MD Anderson IND Sponsor Cover Sheet

Protocol ID	2021-0077
Protocol Title	Phase Ib/II study of grapiprant (IK-007) and eribulin combination treatment for metastatic inflammatory breast cancer (mIBC)
Protocol Version	04
Version Date	11/22/2022
Protocol PI	Sadia Saleem
Department	Breast Medical Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	157135

Protocol 2021-0077: Phase Ib/II study of grapiprant (IK-007) and eribulin combination treatment for metastatic inflammatory breast cancer (mIBC)

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Department/Program: Breast Medical Oncology/Morgan Welch Inflammatory Breast Cancer Research Program and Clinic

Protocol Type: Standard Protocol

Protocol Phase: Phase Ib/II

Version Status: 4.0

2021-0077 Protocol Synopsis

Title	Phase Ib/II study of grapiprant (IK-007) and eribulin combination treatment for metastatic inflammatory breast cancer (mIBC)
Protocol No.	2021-0077
Phase	1b/2
Sponsor	IKENA Onvology
Investigational Product	IK-007
Study Population	Metastatic inflammatory breast cancer
Primary Objectives	• Determine the safety and efficacy of grapiprant and eribulin combination treatment for the patient with mIBC.
Secondary Objectives	• Determine objective response rate (ORR), % of the patients who achieve complete response (CR) or partial response (PR). • Determine the time to progression (TTP) of the proposed treatment. • Determine the duration of response of the proposed treatment (Phase 2 only) • Determine the time to first response of the proposed treatment (Phase 2 only) • Determine progression-free survival (PFS) of the proposed treatment • Determine the overall survival (OS) of the proposed treatment • Investigate the predictive biomarker of the proposed treatment
Exploratory Objectives	• Evaluate the changes in the tumor microenvironment after the proposed treatment
Treatment Regimen	IK-007 (administered orally) and eribulin (administered intravenously)

Study Design	In the phase Ib part, a safety lead-in to the phase II part, the three enrolled patients will initially start grapiprant with 300 mg BID every day and eribulin (1.4 mg/m^2, day 1 and day 8 of every cycle). We will monitor DLT during the 1st cycle of the treatment. If we observe < 2/3 DLT, we will enroll 3 more patients. If we observe 0 or 1/6 DLT, we will start phase II in that dose and roll over the patients to phase II. If we observe DLT ≥ 2/3 or 2/6 patients, we will de-escalate the dosing to 200 mg BID. In de-escalation (200 mg cohort), if we observe < 2/3 DLT, enroll 3 more patients. If we observe 0 or 1/6 DLT, we will start phase II in that dose and roll over the patients to phase II. If we observe DLT ≥ 2/3 or 2/6 patients, we will stop the safety trial. For phase II, the same toxicities that are defined as DLT in phase Ib will be continuously monitored during the first cycle of treatment using the following safety rule: After the first 9 patients (including the first 6 patient rolled over from phase Ib part), if the grade 3/4 toxicity rate >30%, the investigators will inspect the totality of the safety data and potentially terminate the trial for safety. Phase II adopts the Bayesian optimal phase II (BOP2) design with the null hypothesis H0: CBR = 10% versus the alternative hypothesis H1: CBR = 30%. If the phase II part starts with 300 mg dosing, we will enroll 6 patients and evaluate the clinical benefit in 12 patients (including 6 patients from the phase Ib cohort). For the purpose of futility monitoring, the assessment window for CBR is 24 weeks. If we observed 2 or more clinical benefits in 12 patients, we will proceed to enroll 13 patients and claim the study promising if we observed 5 or more clinical benefits in 25 patients. This design yields the power of 86% with the type I error of 10%.
Number of Patients	Total: 25 patients
Number of Sites	1 site

Key Inclusion Criteria	• Male or female ≥ 18 years of age. • Is willing and able to provide written informed consent for the trial. • Has histological confirmation of breast carcinoma with a clinical diagnosis of IBC. • Any prior treatments will be allowed except eribulin and/or any EP2/4 inhibitor . • Has at least 2 weeks of untreated period from the previous treatment. • Any receptor status for ER/PR and HER2. But for HER2+ type, must has failed trastuzumab, pertuzumab, and T-DM1 treatment. • Has a measurable disease per RECIST v1.1 (only applies to phase II part). • Has a distant metastasis site or locoregional recurrence. • Is willing to provide fresh tumor tissue via tumor biopsy before the first dose of the study drug only if participant has a disease can be be safely accessed through a CT-guided/US-guided or percutaneous biopsy for multiple core biopsies judged by the investigator. • Performance status (PS) of 0-2 on the Eastern Cooperative Oncology Group (ECOG) performance scale. • Has adequate organ function as determined by the following laboratory values: • Left ventricular ejection fraction (LVEF) ≥ 50% by ECHO or MUGA scan. • Female patients must not be pregnant or breastfeeding and must be practicing a medically acceptable form of locally approved birth control, be sterile or post-menopausal. Male patients should be using a medically acceptable form of birth control during the trial or be sterile. ○ Female patient: A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: ▪ Not a woman of childbearing potential (WOCBP) OR ▪ A WOCBP agrees to follow the contraceptive guidance during the treatment period and at least 6 months after the last dose of trial intervention and must refrain from breastfeeding for at least 2 months after the last grapiprant treatment. ▪ Additionally, WOCPB must have a negative urine pregnancy test no more than 7 days prior to starting treatment on-study. ○ Male patients: A male patient must agree to use contraception during the treatment period and for at least 6 months after the last grapiprant treatment and refrain from donating sperm during this period. • Patient with known HIV including current or prior infection would be included if with CD4+ T-cell (CD4+) counts ≥ 350 cells/uL and without a history of AIDS-defining opportunistic infections

Key Exclusion Criteria	• Current chronic use of NSAIDs, COX-2 inhibitors. We will allow prior use of those agents if patients stop them at least 2 weeks before accrual. • Is currently participating in a study of an investigational anti-cancer agent or receiving concurrent anti-cancer therapy for metastatic disease. • Has a diagnosis of immunodeficiency, or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy. • Uncontrolled hypertension is defined as a systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg, with or without antihypertensive medications. • Has a history of and/or active cardiac diseases. • Has preexisting neuropathy > Grade 2. • Patients with known hypersensitivity to halichondrin B and/or halichondrin B chemical derivative. • Has medical conditions requiring concomitant administration of strong CYP3A4 or P-glycoprotein inhibitors or inducers. • Potentially life-threatening second malignancy requiring systemic treatment within the last 3 years (i.e., patients with a history of prior malignancy are eligible if treatment was completed at least 3 years before entering the Treatment period and the patient has no evidence of disease) or which would impede evaluation of treatment response. Hormone ablation therapy is allowed within the last 3 years. Patients with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are eligible. • Any other previous malignancies (except for cervical in situ cancers treated only by local excision and basal and squamous cell carcinomas of the skin) within 5 years. • Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. • Active infection requiring systemic therapy. • Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. • Known active Hepatitis B or C.

