treatment combined) unless otherwise specified.
    - In the case of patients who received 1 cycle of R-CHOP [or some component(s) there of] prior to study enrollment, the screening window extends to $\leq$60 days.

6.1.1 ME-401

- Participants will receive ME-401 60 mg by mouth on days 1-4 or days 1-7 of each 21 day cycle. On day 1 MEI will be administered 30 minutes – 90 minutes prior to R-CHOP chemo
- ME-401 is to be taken orally once a day with a glass of water on an empty stomach at least 1 hour prior to food or 2 hours after food at the same time each day. Participants unable to take ME-401 on an empty stomach are allowed to take ME-401 with a light, non-fatty snack. If possible, separate taking ME-401 capsules from that of concomitant medications that have a known effect on p-glycoprotein, Breast Cancer Resistance Protein (BCRP) transporter, and CYP2C8 substrates, as well as concomitant oral medications that have known interactions with drugs that inhibit P-gp, BCRP, and CYP3A4.
- Dose escalation with 2 doses only. Dose level 1 is 60mg daily on days 1-4 of each 21-day cycle. Dose level 2 is 60 mg daily on days 1-7 of each 21 day cycle. See Section 6.2 for dose escalation.

6.1.2 R-CHOP

- Use actual weight when calculating surface area. The start of treatment doses for all drugs can be used for all cycles unless the BSA changes by > 5% in which case doses must be re-calculated. Acetaminophen (650 to 1000 mg) PO and diphenhydramine (25 to 50 mg) PO or IV are to be administered 30 to 60 minutes prior to starting each infusion of rituximab. Hydroxyzine may be substituted in participants intolerant of diphenhydramine..

  a. Prednisone 100 mg orally day 1 through 5 of subsequent cycles.
  b. Rituximab 375 mg/m^2 IV/SQ on day 1 of each cycle (every 21 days). Rituximab biosimilars are allowed as per institutional protocol.
  c. Cyclophosphamide 750 mg/m^2 IV Day 1 of each cycle (every 21 days)
  d. Doxorubicin 50 mg/m^2 IV Day 1 of each cycle (every 21 days)
  e. Vincristine 1.4 mg/m^2 IV (Maximum dose = 2.0 mg) Day 1 of each cycle (every 21 days)
  f. Administration of growth factors as per institutional standards. Pegfilgrastim 6 mg SC day 2 (every 21 days) as per institutional standards. Filgrastim 300 or 480 mcg IV/SC daily days x 5-10 starting day 2 may be substituted if pegfilgrastim is not available. ONPRO™ is also an acceptable method of administration on day 1. Biosimilars may be used per institutional protocols.

6.1.3 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) labs including basic chemistry panel (BMP), LDH, uric acid, calcium and phosphorous will be checked on cycle 1 day 1 prior to starting treatment. Patients at risk for TLS will be managed as per institutional guidelines. Allopurinol 300 mg PO daily for 5-7 days can be used for TLS treatment and/or prophylaxis as per treating investigator's discretion. Other interventions like intravenous fluids can be used at per institutional guidelines. TLS labs should be repeated as per institutional guidelines in high risk patients.

6.1.4 PJP Prophylaxis

Participants should receive either TMP-SMX or Pentamidine for PJP prophylaxis starting from initiation of chemotherapy to 2-6 months after last dose of ME-401. Dapsone is a prohibited drug to use for prophylaxis.

6.1.3.1 Trimethoprim/sulfamethoxazole (TMP-SMX)

Given as 160 mg/800 mg (double strength) orally once daily three days per week.

6.1.3.1 Pentamidine

Given as 300 mg aerosolized once every 4 weeks.

6.1.5 VZV Prophylaxis

Participants should receive acyclovir 400mg BID for VZV prophylaxis from initiation of chemotherapy (cycle 1, day 1) to 6 months after last dose of ME-401.

6.1.4.1 Acyclovir

Given as 400 mg orally twice daily.

6.2 Phase I Dose Escalation

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined in section 6.3.

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
1 out of 3	Enter 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). If 2 or more DLT observed in 3 or 6 participants at dose level 1, MTD is exceeded, and the study will be discontinued (see section 14.0). If this occurs in dose level 2, three (3) additional participants will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose or at highest dose level if able to escalated to dose level 2	This is generally the recommended maximally tolerated dose. At least 6 participants should be entered at the recommended phase 2 dose.

6.3 Definition of Dose-Limiting Toxicity

Management and dose modifications are outlined in Section 7.

Dose limiting toxicity will be defined as any of the following AEs that occur during cycle 1 (first 21 days) for all dose levels with severity graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0:

Non-hematologic DLTs

- Grade ≥3, non-hematologic toxicity. This excludes fatigue or anorexia lasting < 7 days.

Hematologic DLTs

- Grade 4 neutropenia lasting ≥ 7 days despite G-CSF
- Grade 4 thrombocytopenia
- Grade ≥3 thrombocytopenia with ≥ Grade 2 bleeding

In addition, the following will be considered DLTs:

- Any toxicity that requires a participant to come off study will be considered a DLT
- *For patients with any toxicity that requires ME-401 to be held for the 2nd consecutive cycle, the DLT window will extend to 42 days. If ME-401 cannot be restarted by the 3rd consecutive cycle, that will be considered a DLT.

6.4 General Concomitant Medications and Supportive Care Guidelines

The following medications/therapies are prohibited during the study:

- Other investigation agents; and
- Cancer therapies not mentioned in this protocol.

The following medications/therapies should be used with caution:

- Drugs that affect the CYP2C8 (See Appendix D)
- Drugs that affect the QT/QTc interval (See Appendix E)
- Orally administered drugs known to interact with drugs that inhibit CYP3A4 (https://drug-interactions.medicine.iu.edu/Main-Table.aspx)
- Orally administered drugs known to interact with drugs that inhibit the intestinal transporters BCRP and P-gp

6.5 Criteria for Removal from Study (See Section 3.4.1)

6.6 Duration of Follow Up (see Section 3.4.2)

7.0 DOSE DELAYS/DOSE MODIFICATIONS

All scheduled visits will have a ±3-day window due to unanticipated or unavoidable scheduling conflicts. For hematologic or other toxicity in the opinion of the treating physician attributable to ME-401 but not described elsewhere in the protocol, treatment with ME-401 may be held, after discussion with the study PI.

7.1 ME-401

There will be no dose reduction based on toxicity, only dose delays or discontinuation as needed below.

7.1.1 Hematologic Toxicity

- ANC ≥ 1000, and platelets ≥ 75,000 on day 1 of new cycle: No change in dose
- ANC ≤1000, and platelets < 75,000 on day 1 of new cycle: Hold until resolves. Resume at same dose level.
- Grade 4 thrombocytopenia or Grade 4 neutropenia with associated symptoms (e.g. fever) anytime during a cycle. If noted on days 1-7 then hold ME-401 for the completion of current cycle. If toxicity

resolves to grade ≤1, ME-401 can be resumed with the subsequent cycle. If toxicity does not resolve then continue to hold ME-401 until toxicity is grade ≤1 or less.

- If there is a persistent or recurrent hematologic toxicity and as per the Investigator's assessment this is deemed intolerable and not related to the disease, discontinue ME-401.

7.1.2 Non-Hematologic Toxicity

***Note, for Phase I, grade 3 and 4 events are considered a DLT.**

ME-401 Dose Modifications and Toxicity Management			
Toxicity	Grade	Management of ME-401	Management of Toxicity
Diarrhea/Colitis	2	Hold ME-401 unless diarrhea confirmed to be due to an infectious agent. If ME-401 is held, once diarrhea resolves to Grade ≤ 1, resume ME-401 at start of next cycle.	The cause of diarrhea should be investigated to rule out an infectious cause, including clostridium difficile. Hold ME-401 and start loperamide or similar anti-diarrheal agent. If no improvement occurs within 48 hours, start prednisolone 0.5-1 mg/kg IV or oral budesonide 9 mg daily. Based on data from the Phase 1b study, participants with diarrhea that was preceded by rash in the prior 1-2 weeks often experienced more prolonged and severe diarrhea. Thus, if diarrhea is preceded by rash in the prior weeks, start prednisolone 0.5-1 mg/kg IV or oral budesonide 9 mg daily.
Diarrhea/Colitis	3	Hold ME-401 until AE resolves to Grade ≤ 1, then, if clinically indicated, resume ME-401 at start of next cycle. For recurrence of Grade 3 diarrhea/colitis, discontinue study drug permanently.	The cause of diarrhea should be investigated to rule out an infectious cause, including clostridium difficile. A colonoscopy is appropriate to document evidence of colitis Participants should be hydrated as clinically indicated and administered (methyl) prednisolone 1-2 mg/kg/day IV or equivalent oral systemic steroids. • If no improvement occurs within

