Masonic Cancer Center, University of Minnesota
Cancer Experimental Therapeutics Initiative
Blood and Marrow Transplantation Program

Study of the ADAM17 Inhibitor INCB7839 Combined With Rituximab After Autologous Hematopoietic Cell Transplantation (HCT) For Patients With Diffuse Large B Cell Non-Hodgkin Lymphoma (DLBCL)

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Revision History

Revision #	Version Date	Summary Of Changes	Consent Changes
	11/06/2013	original to CPRC	
	12/26/2013	in response to CPRC's review	
	01/30/2014	• change study design from Simon's optimal two-stage phase II to a phase I/II with INCB7839 dose escalation component – revisions throughout the protocol; • revise rituximab dose schedule adding 1 dose - rituximab is at 28 days post- transplant and then 1 and 7 weeks; • delay start of INCB7839 until day of 2nd rituximab dose; • change primary endpoint from disease free survival to progression free survival; • update and expand background; • edit and update inclusion/exclusion criteria; • clarify required DVT prophylaxis; • update standard of care and research "x" chart; • limit enrollment to 18 years and older; • other edits and clarifications throughout.	n/a
	3/14/2014	In response to FDA email dated 3/11/2014 • convert from fast-track (accelerated titration design) to 3+3 design after observing a grade 2 or greater treatment emergent toxicity (previously written as grade 3 or greater) • expand the definition of dose limiting toxicity to include selected hematologic toxicity, lower the threshold for DLT from grade 4 to grade 3 • section 10.2 – document "unlikely" related adverse events leaving only "unrelated" adverse events not recorded, edit section 10.3 table for expedited reporting	
1	06/04/2014	• Study schema and section 8: convert study schedule from week based to day based, clarify f/u visits will coincide with transplant/SOC clinic visits (data obtained from BMT database), move PT/INR and D-dimer testing from SOC to research x chart • Section 10.2: correct definition of non-hematologic toxicity to match rest of protocol • Study schema, Sections 10.2 and 13.5: modify hematologic stopping rule to require persistence of 7 or more days • Section 9.1 – remove dose reference, delete 300 mg tablets (only 100 mg tablets are provided by manufacturer) • Other minor edits (all tracked)	yes
2	04/26/2016	• Through-out document: mark the phase I component as enrollment completed March 2016 and set phase II dose at 300 mg bid • Sections 7.2.1 and 8.2: reduce the frequency of D-dimer monitoring in the phase II component as abnormalities were not seen during phase I with a supportive care plan if > 3-fold increase • Section 7.2.3: add a statement that dose modifications are allowed for individual patients and label current - modifications as guidelines	yes

Revision #	Version Date	Summary Of Changes	Consent Changes
		• Section 8.1: standard of care – clarify screening may occur anytime post-transplant until day +60 • Section 8.2: research related – decrease d-dimer testing to screen, day 22 and final treatment visit; delete all PT/INR except baseline and final treatment visit; delete day 50 column (PT/INR and d-dimer deleted).add footnote number for day 64 and day 92 column; label day 99 column as last day of study drug • Section 10: update to current IRB reporting requirements • Remove Linda Burns from the cover page as no longer at this institution	
3	02/12/2018	• Expand study enrollment window from through Day 60 post-transplant to through Day 75 post-transplant • Add a window of ±7 days for the administration of the 3rd dose of rituximab • Remove Dr. Lazayan as Co-I from the cover page as no longer at this institution • Updates to the current protocol template	yes

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Protocol Synopsis

Study of the ADAM17 Inhibitor INCB7839 Combined With Rituximab After Autologous Hematopoietic Cell Transplantation (HCT) For Patients With Diffuse Large B Cell Non-Hodgkin Lymphoma (DLBCL)

Study Design:

This is a single institution phase I/II study using an ADAM17 inhibitor (INCB7839) with rituximab as consolidation therapy after an autologous hematopoietic cell transplant (HCT) for patients with diffuse large B cell lymphoma (DLBCL). The study consists of two phases. The dose finding phase is a modified version of a phase I trial and the extended phase is a modified version of a phase II trial.

Rituximab (375 mg/m^2) is given at 3 time points post-transplant - the 1st shortly after the day 28 (but as late as day 75), with the 2nd and 3rd doses 1 and 7 weeks later. The oral ADAM 17 inhibitor INCB7839 is taken twice daily at the assigned dose for 90 days beginning at the time of 2nd rituximab.

The primary goal of the dose finding phase is to determine the maximum tolerated dose (MTD) of INCB7839. Up to three dose levels will be tested (100 mg bid, 200 mg bid, and 300 mg bid). As the 300 mg bid has been proven safe in the non-transplant setting, dose escalation follows a Fast-Track Design with 1 patient enrolled per dose level unless a grade 2 or greater treatment emergent event occurs within the 1st 14 days of INCB7839. At that point, dose escalation converts to a standard 3+3 design and two additional patients are enrolled at the current dose level. If dose level 3 is completed without dose limiting toxicity (DLT) in the 1st 3 patients, an additional 3 patients will be enrolled at this level (without the staggering required by the DLT rules) prior to moving to the phase II component.

Once the phase I dose escalation is completed, an additional 12 patients will be enrolled at the MTD (or dose level 3, if no DLT) to obtain a more detailed toxicity profile as well as a preliminary estimate of progression free survival at 6 months post-transplant.

Primary Objective:

Phase I Dose Finding: To determine the maximum tolerated dose (MTD) of INCB7839 when given in combination with rituximab as consolidation therapy after an autologous hematopoietic cell transplant (HCT) for diffuse large B cell lymphoma (DLBCL).

Phase II Extension: To establish a preliminary estimate of progression free survival (PFS) at 6 months post autologous HCT while gaining a more detailed toxicity profile of INCB7839 when administered with rituximab as consolidation therapy

Secondary Objectives:

- To evaluate the safety and tolerability of INCB7839 in combination with rituximab
- To determine incidence of serious adverse events
- To evaluate 1 year disease-free survival
- To evaluate 1 year overall survival
- To determine time to relapse/progression

Correlative Objectives:

- To compare expression of CD16 and CD62L on natural killer (NK) cells and NK cells function after INCB7839 plus rituximab versus rituximab only and the baseline.
- To correlate clinical response with NK frequencies, phenotype, and function

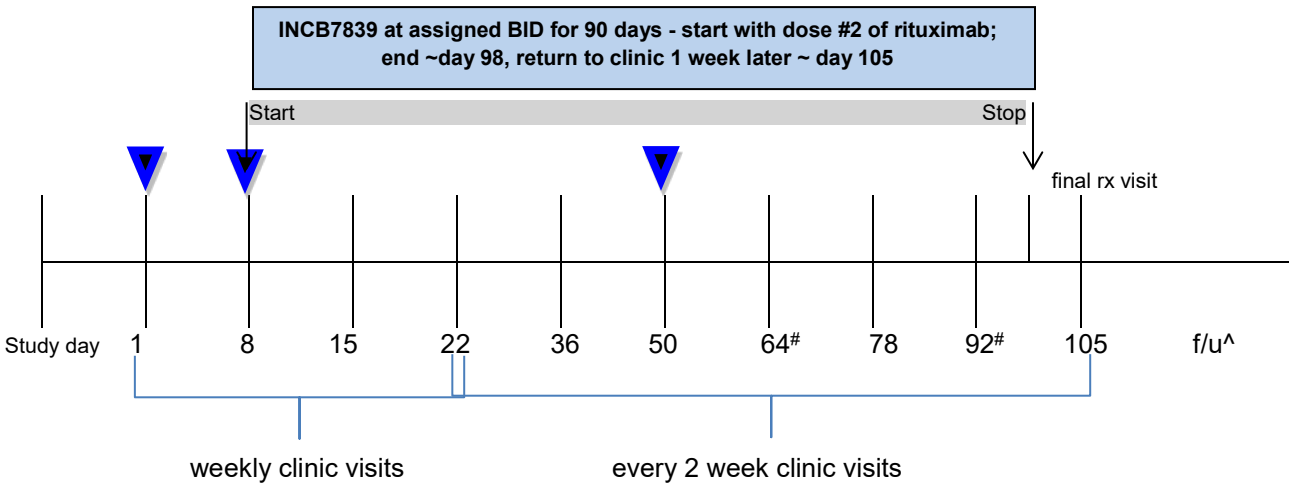
Patient Population:

Patients 18 years and older with DBLCL who underwent an autologous HCT and are in remission (CR, PR) or have stable disease at the day 28 post-transplant reassessment

Enrollment:

Phase I Dose Finding: 6 to 18 patients (Enrollment completed March 2016)
Phase II Extension: enroll an additional 12 patients at the phase I MTD

Study Schema



* also begin aspirin prophylaxis with the 1st dose of INCB7839 (unless on other anti-coag) and continue daily until 1 week after the last dose of INCB7839 (per section 7.2.1)

Rituximab 375 mg/m^2 IV after day +28 re-staging and again 1 and 7 weeks later
Note: the 1st dose of rituximab may begin as late as day 75 post-transplant, refer to section 7
INCB7839 at assigned dose twice daily for 90 days – begin the morning of the 2nd dose of rituximab

day 64 and day 92: study coordinator to check in with patient, no clinic visit unless medically indicated
Final treatment visit day 105 or 1 week after last dose of INCB7839 if discontinued earlier
^F/U for disease and survival status will link to transplant related milestones and/or SOC visits with information obtained from BMT database