Dose Limiting Toxicity	The DLT will be defined as any of the following be "probable," "possible," and "definite events occurring in the first 21 days (cycle 1): • Any Grade 3 hematologic toxicity with the following changes: grade 3 platelet count (< 50,000/mm^3–25,000/mm^3) with associated bleeding (without bleeding, grade 4 platelet count [< 25,000/mm^3] will be defined as DLT); grade 3 absolute neutrophil count (<1,000–500/mm^3) that persists for 7 or more days despite of the use of the grown factor support or that is associated with fevers (febrile neutropenia). (Otherwise, grade 4 absolute neutrophil count [< 500/mm^3] will be defined as DLT.) • Hepatocellular injury is indicated by 3-fold or greater elevations above the ULN of ALT or AST in addition to the elevation of serum total bilirubin > 2 x baseline. In such cases, no other reason can be found to explain the combination of increased transaminases and total bilirubin such as viral hepatitis, preexisting or acute liver disease, or another drug capable of causing the observed injury (Hy's Law). For patients with liver metastasis, 6-fold or greater elevations above the baseline of ALT or AST in addition to the elevation of serum total bilirubin > 4 x baseline. • Grade 3 nausea or vomiting that does not improve to Grade 1 within 72 hours of initiating supportive therapy. • Any other non-hematologic grade ≥ 3 toxicity deemed to be related to the study drug that lasts 72 hours or more will be considered a DLT. • A grade ≥ 3 laboratory abnormality that is determined to be of no clinical significance by the investigators will not necessarily constitute a DLT. • Any death not clearly due to the underlying disease or extraneous causes.

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1.0 TRIAL SUMMARY

Abbreviated Title	Grapiprant for metastatic IBC
Trial Phase	Ib/II
Clinical Indication	Anti-inflammation therapy for metastatic IBC
Trial Type	Open-label, non-randomized, single-center
Type of control	None
Route of administration	Oral
Trial Blinding	No
Treatment Groups	One
Number of trial subjects	25
Estimated duration of trial	2-3 years
Duration of Participation	2 years

2.0 OBJECTIVES & HYPOTHESIS

2.1 Primary Objective

To determine the safety and efficacy of grapiprant and eribulin combination treatment for the patient with metastatic inflammatory breast cancer (mIBC).

2.2 Secondary Objectives

(1) To determine objective response rate (ORR), % of the patients who achieve complete response (CR) or partial response (PR).

(2) To determine the time to progression (TTP) of the proposed treatment.

(3) To determine the duration of response of the proposed treatment (Phase 2 only)

(4) To determine the time to first response of the proposed treatment (Phase 2 only)

(5) To determine progression-free survival (PFS) of the proposed treatment

(6) To determine the overall survival (OS) of the proposed treatment

(7) To investigate the predictive biomarker of the proposed treatment

2.3 Exploratory Objective

To evaluate the changes in the tumor microenvironment after the proposed treatment

3.0 BACKGROUND & RATIONALE

3.1 Inflammatory breast cancer (IBC)

Definition of IBC

IBC is currently defined as diffuse erythema, edema (*peau d'orange*) of the breast, often without an underlying tumor mass, in the presence of pathologic evidence of breast cancer according to the clinical criteria outlined in the seventh edition of the *AJCC Cancer Staging Manual* of the American Joint Committee on Cancer [1]. Histologic evidence of dermal lymphatic invasion confirms the diagnosis but is not mandatory [2].

Metastatic IBC

Although IBC accounts for a mere 2-6% of all breast cancers in the United States, IBC is responsible for a disproportionate 7% of breast cancer-related deaths [3-5]. Approximately 20% to 30% of patients with IBC present with distant metastasis at diagnosis (*de novo* metastasis, classified as stage IV disease) [6-8], compared to 6% to 10% of patients with non-inflammatory breast cancer (non-IBC) [9, 10].

We have tested the hypothesis that OS is worse in patients with IBC than in non-IBC among patients with distant metastasis at diagnosis (stage IV disease). Survival curves were compared among 1504 consecutive patients with stage IV breast cancer (IBC: 206; non-IBC: 1298) treated at our institution from 1987 through 2012. The Cox proportional hazards model was used to determine predictors of OS. IBC was associated with a shorter median OS time than non-IBC (2.3 years vs. 3.4 years; P = .01, log-rank test). In a multivariate Cox model that included 1,389 patients, the diagnosis of IBC was a significant independent predictor of worse OS (hazard ratio = 1.4, P = .00). In summary, IBC is associated with shorter OS than non-IBC in patients with distant metastasis at diagnosis (unpublished data). These data support the prognostic impact of IBC among patients with stage IV breast cancer.

3.2 Pharmaceutical and Therapeutic Background

Inflammation is the key component for the biology of IBC. Compared with non-IBC, IBC overexpresses the PTGS2 gene, which encodes cyclooxygenase (COX)-2 [11, 12]. COX-2 is an enzyme that catalyzes the generation of eicosanoid products, and it mediates pain and inflammation. Overexpression of COX-2 in breast cancer correlates with a more aggressive breast cancer profile characterized by higher proliferation rates, larger tumors, higher pathologic grade, hormone receptor negativity, and HER2 overexpression [13, 14]. The production of COX-2, prostaglandin E2 (PGE2), is also upregulated in the primary IBC and metastatic regions [15]. Our study has shown that a significant association between IBC progression and the COX-PGE2 pathway [16]**.** IBC cells have higher levels of COX-2's enzymatic products, PGE2 and PGF2α, than non-IBC cells. Also, high COX-2 expression in tumor specimens correlates with poor overall survival outcome (n = 44). Intriguingly, PGE promoted the expression of cancer stem-like markers in IBC cell lines. PGE2 and PGF2α increased the CD44+/CD24-/low population of SUM149 cells and ALDH1 activity. Moreover, inhibition of the COX-PGE2 pathway decreased cancer stem-like marker and mammosphere formation. Celecoxib treatment decreased ALDH1 activity and mammosphere formation of SUM149 cells. Thus, the COX-2-PGE2 inflammatory pathway is a potential target for IBC treatment.