			2–3 days, the corticosteroid dose should be increased to 2 mg/kg/day IV or equivalent oral systemic steroids. Once improved to Grade ≤ 1, start tapering the corticosteroid as clinically indicated.
Diarrhea/Colitis	4	Permanently discontinue ME-401.	Same as grade 3 management.
Cutaneous Reactions and Mucositis	2	Hold ME-401 unless rash ascertained to be unrelated to study drug. If ME-401 is held, once AE resolves to Grade ≤ 1, resume ME-401 at start of next cycle.	Monitor participants with increased frequency. Per Investigator's discretion, anti-histamines, topical steroids, and systemic steroids may be given.
Cutaneous Reactions and Mucositis	≥3	Hold ME-401 until AE resolves to Grade ≤ 1, then, if clinically indicated, resume ME-401 at start of next cycle. For recurrence of Grade 3, permanently discontinue ME-401.	Monitor participants s as clinically indicated until resolution. Oral antihistamines and systemic corticosteroids such as prednisone 0.5 – 1 mg/kg/day (or equivalent dose of methylprednisolone) should be given until rash resolves to Grade ≤ 1.
Cutaneous Reactions and Mucositis	Any	Permanently discontinue ME-401 for life-threatening toxicity, Stevens-Johnson syndrome of any grade, and toxic epidermal necrolysis syndrome (TENS) of any grade.	Treat per institutional standard of care.
Hepatotoxicity	2	For ALT/AST > 3-5 x ULN but < 5 x ULN, maintain ME-401 dose.	Monitor weekly with until resolved to Grade ≤ 1 x ULN.
Hepatotoxicity	3	For ALT/AST > 5-20 x ULN, hold ME-401 and monitor twice least weekly until resolved to Grade ≤ 1 x ULN. Then, resume ME-401 at start of next cycle For recurrence of Grade 3,	Treat per institutional standard of care, which may include a course of corticosteroids in clinically indicated.

		permanently discontinue ME-401.	
Hepatotoxicity	4	For ALT/AST > 20 x ULN, permanently discontinue ME-401.	Treat per institutional standard of care, which may include a course of corticosteroids in clinically indicated.
Non-infectious pneumonitis (NIP)	2	Hold ME-401 until AE resolves to Grade ≤ 1. Resume ME-401 at start of next cycle.	Treat per institutional standard of care.
Non-infectious pneumonitis (NIP)	≥3	Permanently discontinue ME-401.	Treat per institutional standard of care, including systemic corticosteroids.
Other, not listed above	2	Holding ME-401 is not required.	Treat per institutional standard of care.
	3	For an AE related to ME-401, hold ME-401 until AE resolves to Grade ≤ 1. However, for an AE not related to ME-401, this will be upon the discretion of the treating physician. Resume ME-401 at start of next cycle. For recurrence of Grade 3, discontinue permanently ME-401.	Treat per institutional standard of care.
	4	Permanently discontinue ME-401.	Treat per institutional standard of care.

Participants who interrupt dosing for ≥ 8 weeks will have ME-401 permanently discontinued.

7.2 R-CHOP

7.2.1 Hematologic Toxicity

On the day of starting each cycle, hematologic (absolute neutrophil count, hemoglobin and platelet) parameters must have resolved to baseline or grade 1. If these criteria are not met, therapy will be held by 1 week increments for a maximum of 4 weeks. If treatment cannot be given during that time frame the

participant will be removed from study.

- ANC $\geq$ 1000, and platelets $\geq$ 75,000 on day 1 of new cycle: No change in dose
- ANC $\leq$ 1000, and platelets < 75,000 on day 1 of new cycle: Hold until resolves. Resume at same dose level.

7.2.2 Non-Hematologic Toxicity

Grade 2-4 non-hematologic toxicity (except fatigue or anorexia lasting < 7 days or Grade 3 nausea and/or vomiting that persists for < 2 days following appropriate supportive care or non-clinically significant grade 3 electrolyte abnormalities that have been corrected) that is treatment-related must return to a grade 1 or better prior to continuing treatment. If these criteria are not met, therapy will be held for a maximum of 4 weeks. If treatment cannot be given during that time frame the participants will be removed from study.

For toxicities deemed to be related to R-CHOP, dose reductions will be given as indicated below. In the case of recurrence of the specific grade 3-4 non-hematologic toxicity, the participant will be removed from study. In the case of recurrence of grade 2 non-hematologic toxicity, continuation on the study will be at the discretion of the principal investigator.

7.2.2.1 Neuropathy

. Given the well-documented and relatively high incidence of vincristine-induced peripheral neuropathy, dose modification of vincristine can be performed any time during treatment at the discretion of the investigator in accordance with institutional practices.

7.2.2.2 Hemorrhagic Cystitis

Intravenous hydration for cyclophosphamide as per institutional standard. Should gross hematuria develop, cyclophosphamide will be withheld until resolution of cystitis. Subsequent cycles will be given at 50% of the initial dose of cyclophosphamide for one cycle and, if tolerated, increased to 75% of the full dose for remaining cycles.

7.2.2.3 Cardiac Monitoring

. Participants will be monitored closely for clinical signs and symptoms of hypervolemia, pulmonary edema or indications of congestive heart failure or suspected cardiac event. If clinical suspicion arises, further evaluation is at the discretion of the investigator but may include EKG, N-terminal pro-brain natriuretic peptide (NTp-BNP) measurement and possibly echocardiogram. If cardiac assessment reveals significant changes from baseline in cardiac function or significant elevations in NTp-BNP, further dosing with doxorubicin can only proceed after with approval from the principal investigator and the sponsor.

7.2.2.4 Hepatic Toxicity

. If the bilirubin is between 1.5 and 3.0 mg/dl on day 1 of any cycle 2-6,

doxorubicin dose will be reduced by 25% and vincristine dose must be reduced by 50%. If the hepatic function has returned to normal by day 1 of the subsequent cycle, full doses will be given. If bilirubin is > 3.0 mg/dl, doxorubicin and vincristine should delayed in 1 week increments for up to 2 weeks until < 3.0 mg/dl and then given with the above dose reductions. If bilirubin remains > 3.0 mg/dl, the Study Monitor must be contacted and the Study PI (or designee) will be notified and the participant will be discontinued from therapy.

7.2.2.5 Rituximab Hypersensitivity/Infusion Reactions

Because rituximab is known to cause hypersensitivity and infusion reactions, it will be infused with graduated incremental rates depending on whether it is being given as an initial dose (cycle 1) or subsequent dose (2-6), per institutional guidelines. As the severity of infusion reactions increase, the infusion of rituximab will be either slowed or held, as indicated per institutional standards.

7.2.2.6 Non-Hematologic Toxicity attributable to doxorubicin and/or cyclophosphamide, excluding neuropathy, suspected rituximab reactions and hemorrhagic cystitis.

If non-hematologic toxicity is deemed to be due to the components of R-CHOP rather than ME-401 and is not neuropathy, a rituximab reaction or hemorrhagic cystitis, the doses of doxorubicin and cyclophosphamide will be modified as indicated below.

If the investigator cannot determine whether non-hematologic toxicities are due to ME-401 or R-CHOP, it will be assumed that they are due to ME-401 and managed as discussed above. As above, R-CHOP should be held until toxicity returns to grade 1 or better.

Non-Hematologic Toxicity attributable to R-CHOP, excluding neuropathy, suspected rituximab reactions and hemorrhagic cystitis			
Event Grade	**Management/Next Dose for Doxorubicin**	**Management/Next Dose for Cyclophosphamide**	**Management/Next Dose for Vincristine**
≤ Grade 1	No change in dose.	No change in dose.	No change in dose.
Grade 2	Hold until ≤ Grade 1 unless symptoms were not optimally medically managed. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.	No change in dose.
Grade 3	Hold Doxorubicin until < Grade 2.* Resume at 75% of previous dose.**	Hold Cyclophosphamide until < Grade 2.* Resume at 75% previous dose.**	No change in dose.

Grade 4	Discontinue Doxorubicin and treat patient with off protocol therapy.	Discontinue Cyclophosphamide and treat patient with off protocol therapy.	Discontinue vincristine and treat patient with off protocol therapy.
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring two dose reductions should go off protocol therapy.			

8.0 ADVERSE EVENTS AND POTENTIAL RISKS

8.1 Adverse Events and Potential Risk

8.1.1 ME-401

Toxicities included neutropenia, thrombocytopenia, and immune related adverse events (skin rash, diarrhea/colitis, hepatotoxicity, pneumonitis). Discussion regarding management of these toxicities can be found in Section 7.1.

8.1.2 Cyclophosphamide

Toxicities include myelosuppression, nausea and vomiting, hemorrhagic cystitis, and alopecia. Cystitis can be largely prevented by maintaining a good state of hydration and good urine flow during and after drug administration using the following. Please refer to the package insert for a complete listing of all toxicities.