INCB7839 Dosing Scheme
Phase I Dose Finding: ENROLLMENT COMPLETED MARCH 2016 – 300 mg BID for Phase II

Dose Level	INCB7839 Dose (taken twice daily)	Minimum # of Patients*
1	100 mg	1
2	200 mg	1
3	300 mg	6

Fast Track Design until ≥grade 2 treatment emergent event or dose level 3 is reached, then convert to 3+3 Design

3+ 3 Design dose limiting toxicity (DLT) is defined as any of the following within the 1st 14 days of INCB7839:
- any grade 3 or greater non-hematologic, non-infectious toxicity including thromboembolic complications
- selected hematologic toxicity
  - grade 4 neutropenia lasting for ≥ 7 days
  - febrile neutropenia
  - grade 4 thrombocytopenia lasting for ≥ 7 days despite dosing delay
  - grade 3 thrombocytopenia associated with bleeding
- inability to complete at least 10 days (20 doses) of twice daily INCB7839 therapy within the 1st 14 days due to treatment related toxicity

If dose level 3 is reached without DLT in the 1st 3 patients, an additional 3 patients (for a total of 6) will be enrolled without the 14 day waiting period
Phase II Extension: Enroll an additional 12 patients - INCB7839 at the maximum tolerated dose (MTD) established during phase I component or dose level 3 if no DLT

1 Objectives

1.1 Primary Objective

Phase I dose finding: To determine the maximum tolerated dose (MTD) of INCB7839 when given in combination with rituximab as consolidation therapy after an autologous hematopoietic cell transplant (HCT) for patients with diffuse large B cell lymphoma (DLBCL)

Phase II expansion phase: To establish a preliminary estimate of progression free survival (PFS) at 6 months post autologous HCT while gaining a more detailed toxicity profile of INCB7839 when administered with rituximab as consolidation therapy

1.2 Secondary Objectives

- To evaluate the safety and tolerability of the ADAM17 inhibitor INCB7839 in combination with rituximab
- To determine incidence of serious adverse events
- To evaluate 1 year disease-free survival
- To evaluate 1 year overall survival
- To determine time to relapse/progression

1.3 Correlative Objectives

- To compare expression of CD16 and CD62L on natural killer (NK) cells and NK cell function after ADAM17 inhibitor INCB7839 plus rituximab versus rituximab only versus baseline
- To correlate clinical response (relapse versus remission) with NK phenotype and function

2 Background

2.1 Enhancing Cure Rate Of DLBCL After Autologous Hematopoietic Cell Transplant

Non-Hodgkin lymphoma (NHL) is the second most common hematologic malignancy. Diffuse large B cell lymphoma (DLBCL), the most common lymphoma subtype (30-40%), is an aggressive cancer that is rapidly fatal unless promptly treated. In the US, approximately 440,000 patients were treated for NHL in 2010 (SEER.gov). Patients with DLBCL experience frequent relapse and estimated 5-year survival rate is less than 50%.[1, 2]

Standard treatment includes the use of high-dose chemotherapy with autologous hematopoietic cell transplantation for patients with

chemosensitive recurrence. Although most patients initially achieve a remission, treatment fails for most patients. The relapse incidence is particularly high during the first 6 months after transplant[3] (**Figure 1**). There is an urgent need to develop well-tolerated and effective therapies to sustain remission in DLBCL. In this proposal, we hypothesize that chemoresistant lymphoma cells surviving post autologous transplantation retain sensitivity to cellular immune-mediated killing. This hypothesis is supported by clinical evidence that human natural killer (NK) and T cells can be used to treat cancer.[4,5] NK cells (defined as $CD3^-CD56^+$) are capable of killing virally infected or transformed cells without prior sensitization; however, autologous NK cells have to be activated to kill. Proposed trial presents the novel approach of combining monoclonal antibody therapy with the newly discovered strategy of augmenting both NK cell function and tumor homing. The treatment goal is to eliminate chemoresistant lymphoma cells after autologous transplantation.

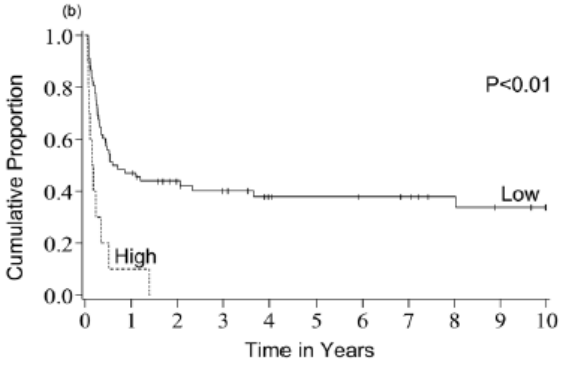


Figure 1. Progression free survival in DLCBL after autologous transplant in low and high risk groups defined by International Prognostic Index at relapse[1]

2.2 Rituximab Use After Autologous Transplantation In DLBCL

Rituximab's key anti-cancer mechanism of action is mediated through FcγRIII (CD16) on NK cells; this receptor is by far the most potent NK activating receptor.[6] Rituximab crosslinks CD16 and triggers vigorous production of cytokines and NK cell degranulation, leading to target cell killing (a process referred to as antibody-dependent cellular cytotoxicity; ADCC). Targeting CD20 on lymphoma cells with rituximab dramatically improves initial remission rates (by 10-20%), but resistance is common. The international CORAL study tested the impact of maintenance rituximab after autografting by evaluating DLBCL patients treated with rituximab or controls.[6] The 4-year event-free survival rates were identical in the two groups (52% and 53%). The limitations of rituximab efficacy may be due to poor NK cell function post transplantation. The mechanism of rituximab resistance to be tested in this study presents a new therapeutic opportunity. We hypothesize that targeting CD16 with the ADAM17 inhibitor may potently improve rituximab efficacy after autologous transplantation.

2.3 Inhibition of ADAM17 Enhances NK Cell Function

NK cells contain a germ line encoded set of receptors governing both their development and function. These receptors are either activating or inhibitory. Integration of downstream signaling pathways dictates how an NK cell will respond when interacting with its target. The most notable inhibitory receptors are the killer-immunoglobulin like (KIR) receptors which recognize the human leukocyte antigen (HLA) class I proteins (HLA-A, -B, and –C). The most potent NK activating receptor is FcRγ IIIA (CD16), present on most peripheral blood NK cells and all $CD56^{dim}$ NK cells. CD16 mediates ADCC upon recognition of antibody-coated tumor cells, leading to target elimination through direct killing and cytokine production. Other activating receptors include NKG2D, which recognize "stress ligands" expressed on tumor cells. We recently identified a novel mechanism by which activated NK cells rapidly downregulate CD16.[7] Loss of CD16 is an enzymatically regulated process limiting ADCC. Importantly, our group recently discovered that CD16 is clipped by a desintegrin and metalloproteinase-17 (ADAM17). We showed that inhibition of ADAM17 with the small, orally available molecule INCB7839 consistently increased the killing of rituximab-coated lymphoma cells by preserving CD16 on NK cells. For the first time our data identified a novel target, ADAM17, that modifies the potency of monoclonal antibodies inducing ADCC. Importantly, the ADAM family enzymes including ADAM17 and ADAM10 are highly expressed in lymphoma tumor stroma.[8] Additionally, others showed that lymphoma-associated stress ligands (ULBP3, MICA, MICB, and B7-H6) capable of activating NK cells are also ADAM17 targets[9]

ADAM17 clips CD16 and L-selectin from NK cells and limits NK cell function. The anti-CD20 monoclonal antibody rituximab interacts with FcRIIIya/CD16 on NK cells to induce ADCC. Upon antibody recognition, this activating NK cell receptor induces potent signals that result in cytokine production (IFNγ and TNFα) and cell cytotoxicity[7,9] CD16 is rapidly down-regulated when the NK cell is activated by various triggers (PMA, cytokines IL12+IL18, and HLA-class I negative cell target K562; **Figure 2**). This process, referred to as ectodomain clipping, is a proteolytic event that occurs at an extracellular site proximal the plasma membrane resulting in

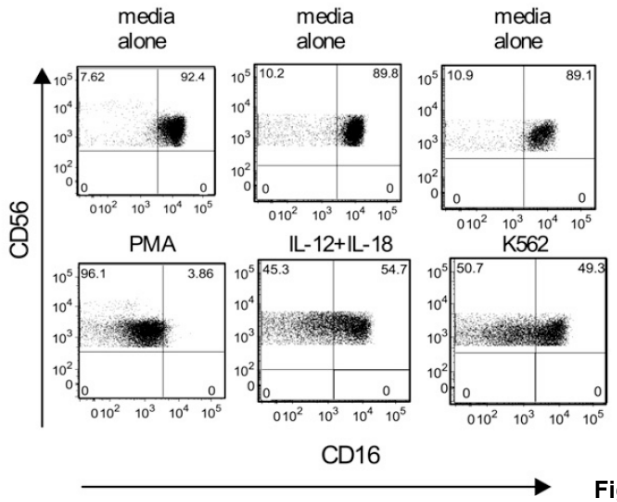


Figure 2

soluble CD16 release. We were the first to report that the membrane metalloproteinase ADAM17 is expressed by human NK cells and clips off CD16 and the homing molecule L-selectin (CD62L) upon NK cell activation.[7]

CD16 expression is decreased after treatment with rituximab in vivo. In a control experiment (**Figure 3, top panel**), we incubated $CD56^{dim}$ NK cells with rituximab (10 µg/ml) in vitro and showed that it does not block CD16 binding. We then tested peripheral blood from patients with DLBCL before and after the therapy with rituximab (375mg/m^2 x 4 doses). At baseline $CD56^{dim}$ NK cells expressed high levels of CD16. After rituximab therapy, a large proportion of blood NK cells (46%) downregulated CD16 and became CD16 negative (**Figure 3, lower panel**) demonstrating that rituximab treatment doses clip CD16 off NK cells in vivo.