3.3 Preclinical and Clinical Trial Data

Preclinical Data (See Investigator's Brochure for details)

Grapiprant is an antagonist of the prostaglandin E2 prostanoid 4 (EP4) receptor. EP4 belongs to the prostanoid receptor sub-family, a class of seven-transmembrane G protein-coupled receptors. EP4 is one of four E2 prostanoid receptors that bind to and are activated by the metabolite PGE2. COX-

1 and COX-2 synthesize PGE2 from the fatty acid precursor arachidonic acid. PGE2 is a well-described modulator of the immune response and can be both pro- or anti-inflammatory depending on the specific context. EP4, a high-affinity PGE2 receptor, and EP2, a related low-affinity PGE2 receptor, predominantly mediate the anti-inflammatory and suppressive activities of PGE2.

The anti-tumor activity of Grapiprant as a single agent and combined with a mouse anti-CTLA4 antibody was evaluated in the 4T1 mouse breast cancer model grown in BALB/c mice. Mice were inoculated subcutaneously in the right flank with 3 x 10^5 tumor cells. When tumors reached an average size of 100 mm^3 (7 days after tumor cell inoculation), dosing was initiated. During dosing, the tumor growth kinetics in mice treated with grapiprant dosed at 15 mg/kg BID and anti-CTLA4 were decreased relative to the vehicle-treated mice. Moreover, the tumor growth kinetics in mice treated with grapiprant and anti-CTLA4 combined was decreased relative to either agent when dosed alone. The mice tolerated each dosing regimen as indicated by an average increase in body weight in each cohort during the treatment period and after treatment was discontinued. After treatment was discontinued, mice treated with grapiprant at 15 mg/kg BID combined with anti-CTLA4 demonstrated improved survival relative to either single agent alone. After monitoring the mice for 41 days after tumor inoculation, 9 of 10 mice were still alive. Only 1 out of 10 mice were treated with anti-CTLA4 as a single agent, and 2 out of 10 mice were treated with grapiprant were still alive 41 days after tumor inoculation.

Grapiprant was evaluated in various animal models to characterize its pharmacologic safety profile, and there were no nonclinical findings that would preclude testing of grapiprant in clinical trials.

Clinical Data

Grapiprant has been evaluated in approximately 1000 humans in studies conducted in the United States comprising single-ascending dose and multi-ascending dose studies, a food-effect study, a safety evaluation study in elderly subjects with renal impairment, an endoscopic gastrointestinal safety study, and in two Phase II studies in patients with osteoarthritis pain. For the solid malignancy, two Phase 1 studies, ARYS-001 and ARYS-002, are ongoing:

1) ARYS-001: Safety and Efficacy of Grapiprant in Combination with Pembrolizumab in Advanced or Progressive microsatellite stable (MSS)-colorectal cancer (CRC).

ARYS-001 is a multicenter, open-label single-arm Phase 1b study designed to evaluate the safety and efficacy of grapiprant combined with pembrolizumab. Participants receive treatment with grapiprant and pembrolizumab during the Combination Treatment period. Each 21-day treatment cycle comprises 21 consecutive days of grapiprant treatment and a single dose of pembrolizumab, administered on Day 1 of each cycle. Approximately 63 patients are planned to be screened for this study. Following the continuous safety assessment phase, 53 participants will be assessed to establish an estimate of efficacy. Cohort 1 enrolled participants at 300 mg BID, 450 mg every 12 hours (Q12h), 600 mg Q12h, and 900 mg Q12h before enrolling participants into Cohort 2. <u>There have been no DLTs observed in the ARYS-001 study</u>.

2) ARYS-002: Safety and Efficacy of Grapiprant in Combination with Pembrolizumab in Advanced or Metastatic Post-PD-1/L1 non-small cell lung cancer (NSCLC) Patients.

This study is an open-label, single-arm, Phase 1b/2 study designed to evaluate the safety and objective response rates in NSCLC subjects who have progressed on anti-PD-1 or anti-PD- L1 therapy. A grapiprant dose of 300 mg BID was initially explored, and then, based on safety established in the ARYS-001 study, 900 mg every 12 hours (Q12h) has also been investigated. If

the 900 mg Q12h dose is unsafe in this study, intermediate doses may be considered.. As of December 15, 2020, this study has been evaluating grapiprant 18 patients with NSCLC have been enrolled to date. Of the 18 subjects enrolled, 4 were treated with 900 mg q12h and 14 were treated with 300 mg BID of grapiprant in combination with a single dose of pembrolizumab. The 900 mg q12h dose level was not well tolerated in the 4 patients treated. One patient experienced a dose limiting toxicity and the 2 other patients withdrew due to hepatic toxicity events. After review of the safety data and discussion with the Investigators, the 900mg q12 dose level was deemed not tolerable. Additionally, while the 300 mg BID dose was well tolerated, there was no efficacy observed in 12 evaluable subjects. Based on the totality of the data, Ikena Oncology has decided to not explore further lower doses of grapiprant in combination with pembrolizumab in patients with NSCLC and is terminating the study ARYS-002. There are no subjects on study drug at this time and the follow-up period of the study has been completed. A clinical study report will be written and provided to the FDA as soon as available.

Among the SAEs currently reported for the two ongoing oncology studies, 8 SAEs were reported by 6 subjects related to the investigational drug as assessed by the investigator. The preferred terms of myositis and colitis were reported as treatment-related SAEs in Study ARYS-001. In Study ARYS-002, the preferred term of colitis was reported, and there were 2 SAEs reported related to liver abnormalities. The subject who experienced hepatic failure also reported treatment-related SAEs of hyponatremia and confusion. A previously reported SAE of intermittent junctional tachycardia occurred twice after treatment with grapiprant in the patient who had a prior history of arrhythmia-related to grapiprant.

3.4 The rationale for the Trial and Selected Subject Population

The prognosis for metastatic breast cancer (MBC) patients is poor, with an estimated 5-year survival of only 26%. Distant metastasis remains the main cause of death in patients with breast cancer despite important medical advances [17]. Therefore, MBC remains the most challenging task facing both cancer researchers and oncologists. IBC is associated with younger age at diagnosis, premenopausal status, African American race, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer, BRCA1 mutations, and more aggressive behavior than other breast cancer subtypes [4, 18]. To date, no IBC-specific targeted therapeutic options exist for the treatment of mIBC. Unfortunately, the median survival is only 2.3 years indicating that all patients will not maintain disease control after achieving a clinical response to systemic chemotherapy or endocrine therapy. The median survival is only 2.3 years for IBC, indicating that all patients will not maintain disease control after achieving a clinical response to systemic chemotherapy or endocrine therapy. To date, no specific targeted therapeutic options exist for the treatment of mIBC [3, 19].