8.1.3 Doxorubicin

Toxicities include myelosuppression, stomatitis, alopecia, nausea and vomiting, and acute and chronic cardiac toxicity, manifested as arrhythmias or a congestive cardiomyopathy, the latter uncommon at total cumulative doses less than 500 mg/m2. The drug causes local necrosis if infiltrated into subcutaneous tissue. Please refer to the package insert for a complete listing of all toxicities.

8.1.4 Pegfilgrastim

Toxicities include rare anaphylactic reactions with the first dose; bone pain at sites of active marrow with continued administration. Local reactions at injection sites. Constitutional symptoms, increased alkaline phosphatase, LDH, uric acid; worsening of pre-existing inflammatory conditions. Please refer to the package insert for a complete listing of all toxicities.

8.1.5 Prednisone

Toxicities include insomnia, agitation, proximal muscle weakness, glucose intolerance, thinning of skin, redistribution of body fat, Cushingoid facies, immunosuppression, and propensity to gastrointestinal ulceration. Please refer to the package insert for a complete listing of all toxicities.

8.1.6 Rituximab

Reported adverse events including fever, chills, headache, nausea, vomiting, rhinitis, asthenia, and hypotension, occurred primarily during rituximab infusions and typically responded to an interruption of the infusion and resumption at a slower rate. Fatal Infusion Reactions: Severe and fatal cardiopulmonary events, including angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have been reported. Other reactions include tumor lysis syndrome, cytopenias including prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia. There is an increased rate of infectious events, hepatitis B reactivation. Please refer to the package insert for a complete listing of all toxicities.

8.1.7 Vincristine

Toxicities include peripheral neuropathy, constipation, autonomic neuropathy, and alopecia. Local necrosis if injected subcutaneously. Please refer to the package insert for a complete listing of all toxicities.

8.1.8 Trimethoprim/sulfamethoxazole (TMP-SMX)

Toxicities for trimethoprim/sulfamethoxazole can include blood dyscrasias, dermatologic reactions, hepatic necrosis, hyperkalemia and thrombocytopenia. However, at the prophylactic dosing it is usually well tolerated with rare toxicities. Please refer to the package insert for a complete listing of all toxicities.

8.1.9 Pentamidine (aerosolized)

Toxicities include fatigue, dizziness, decreased appetite, respiratory symptoms (such as cough and SOB) but it is generally well tolerated. Please refer to the package insert for a complete listing of all toxicities.

8.1.10 Acyclovir

Toxicities include neurologic toxicity including agitation, tremors, delirium, hallucinations, and myoclonus, with higher risk in patient with renal insufficiency. Please refer to package insert for a complete listing of all toxicities.

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the participant; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the participant.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the participant was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

For the purpose of this study the following events would not be considered adverse events and would not be recorded in the database:

- Abnormal laboratory findings considered associated to the original disease

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the participant which occur after the participant has signed the informed consent are fully recorded in the participant's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the participant to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the participant. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the participant.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.3 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur on or after Cycle 1 Day 1 through 30 days after the final dose of study drug, **and** 90 days for evaluation and capture of pre-specified AESIs after their final dose of MEI-401. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es). Related AEs and all AESIs will be followed until resolution to baseline or grade 1 or stabilization.

All AESIs are listed in the most recent version of the Investigator Brochure.

8.4.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events and adverse events of special interest (AESIs) to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - PI: Deepa Jagadeesh, MD (see front page for contact information)
    - [redacted] and the lead study coordinator (see front page for contact information)
- The Lead Site Principal Investigator will review the SAE and/or AESI and report the event to the FDA, MEI Pharma, external collaborator(s), and IRB as applicable. Only AEs and AESIs meeting the regulatory definition of a serious adverse event should be reported to MEI Pharma as discussed below under MEI Pharma Reporting Requirements.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

MEI Pharma Reporting Requirements:

- All SAEs, regardless of relationship to study drug, must be reported to MEI Pharma at [redacted] within 1 business day of study Investigator's knowledge of the event, during the study and through 30 days after receiving the last dose of study treatment. SAEs must be reported in agreement with terms set forth in the study contract.
- Reports will be submitted using Form FDA 3500A (MedWatch) and include a narrative description of the SAE(s), severity grade, applicable seriousness criteria, start and stop dates of the event, outcome of the event, and the Investigator's assessment of the causal relationship between the SAE(s) and ME-401.

- The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF.
- It is the responsibility of the Sponsor-Investigator (Cleveland Clinic Principal Investigator) to report serious adverse events to the drug supplier (MEI Pharma) and to the US FDA, as required.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.5 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0.

9.1 ME-401 (Zandelisib)

Other Names: PWT-143

Classification: PI3Kdelta inhibitor

Product description: Capsules of 45mg and 60mg.

Solution preparation: No preparation required.

Storage requirements: ME-401 should be stored in a cool place or at controlled room temperature, 15-25°C (59-77°F). Some US sites will store between 20-25°C (68 - 77°F) per ME-401 product label.

Route of administration: ME-401 is to be taken orally once a day with a glass of water on an empty stomach at least 1 hour prior to food or 2 hours after food at the same time each day. Participants unable to take ME-401 on an empty stomach are allowed to take ME-401 with a light, non-fatty snack. If possible, separate taking ME-401 capsules from that of concomitant medications that have a known effect on p-glycoprotein, Breast Cancer Resistance Protein (BCRP) transporter, and CYP2C8 substrates, as well as concomitant oral medications that have known interactions with drugs that inhibit P-gp, BCRP, and CYP3A4.

Drug Procurement: ME-401 will be supplied by MEI Pharma Inc.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction: At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

9.2 Cyclophosphamide

Chemical Name:	2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate.
Other Names:	Cytoxan™
Classification:	Nitrogen Mustard, Antineoplastic Agent
Molecular Formula:	$C_7H_{15}Cl_7N_2O_2P \cdot H_2O$
Mode of Action:	An activated form of cyclophosphamide, phosphoramide mustard, alkylates or binds with many intracellular molecular structures, including nucleic acids. Its cytotoxic action is primarily due to cross-linking of strands of DNA and RNA, as well as inhibition of protein synthesis.

Metabolism:

Absorption: Systemic: Bioavailability: > 75%
Metabolism: Systemic: Hepatic
Excretion: Systemic Renal, 5 to 25% unchanged. In dialysis: cyclophosphamide is dialyzable.
Elimination Half Life: 3 to 12 hours.

Product description: white crystalline powder

Solution preparation: reconstitute with NS to inject directly, (infusion) dissolve in Sterile Water for Injection, USP (25 mL for 500 mg, 50 mL for 1 g, 100 mL for 2 g); then dilute in D5W, 5% dextrose in 0.9% normal saline (D5NS) or lactated ringers (D5LR or LR).

Storage requirements: Storage at or below 77°F (25°C) is recommended; this product will withstand brief exposure to temperatures up to 86°F (30°C) but should be protected from temperatures above 86°F (30°C).

Stability: Reconstituted lyophilized cyclophosphamide is chemically and physically stable for 24 hours at room temperature or for six days when refrigerated.

Route of administration: Short intravenous infusion over 30-60 minutes.

Drug Procurement: Cyclophosphamide will be obtained from commercial sources.

9.3 Doxorubicin

Chemical Name: 14-Hydroxydaunomycin

Other Names: Doxorubicin Hydrochloride

Classification: Anthracycline, Antineoplastic Agent

Molecular Formula: C27H29NO11

Mode of Action: DNA Intercalation

Metabolism:

A) Distribution Sites
   1) Protein Binding: 74% to 76%
   2) Other Distribution Sites Placenta: Placenta concentrations of doxorubicin were 1.2nmol/g of tissue when a single patient received doxorubicin about 48 hours before delivery. Umbilical cord concentrations were 0.08 nmol/g in the same patient.

B) Distribution Kinetics
   1) Distribution Half-Life: 5 minutes
   2) Volume of Distribution: 20 to 30 liters/kilogram

C) Metabolism Sites and Kinetics Liver, extensive Changes in liver

function caused by hepatocellular carcinoma result in elevated plasma concentrations of doxorubicinol rather than doxorubicin

D) Metabolites
    1) Doxorubicinol, active.
    2) Adriamycin aglycones.

E) Kidney
    1) Renal Excretion: 5% to 12%
    2) Only 1% appears in the urine over 5 days; less than 1% appears in the urine as aglycones.

F) Other
    (1) Bile, 40% and (2) Feces, 50%

G) Parent Compound
    1) Elimination Half-life: 20 to 48 hours.

H) Metabolites: Doxorubicinol, 20 to 48 hours.

Product description: Doxorubicin Hydrochloride Injection is a sterile parenteral, isotonic solution in either single dose of multi-dose vials.