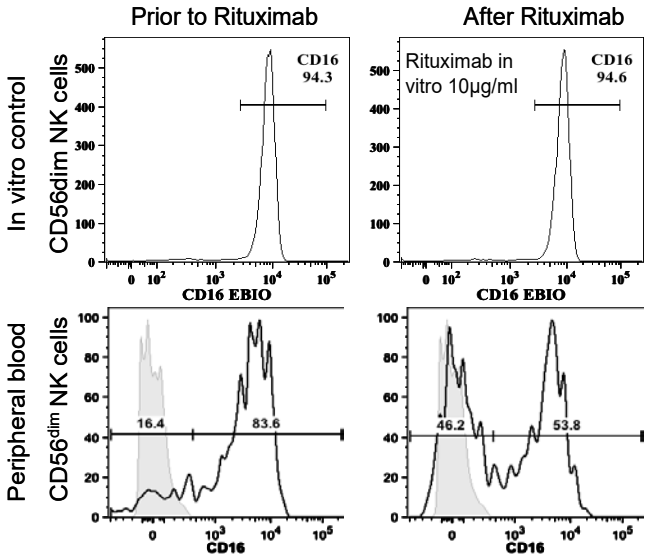


Figure 3

2.4 Lymphoma-Associated Stress Ligands

Others showed that ADAM family enzymes including ADAM10 and ADAM17 are expressed in lymphoma tumor stroma. Furthermore lymphoma-associated stress ligands (such as ULB, MICA, MICB and B7-H6) are also ADAM17 protease targets.[9] The significance of these findings is that therapeutic blockade of ADAM10 and ADAM17 seems promising for cancer treatment by targeting immune escape of tumors.

2.5 INCB7839 Is An Orally Bioavailable Small Molecule Selective Inhibitor Of ADAM17/ADAM10

INCB7839 was recently developed by Incyte as an inhibitor of HER2 (also an ADAM17 target). The drug was tested in phase 1 studies in over 100 patients. Results of these studies are summarized in below.

ADAM17 inhibitor INCB7839 plus rituximab augments NK cell cytokine production and cytotoxicity in vitro[7]

We recently demonstrated that pharmacological inhibition of ADAM17 enhanced CD16-mediated NK cell function by preserving CD16 on the NK cell surface and thus increased the killing of rituximab-coated lymphoma cells. In in-vitro assays, we purified human NK cells and incubated them with media alone, the B cell lymphoma line Raji, or Raji cells pre-incubated with 10 mg/mL rituximab. Expression of CD16, CD62L (panel A), and intracellular IFNγ and TNFα (panel B) were measured after 5 hours (**Figure 4**). Inhibition of ADAM17 significantly attenuated clipping of both CD16 and CD62L from NK cells after incubation with rituximab-coated Raji cells (**Figure A**). In addition, ADAM17 inhibition significantly increased intracellular levels of IFN-g and TNF-a (**Figure B**).

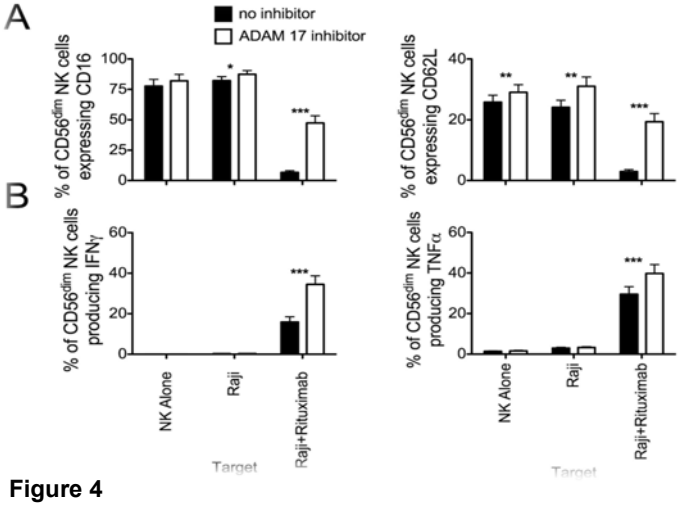


Figure 4

Clinical Safety

Phase 1 studies using INCB7839

INCB7839 is methyl (6S,7S)-7-[(hydroxyamino) carbonyl]-6-[(4-phenylpiperazin-1-yl)carbonyl]-5-azaspiro[2,5]octane-5-Carboxylate).

INCB7839 is an orally bioavailable selective small molecule inhibitor of ADAM17/ADAM10 developed by Incyte (Wilmington, DE). It prevents clipping of the tumor ligands HER2 and ErbB by inhibiting the ADAM17 protease in a dose-dependent manner. The half-life of dosing with the extended release tablet is 10-14 hours. Single and multiple-dose studies have been completed with INCB7839 in healthy volunteers. Adverse events were mild and self-limiting. INCB7839 (dosed 100-500mg twice a day; bid) was tested in an open label, dose-escalation, phase 1 study for solid tumors. A dose of 500mg bid was determined to be the maximum tolerated dose. The dose-limiting toxicity was deep venous thrombosis (DVT) with a total of 9 thrombotic events (in 41 patient months); however, nearly all patients had added thrombotic risk factors of advanced malignancy. However, there was not a clear relationship between the frequency of thrombosis and the dose administered. In patient without prophylaxis (low

dose ASA) the risk of DVT was 25%. The most recent phase 1 study combined INCB7839 (100-300mg bid) with the anti-HER-2 monoclonal antibody trastuzumab in 46 patients with previously untreated metastatic HER2+ breast cancer. [13] (poster in Appendix III) The highest dose administered was 300mg bid, and side effects were modest. The most reported events (all causes) occurring in ≥ 10% of patients were: vomiting, pyrexia, anorexia, pain, diarrhea, dyspnea, asthenia, headache, cough, arthralgia, vascular events, abdominal pain, and back pain. Most were not serious. The incidence of DVT was 10%, and thus, prophylactic measures are warranted to reduce the risk of thrombosis associated with INCB7839.

CD16 plasma levels before and after therapy with INCB007839. We tested plasma levels of soluble CD16 in 11 patients enrolled to the trastuzumab+INCB7839 clinical trial by ELISA. Soluble CD16 levels were significantly reduced after therapy with INCB7839 (**Figure 5**).

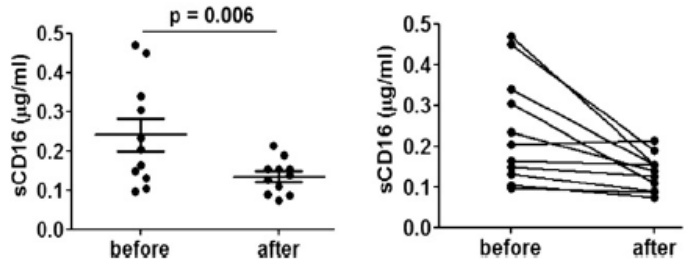


Figure 5: mean and standard deviation are shown.[14]

2.6 NK Cells Rapidly Develop After Autologous HCT And Express CD16

The recovery of NK cells after autologous HCT is vigorous and prompt. Four weeks after HCT, NK cells represent about 15-45% of lymphocytes (**Figure 6**) and are composed almost exclusively of $CD56^{dim}$ NK cells characterized by CD16 expression. CD16 expression on $CD56^{dim}$ NK cells is 65-70% at all time-points after transplant, however NK function is often decreased.

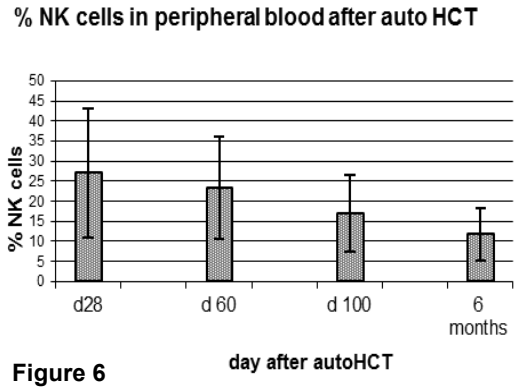


Figure 6

2.7 NK Cell Therapy Trial At University of Minnesota

We have tested various strategies to enhance the cytotoxicity of NK cells to treat patients with lymphoma. We tested outpatient low-dose IL2 based immunotherapy in three clinical trials encompassing >75 patients to date.(9) Patients undergoing autologous HCT therapy including NHL patients were subsequently enrolled to a clinical trial combining daily subcutaneous IL2 administration with infusion of autologous NK cells incubated ex vivo with IL-2 and combinations of IL-2 with Rituximab post autologous HCT.[5,11,12] There was significant clinical benefit of these therapies. More recently, we used allogeneic donor derived NK cells followed by IL-2 to treat refractory non-Hodgkin lymphoma patients (12) We treated 12 patients on this regimen and observed clinical remission in 40%, however the cost and complexities of production of NK cell product limited the large scale use.[10]

This study builds on the established NK cell therapy program at University of Minnesota and explores novel platform to augment the activity of autologous NK cells with the use of the ADAM17 inhibitor INCB7839.