Given the preclinical findings and clinical trial results, EP4 inhibitor has the potential to be a treatment option for mIBC since the COX-PGE pathway has a major role in driving IBC progression. In summary, IBC is associated with upregulated COX2 and PGE2, which can promote tumor progression. The downstream receptor of the COX-PGE pathway, EP4, is a highly potential candidate of the druggable target for mIBC. Taken together, the previous safety and preclinical data provide the rationale for conducting a clinical trial using grapiprant in mIBC treatment.

3.5 Study Endpoint

This clinical trial aims to confirm the safety and efficacy of grapiprant and eribulin mesylate (eribulin) combination treatment in patients with mIBC. The safety endpoint is dose-limiting toxicity, and the efficacy endpoint is the clinical benefit rate. We also aim to prove our concept that grapiprant modulates tumor microenvironment to an immune active status by conducting the correlative study. Also, we are going to evaluate the predictive biomarker of the proposed treatment.

4.0 METHODOLOGY

4.1 Outcomes

Primary outcomes

- Dose-limiting toxicity (See section **4.4.2 Dose modification**)
- Clinical benefit rate (CBR): CR + PR + SD (>24weeks)

Secondary outcomes

- Overall objective response (ORR): % of the patients who achieve CR or PR.
- Time to progression (TTP): the time from starting grapiprant treatment until objective tumor progression (PD).
- Duration of response of the proposed treatment (Phase 2 only): the time from observing the response to the grapiprant treatment until objective tumor progression (PD)
- Time to first response of the proposed treatment (Phase 2 only): the time from starting grapiprant treatment until observing the response.
- Progression-free survival (PFS): the time from starting grapiprant treatment until objective tumor progression (PD) or death with any cause.
- Overall survival (OS): the time from starting grapiprant treatment until death with any cause.
- Association between the treatment response and the urine prostaglandin E2 metabolite in urine samples after the proposed treatment.

Exploratory outcome

- Change in 1) immune cell markers (M1/M2 macrophage, T lymphocyte, regulatory T cell, myeloid-derived suppressor cell, NK cell, dendritic cell, endothelial cell, fibroblast). 2) PD-L1, PD-1, and ALDH1 on tumor and immune cells.

4.2 Entry Criteria

To be eligible for participation in this trial, the subject must meet the following criteria.

4.2.1 Inclusion Criteria

1. Male or female ≥ 18 years of age.
2. Is willing and able to provide written informed consent for the trial.

3. Has histological confirmation of breast carcinoma with a clinical diagnosis of IBC based on the presence of inflammatory changes in the involved breast, including diffuse erythema and edema (peau d'orange), with or without an underlying palpable mass involving the majority of the skin of the breast. Or the diagnosis confirmed by the MD Anderson IBC specialists. Pathological evidence of dermal lymphatic invasion should be noted but is not required for the diagnosis of IBC.

4. Any prior treatments will be allowed except eribulin and/or any EP2/4 inhibitor .

5. Has at least 2 weeks of untreated period from the previous treatment.

6. Any receptor status for ER/PR and HER2. But for HER2+ type, must has failed trastuzumab, pertuzumab, and T-DM1 treatment.

   NOTE:

   HER2 positive status is defined as strongly positive (3+) staining score by IHC, or gene amplification using FISH, if performed. If IHC is equivocal (2+), please refer to Appendix H for current ASCO guidelines algorithm for evaluation of HER2.

   HER2 negative status, which is determined by assays using IHC require negative (0 or 1+) staining score. If IHC is equivocal (2+) staining score, please refer to Appendix H for current ASCO guidelines algorithm for evaluation of HER2.

7. Has a measurable disease per RECIST v1.1 (only applies to phase II part).

   NOTE:

   Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one-dimension (longest diameter to be recorded) as ≥ 20mm by chest X-ray, ≥ 10mm by computed tomography (CT) scan, ≥ 10mm with calipers by clinical exam.

   Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT scan.

   Non-measurable disease: All other lesions (or sites of disease), including small lesions, are considered non-measurable. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis, cutis/pulmonitis, inflammatory breast disease, and abdominal masses [not followed by CT or magnetic resonance imaging (MRI)] are considered non-measurable.

8. Has a distant metastasis site or locoregional recurrence.

9. Is willing to provide fresh tumor tissue via tumor biopsy before the first dose of the study drug only if participant has a disease can be be safely accessed through a CT-guided/US-guided or percutaneous biopsy for multiple core biopsies judged by the investigator. If participant doesn't have a disease that can be safely accessed, they are still eligible.

10. Performance status (PS) of 0 to 2 on the Eastern Cooperative Oncology Group (ECOG) performance scale.

11. Has adequate organ function as determined by the following laboratory values:

    - Absolute neutrophil count (ANC) ≥ 1,200 /mcL
    - Platelets ≥ 100,000 /mcL
    - Hgb ≥ 9 g/dL
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (up to ≤ 3 x ULN for patients with liver metastasis)
    - ALT and AST ≤ 2.5 x ULN (up to ≤ 5 x ULN for patients with liver metastasis)
    - Cockcroft-Gault GFR (mL/min/1.73 m^2) ≥ 50. Cockcroft-Gault GFR Creatinine Clearance Value = [(140-age) x weight (kg)]/(Scr x 72) (x 0.85 *for females*).

12. Left ventricular ejection fraction (LVEF) ≥ 50% by ECHO or MUGA scan.

13. Female patients must not be pregnant or breastfeeding and must be practicing a medically acceptable form of locally approved birth control, be sterile or post-menopausal. Male patients should be using a medically acceptable form of birth control during the trial or be sterile.
    - Female patient: A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
      - Not a woman of childbearing potential (WOCBP)

        OR
      - A WOCBP agrees to follow the contraceptive guidance during the treatment period and at least 6 months after the last dose of trial intervention and must refrain from breastfeeding for at least 2 months after the last grapiprant treatment.
      - Additionally, WOCPB must have a negative urine pregnancy test no more than 7 days prior to starting treatment on-study.
    - Male patients: A male patient must agree to use contraception during the treatment period and for at least 6 months after the last grapiprant treatment and refrain from donating sperm during this period.