Solution preparation: After reconstitution, solution is stable at room temperature for 7 days and in the refrigerator between 2 and 8 degrees C for 15 days. Protect from sunlight.

Storage requirements: Store powder at controlled room temperature between 15 and 30 degrees C (59 and 86 degrees F). Store in original carton to protect from light. Discard any unused portion

Stability: Doxorubicin 8 mg/500 mL in glucose 5% was stable for 7 days when stored in PVC (polyvinyl chloride) bags at 4 degrees C with light protection. There was also no loss of doxorubicin when infused via PVC infusion bags with PVC administration.
Doxorubicin 2 mg/mL was stable for up to 14 days at 3 or 23 degrees C and for an additional 28 days at 30 degrees C in portable pump reservoirs.
Doxorubicin was stable (less than 10% loss of potency) for 24 days in 0.9% sodium chloride stored at 25 degrees C in PVC (polyvinyl chloride) mini bags and syringes at a pH of 6.47. Also, doxorubicin was stable for at least 43 days in 0.9% sodium chloride (pH, 6.47) and 5% dextrose (pH, 4.36) at 4 and -20 degrees C.
Although doxorubicin does react with aluminum, the reaction is slow and does not result in a substantial loss of potency. Doxorubicin reconstituted with 0.9% sodium chloride injection or sterile water for injection to a concentration of 2 mg/mL and combined with steel, plastic, or aluminum was examined for color, pH, and potency. In the first 24 hours, pH changed from 4.8 to 4.9 in solutions containing plastic or steel. In the aluminum-containing solution, the pH changed from 4.8 to 5.2 and the solution changed to a darker ruby red. There was no change in potency in any of the solutions containing steel and aluminum, respectively. No precipitation was noted; therefore, doxorubicin may be safely injected through an aluminum-hubbed needle. However, reconstituted doxorubicin should not be stored in syringes capped with aluminum-hubbed needles.

Route of administration:
(1). For IV use only; do not administer IM or subcutaneously (SC)
(2). Administer slowly into freely running IV of Sodium Chloride Injection, USP or D5W over not less than 3 to 5 minutes, depending on the size of the vein and the dosage; avoid veins over joints or those with poor drainage; Butterfly(R) needle inserted into a large vein is preferable.
(3). Care should be taken to avoid extravasation as severe local tissue necrosis will occur; extravasation may occur with or without burning or stinging, and even if there is blood return on aspiration of the needle
(4). If extravasation is suspected, immediately stop administration and restart in another vein; intermittently apply ice to the site for 15 minutes, 4 times daily for 3 days.

Drug Procurement: Doxorubicin to be obtained from commercial sources.

9.4 Pegfilgrastim

Chemical Name:	N-(3-hydroxypropyl)methionylcolony-stimulating factor (human), 1-ether with α-methyl-ω- hydroxypoly(oxyethylene)
Other Names:	Neulasta™, recombinant methionyl human granulocyte colony-stimulating factor (G-CSF)
Classification:	Hematopoietic Growth Factor
Molecular Formula:	$C_{849}H_{1348}N_{223}O_{244}S_9 \bullet (C_2H_4O)$
Mode of Action:	Biosynthetic hematopoietic agent that affects the proliferation and differentiation of neutrophils within bone marrow.
Metabolism:	Renal. Neutrophil receptor binding is an important factor in pegfilgrastim clearance. Serum clearance is related to the number of circulating neutrophils; serum concentrations of the drug decline rapidly with resolution of neutropenia.

Product description: Pegfilgrastim is provided in a dispensing pack containing one syringe.

Solution preparation: Pegfilgrastim is supplied as a preservative- free solution containing 6 mg (0.6 mL) at a concentration of 10 mg/mL in a single-dose syringe with a 27 gauge, 1/2 inch needle with an UltraSafeÒ Needle Guard.

Storage requirements: Pegfilgrastim should be stored refrigerated at 2° to 8°C (36° to 46°F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light.

Stability: Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, pegfilgrastim should be discarded.

Route of administration: Subcutaneous injection

Drug Procurement: Pegfilgrastim will be from commercial sources.

9.6 Prednisone

Chemical Name: 17, 21-dihydroxypregna-1, 4-diene-3,11,20-trione
Other Names: None
Classification: Adrenal Glucocorticoid, Immune Suppressant
Molecular Formula: $C_{21}H_{26}O_5$

Mode of Action: Prednisone is an adrenocortical steroid with salt-retaining properties. It is a synthetic glucocorticoid analog, which is mainly used for anti-inflammatory effects in different disorders of many organ systems. It causes profound and varied metabolic effects, modifies the immune response of the body to diverse stimuli and is also used as replacement therapy for adrenocortical deficient patients .

Metabolism:

A) Bioavailability
    1) Oral, regular release: 92%
B) Distribution Sites
    1) Protein Binding 70%, The active metabolite, prednisolone, is nonlinearly bound to transcortin and albumin .
C) Distribution Kinetics
    1) Volume of Distribution 0.4 to 1 L/kg
D) Metabolism Sites
    1)Liver, extensive.
        a) The liver reduces the 11-oxo group of prednisone to form the biologically active steroid, prednisolone.

        b) Historically, prednisolone has been recognized as the primary metabolite of prednisone; however, some work has established that prednisone and prednisolone undergo complex reversible metabolism. After oral doses of prednisone or prednisolone, the plasma concentration- time profiles for both agents are superimposable.

Product description: Available as 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets and as oral solution (5 mg/5 ml)

Solution preparation: Available as commercially-available oral tablets or pre-prepared oral solution.

Storage requirements: Store at controlled room temperature at 25 degrees C (77 degrees F), with excursion permitted between 15 and 30 degrees C (59 and 86 degrees F). Protect tablets from moisture.

Stability: Tablets are stable at room temperature until the date noted on the packaging.

Route of administration: Oral

Drug Procurement: Prednisone will be from commercial sources.

9.7 Rituximab

Chemical Name:	IDEC-C2B8, Chimeric anti-CD20 monoclonal antibody,
Other Names:	Rituxan™, Mabthera™
Classification:	Monoclonal antibody, antineoplastic agent
Molecular Formula:	$C_{6416}H_{9874}N_{1688}O_{1987}S_{44}$
Mode of Action:	Rituximab binds with high affinity to CD20-positive cells, performs human effector functions in vitro, and depletes B cells in vivo. The FAb domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B cell lysis in vitro. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.
Metabolism:	Not fully understood. Generally believed to be degraded nonspecifically in the liver.

Product description: Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration.

Rituximab biosimilar use is permitted for this study per institutional standards.

Solution preparation: Using appropriate aseptic technique, withdraw the necessary

amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

Storage requirements: Rituximab is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

Stability: Rituximab is biologically and chemically stable at 2°C to 8°C (36°F to 46°F) and has a proposed shelf life stability of 30 months. Once reconstituted into IV bags, rituximab is chemically stable for up to 24 hours at 2°C to 8°C (36°F to 46°F), followed by up to 24 hours at room temperature (23°C). However, since rituximab solutions do not contain preservative, diluted solutions should be stored refrigerated (2°C to 8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed. Rituximab vials should be protected from direct sunlight. Rituximab vials are intended for single use only. Do not use beyond the expiration date stamped on the carton.

Route of administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Do not infuse rituximab Concurrently with another IV solution or other IV medications. Premedication, consisting of acetaminophen 650 mg to 1000 mg PO and diphenhydramine 25 to 50 mg IV or PO, will be administered before each infusion of rituximab. Premedication may attenuate infusion-related events. Since transient hypotension may occur during rituximab infusion, anti-hypertensive medications will be withheld 12 hours prior to rituximab infusion.

Rituximab is administered intravenously. An in-line filter is not required. The initial rate is 50 mg/hr for the first hour. If no toxicity is seen, the rate may be escalated gradually in 50 mg/hour increments at 30-minute intervals to a maximum of 400mg/hr. If the first dose is well tolerated, the initial rate for subsequent dose is 100mg/hr, increased gradually in 50 mg/hr increments at 30-minute intervals, not to exceed 400 mg/hr. Rituximab infusion must be interrupted for severe reactions. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects will be evaluated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100mg/hr to 50mg/hr) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of rituximab therapy.

Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued. The patient should be treated according to the best available local practices and procedures. In patients with detectable circulating

lymphoma cells, the initial infusion rate must be reduced to 25 mg/hr; these patients may experience more frequent and severe transient fever and rigors, shortness of breath, and hypotension.

NOTE: In addition, alternative rituximab infusion rates (i.e., "rapid rituximab infusion") can be used per institutional guidelines as long as the total number of milligrams of rituximab is the same and that "rapid infusion" is not administered with the patient's first rituximab cycle. Further, a rituximab infusion time should not be less than 90 minutes in duration.