3 Summary and Rationale

Our **hypothesis** is that the ADAM17 inhibitor INCB7839 will enhance the efficacy of rituximab-mediated autologous NK cell killing, resulting in a 20% improvement in progression free survival in DLBCL patients treated with autologous HCT.

3.1 INCB7839 Dose Rationale

In this dose escalation plan, three dose levels of INCB7839 will be tested (100 mg bid, 200 mg bid, and 300 mg bid). The previous INCB7839 plus trastuzumab study showed that the 300 mg bid dose was safe; however this was in a non-transplant setting. Therefore this study will proceed cautiously, starting with a 100 mg dose but using a fast track design to minimize the number of patients exposed to a potentially non-therapeutic dose. With the fast-track design, one patient will be enrolled per dose level until a grade 2 or greater treatment emergent toxicity is encountered. At that point, dose escalation will convert to a 3+3 design and three additional patients will enroll at the current dose level. Unless there is an interaction with the milieu seen in the post-transplant setting, it is expected all 3 dose levels will be completed without DLT and the 300 mg bid dose level will move to the phase II.

4 Study Design

This is a single institution phase I/II study using an ADAM17 inhibitor (INCB7839) with rituximab as consolidation therapy after an autologous hematopoietic cell transplant (HCT) for patients with DLBCL. The study consists of two phases. The dose finding phase is a modified version of a phase I trial and the extended phase is a modified version of a phase II trial.

The study is open to persons 18 years and older who are in a complete response, partial response or have stable disease at their 28 days post-transplant reassessment. Three doses of rituximab (375 mg/m^2) will be given post-transplant. The first dose will be given at the day 28 post-transplant follow-up (but permitted through day 75), the 2nd dose 1 week later, and the 3rd dose 7 weeks after the 1st. The oral ADAM 17 inhibitor INCB7839 at the assigned dose will be taken twice daily for 90 days (12 weeks). The 1st dose will be taken the morning of the 2nd rituximab dose after the research related labs are drawn.

The primary goal of the dose finding phase is to determine the maximum tolerated dose (MTD) of INCB7839. Up to three dose levels of INCB7839 will be tested (100 mg bid, 200 mg bid, and 300 mg bid). As the 300 mg bid has been proven safe in the non-transplant setting, dose escalation will follow a Fast-Track Design with 1 patient enrolled per dose level until a grade 2 or greater treatment emergent adverse event occurs. A treatment emergent adverse event is any event not present prior to the initiation of the treatment (INCB7839) or any event already present that worsens in either intensity or frequency following exposure to the treatment. At that point, dose escalation will convert to a standard 3+3 design with two additional patients enrolled at the same dose level. If dose level 3 is completed without dose limiting toxicity (DLT) in the 1st 3 patients, an additional 3 patients will be enrolled at this level (without the staggering required by the DLT rules) prior to moving to the phase II component. DLT is defined in section 7.2.2 of the protocol.

Once the phase I dose escalation is completed, an additional 12 patients will be enrolled at the MTD (or dose level 300mg bid, if no DLT) to obtain a more detailed toxicity profile as well as a preliminary estimate of progression free survival at 6 months post-transplant. Persons receiving less than 10 weeks of INCB7839 and/or fewer than 2 doses of rituximab will be replaced for the primary endpoint analysis.

Patients will be followed for 1 year from transplant for progression free survival (PFS) and overall survival (OS).

5 Patient Selection

Study entry is open to patients 18 years and older regardless of gender or ethnic background. While there will be every effort to seek out and include women and minority patients, the patient population is expected to be similar to that of autologous HCT studies at the University Of Minnesota since this is a requirement for study entry.

Inclusion Criteria

5.1 Patients 18 years or older who have undergone an autologous HCT for the treatment of DLBCL and are in a complete remission (CR), partial remission (PR) or have stable disease (SD) at the day 28 post-transplant reassessment

5.2 Karnofsky Score of ≥ 70% (appendix II)

5.3 Able to start the protocol therapy (1st dose of rituximab) between day 28-75 post-transplant

5.4 Adequate organ function defined as:

Hematologic: platelets ≥ 50,000 x 10^9/L; ANC ≥ 1000 x 10^9/L unsupported by G-CSF or GM-CSF for 3 days

Renal: creatinine < 1.5 mg/dl or glomerular filtration rate > 50 ml/min

Hepatic: Alanine transaminase (ALT, SGPT) and aspartate aminotransferase (SGOT, AST) < 3 x upper limit of institutional normal and total bilirubin < 3.0 mg/dl (if total bilirubin is ≥ 3.0 patient is eligible if direct bilirubin is within normal limits)

Pulmonary: clinically no evidence of pulmonary disease

Cardiac: no symptoms of uncontrolled cardiac disease

5.5 If post-transplant consolidation radiation therapy is given, the patient must be at least 14 days between last radiation treatment and 1st dose of rituximab

5.6 Able to take daily aspirin (325 mg) for the duration of INCB7839 treatment and 1 week after the last dose to reduce the risk of thrombosis (not applicable if on other anti-coagulant therapy at time of study enrollment – see section 5.11)

5.7 Females are either postmenopausal for at least 1 year, are surgically sterile for at least 3 months, or must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 12 months after the last dose of rituximab if of childbearing potential. (Note: Permitted

methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their understanding confirmed).

5.8 Males must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from screening through 12 months after the last dose of rituximab. (Note: Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the participants and their understanding confirmed).

5.9 Voluntary written consent signed before performance of any study-related procedure not part of normal medical care

Exclusions

5.10 Pregnant or lactating – Studies to evaluate the potential for embryo toxicity and teratogenicity have not been performed for INCB7839. Until additional information is available, women of childbearing potential should use appropriate precautions to avoid becoming pregnant. Rituximab is Pregnancy Category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Females of childbearing potential must have a negative urine or serum pregnancy test within 14 days of study treatment start

5.11 Recent venous thrombosis within 4 weeks prior to study enrollment. Patients at high risk for thrombotic events due to inherited risk factors (i.e. factor V Leiden) or DVT/PE in the past 12 months should be on secondary prophylaxis with anti-coagulant therapy (i.e. warfarin or low molecular weight heparin) prior to enrollment

5.12 Active uncontrolled infection

5.13 Active CNS disease

5.14 Previous severe or life-threatening allergic reaction with rituximab or known allergy to the compounds found in INCB7839

5.15 Any gastrointestinal condition causing malabsorption or obstruction (eg, celiac sprue, gastric bypass surgery, strictures, adhesions, history of small bowel resection, blind loop syndrome)

5.16 Unwilling or unable to swallow tablets BID

5.17 Serologic or clinical evidence of current active hepatitis B or C infection, defined as elevated levels of Hep B antigen or Hep C antibody (unless active infection is ruled out by nucleic acid tests)

5.18 Known HIV infection

6 Patient Screening and Enrollment/INCB7839 Dose Level Assignment

Written consent must be obtained prior to the performance of any research related tests or procedures. Consent is usually obtained before final eligibility is determined.

Enrollment in the study and the 1st dose of rituximab may occur up to day 75 post-transplant.

6.1 Consent and Study Screening in OnCore

Any patient who has been consented is to be entered in OnCore by the Primary Clinical Research Coordinator (PCRC) or designee. If a patient is consented, but not enrolled, the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

6.2 Study Enrollment

To be eligible for study enrollment, the patient must sign the treatment consent and meet each of the inclusion criteria and none of the exclusion on the eligibility checklist (Appendix I) based on the eligibility assessment documented in the patient's medical record.

The Primary Clinical Research Coordinator (PCRC) or designee will assign the study treatment arm and add the on-treatment date to complete enrollment.

6.3 INCB7839 Dose Level Assignment

The PCRC or designee will assign each patient to the current dose level of INCB7839 no later than the day of the 2nd rituximab dose.

In March 2016, enrollment to the phase I dose escalation component was completed with INCB7839 at 300 mg twice a day deemed the phase II dose.

6.4 Patients Who Are Registered and Do Not Receive Study Treatment

If a patient is registered to the study, and is later found not able to receive the 1st dose of rituximab by day 75 post-transplant, for whatever reason, the patient will be removed from study and treated at the physician's discretion. The PCRC or designee will update OnCore of the patient's non-treatment status and notify the Principal Investigator. Study data will be collected until the time the patient is off study. The reason for removal from study will be clearly in OnCore. The patient will be replaced to complete enrollment.