14. Patient with known HIV including current or prior infection would be included if:

    - with CD4+ T-cell (CD4+) counts ≥ 350 cells/uL
    - without a history of AIDS-defining opportunistic infections

4.2.2 Exclusion Criteria

1. Current chronic use of NSAIDs, COX-2 inhibitors. We will allow prior use of those agents if patients stop them at least 2 weeks before accrual.

2. Is currently participating in a study of an investigational anti-cancer agent or receiving concurrent anti-cancer therapy for metastatic disease.

3. Has a diagnosis of immunodeficiency, or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy.

4. Uncontrolled hypertension is defined as a systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg, with or without antihypertensive medications.

5. Has a history of and/or active cardiac diseases.

   History of cardiac diseases including:

   - active myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of left ventricular function.
   - history of documented chronic heart failure; and documented cardiomyopathy.
     Active cardiac diseases including:
   - symptomatic angina pectoris within the past 180 days that required the initiation of or increase in anti-anginal medication or other intervention.
   - ventricular arrhythmias except for benign premature ventricular contractions.
   - supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication.
   - conduction abnormality requiring a pacemaker.
   - valvular disease with documented compromise in cardiac function.
   - symptomatic pericarditis.

6. Has preexisting neuropathy > Grade 2.

7. Patients with known hypersensitivity to halichondrin B and/or halichondrin B chemical derivative.

8. Has medical conditions requiring concomitant administration of strong CYP3A4 or P-glycoprotein inhibitors or inducers.

9. Potentially life-threatening second malignancy requiring systemic treatment within the last 3 years (i.e., patients with a history of prior malignancy are eligible if treatment was completed at least 3 years before entering the Treatment period and the patient has no evidence of disease) or which would impede evaluation of treatment response. Hormone ablation therapy is allowed within the last 3 years. Patients with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are eligible.

10. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate if they are stable and have no evidence of new or enlarging brain metastases. They are not using steroids for at least 28 days before trial treatment.

11. Active infection requiring systemic therapy.

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

13. Known active Hepatitis B or C.

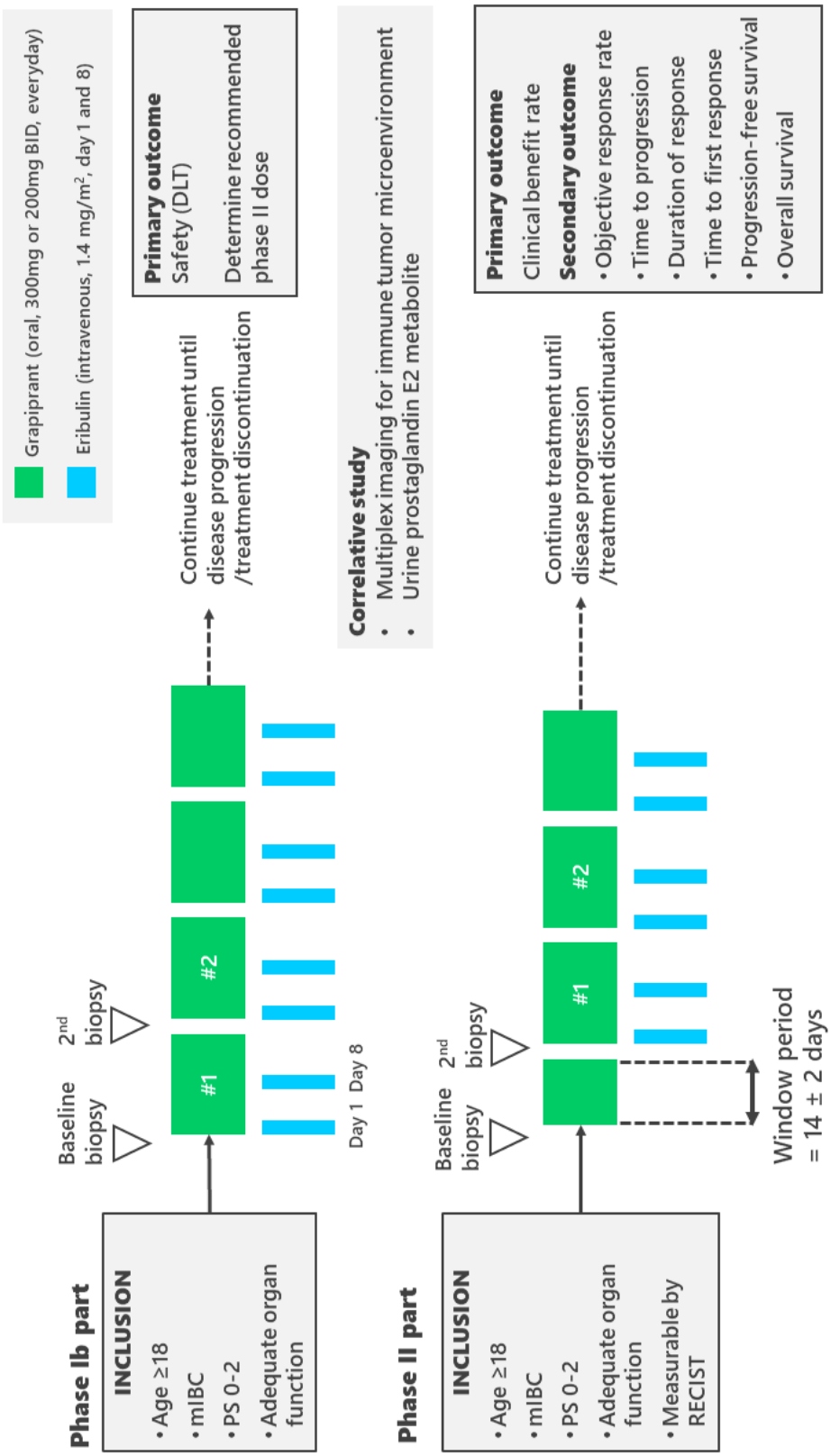
4.3 Study Design

The design of this study is a single-arm, phase Ib/II study. The overview of the study is shown in **Figure 1**. A total of 25 patients will be enrolled in the study. Once the recommended phase II dose of grapiprant in combination with eribulin is determined, the remaining patients will be treated in the phase II portion, which adds 14 ± 2 days window period of grapiprant treatment alone before the main study to evaluate the effect of grapiprant treatment in the tumor microenvironment and urine prostaglandin E2 metabolite. We will perform a correlative study by collecting tumor and urine samples at pre-and post-window periods. We will ensure the safety of grapiprant and eribulin combination by phase Ib part and determine efficacy in the phase II part—the detail of the trial design described in the **statistical analysis plan (7.0)**.