Hycela (SQ rituximab/hyaluronidase human)

Product description: RITUXAN HYCELA is a combination of rituximab and hyaluronidase human. Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM. Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium that may contain the antibiotic gentamicin. Gentamicin is not detectable in the final product. Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of coadministered drugs when administered subcutaneously. It is produced by mammalian (Chinese Hamster Ovary) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

RITUXAN HYCELA (rituximab and hyaluronidase human) Injection is a colorless to yellowish, clear to opalescent solution supplied in sterile, preservative-free, single-dose vials for subcutaneous administration. Each mL of solution contains rituximab (120 mg), hyaluronidase human (2,000 Units), L-histidine (0.53 mg), L-histidine hydrochloride monohydrate (3.47 mg), L-methionine (1.49 mg), polysorbate 80 (0.6 mg), α,α-trehalose dihydrate (79.45 mg), and Water for Injection.

Product Instructions/Details:

- Rituximab-hyaluronidase (Rituxan Hycela) 1400 mg-23,400 units/11.7 mL
- Patient's must have tolerated at least 1 full dose of IV rituximab without a serious reaction
- Prior to each dose premedicate patients with acetaminophen 650mg and diphenhydramine 50mg
- 11.7 mL is given subcutaneously over approximately 5 minutes on Day 1 of a 28 day cycle, beginning in Cycle 2.
- Injection should be given into the subcutaneous tissue of the abdomen. Never inject into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.
- If administration is interrupted, continue administering at the same site, or at a different site, but restricted to the abdomen.

- To avoid clogging, attach administration needle, or catheter, only when the patient is ready for injection.
- If not used immediately, prepared syringe may be stored in the refrigerator at 2-8 ◦C for up to 48 hours and subsequently for 8 hours at room temp up to 30 ◦C
- Patients must be observed for at least 15 minutes following administration

Drug Procurement: Rituximab must be obtained from commercial sources.

9.8 Vincristine

Chemical Name: (3aR,3a1R,4R,5S,5aR,10bR)-methyl 4-acetoxy-3a-ethyl- 9-((5S,7S,9S)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-2,4,5,6,7,8,9,10-octahydro-1H-3,7-methano[1] azacycloundecino[5,4-b]indol-9-yl)-6-formyl-5-hydroxy- 8-methoxy-3a,3a1,4,5,5a,6,11,12-octahydro-1H- indolizino[8,1-cd]carbazole-5-carboxylate

Other Names: OncovinTM

Classification: Vinca alkaloid, mitotic inhibitor, antineoplastic agent

Molecular Formula: $C_{46}H_{56}N_4O_{10}$

Mode of Action: Vincristine sulfate, an oncolytic vinca alkaloid, has an unknown mechanism of action, although it is thought to be related to the arrest of replicating cells at the metaphase stage through prevention of microtubule formation in the mitotic spindle.

Metabolism: Absorption: Protein binding – yes
Metabolism: Hepatic: CYP3A4P450 subfamily
Excretion: Fecal: about 80% Renal: 10% to 20%
Dialyzable: no
Elimination Half Life 85h (19 to 155h)

Product description: Vincristine sulfate is a white to off-white powder. Each mL contains vincristine sulfate, 1 mg (1.08 µmol); mannitol, 100 mg; and water for injection, qs. Acetic acid and sodium acetate have been added for pH control. The pH of Vincristine Sulfate Injection, USP ranges from 3.5 to 5.5.

Solution preparation: Dilute only in NS or D5W; do not dilute in solutions that raise or lower the pH outside the range of 3.5-5.5. Dispense with provided sticker or overwrap that states "FATAL IF GIVEN INTRATHECALLY. FOR INTRAVENOUS USE

ONLY".

Storage requirements: The ready-to-use solution should be refrigerated during storage, however, no specific temperature recommendations are provided by the manufacturer. Protection from light has been recommended. If stored at room temperature (15 to 30 degrees C) or in a cool place (8 to 15 degrees C), vincristine sulfate is stable for 1 month. If then refrigerated, the stability of vincristine sulfate is as originally labeled by the manufacturer (Lilly).

Stability: Vincristine sulfate in 5% dextrose injection is stable for 24 hours in both glass and PVC containers

Route of administration: Syringes should not be used for vincristine administration. Administering via a mini bag infusion is recommended to protect against accidental intrathecal administration. Administer via free-flowing intravenous (IV) needle or catheter; inject directly into vein or into tubing of a running IV infusion within 1 minute. Vincristine is considered a vesicant. Care should be taken to avoid extravasation.

Drug Procurement: Vincristine will be obtained from commercial sources.

10.0 CORRELATIVE STUDIES

10.1 Molecular Subtyping

See Section 2.3

10.1.1 Background

See Section 1.5.

10.1.2 Rationale for Analysis

See Section 1.5.

10.1.3 Tissue Procurement

The following materials should be collected within 90 days of registration and sent for each patient that signs consent. The slides and/or tissue scrolls should be prepared after the patient has signed the consent form to participate in the study and within 4 weeks of starting study treatment. We prefer tissue scrolls, but unstained slides are acceptable if scrolls are not available.

1. Fifteen 4 micron unstained sections on charged (plus) slides
2. Four 10 micron sections/tissue scrolls (if an incisional or excisional biopsy) or eight 10 micron sections/tissue scrolls (if needle biopsy) preferably in a tube to minimize degradation. Otherwise, on slides is acceptable.

10.1.4 Blood Sample

Two 10ml heparinized green top tubes (20 ml total) of peripheral blood will be obtained at the time of sample collection (screening/prior to treatment, prior to treatment of cycle 4, and then end of treatment).

The green top heparin tubes will be processed into aliquots of plasma and viable mononuclear cells.

2(or quantity needed obtain 5ml total plasma) lavender top EDTA or, Streck (if available), tubes will also be used to collect a whole blood sample at Screening/Baseline, EOT, and 12-month follow-up visits.

10.1.5 Shipment

Please ship the slides/tube to the Cleveland Clinic Biorepository at the address provided below:

Robert J. Tomsich Pathology and Laboratory Medicine Institute (RT-PLMI)
ATTN: Dr. Genevieve Crane
2119 East 93 Street, L25
Cleveland, Ohio 44106

Please ship the blood samples to the Cleveland Clinic Pharmacology Lab. The Manual of Operating Procedures (MOP) contains more detailed instructions on shipment of the slides and blood samples.

10.1.6 Analytical Laboratory

The specimen will be analyzed via next generation sequencing and RNA sequencing as described by Chapuy et al. [13]. The assay is not currently available but when it is, we will perform testing in the laboratory at Cleveland Clinic or through use of a third party laboratory.

Further information about the planned analyses concerning these correlative studies will be added in a protocol amendment.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluation

Screening studies and evaluations will be used to determine eligibility of each participant for study inclusion. All evaluations must be completed ≤ 45 days prior to administration of protocol therapy, except where otherwise indicated or - in the case of patients who received 1 cycle of R-CHOP [or some component(s) there of] prior to study enrollment (in this case, window extends to ≤60 days), a

CT and/or PET/CT, echocardiogram and bone marrow biopsy must have been obtained prior to treatment.

- Informed Consent
- Medical History
- Complete Physical Exam
- Height
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over the counter (OTC) medications and natural/herbal supplements
- ECOG Performance Status
- Baseline Symptoms Assessment
- IPI score documented
- Laboratory Studies:
    -Complete blood count (CBC) with differential and platelets
    -Serum chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST (SGOT), ALT (SGPT), sodium
    - Lactate dehydrogenase (LDH), uric acid, phosphorus
    - Calculated creatinine clearance will be determined using Cockcroft-Gault formula if creatinine and/or BUN are abnormal
    -Serum B-HCT for women of childbearing potential
    -Urinalysis
    -Remote Hepatitis panel (Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody, Hepatitis C Antibody)
        *If hepatitis B surface antigen and/or B core antibody is positive then Hep B PCR assay is required
        *If hepatitis C virus antibody. If positive need hepatitis C PCR is needed
    -HIV testing
    -CMV PCR testing
- EKG
- MUGA or echocardiogram (must be completed < 6 months prior to administration of protocol therapy) unless there is clinical evidence for new cardiac symptoms within period of time since the cardiac assessment.
- CT scan of neck, chest, abdomen and pelvis with oral and IV contrast (neck may be omitted at discretion of treating physician).
- PET/CT scan as baseline tumor imaging assessment
- Bone Marrow Aspirate and Biopsy (within 90 days of registration)
- Diagnostic biopsy material sent to Cleveland Clinic for subgroup analysis.
- Correlative blood draw

11.1.2 Treatment Period

- Treatment cycles are 21 days long.
- A visit window of ± 3 days is allowed for labs
- A visit window of ± 3 day is allowed for treatment
- A visit window of ± 14 days is allowed for follow up visits

Cycle 1, Day 1

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG performance status
- Laboratory Studies:
  - Complete Blood Count (CBC) with differential and platelets.
  - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
  - LDH, uric acid, phosphorous
  - Pregnancy test, serum B-HCT, for females of childbearing potential (on day 1)
  - CMV PCR
- EKG
- R-CHOP administration
- ME-401 started (days 1-7; *note: days 1-4 for dose level 1 of phase 1)
- Start Trimethoprim/sulfamethoxazole three days a week or Pentamidine (aerosolized) monthly
- Start acyclovir 400mg BID

Cycle 1, Day 2

- Pegfilgrastim administration or ONPRO™ wearable device as per institutional standard
  - Pegfilgrastim 6 mg SC day 2 (every 21 days). Filgrastim 300 or 480 mcg IV/SC daily days x 5-10 starting day 2 may be substituted if pegfilgrastim is not available. ONPRO™ is also an acceptable method of administration on day 1. Biosimilars may be used per institutional protocols.