7 Treatment Plan

The first dose of rituximab will be considered study week 1 regardless of whether it is given at post-transplant day 28 or as late as post-transplant day 75. Routine post-transplant follow-up will continue as planned, independent of this study, although during active treatment study visits will be scheduled to coincide with transplant related visits (i.e. day 60, 100). Follow-up time points for disease and survival status will remain linked with a post-transplant visit at 6 and 12 months regardless of when the 1st dose of rituximab in given.

7.1 Rituximab

Rituximab 375 mg/m^2 IV will be administered per institutional guidelines at the following time points:

- On (or shortly after) the day 28 post-transplant re-assessment, but no later than post-transplant day 60
- 1 week (+/- 3 days) after the 1st dose
- 7 weeks (+/- 7 days) after the 1st dose

The first dose will be infused over 6 hours. Infusion should start at 50 mg/hour and increase by 50 mg/hour every 30 minutes as tolerated to a maximal infusion rate at 400 mg/hour. If the infusion is well tolerated, the next two doses at 1 and 7 weeks may be administered at 100 mg/hour with 100 mg/hour increments at 30 minutes intervals up to 400 mg/hour.

Premedication: Acetaminophen 650 mg PO and diphenhydramine (e.g. Benadryl) 25 mg PO 30 minutes before each infusion.

Persons receiving fewer than 2 doses of rituximab will be considered unevaluable and replaced.

7.2 INCB7839

Patients will begin INCB7839 orally at the assigned dose bid the morning of the 2nd rituximab dose and after the research related blood samples are collected. In April 2016 the study moved to the phase II component with the INCB7839 dose set at 300 mg bid. Dose modifications in individual patients are permitted per section 7.2.3.

The tablets are taken twice daily, morning and night, approximately 12 hours apart for 90 days (+/- 3 days) with food.

If the morning or evening dose is missed by more than 4 hours, the patient will skip that dose and take the next scheduled dose at the usual time. Skipped doses will not be made up.

The patient will be provided with a daily drug log to record times of administration, side effects, and missed doses. The patient will be instructed to bring the drug log and study drug bottles (including any empties) to each appointment for reconcilement.

No pre-medications are recommended with the INCB7839 dosing, although side effects may be treated as needed (i.e. acetaminophen for headache, diphenhydramine for nausea).

7.2.1 Supportive Care

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. anti-emetics, anti-pyretics).

DVT prophylaxis (all patients): On the same day that INCB7839 dosing is started, all patients will begin taking aspirin tablet (325 mg) once a day or on anticoagulant therapy (e.g. warfarin, low-molecular-weight heparin (LMWH) for the duration of INCB7839 administration and for 1 week afterwards as prophylactic measure to reduce the risk of thrombosis.

In the event of "excessive DVT" defined as >20% thrombotic events in patients taking aspirin, all patients (current and future) will be discontinued from aspirin and begin anti-coagulation therapy (e.g. warfarin or LMWH at prophylactic dose) at the time of their next scheduled appointment. Patients within 1 week of discontinuing INCB7839 may continue aspirin as planned.

Serum D-dimer levels will be checked prior to the 1st dose of rituximab, at Day 22, and at the final study visit effective with the April 2016 protocol revision. The frequency was decreased from the phase I monitoring schedule as abnormalities were not seen. If D-dimer level increase >3-fold, than the patient will be considered at high risk of developing DVT/PET and will be switched to warfarin or LMWH for anticoagulation.

7.2.2 INCB7839 Dose Level Assignment

Dose Finding Phase (COMPLETED MARCH 2016)

INCB7839 dose level assignment will occur at the time of study registration based on the following Dose Level cohorts:

Dose Level	INCB7839 Dose (taken twice daily)	Minimum # of Patients*
1	100 mg	1
2	200 mg	1
3	300 mg	6

Initially the Fast Track Design of 1 patient per dose level will be used until a grade 2 or greater treatment emergent adverse event is experienced. At that point, three additional patients will be enrolled at the same dose level and a standard dose escalation design will be used per section 13.2.

Dose Limiting Toxicity is defined as any of the following within the 1st 14 days of INCB7839 dosing:

- any grade 3 or greater non-hematologic, non-infectious toxicity including thromboembolic complications
- selected hematologic toxicity
  - grade 4 neutropenia lasting for ≥ 7 days
  - febrile neutropenia
  - grade 4 thrombocytopenia lasting for ≥ 7 days despite dosing delay
  - grade 3 thrombocytopenia associated with bleeding
- inability to complete at least 20 doses of twice daily INCB7839 therapy within the 1st 14 days due to treatment related toxicity

Dose escalation to the next level cannot proceed until the following conditions are met:

- At least 14 days has passed since the last patient within a dose level began INCB7839
- The maximum tolerated dose (MTD) has not been exceeded

If dose level 3 is reached without DLT in the 1st 3 patients, an additional 3 patients (for a total of 6) will be enrolled without the 14 day waiting period.

Phase II Extension (OPENED TO ENROLLMENT APRIL 2016)

In March 2016 INCB7839 at 300 mg bid was declared the phase II dose level. An additional 12 patients will be enrolled at the MTD established during the phase I component adhering to the early stopping rules found in section 13.4.

7.2.3 INCB7839 Dose Modification/Interruptions

Refer to section 7.2.1 for prevention and management of thromboembolic complications.

With activation of the Phase II extension in April 2016, both dose reductions and dose interruptions are permitted in individual patients at the discretion of the treating physician if the 300 mg bid dose is not well tolerated.

Dose reductions will follow the phase I dose levels (i.e. 300 mg bid reduced 200 mg bid reduced 100 mg bid).

Dose interruptions of up to 14 days are permitted, restarting with or without a dose reduction.

General Guidelines:

Grade 1 and 2 adverse events will be treated as medically appropriate and the INCB7839 dose may be reduced by one phase I dose level (i.e. 300 mg bid may be reduced to 200 mg bid).

INCB7839 administration should be interrupted in the event of a CTCAE v4 **grade 3 or 4 treatment related toxicity** despite best medical support, until resolution to grade 1 or better. The patient may be restarted on INCB7839 at 1 dose level lower (i.e. 300 mg reduced to 200 mg bid).

Skipped doses will not be made up.

In general a patient would be taken off treatment if any of the following occurs:

- a treatment break is for more than 14 days
- the patient is unable to tolerate INCB7839 at 100 mg bid
- if the toxicity recurs (≥ grade 3) despite a dose reduction

Note: any treatment related grade 4 or 5 event may count toward the study's early stopping rules per section 13.5.

7.3 Duration of INCB7839

Patients will take INCB7839 twice a day beginning with the 2nd dose of rituximab and continuing for 90 days (+/- 3 days) unless:

- consent is withdrawn
- patient refuses INCB7839 or is non-compliant
- more than 14 days pass without dosing (regardless of reason), the patient is unable tolerate INCB7839 at the100 mg bid level or a toxicity recurs (≥ grade 3) after a dose reduction
- disease progression
- unacceptable toxicity
- in the treating physician's medical judgment, continuing with INCB7839 is not in the best interest of the patient's health or well-being

During the extension phase, patients receiving less than 10 weeks of INCB7839 or less than 2 doses of rituximab for reasons other than toxicity will be replaced.

7.4 Duration of Study Participation

Active study participation will end 1 week after the last dose of INCB7839 unless there is ongoing treatment related toxicity, which will be treated as medically appropriate with follow-up until toxicity resolves to grade 1 or better or is stable for 3 months.

Patients will be seen at 6, 9 and 12 months post-transplant as part of the standard of care follow-up with information regarding disease status and survival recorded for this study unless one of the following occurs:

- consent is withdrawn
- patient is unevaluable – if a patient is not evaluable, follow only until the resolution or stabilization of treatment related toxicity

8 Schedule of Patient Activities

For patient convenience and unnecessary clinic visits; some flexibility is permitted in scheduling study related visits and activities. Through the day 22 visit a window of ± 3 days is permitted. A window of ± 7 days is permitted for the 3rd dose of rituximab. After day 22, visits will coordinate with BMT anniversary visits whenever feasible; however a window of ± 7 days is permitted for any study visits not linked to a BMT anniversary visit. After the end of treatment visit, disease and survival status will be obtained from the BMT database.

8.1 Standard of Care

Study Time Point	Screening (any time between day +28 and +60))	Day 1[1]	Day 8	2- 4 days after 2nd rituximab dose (refer to 8.2)	Day 15	Day 22	Day 36	Day 50	Day 78	End Of Treatment Visit Day 105	F/U for Disease and Survival Status[3]
Consent	X										
Medical History	X				X	X	X	X	X	X	
Physical Exam	X				X	X	X	X	X	X	
Height	X										
Weight		X	X					X		X	
Review of transplant related side effects	X										
Karnofsky PS	X				X	X				X	
CBC/diff/plt	X	X	X		X	X	X	X	X	X	
Comprehensive Metabolic panel	X	X	X		X	X	X	X	X	X	
Pregnancy test if applicable	X										
Disease Evaluation[2]	X								X		X[3]
Rituximab		X	X					X			

1 – day 1 may occur anytime between day 28 and day 75 post-transplant

2 – disease evaluations are the results of the transplant related follow-ups at approximately day +28 and day +100 post-transplant

3 – follow-up after the final treatment visit is linked to transplanted related milestones and/or standard of care visits – information for this study will be obtained from routine data collected by the BMT database

8.2 Research Related Procedures and Activities

Study Time Point	prior to 1st dose of rituximab	Day 8 prior to 2nd dose of rituximab	2-4 days post 2nd dose of rituximab	Day 15	Day 22	Day 36	Day 64 and Day 92[3]	Day 78	Day 99 (last dose of drug)[2]	Day 105[4]
PT/INR	X									X
D-dimer refer section 7.2.1	X				X					X
Review of drug log (AEs)/ tablet count		X				X	X[3]	X		X
Monitor for stopping rules (phase II)	Per section 13.5 by 4 months post-transplant									
five 10 ml heparin (green top) tubes, one 10 ml serum (red top) tube	X	X	X		X			X		X
INCB7839		begin assigned dose bid daily for 90 days (+/-3 days)								

1 – all blood samples go to TTL

2- day 99 is not a scheduled clinic visit but instead the time point where the patient discontinues drug

3- at day 64 and 92 – research nurse or designee will contact the patient; visits are not required.