The starting dose of grapiprant will be 300 mg BID daily orally. Eribulin will be intravenously administered on day 1 and day 8 of every cycle (starting at the FDA-approved dose of 1.4 mg/m^2). We define one cycle as 21 days. We will continue the treatment until disease progression, discontinuation by severe toxicity, death, and patient withdrawal. If the patients cannot continue the eribulin because of its toxicity, they will stop eribulin but continue grapiprant as a single treatment until progression or discontinuation. If the patients cannot continue the grapiprant because of its toxicity, they will be off treatment. We will follow-up with the patients up to 5 years after off-treament (see section 4.9). The follow-up can be performed in the clinic in MD Anderson Cancer Center. If the patient is unwilling to come to the clinic, the follow-up would be done by phone.

We will perform imaging analysis by PET-computed tomography (CT) or CT/bone scan at baseline, after the 2 cycles of proposed treatment (does not includes window period), then at the end of every 3 cycles. The Quantitative Imaging Analyzing Core (QIAC) in MD Anderson Cancer Center will independently evaluate the treatment response based on the imaging results.

Figure 1. Overview of the trial design



4.4 Treatment Plan

The dosing levels to be applied in this trial is outlined in **Table 1** below.

Table 1. Dosing level for grapiprant and eribulin in the phase Ib and II part

Phase Ib (dosing level)		Phase II (dosing level)	
Grapiprant (experimental)	**Eribulin (standard of care)**	**Grapiprant (experimental)**	**Eribulin (standard of care)**
300 mg BID, PO daily (0)	1.4mg/m^2, iv, day 1 and day 8 (0)	300 mg BID, PO daily (to be determined by phase Ib part)	1.4mg/m^2, iv, day 1 and day 8 (0)
200 mg BID, po daily (-1)	1.1mg/m^2, iv, day 1 and day 8 (-1)	200 mg BID, po daily (to be determined by phase Ib part)	1.1mg/m^2, iv, day 1 and day 8 (-1)
	0.7mg/m^2, iv, day 1 and day 8 (-2)	100 mg BID, po daily*	0.7mg/m^2, iv, day 1 and day 8 (-2)

*The dosing of 100 mg BID grapiprant will be used in phase II part only for the toxicity management.

4.4.1 Dose Selection

The RP2D of Grapiprant is suggested as 300 mg BID (twice a day) from the ongoing phase I clinical trial for colorectal cancer (CRC) and non-small cell lung cancer (NSCLC). Those trials observed acceptable tolerability when it was combined with an immune-checkpoint inhibitor. The most frequent adverse event was liver toxicity (elevated GGP and ALP). Also, a G2/3 hepatic event was observed for 18.5% at 300 mg BID in the CRC study and 14.3% in the NSCLC study (See the investigator brochure). Base on the result from phase I trials, we will start the grapiprant from 300 mg in phase Ib If we observe dose-limiting toxicity (DLT) with 300 mg BID, the dosing will go down to 200 mg BID and re-evaluate the safety (see the section of **statistical analysis plan [7.0]**). One cycle is defined as 21 days. Grapiprant will be administered orally every day of each cycle. A research medication diary will be used for source documentation. Patients will follow dosing instructions as below:

- Patients will take grapiprant daily as instructed dependent on their assigned dose. Patients are encouraged to take study drug with food or within 2 hours after eating as food is known to decrease common mild gastrointestinal adverse events in drugs of a similar class (COX-2 inhibitors). Patients are to maintain a normal diet.

- Patients should take grapiprant every 12 hours at approximately the same time each day and evening, and not to take more or less than the prescribed dose at any time.

- Patients should swallow the tablets whole and not chew, crush, or break them with about 8 oz water.

- The date, amount taken, and time of study drug administration will be recorded daily in a research medication diary.

- If vomiting occurs, the patient should not take a replacement dose but should attempt to take their next scheduled dose if they are able. Any dose variations due to vomiting should be recorded on the research medication diary.

- If the patient forgets to take a dose at the scheduled time, the patient can take the scheduled dose if less than 3 hours have passed from the regularly scheduled time. If more than 3 hours have passed after the scheduled time, then that missed dose should be omitted and the patient should continue treatment with the next scheduled dose. Any missed doses should be recorded in the research medication diary.

Eribulin 1.4 mg/m^2 will be administered on day 1 and day 8 of each cycle per institutional guidelines in the outpatient setting at MD Anderson or at the local clinic/hospital. The day 8 dose may be delayed for up to 1 week in patients with toxicities. Please refer to Table 3 for recommended eribulin dose modifications and criteria for treatment interruption and re-initiation with treatment-related adverse events. The toxicities requiring dose delays will be documented in the subject's chart.

4.4.2 Dose Modification

For patients who do not tolerate the protocol-specified dosing schedule, adjustments in grapiprant and eribulin doses are permitted to allow the patient to continue the study treatment. All dose modifications must be based on the worst preceding toxicity as graded by the NCI-CTCAE version 5.0. Those will also be counted as DLT when it meets DLT definition. The DLT will be defined as any of the following be "probable," "possible," and "definite events occurring in the first 21 days (cycle 1):

- Any Grade 3 hematologic toxicity with the following changes: grade 3 platelet count (< 50,000/mm^3–25,000/mm^3) with associated bleeding (without bleeding, grade 4 platelet count [< 25,000/mm^3] will be defined as DLT); grade 3 absolute neutrophil count (<1,000–500/mm^3) that persists for 7 or more days despite of the use of the grown factor support or that is associated with fevers (febrile neutropenia). (Otherwise, grade 4 absolute neutrophil count [< 500/mm^3] will be defined as DLT.)

- Hepatocellular injury is indicated by 3-fold or greater elevations above the ULN of ALT or AST in addition to the elevation of serum total bilirubin > 2 x baseline. In such cases, no other reason can be found to explain the combination of increased transaminases and total bilirubin such as viral hepatitis, preexisting or acute liver disease, or another drug capable of causing the observed injury (Hy's Law). For patients with liver metastasis, 6-fold or greater elevations above the baseline of ALT or AST in addition to the elevation of serum total bilirubin > 4 x baseline.

- All other grade 3+ electrolyte abnormality associated with clinical symptoms, regardless of duration.

- Grade 3 nausea or vomiting that does not improve to Grade 1 within 72 hours of initiating supportive therapy.

- Any other non-hematologic grade ≥ 3 toxicity deemed to be related to the study drug that lasts 72 hours or more will be considered a DLT.