Cycle 1, Day 8 (Phase I Only)

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Laboratory Studies:
  - Complete Blood Count (CBC) with differential
  - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
  - LDH, uric acid, phosphorous

- Adverse event evaluation and documentation

Cycle 1, Day 15 (Phase I Only)

- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential
    - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
- Adverse event evaluation and documentation

Cycle 2-6, Day 1

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG performance status
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.
    - Serum Chemistries: Serum chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
    - LDH
    - CMV PCR
    - *Cycle 2 Day 1 only: uric acid and phosphorous
    - *Cycle 3 Day 1 and Cycle 6 Day 1 only: EKG
    - *Cycle 4 Day 1 only: correlative blood draw
- R-CHOP administration
- ME-401 started (days 1-7; *note: days 1-4 for dose level 1 of phase 1)

Cycle 2-6, Day 2

- Pegfilgrastim administration as per institutional standard. ONPRO™ wearable device on day 2
    - Pegfilgrastim 6 mg SC day 2 (every 21 days). Filgrastim 300 or 480 mcg IV/SC daily days x 5-10 starting day 2 may be substituted if pegfilgrastim is not available. ONPRO™ is also an acceptable method of administration on day 1. Biosimilars may be used per institutional protocols

Cycle 3, Day 15-21

- CT of neck, chest, abdomen, and pelvis with IV and PO contrast for response assessment. Neck CT can be omitted if no involvement at baseline.

End of Treatment Response Assessment – 8 weeks (+/-7days) after the first day of last treatment cycle

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Concurrent Medications Assessment including prescription medications, over-the-counter (OTC) medications and natural/herbal supplements.
- ECOG Performance Status
- Adverse Event evaluation and documentation
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.
    - Serum Chemistries: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
    - LDH
    - CMV PCR
    - Hepatitis B PCR if participant tested positive for hepatitis B surface antigen and/or hepatitis B core antibody during screening
    - Hepatitis C PCR if participant tested positive for hepatitis C antibody on screening
    - Correlative blood draw
- EKG
- Bone marrow biopsy (may be omitted if screening bone marrow biopsy was negative for involvement by lymphoma).
- PET and diagnostic CT of neck, chest, abdomen, and pelvis with IV and PO contrast for response assessment. Neck CT can be omitted if no involvement at baseline. PET scan alone is acceptable if diagnostic CT scans are declined by insurance company.

Follow Up

After completion of the study treatment the participants will be followed for a total of 2 years or until disease progression whichever comes first. The follow up visits will be done at 6, 12, 18, and 24 months after the first day of the last cycle of therapy. If the patient is unable to follow up in person, virtual visits may be used to capture applicable procedures during long-term follow up only. Every attempt should be made to complete the required assessments listed below, although if they are not completed it will not be considered a protocol deviation.

The follow up visits should include the following:

- Physical Examination
- Vital signs
- ECOG performance status
- Adverse event evaluation
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.

    - Serum Chemistries: sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
    - LDH
    - CMV PCR
- Diagnostic CT neck, chest, abdomen and pelvis scan with IV and PO contrast will be done at 6, 12, and 24 months if no disease progression. Neck CT can be omitted if no involvement at baseline
- *Discontinue PJP prophylaxis by 6 month visit (can be stopped between 2-6 months)
- *Discontinue acyclovir at 6 month visit

Patients who have progressive disease or start new treatment are not required to come in for clinical follow up. These patients can be contacted over the phone by the study personnel to obtain the following information:

- Disease status
- Adverse event evaluation only if patients have residual persistent symptoms related to study treatment
- Current lymphoma treatment

Patients will be followed for toxicity for 30 days, and 90 days for evaluation and capture of pre-specified AESIs, after treatment with ME-401 has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until has been determined that the study treatment or participation is not the cause.

Serious adverse events (SAE) that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

11.2 Calendar

Procedures	Screening	Cycle 1				Cycle 2		Cycle 3			Cycles 4-6		End of Treatment	Follow Up[o]
	Days -45 -0	Day 1	Day 2	Day 8[a]	Day 15[a]	Day 1	Day 2	Day 1	Day 2	Days 15-21	Day 1	Day 2	8 weeks after last treatment	6,12,18,24 months after last treatment[k]
Informed Consent	X													
Inclusion/Exclusion	X													
Medical History	X													
Physical Exam	X	X				X		X			X		X	
Vital Signs	X	X		X	X	X		X			X		X	X
Height/Weight[m]	X	X				X		X			X		X	X
Concurrent Meds Assessment	X	X				X		X			X		X	
Baseline Symptom Assessment	X	X												
Adverse Event Evaluation				X	X	X		X			X		X	X
ECOG Performance Status	X	X				X		X			X		X	X
CBC with differential	X	X		X	X	X		X			X		X	X
Serum Chemistry	X[b]	X[b]		X[b]	X[b]	X[b]		X[b]			X[b]		X[b]	X[b]
LDH	X	X		X		X		X			X		X	X
Uric Acid	X	X		X		X								
Phosphorous	X	X		X		X								
Pregnancy Test (WOCBP)	X	X												
Urinalysis	X													
Remote Hepatitis Panel	X													
Hepatitis B and C PCR	X[f]													
HIV	X													
CMV	X	X				X		X			X		X	X
ECG	X	X						X			X[l]		X	
Echo or MUGA	X													
CT Neck/Chest/ Abdomen/Pelvis	X[d]									X[d]			X[d]	X[j]
PET Scan	X[e]													
Bone marrow biopsy	X												X[g]	
R-CHOP		X				X		X			X			
ME-401		X[c]				X[c]		X[c]			X[c]			
Pegfilgrastim or OnPRO™			X				X		X			X		
PJP or VZV prophylaxis		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[i]
Correlative Blood	X										X[n]		X	X[p]

- A visit window of ± 3 days is allowed for labs
- A visit window of ± 3 day is allowed for treatment.
- A visit window of ± 14 days is allowed for follow-up visits.

a. Cycle 1, Day 8 and 15 evaluation is for phase I only. In-person visit may be replaced with a phone call to assess for AEs if investigator believes there would be no increased risk to the subject's safety. Labs should still be drawn in accordance with SOC procedures.
b. Sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, total protein, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]
c. Phase 1: ME-401 will be given on days 1-4 (dose level 1) OR days 1-7 (dose level 2) of a 21 day cycle. . Phase 2: ME-401 will be given on days 1-4 or days 1-7 of a 21-day cycle depending on the RP2D. Participants should take ME-401 on and empty stomach. Participants unable to take ME-401 on an empty stomach are allowed to take ME-401 with a light, non-fatty snack.
d. Neck CT can be omitted if there is no involvement, or suspicion for involvement, at screening per the discretion of the investigator
e. PET and diagnostic CT scan preferred, but PET alone is acceptable if unable to obtain both. Diagnostic CT scans are acceptable if unable to get PET alone.
f. Hepatitis B PCR only required if tested positive hepatitis B surface antigen and/or hepatitis B core antibody during screening OR Hepatitis C PCR only required if participant tested positive for hepatitis C antibody on screening
g. Bone marrow aspiration and biopsy may be omitted if screening bone marrow biopsy was negative for involvement of lymphoma
h. PJP prophylaxis with TMP/SMX three days weekly or pentamindine monthly. Or VZV prophylaxis with Acyclovir BID
i. PJP prophylaxis stopped 2-6 months after last dose of ME-401 or VZV prophylaxis stopped 6 months after last dose of ME-401
j. Diagnostic CT neck, chest, abdomen and pelvis scan with IV and PO contrast will be done at 6, 12, and 24 months if no disease progression. Neck CT can be omitted if no involvement at baseline
k. Participants who have progressive disease are not required to come in for clinical follow up. Participants will be contacted over the phone to obtain the following information at these time points: disease status, adverse event evaluation (for persistent symptoms), and current treatment. Patients are allowed do virtual visits for long term follow up only, if unable to follow up in person.
l. EKG only on Cycle 6 Day 1
m. Height collected only at screening
n. Correlative blood (heparin tubes) collected only on Screening, Cycle 4 Day 1, and EOT.
o. Long term follow-up visits may be completed via virtual visit if necessary. Every attempt should be made to complete the assessments due though if they are not completed this is not considered a protocol deviation.
p. Whole blood correlative sample to be collected at Screening, EOT, and 12-month follow-up.