4 - or 1 week after the last dose of INCB7839 if stopped earlier

All samples go to the Masonic Cancer Center's Translational Therapy Lab (TTL).

Research sample collection is tied to the clinical care schedule of events and their associated window for performance. Therefore, if a clinical time point does not occur or is altered, the research related time point will be adjusted (or eliminated) as appropriate.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this reason, up to 3 extra samples for a total of 180 ml of blood may be drawn at additional time points that are not specified above.

9 Study Drugs

9.1 INCB7839

Classification: ADAM Inhibitor

Dosage and Administration Schedule: For the purposes of the study, INCB7839 will be administered twice daily for 90 days beginning with the 2nd dose of rituximab

Dose Forms and Strengths: 100 mg tablets

Availability: For the purposes of this study INCB7839 will be provided by the manufacturing, Incyte Corporation packaged in HDPE bottles. All bottles of Incyte investigational product contain the following language: "Caution: New Drug—Limited by Federal Law to Investigational Use".

INCB7839 Expected Side Effects: In healthy volunteer studies, mild nausea, headache, dizziness, and tinnitus have been noted which may possibly be due to administration of INCB7839. One patient with a history of hot flashes experienced a hot flash of moderate intensity. One subject experienced a SAE of DVT that was possibly related to drug exposure; this patient was subsequently found to have a deficiency of antithrombin-III.

In studies of cancer patients, INCB7839 has generally shown to be tolerated at doses up to 500 mg bid. Adverse events most frequently occurring in patients receiving INCB7839 include nausea or vomiting, anorexia, fatigue, dyspnea, constipation, pyrexia, cough, asthenia, and headache.

Thrombotic events, primarily venous thromboses, have been observed at a higher than expected rate for the study population; thrombosis is defined as the dose-limiting toxicity. Investigators should discuss the risk with their patients, and maintain a high level of vigilance for signs of possible thromboembolism. Prophylactic anticoagulation is used as a precaution; it is not currently known how effective these measures are in reducing the risk of thromboembolism.

Please refer to the Investigator Brochure for additional information.

Contraindications: INCB7839 is contraindicated in subjects with clinically significant hypersensitivity to any component of its formulation.

9.2 Rituximab

Trade name: Rituxan

Classification: Monoclonal Antibody, Antineoplastic Agent

Category: Biological Response Modifier Agent

Dosage and Administration Schedule: For the purposes of the study, Rituximab 375 mg/m^2 IV administered per institutional guidelines within 4 weeks of the day 28 post-transplant re-assessment and again 2 and 8 weeks later.

Dose Forms and Strengths: 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial

Availability: Available by prescription

Warnings And Precautions:

- Tumor lysis syndrome – administer prophylaxis and monitor renal function
- PML - monitor neurologic function. Discontinue rituximab
- Hepatitis B reactivation with fulminant hepatitis, sometimes fatal – screen high risk patients and monitor HBV carriers during and several months after therapy. Discontinue Rituxan if reactivation occurs.
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor patients with these conditions closely.
- Bowel obstruction and perforation - evaluate complaints of abdominal pain.
- Do not administer live virus vaccines prior to or during Rituxan.
- Monitor CBC at regular intervals for severe cytopenias
- Pregnancy Category C

10 Adverse Event Reporting

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE). A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

10.1 Definitions

Note: throughout this section the generic term "drug" refers to the INCB7839 and rituximab.

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21CFR312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Treatment-Emergent Adverse Event: Any event not present prior to the initiation of the treatment or any event already present that worsens in either intensity or frequency following exposure to the treatment. A treatment emergent AE refers to an event temporally related to the study treatment regardless of the causality assessment by the investigator.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death.

Serious Adverse Event Or Serious Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

If either the IND sponsor or the investigator believes the event is life-threatening or serious, the event must be evaluated by the sponsor for expedited reporting (21CRF 312.32(a)).

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Thus, adverse events that occur as part of the disease process or underlying medical conditions are considered unexpected; however, they will not be reportable per section 10.3.

Unanticipated (unexpected) problems/events as defined by the University Of Minnesota IRB are those that are not already described as potential risks in the consent form, not listed in the Investigator's Brochure or not part of an underlying disease.

Note: The major discord between the FDA and IRB definitions is whether or not the underlying disease is included when considering expectedness.

The following definitions are from the Masonic Cancer Center's Standard Operating Procedure (SOP) Deviation Reporting:

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB, FDA) as

detailed in section 10.3. For the IRB this is 5 business days. For studies under an IND, it is 7 or 15 calendar days.

10.2 Adverse Event Documentation

For the purposes of this study adverse event monitoring will begin with the 1st dose of rituximab. The adverse events associated with rituximab in the post-transplant setting are well characterized and expected events will not be documented. However, any event felt at least possibly related to rituximab and meets the criteria for expedited reporting per section 10.3 will be documented.

Adverse event documentation for INCB7839 will begin with the 1st dose. Events will be recorded onto study specific case report forms based on the following table:

Relation to INCB7839	Grade 1	Grade 2		Grade 3		Grade 4 and 5
	Expected or Unexpected	Expected	Unexpected	Expected	Unexpected	Expected or Unexpected
Unrelated	Not required	Not required	Not required	Not required	Required	Required
Possible Probable Definite Unlikely	Not required	Required	Required	Required	Required	Required

After the final treatment visit approximately 1 week after the discontinuation of INCB7839 formal AE documentation will end, however; the investigator must report upon knowledge any study treatment related event meeting the criteria for expedited reporting in section 10.3 or events related to the study stopping rules.

<u>During the Fast-Track Design:</u> any grade 2 or greater treatment emergent adverse event during the 1st 14 days of INCB7839

<u>Dose Limiting Toxicity:</u> The following events within the 1st 14 days of INCB7839 meet the definition of dose limiting toxicity during the dose escalation phase component and must be reported to the MCC Study Coordinator using the DLT Report Form:

- any grade 3 or greater non-hematologic, non-infectious toxicity including thromboembolic complications
- selected hematologic toxicity within the 1st 14 days of INCB7839
  - grade 4 neutropenia lasting for ≥ 7 days

  - febrile neutropenia
  - grade 4 thrombocytopenia lasting for ≥ 7 days despite dosing delay
  - grade 3 thrombocytopenia associated with bleeding
- inability to complete at least 10 days (20 doses) of twice daily INCB7839 therapy within the 1st 14 days due to treatment related toxicity

Stopping Rule Events: The following events count toward a study stopping rule during the phase II (extension) component per section 13.5 and must be reported to the MCC Study Coordinator using the Early Stopping Rule Report Form:

- Grade 4-5 non-hematologic toxicity by 4 months post-transplant
- Grade 4-5 hematologic toxicity lasting 7 or more days by 4 months post-transplant

Events that count toward dose limiting toxicity or an early stopping rule do not necessarily constitute a serious adverse event requiring expedited reporting and should be reported as such only if they meet the criteria for expedited reporting to the IRB as defined in section 10.3.

In addition, although not always an event requiring expedited reporting, deaths with cause will be recorded in OnCore upon knowledge in the follow-up tab.

10.3 Required Reporting: FDA, IRB, and MCC's SAE Coordinator

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers	Copy AE to:
U of MN IRB	Unanticipated death of a locally enrolled subject(s); New or increased risk; Any adverse event that require a change to the protocol or consent form – refer to the IRB website for complete details	Within 5 business days of event discovery	Report Form	irb@umn.edu	SAE Coordinator mcc-saes@umn.edu and copy to Incyte Corporation
	Clinical deviations per current IRB reporting requirements		OnCore Deviation Form		
FDA	Unexpected fatal or life threatening adverse reaction except those that can clearly be determined to be unrelated to INCB7839	7 Calendar-Day	MCC SAE	Submit to CDER as an amendment to IND	
	1) Serious and unexpected adverse reaction except those that can clearly be determined to be unrelated to INCB7839 or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	15 Calendar-Day			
	All other events per CRF 312.33	At time of IND annual report	Summary format	Submit as part of the IND annual report	n/a
	Note: Events clearly determined to be unrelated to INCB7839 and felt due to the disease under treatment. the recent transplant or an underlying medical condition will not require expedited reporting to the FDA for the purposes of this study				
Masonic Cancer Center SAE Coordinator	Events that count toward a dose limiting toxicity or stopping rule	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu	Not applicable

In each IND safety report, the sponsor must identify all IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of the previous, similar reports.