- A grade ≥ 3 laboratory abnormality that is determined to be of no clinical significance by the investigators will not necessarily constitute a DLT.

- Any death not clearly due to the underlying disease or extraneous causes.

Dose modification at the time of toxicities will be conducted as follows:

Grapiprant

Safety management guidelines, including dose modification algorithms, are provided. Please note, in cases where the investigator is directed to permanently discontinue study treatment, these instructions are mandatory as described in this section. An overview of the available grapiprant dose modification guidelines is presented in **Table 1**. All AEs are to be graded according to NCI-CTCAE, version 5.0 (http://ctep.cancer.gov). All dose modifications and the reason(s) for the dose modification must be documented in the eCRF. The major classes of grapiprant toxicity described in **Table 2** include "Cardiac", "Blood pressure", and "Gastrointestinal", "Renal", and "Hepatic".

Investigators should refer to the grapiprant IB and Eribulin PI for additional information regarding the background of each drug and the management of other AEs or potential safety-related issues.

In case a dose reduction is necessary, the dose level or schedule of grapiprant may be changed as determined by the investigator and IKENA Oncology, consistent with the instructions for dose level and schedule (**Table 2**). If either study treatment is deemed intolerable and requires discontinuation despite optimal management, as described below, the participant must be discontinued from the study treatment, unless clinical benefit has been demonstrated. Any participant who requires a decrease in the grapiprant dose below 100 mg BID will discontinue grapiprant treatment and will come off study. Patients may continue to receive eribulin off study per standard of care if clinical benefit has been demonstrated per attending physicican discretion. Any participant that is required to discontinue eribulin for an AE may only continue on grapiprant if clinical benefit has been demonstrated and with agreement from the IKENA Oncology.

In the phase Ib part, we will set two dosing levels for grapiprant (300 mg and 200 mg). Grapiprant will start from 300mg BID daily and be initially tested in 3 patients. For the main study, we will set 2 dosing levels for grapiprant for dose reduction by the DLT in phase Ib part and 3 dosing levels for toxicity management in phase II part (**Table 1**). The major adverse events of grapiprant from previous clinical trials were not overlapped to those in eribulin; therefore, we will modify dosing based on the type of events. In the event of hepatic toxicity, we will modify the grapiprant first. The major reported adverse events for grapiprant from the phase I study include elevation of liver enzymes, colitis, myositis, and supraventricular tachycardia. The dosing modification for grapiprant will follow the instruction which is described later in this section. In case the patient had uncommon side effects, PI and clinical staff will discuss the event and determine which drug should be reduced dosing. the discussion of the event with the PI and the rationale (which drug to reduce) will be documented in the subject's chart. **Table 2** (grapiprant) and **Table 3** (eribulin) show the summary of dose modification and criteria for treatment interruption and re-initiation.

Table 2. Recommended grapiprant dose modifications and criteria for treatment interruption and re-initiation with treatment-related adverse events

DOSE MODIFICATIONS FOR GRAPIPRANT	
Toxicity (CTCAE 5.0 Grade)	**Grapiprant Dose Modifications**
Non-Hematologic Adverse Events Not Otherwise Specified	
Grade 1	Administer symptomatic treatment as appropriate Continue study treatment at same dose Follow-up:

	Symptoms resolve to baseline within 7 days: Provide close follow-up to evaluate for increased severity. *Symptoms ongoing >7 days*: Consider following algorithm for Grade 2 events.
Grade 2	Administer symptomatic treatment Investigate etiology Consider consulting subspecialist, biopsy, and/or diagnostic procedure Discuss with IKENA Oncology Follow-up: *Symptoms ongoing >7 days or worsening* • Consider interruption of study treatment • Resume study treatment at the same or lower dose if symptoms have improved to Grade 1 • If potentially related to cumulative toxicity (past first cycle), consider changing administration of grapiprant to 2 weeks on/ 1 week off • If symptoms continue or worsen to Grade 3-4, follow algorithm for Grade 3-4 events
Grade 3-4	Interrupt or discontinue study treatment Consult sub-specialist Discuss with IKENA Oncology Follow-up: *Symptoms improve to Grade ≤1:* • Restart study treatment at a lower dose of grapiprant • If potentially related to cumulative toxicity (past first cycle), consider changing administration of grapiprant to 2 weeks on/ 1 week-off *Symptoms ongoing:* • Discuss further management with consultant and IKENA Oncology • Consider alternative therapy
CARDIAC	
Arrhythmia (tachycardia: supraventricular tachycardia, atrial fibrillation)	
	First Occurrence: Omit grapiprant Perform a repeat ECG within 1 hour of the first occurrence. Seek cardiologist input; address electrolytes, calcium, and magnesium abnormalities; concomitant medication must be reviewed. Second Occurrence: Permanently discontinue patient from grapiprant
Other Cardiac Events	
Grade 1 or 2	Continue study treatment at same dose

Grade 3	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level
Grade 4	Permanently discontinue patient from grapiprant
BLOOD PRESSURE	
Hypertension * true uncontrolled hypertension, not present at baseline, judged by the investigator to warrant a dose reduction	
Grade 1: systolic BP (sBP) 120-139 mmHg or diastolic BP (dBP) 80-89 mmHg	Continue study treatment at same dose
Grade 2: sBP 140-159 mmHg or dBP 90-99mmHg	Omit dose until resolved to ≤ Grade 1 Perform an ECG and seek cardiologist input per physician discretion; address electrolytes, calcium, and magnesium abnormalities; review concomitant medication. Once hypertension was resolved, the grapiprant may be restarted by decreasing 1 dose level. Continue measuring blood pressure daily at home.
Grade 3: sBP ≥ 160mmHg or dBP ≥ 100 mmHg	Omit grapiprant Perform an ECG and seek cardiologist input per physician discretion; address electrolytes, calcium, and magnesium abnormalities; review concomitant medication. Permanently discontinue patient from grapiprant
GASTROINTESTINAL	
Colitis	
Grade 1	Continue study treatment at same dose
Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at the same dose.
Persistent > Grade 2 regardless of etiology	Permanently discontinue patient from grapiprant
RENAL	
Serum creatinine	
< 2 x ULN	Continue study treatment at same dose
2–3 x ULN	Omit dose until resolved to ≤ Grade 1, then resume
HEPATIC	
Grade 1	Administer symptomatic treatment as appropriate Continue study treatment at same dose Follow-up: *Symptoms and laboratory abnormalities resolve to baseline within 7 days:* Provide close follow-up to evaluate for increased severity *Symptoms or laboratory abnormalities ongoing >7 days*: Consider following algorithm for Grade 2 events