12.0 RESPONSE ASSESSMENT

Response assessments will be evaluated based on Lugano Criteria (refer to Appendix C). Patients will have a PET/CT 8 weeks +/-7 days after end of treatment. Please see section 10 for the schedule of the imaging studies. Patients will have pre-treatment and end of treatment FDG-PET and/or CT to monitor their response to treatment. Interim response will be assessed after cycle 3 using CT scans. During follow up patients will have CT scans done at 6, 12, and 24 months after completion of therapy.

All patients will be evaluable for toxicity from the time of their first treatment with ME-401.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest dominant nodes or extranodal masses must be identified at baseline.
- If there are 6 or fewer nodes and extranodal masses, all must be listed as dominant.
  If there are more than 6 involved nodes or extranodal masses, the 6 largest dominant nodes or extranodal masses should be selected according to the following features:
  - nodes should be clearly measurable in at least two perpendicular measurements
  - nodes should be from as disparate regions of the body as possible
- Measurements for all dominant nodes and extranodal masses will be reported at baseline. Measurements on non-dominant nodes are not required. The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1cm, 2.2 cm, etc.)

12.1 Definitions

12.1.1 Progression Free Survival

Progression free survival (PFS) is defined as the time from first dose of study treatment to documented disease progression, or death from any cause, whichever occurs first. Data for participants who are still alive and free from progression at the time of data cutoff date, lost to follow-up, have discontinued the study, or have initiated NPT will be censored on last assessment (or, if no post-baseline tumor assessment, at the time of first dose plus 1 day).

12.1.2 Overall Response Rate

Overall response rate (ORR) is defined as all patients that achieve a CR or PR based on end of treatment scans, using the Lugano Criteria.

12.1.3 Complete Remission Rate

Complete response (CR) rate is defined as all patients that achieve a CR based on end of treatment scans, using the Lugano Criteria.

12.1.4 Partial Remission Rate

Partial response rate (PRR) is defined as all patients that achieve a PR based on end of treatment scans, using the Lugano Criteria.

12.1.5 Duration of Response

Duration of response (DOR) is only measured in responders. DOR is defined as the time from documented response (CR or PR) to the time of confirmed disease progression or death due to any cause, whichever occurs first participants who are still alive and free from progression at the time of data cutoff date, lost to follow-up, have discontinued study, or have initiated other non-protocol anti-tumor therapy (NPT) will be censored at the last tumor assessment when participants are progression-free.

12.1.6 Overall Survival

Overall survival (OS) is defined as the time from first dose of study treatment to death from any cause. Data for participants who are still alive at the time of data cutoff date, lost to follow-up, have discontinued the study (or, if no post-baseline assessment, at the time of first dose plus 1 day) will be censored on last assessment.

12.1.7 Time to Treatment Failure

Time to treatment failure (event-free survival) is measured from the time from study entry to any treatment failure including discontinuation of treatment for any reason, such as disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death.

12.2 Response Review

Responses will be reviewed by the investigator (PI or co-investigator) who is treating the patient at each participating site. Patients who have been treated with 3 or more cycles of R-CHOP in combination with ME-401 will be available for response assessment.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The Advarra™ EDC and OnCore® databases will be utilized, as required by the Case Comprehensive Cancer Center and Cleveland Clinic, to provide data collection for both accrual entry and trial data management. Advarra™ EDC and OnCore® are Clinical Trials Management Systems housed on secure servers. Access to data through Advarra™ EDC and OnCore® is restricted by user accounts and assigned roles. Once logged into the Advarra™ EDC or OnCore® system with a user ID and password, Advarra™ EDC and

OnCore® define roles for each user which limits access to appropriate data. Applications for user accounts can be obtained by contacting the OnCore® Administrator at OnCore-registration@case.edu for OnCore® access, and taussigoncore@ccf.org for Advarra™ EDC access.

Advarra™ EDC is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. When properly utilized, Advarra™ EDC is 21 CFR 11 compliant. This study will utilize electronic Case Report Form completion in the Advarra™ EDC database. A calendar of events and required forms are available in Advarra™ EDC.

13.2 **Regulatory Considerations**

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.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the participant's financial responsibility. Participants must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the participant. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Participant Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a participant must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including participants' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform

audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

Phase I

- The primary endpoint of phase I is DLT during the first cycle. The target toxicity rate is no more than 30%. Standard "3+3" design will be used for phase I part with 2 pre-specified dose levels, starting from level 1. If 0/3 DLT observed, dose level will be escalated. If 1/3 DLT observed, additional 3 participants will be enrolled on the current level. If 2 or more DLT observed in 3 or 6 participants, MTD is exceeded, and dose level will de-escalate. If this happens in dose level 1, the study will be discontinued as there MEI is only manufactured as 60 mg tablets currently. Since there is no lower dose to deescalate, we will discontinue the study. If 1/6 DLT observed, dose level will escalate. RP2D is defined as the dose level with 1 or less DLT out of 6 patients.
- The secondary endpoints, TRAEs and treatment delays, will be characterized with descriptive statistics.

Phase II

- The primary endpoint for the phase II is 1 year PFS. The null rate was set as 65% and we expect ME401 + CHOP will increase 1-year PFS to 80%. A total of 54 participants treated on RP2D (with the anticipation of no more than 5 patients lost to follow up by 1 year) will ensure a power of 80% at one-sided type I error rate of 5% to detect such a difference using a one sample log-rank test[46] against the null 1-yr rate.
- Secondary endpoints are defined in Section 12.1.
    - To estimate the response rates (complete and partial remission), duration of response (DOR), time to progression (TTP), and overall survival (OS) with ME-401 plus R-CHOP. Response rates will be reported as proportions along with exact 95% confidence intervals. DOR, TTF, and OS will be estimated using Kaplan-Meier methods.
    - To characterize treatment-related AEs in participants treated with ME-401 plus R-CHOP. TRAEs will be summarized by cycle and grade using descriptive statistics.

Bayesian Monitoring Rule for Safety (Phase II Only).

To ensure participants safety, a Bayesian rule[49] will be used to monitor DLT rate and stop the trial early if excessive toxicity rate is observed. We use a Beta (0.3,0.7) prior for the

true rate of DLT, which corresponds to the target toxicity rate of 30%. We will stop the trial for toxicity if Pr(DLT rate > 30%|data) > 0.9, i.e. stop the trial if posterior probability of DLT rate higher than 30% given data is greater than 0.9. All 54 patients treated on R2PD will be monitored by this rule in cohorts of 6. Table 1 summarizes early stopping rules and table 2 summarizes operating characteristics.

Table 1. Safety stopping boundaries for toxicity monitoring in phase II. Patients will be monitored in cohorts of 6. Trial will be stopped early due to excessive toxicity if number of DLTs observed was greater or equal to the boundaries. E.g. if 6 out of the first 12 patients experienced DLT, we will stop early for toxicity. Similarly, if 9/18, 11/24, 13/30, 15/36, 17/42, or 19/48 DLTs observed, we will stop the trial early.

Total Number of Patients Treated	6	12	18	24	30	36	42	48
Stop if Number of DLT observed >=	4	6	9	11	13	15	17	19

Table 2. Summary of operating characteristics based on 10,000 simulations using monitoring rules specified in table 1. E.g. If the true DLT rate is 50%, the early stopping probability is 0.97.

Scenario	True DLT Rate	Pr(Early Stoppping)	Average Sample Size	Average Number of DLTs Observed
1	0.2	0.03	52.5	10.5
2	0.3	0.24	45.4	13.6
3	0.4	0.71	30.1	12.0
4	0.5	0.97	16.7	8.4

Analysis Plan

Descriptive statistics will be used for toxicity profile and response status. Logistic regression model will be used to associate patient characteristics with response status. PFS and OS will be estimated using Kaplan-Meier method. One-sample log-rank test will be used to compare observed 1-year PFS rate against null rate. Cox proportional hazard model will be used to associate patient characteristics with PFS and OS. Other statistical analyses will be carried out as appropriate.

Correlatives

- PFS based on molecular subtype will be explored using Kaplan-Meier method depending on the number of participants in each subtype.