The SAE Coordinator will provide the Masonic Cancer Center's Data and Safety Monitoring Council (DSMC) with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

11 Study Data Collection and Monitoring

11.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore® (Online Enterprise Research Management Environment).

The Oncore database resides on dedicated secure and PHI compliant hardware consisting of 3 physical servers: dev, DR, and production. The dev server is located in the University of Minnesota (UMN) datacenter (WBOB) and houses six database instances (test, train, sandbox, mcc reports, oncdm, and vendor) that are backed up locally because the data is refreshed from Oncore production data. The production server is located in the UMN datacenter (WBOB). All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. This real-time clustering is physically limited to the UMN data center. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to Oncore databases.

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The data will be integrated and extracted to researchers through the CTSI Informatics team and will be delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, sftp, etc). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data.

Additional data about correlative laboratory samples generated by the Masonic Cancer Center Translational Therapy Laboratory (TTL) from the protocol-directed correlative research samples is stored in their Laboratory Information Management System (LIMS).The LIMS database application is also stored on a production server located in the UMN datacenter (WBOB) and is managed by the Academic Health Center

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

11.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRF) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Primary Clinical Research Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRF based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

11.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp.

For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND). Therefore the following requirements will be fulfilled:

- The PI will complete and submit a quarterly Trial Progress Report to the Masonic Cancer Center Data and Safety Monitoring Council (DSMC) with the understanding the Cancer Protocol Review Committee (CPRC) may require more frequent reporting.
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable adverse events per the definition of reportable in section 10.3 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, and the FDA.

11.4 IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the sponsor-investigator with assistance from the MCC Clinical Trials Office (CTO) will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect.

11.5 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the Masonic Cancer Center or their designee, IRB, government regulatory bodies, and University of Minnesota compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments,

study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

11.6 Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at 6 years after the study file is closed with the IRB and FDA.

In addition, the Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient.

Please contact the CTO before destroying any study related records.

12 Correlative Endpoints

To compared expression of CD16 and CD62L on natural killer (NK) cells and ADCC and IFN gamma production prior and after treatment with rituximab and after rituximab + INCB7839 (each patients is his/her own control). We will also determine the soluble CD16 and CD62L levels in vivo and soluble level of stress ligands MICa, MICb, UPBP3 before and after INCB7839 therapy.

13 Statistical Considerations

13.1 Rationale

We recently analyzed outcomes of 80 patients with diffuse large B cell lymphoma (DLBCL) who received autologous hematopoietic stem cell transplant at University of Minnesota between 1984 and 2002 (5). The median age was 47 years and most patients were in complete or partial remission. Post-transplant, the progression free survival at 5 years was 32% (95%CI 22-42%). We identified high risk group (high risk features defined by IPI score) and low risk group with widely different median PFS of 2 months (high risk group) versus 8 months (low risk). Based on Kaplan – Meyer PFS curve, we expect 65% of patients to be progression-free at 6 months.[3]

Recent prospective multicenter study comparing two different conditioning regimen prior to autograft for DLBCL demonstrated similar 6 months progression free survival of 65-70%.[1,2.] The most common cause of treatment failure is lymphoma progression/relapse.

13.2 Study Design

The study is a Phase I/II trial consisting of two phases. The first phase is a dose escalation phase with the aim of establishing a maximum tolerated dose (MTD) of Adam17 inhibitor INCB7839 with rituximab as consolidation therapy after autologous HCT for patients with diffuse large B cell lymphoma. In the second phase, a larger group will be enrolled in order to obtain a more detailed toxicity profile of the chosen MTD from the first phase as well as establish a preliminary estimate of the rate progression free survival at 6 months.

In the dose escalation phase, three dose levels of INCB7839 will be tested (100mg, 200mg, and 300mg). Since we are starting the experiment at a very low dose at which expected toxicity impacts are low using the standard dose escalation design would expose more subjects to ineffective doses with no expected efficacy. Therefore we decided to conduct the dose escalation phase following a Fast-Track Design. With the fast tract design, 1 patient is entered per dose level until a grade 2 or greater treatment emergent event is experienced within the 1st 14 days of INCB7839 is experienced. At that point, two additional patients will be enrolled at the same dose level and standard dose escalation design will be used as follows:

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule (see section 7.2 for dose levels)
0 out of 3	Enter 3 new patients at the next higher dose level
≥ 2 out of 3	This dose level is declared to be above the maximum tolerated dose (MTD) an dose escalation is stopped. Declare the next lower dose the MTD if 6 patients have already been treated at that dose. Enter 3 additional patients at the next lower dose level if only 3 patients have been treated at the dose, and if ≤ 1 out of 6 patients has DLT then declare this dose the MTD. If ≥ 2 out of 6 patients have DLT then dose de-escalation continues according to the same scheme.
1 out of 3	Enter 3 additional patients at this dose level. • If 0 of these 3 patients (i.e. 1 out of all 6 patients) experience DLT, proceed to the next higher dose level. • If ≥ 1 of these 3 patients (i.e.≥ 2 out of all 6 patients) experience DLT, then this dose is declared to be above the MTD and dose escalation is stopped. Declare the next lower dose the MTD if 6 patients have already been treated at that dose. Enter 3 additional patients at the next lower dose level if only 3 patients have been treated at the dose, and if ≤ 1 out of 6 patients has DLT then declare this dose the MTD. If ≥ 2 out of 6 patients have DLT then dose de-escalation continues according to the same scheme.

The Phase I design will continue until the MTD is declared or until the first dose is declared to be above MTD. After the MTD is declared, the study will proceed to the Phase II.

Phase I dose limiting toxicity (DLT) is defined as any of the following with the 1st 14 days of INCB7839:

- Grade 3-5 non-hematologic, non-infectious toxicity including thromboembolic complications
- Select hematologic events including:
  - grade 4 neutropenia lasting for ≥ 7 days
  - febrile neutropenia
  - grade 4 thrombocytopenia lasting ≥ 7 days despite dose delay
  - grade 3 thrombocytopenia associated with bleeding
- The inability to complete at least 10 days (20 doses) of twice daily INCB7839 therapy within the 1st 14 days due to treatment related toxicity

If dose level 3 is reached without DLT in the 1st 3 patients, an additional 3 patients (for a total of 6) will be enrolled without the 14 day waiting period

Once the MTD is declared, additional 12 patients will be enrolled at the phase I MTD or dose level 3 if no DLT, to obtain a total of 18 patients treated at the designated dose. The specific aim of this second phase is to obtain a more detailed toxicity of the newly established MTD and to make sure the preliminary estimate of 6-month progression free survival.

13.3 Phase II Power Calculation

If all three dose levels are tested, 3-18 patients will be enrolled in the first phase of the trial in order to establish the MTD. Additional 12 patients will be enrolled in the phase II component to obtain 18 patients treated at MTD. Therefore a maximum total of 15 to 30 patients will be involved in the study. In Phase II the designed sample size of 18 for 6 month progression free survival comparison will have a power of 79% to detect the difference between the null hypothesis 6 month progression free survival rate of 65% and the alternative hypothesis of progression free survival of 85% (this is equivalent test the null hypothesis of median disease survival time of 9.7 months and the alternative hypothesis median disease survival time of 25.5 months) at a 0.05 significance using two-sided test. The accrual time will be 18 months and follow up time is 6 months.

13.4 Analysis

The primary endpoint of progression free survival (PFS) and the secondary endpoint of overall survival (OS) will be estimated with Kaplan-Meier curves.[15] Cumulative incidence will be used to estimate the probability of relapse/disease progression treating non-relapse death as a competing risk.[16] Safety measures will be measured descriptively with frequencies and proportions.

13.5 Early Study Stopping Rules – Phase II Component

For phase II component, early stopping rules will be used to monitor the excess toxicity for the additional 12 patients. Stopping rules were developed using Pocock stopping boundaries.[17]

Grade 4-5 non-hematologic toxicity by 4 months

Stopping rules were developed for excessive Grade 4-5 non-hematologic toxicity. The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the toxicity rate is equal to 10% and our sample size is 12 in phase II component. Given these parameters, the upper stopping boundary for toxicity is 2 events out of 4 patients, 3 out of 10, and 4 at any time. If the true toxicity rate is as high as 40% then the chance of early stopping is 87% and the expected sample size is 6.0.

Grade 4-5 hematologic toxicity lasting for ≥ 7 days by 4 months

Stopping rules were developed for excessive Grade 4-5 hematologic toxicity lasting for ≥ 7 days. The goal is to construct a boundary based on toxicity such that the probability of early stopping is at most 10% if the toxicity rate is equal to 30% and our sample size is 12 in phase II component. Given these parameters, the upper stopping boundary for toxicity is 3 events out of 3 patients, 4 out of 5, 5 out of 8, 6 out of 10, and 7 at any time. If the true toxicity rate is as high as 60% then then chance of early stopping is 75% and the expected sample size is 7.7.

14 Conduct of the Study

14.1 Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained

for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

14.3 Informed Consent

All potential study participants will be given a copy of the IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

15 References

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Appendix I – Eligibility Checklist

Study of the ADAM17 Inhibitor INCB7839 Combined With Rituximab After Autologous Hematopoietic Cell Transplantation (HCT) For Patients With Diffuse Large B Cell Non-Hodgkin Lymphoma (DLBCL) - HM2013-24

Eligibility Checklist – page 1 of 2

Patient initials ☐☐☐☐ (1st 2 initials of first name + 1st 2 initials of last name) Patient ID ☐☐☐☐ (Seq #)

INCLUSION CRITERIA

A "NO" response to any of the following disqualifies the patient from study entry.

		Yes	No
1.	Patients 18 years or older who have undergone an autologous hematopoietic cell transplant for the treatment of diffuse large B cell lymphoma with disease response (CR, PR) or stable disease at the day 28 post-transplant reassessment	☐	☐
2.	Karnofsky Score of ≥ 70%	☐	☐
3.	Able to start the protocol therapy (1st dose of rituximab) between day 28-75 post-transplant	☐	☐
4.	Adequate organ function defined as:	☐	☐

test	requirement	patient value	date
platelets	≥ 50,000 x 10^9/L	☐☐☐☐☐☐	☐☐/☐☐/☐☐
ANC	≥ 1000 x 10^9/L unsupported by G-CSF or GM-CSF for 3 days	☐☐☐☐	☐☐/☐☐/☐☐
renal function	creatinine < 1.5 mg/dl or glomerular filtration rate > 50 ml/min	☐.☐ or ☐☐.☐	☐☐/☐☐/☐☐
AST	< 3 X UNL	☐☐☐☐	☐☐/☐☐/☐☐
ALT	< 3 X UNL	☐☐☐☐	☐☐/☐☐/☐☐
total bilirubin	< 3.0 mg/dl (if total bilirubin is ≥ 3.0 patient is eligible if direct bilirubin is WNL)	☐.☐ ☐ if direct bili is used	☐☐/☐☐/☐☐
pulmonary function	clinically no evidence of pulmonary disease		☐☐/☐☐/☐☐
cardiac function	no symptoms of uncontrolled cardiac disease		☐☐/☐☐/☐☐

5.	If post-transplant consolidation radiation therapy is given, the patient must be at least 14 days between last radiation treatment and 1st dose of rituximab ☐ check if n/a	☐	☐
6.	Able to take daily aspirin for the duration of INCB7839 treatment and 1 week after the last dose to reduce the risk of thrombosis (unless of warfarin or LMWH at the time of treatment start)	☐	☐
7.	Females are either postmenopausal for at least 1 year, are surgically sterile for at least 3 months, or must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 12 months after the last dose of rituximab if of childbearing potential. Males must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from screening through 12 months after the last dose of rituximab.	☐	☐
8.	Voluntary written consent signed before performance of any study-related procedure not part of normal medical care	☐	☐

Study of the ADAM17 Inhibitor INCB7839 Combined With Rituximab After Autologous Hematopoietic Cell Transplantation (HCT) For Patients With Diffuse Large B Cell Non-Hodgkin Lymphoma (DLBCL) - HM2013-24

Eligibility Checklist – page 2 of 2

Patient initials ☐☐☐☐ Patient ID☐☐☐☐

EXCLUSION CRITERIA

A "YES" response to any of the following disqualifies the patient from study entry.

		Yes	No
9.	Pregnant or breast feeding - Females of childbearing potential must have a blood test or urine study within 14 days prior to enrollment to rule out pregnancy ☐ check if n/a	☐	☐
10.	Recent venous thrombosis within 4 weeks prior to study enrollment. Patients at high risk for thrombotic events due to inherited risk factors (i.e. factor V Leiden) or DVT/PE in the past 12 months should be on secondary prophylaxis with anti-coagulant therapy (i.e. warfarin or low molecular weight heparin) prior to enrollment ☐ check if n/a	☐	☐
11.	Active uncontrolled infection	☐	☐
12.	Active CNS disease	☐	☐
13.	Previous severe or life-threatening allergic reaction with rituximab or known allergy to the compounds found in INCB7839	☐	☐
14.	Any gastrointestinal condition causing malabsorption or obstruction (eg, celiac sprue, gastric bypass surgery, strictures, adhesions, history of small bowel resection, blind loop syndrome)	☐	☐
15.	Unwilling or unable to swallow tablets BID	☐	☐
16.	Serologic or clinical evidence of current active hepatitis B or C infection, defined as elevated levels of Hep B antigen or Hep C antibody (unless active infection is ruled out by nucleic acid tests)	☐	☐
17.	known HIV infection	☐	☐

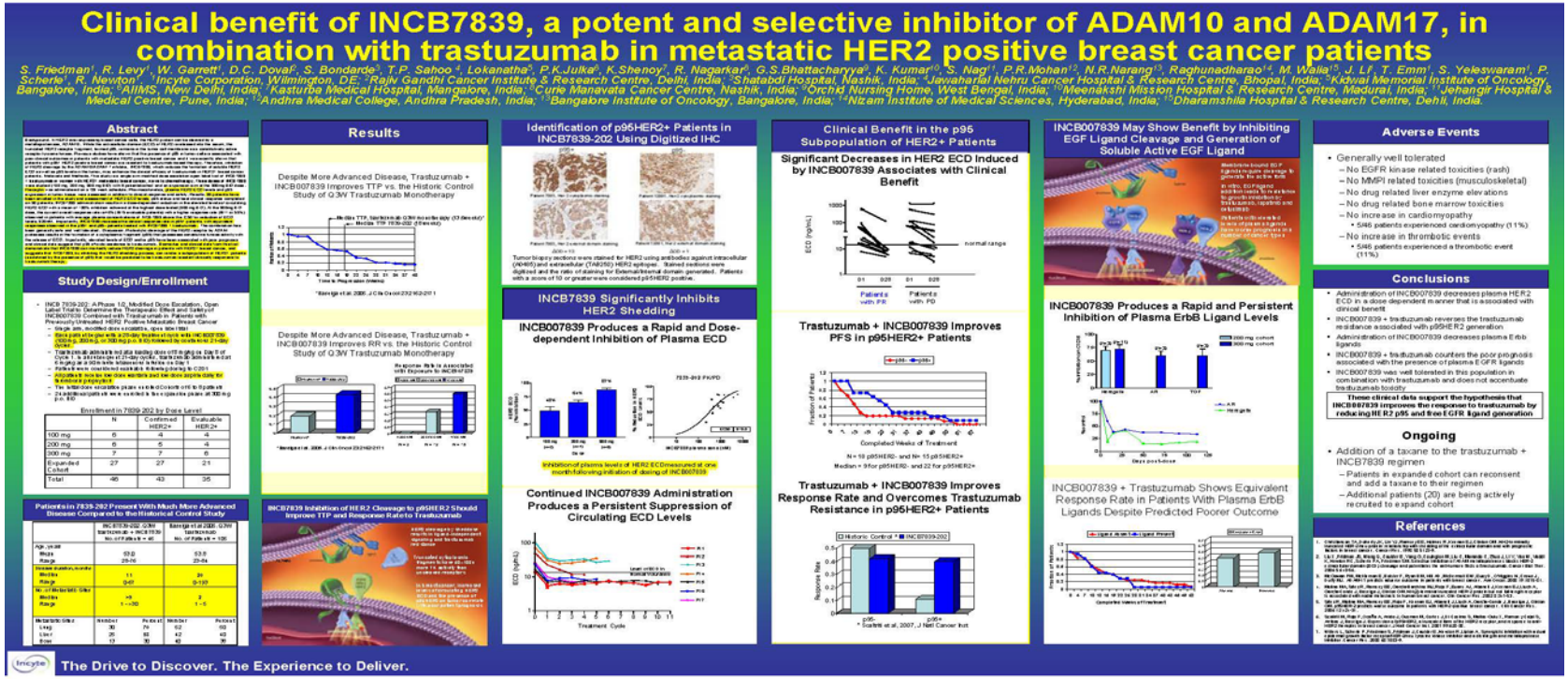
Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is eligible.

Signature of enrolling investigator Date

Appendix II – Performance Status Criteria

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Appendix III – Phase 1-2 Study Combining INCB007839 Plus Trastuzumab In Patients With Previously Untreated Metastatic HER2+ Breast Cancer



Appendix IV - INCB7839 Drug Log

Patient ID: _____

The study drug INCB7839 should be taken with food two times a day approximately 12 hours apart, every day until you are told to stop. If you forget to take a dose by more than 2 hour after the scheduled time or vomit after you take a dose, you should skip the dose and only take the next schedule dose. If this occurs, record a "0" in the time taken column and indicate the reason the dose was missed under the notes column. One 325 mg aspirin (if not taking other anti-coagulant therapy) is also taken each day during INCB7839 administration and continuing until 1 week after the last dose of INCB7839.

Please bring this completed drug log and your study drug bottles (including any unused medication) with you to each appointment. If you have any questions, please contact the study coordinator _____ at _____.

date	**morning (a.m.) time**	**evening (p.m.) time**	**daily aspirin or other anti-coagulant** (warfarin, l low-molecular-weight heparin) check box each day taken	**side effects and notes**
			☐	
			☐	
			☐	
			☐	
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			☐	
			☐	
			☐	

Upon return of the completed log and drug reconciliation:

Research Staff Signature: _____ Date Reviewed: _____