Accrual Rate

- The phase I portion of the trial aims to accrue patients at 2 large academic centers in Ohio with participation of both the Cleveland Clinic and University

Hospitals through the Case Comprehensive Cancer Center. At the Cleveland Clinic Taussig Cancer Center, we have seen over 120 newly diagnosed DLBCL patients per year for the last 3 years. A recently completed phase I study in newly diagnosed DLBCL that required 24 participants completed enrollment in 2 years. We need fewer patients and estimate that we will accrue 1-2 patients per month during the phase I portion of the study and complete enrollment within 12-18 months.

- The phase II portion of the trial will add 1-3 additional sites. During the phase II portion of the study, we estimate we will accrue 2-4 participants per month and complete enrollment in less than 24 months. For completion of the phase I and II portion of the study with at least a year of follow up we estimate it will take 3-4 years.

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APPENDIX A

Performance Status Criteria [50]

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Full active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% if waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B

PARTICIPANT CAPSULE DIARY

Participant Name _____Protocol #_____ Participants Study ID _____

Cycle #: _____ Month #: _____

Date	Day	# of _____ mg *ME-401* capsules and time taken	Comments
	1		
	2		
	3		
	4		
	5		
	6		
	7		

APPENDIX C

Assessment of Responses based on Lugano Criteria as defined by Cheson et al [51]

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology, if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX D

List of CYP2C8 Inhibitors and Inducers

Following is a table of known inducers and inhibitors of CYP2C8.

Inhibitors of CYP2C8 can be classified by their potency, such as:

- **Strong inhibitor** being one that causes at least a five-fold increase in the plasma AUC values, or more than 80% decrease in clearance.
- **Moderate inhibitor** being one that causes at least a two-fold increase in the plasma AUC values, or 50-80% decrease in clearance.
- **Weak inhibitor** being one that causes at least a 1.25-fold but less than two-fold increase in the plasma AUC values, or 20-50% decrease in clearance.

Inhibitors	Inducers
Strong inhibitor gemfibrozil **Moderate inhibitor** trimethoprim glitazones montelukast quercetin	**Unspecified potency** rifampin

Note: Medicines on this list must be reviewed by Principal Investigators on an ongoing basis to assure updates.

Please note the following: This is not an exhaustive list. For an updated list, see the following links:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4

http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX E
List of Drugs Known to Prolong QT/QTc Interval

MEDICATIONS THAT MAY CAUSE QTc PROLONGATION

This table lists drugs that may prolong the QTc interval.

Drugs labeled "Use discretion" may be co-administered in the absence of other risk factors and with appropriate monitoring. Drugs with a weak association may be administered at usual doses with appropriate monitoring.

Compound	Compound Half Life	QTc Prolongation Association/ Concurrent Administration	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzocin	~10 hours	Some/Use Discretion		7
Amantadine	17 +/- 4 hours (10-25)	Some/Use Discretion		4
Amiodarone (cordarone)	**58 days (15-142) 36 days (active metabolite)**	**Strong/Prohibited**		**180**
Amitriptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Amoxapine	~ 8 hours	Weak/At usual doses	40 hours	2 days
Ampicillin	1 to 1.5 hours	Weak/At usual doses		
Arsenic trioxide	**Not characterized; may be weeks**	**Strong/Prohibited**		
Azithromycin	40 hours	Some/Use Discretion		
Bepridil	**42 hr (26-64)**	**Strong/Prohibited**		**10**
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	Some/Use Discretion	48	
Chloroquine	**6 to 60 days; mean 20 days**	**Strong/Prohibited**		
Chlorpromazine	**30 +/- 7 hours**	**Strong/Prohibited**		**7**
Ciprofloxacin	3.5 to 4.5 hours	Weak/At usual doses		
Cisapride	**6 – 12 hour, up to 20 hour**	**Strong/Prohibited**	**60**	
Citalopram		Weak/At usual doses		
Clarithromycin	**Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)**	**Strong/Prohibited**	**36**	**3**
Clomipramine	~ 21 hours	Weak/At usual doses		
Clozapine	12 hours at steady state	Some/Use Discretion		
Desipramine*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Disopyramide	**6.7 hr (4-10)**	**Strong/Prohibited**	**36**	
Dofetilide	**10 hr**	**Strong/Prohibited**	**48**	
Dolesetron	8.1 hr	Some/Use Discretion		
Domperidone	**7-8 hr**	**Strong/Prohibited**	**48**	
Doxepin*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Droperidol	**2.2 hours**	**Strong/Prohibited**	**10**	
Erythromycin	*** Each salt form has different Half life***	**Strong/Prohibited**		
Felbamate	20-23 hr	Some/Use Discretion		5

Fluconazole	~ 30 hours	Weak/At usual doses		
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*	Some/Use Discretion		20
Fosphenytoin	12-29 hr	Some/Use Discretion		6
Galantamine		Weak/At usual doses		
Gatifloxacin	7-14 hr	Some/Use Discretion	48	
Gemifloxacin	7 hours	Some/Use Discretion	48	
Granisetron	3 to 4 hours	Some/Use Discretion		
Grepafloxacin	16 hr	Some/Use Discretion		3
Halofantrine	**6-10 days (variable among individual)**	**Strong/Prohibited**		**45**
Haloperidol	**18 +/-5 hr**	**Strong/Prohibited**		**5**
Ibutilide	**6 hours (2-12) * variable among subject***	**Strong/Prohibited**	**36**	**3**
Imipramine*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Indapamide	14 hours (biphasic elimination)	Some/Use Discretion		3
Isradipine	8 hours (multiple metabolites)	Some/Use Discretion	48	
Itraconazole	20 hours, increasing to 40 hours	Weak/At usual doses		
Ketoconazole	2 hours, increasing to 8 hours	Weak/At usual doses		
Levofloxacin	6-8 hours	Some/Use Discretion	48	
Levomethadyl	**Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM**	**Strong/Prohibited**		**20**
Lithium	24 hour (10-50)	Some/Use Discretion		7
Mefloquine	13 to 24 days	Weak/At usual doses		
Mesoridazine	**24-48 hours (animal study)**	**Strong/Prohibited**		**10**
Methadone	**15-30 hours**	**Strong/Prohibited**		**7**
Mexiletine	>10 hours	Weak/At usual doses		
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	Some/Use Discretion	48	
Moxifloxacin	12 +/-1.3 hours	Some/Use Discretion	72	
Naratriptan	6 hours		36	
Nicardipine	~ 2 hour post IV infusion	Some/Use Discretion	12	
Nortriptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Octreotide	1.7 hours	Some/Use Discretion	12	
Ofloxacin	5 to 7.5 hours	Some/Use Discretion		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)	Some/Use Discretion		1 to 3
Paroxetine		Weak/At usual doses		
Pentamidine	**6.4+/-1.3 hours**	**Strong/Prohibited**	**36**	
Pimozide	**55 hours**	**Strong/Prohibited**		**10**
Procainamide	**3-4 hour for PA and NAPA (active metabolite)**	**Strong/Prohibited**	**24**	**3**
Protiptyline*	> 24 hours, wide interpatient variability	Weak/At usual doses		
Quetiapine	6 hours	Some/Use Discretion	36	

Quinidine	**6-8 hours in adult; 3-4 hours in children**	**Strong/Prohibited**	**36**	
Quinine	4-5 hours	Weak/At usual doses		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)	Some/Use Discretion		4
Roxithromycin		Some/Use Discretion		
Salmeterol	5.5 hours (only one datum)	Some/Use Discretion	36	
Sertraline	~ 26 hours	Weak/At usual doses		
Solifenacin	40 to 68 hours	Weak/At usual doses		
Sotalol	**12 hours**	**Strong/Prohibited**	**72**	
Sparfloxacin	**20 hours (16-30)**	**Strong/Prohibited**		**4**
Sumatriptan	2.5 hours		12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant	Some/Use Discretion		7
Tamoxifen	5-7 days (biphasic)	Some/Use Discretion		30
Telithromycin	2-3 hr	Some/Use Discretion	24	
Thioridazine	**20-40 hours (Phenothiazines)**	**Strong/Prohibited**		**7**
Tizanidine	2.5 hours	Some/Use Discretion	12	
Trimethoprim/sulfa	6 to 17 hours	Weak/At usual doses		
Trimipramine	~ 23 hours	Weak/At usual doses		
Vardenifil	4 to 5 hours	Some/Use Discretion		
Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	Some/Use Discretion	60	
Voriconizole	6 hours; dose dependent	Some/Use Discretion		
Ziprasidone	7 hr	Some/Use Discretion	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	Weak/At usual doses	18	

***These agents are tricyclic antidepressants; traditionally, they have only been associated with QTc interval prolongation at serum levels approaching or into the range of toxicity. Special caution is advised is the elderly and children/adolescents.**

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Disclaimer: This chart was updated on August 23, 2005. It may not include all drugs associated with QTc prolongation. Prescribers are advised to do further research if they have additional questions.