Grade 2	Administer symptomatic treatment Monitor liver chemistries (ALT, AST, bilirubin) weekly until they resolve, stabilize or return to within baseline Investigate etiology Consider consulting subspecialist, biopsy, and/or diagnostic procedure Discuss with IKENA Oncology Follow-up: *Symptoms or laboratory abnormalities ongoing >7 days or worsening:* Consider interruption of study treatment • If interrupted, when symptoms and laboratory abnormalities have improved to Grade 1, resume study treatment at a lower dose of grapiprant (≤200 mg Q12h following the first dose reduction, and ≤100 mg Q12h following the second dose reduction) • With a second dose reduction, change administration of grapiprant to 2 weeks on/ 1 week off If symptoms continue or worsen to Grade 3-4, follow algorithm for Grade 3-4 events
Grade 3	Interrupt or discontinue study treatment Consult subspecialist Monitor liver chemistries (ALT, AST, bilirubin) at least twice weekly until they return to Grade 2, then follow Grade 2 guidelines Discuss with IKENA Oncology Follow-up: *Symptoms* and laboratory abnormalities *improve to Grade ≤1:* • Resume study treatment at a lower dose of grapiprant (≤200 mg Q12h following the first dose reduction, and ≤100 mg Q12h following the second dose reduction) • With a second dose reduction, change administration of grapiprant to 2 weeks on/ 1 week off *Symptoms* or laboratory abnormalities *ongoing >7 days after Interruption:* • Discuss further management with consultant and IKENA Oncology • Permanently discontinue study treatment
Grade 4	Permanently discontinue study treatment Monitor liver chemistries (ALT, AST, bilirubin) at least twice weekly until they return to Grade 2, then follow Grade 2 guidelines Immediately inform IKENA Oncology and MD Anderson Follow-up:

	Symptoms and laboratory abnormalities *resolve to baseline within 7 days:* Provide close follow-up to evaluate for increased severity *Symptoms* or laboratory abnormalities *ongoing >7 days*: Discuss further management with consultant and IKENA Oncology
Management of Hepatotoxicity	
In the event of treatment-emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis and other infectious causes, choledocholithiasis, hepatic metastases, and myositis should be investigated. Concomitant medications or substances (eg, alcohol) known to be hepatotoxic which may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function. As generally understood, AST or ALT >3x ULN and concomitant bilirubin ≥2.0 x ULN (>35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggests significant liver injury. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy. Report all Grade 4 and serious hepatotoxicity events to the IKENA Oncology within 24 hours. Complete liver event eCRF forms and SAE forms if the event also meets the criteria for SAE reporting. For dose reductions related to hepatotoxicity, the grapiprant dose will not exceed 200 mg Q12h following the first dose reduction, and 1000 mg Q12h following the second dose reduction, in addition to a change to a 2 week on/1 week off schedule for grapiprant with the second dose reduction.	

Eribulin

We will administer eribulin with 1.4mg/m^2 on day 1 and day 8 in every cycle. We will assess eribulin's adverse reactions by obtaining the blood sample and physical examination, especially for peripheral neuropathy. We will not administer eribulin on day 1 or day 8 in patients with ≥ grade 3 neutropenia, ≥ grade 2 thrombocytopenia, or grade 3/4 nonhematologic toxicities. The day 8 dose may be delayed for up to 1 week in patients with toxicities. If toxicities resolve or improve to grade 2 or less by day 15, we will administer eribulin at a reduced dose and initiate the next cycle no sooner than 2 weeks later. If toxicities do not resolve or improve to grade 2 or less by day 15, we will omit the dose. If a dose has been delayed for toxicities that have recovered to the severity of grade 2 or less, resume the recommended reduced dose. If a dose has been reduced due to toxicities, we will not re-escalate.

Table 3. Recommended eribulin dose modifications and criteria for treatment interruption and re-initiation with treatment-related adverse events

DOSE MODIFICATIONS FOR ERIBULIN	
Toxicity (CTCAE 5.0 Grade)	**Eribulin Dose Modifications**
HEMATOLOGICAL	
Neutropenia (ANC)	
ANC < 500/mm^3 for > 7 days or ANC < 1,000/mm^3 with fever or infection	Hold eribulin until ANC is ≥ 1,000 and platelet count is ≥ 75 x 10^9/L, then decrease 1 dose level permanently

Any event requiring permanent dose reduction while receiving 1.1 mg/m^2	Hold eribulin until ANC is ≥ 1,000 and no fever, then decrease 1 dose level
Any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue eribulin
Anemia (Hemoglobin)	
Grade 1	Maintain dose level and continue eribulin with caution
Grade 2	Hold eribulin until hemoglobin is Grade 1.
Grade 3-4	Hold eribulin until hemoglobin is Grade 1, then decrease 1 dose level
Thrombocytopenia (Platelet)	
Platelets < 25,000/mm^3 or platelets < 50,000/mm^3 requiring transfusion	Hold eribulin until platelet (g/dL) is ≥ 100,000, then decrease 1 dose level permanently
Any event requiring permanent dose reduction while receiving 1.1 mg/m^2	Hold eribulin until platelet (g/dL) is ≥ 100,000, then decrease 1 dose level
Any event requiring permanent dose reduction while receiving 0.7 mg/m^2	Discontinue eribulin
NEUROLOGICAL	
Peripheral neuropathy	
Grade 1	Maintain dose level.
Grade 2	Omit dose until resolved to ≤ Grade 1, then restart at the same dose.
Grade > 3	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level.
HEPATIC	
AST or ALT	
Grade 1 (> ULN–3.0 x ULN)	Maintain dose level with liver function tests (LFTs)** monitored per protocol
Grade 2 (> 3.0– 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then -If resolved in ≤ 7 days, maintain dose level -If resolved in > 7 days, decrease 1 dose level
Grade 3 (> 5.0– 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	Permanently discontinue patient from eribulin
AST and/or ALT and Albumin	

AST and/or ALT > ULN–3.0 x ULN (grade 2) and albumin < LLN – 3 g/dL (grade 1)	Omit dose until resolved to ≤ Grade 1, then -If resolved in ≤ 7 days, maintain dose level -If resolved in > 7 days, decrease 1 dose level
AST and/or ALT > 3.0– 5.0 x ULN and albumin < 3 - 2 g/dL (grade 2) without total bilirubin elevation to > 2.0 x ULN	Permanently discontinue patient from eribulin
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 1 (> ULN–1.5 x ULN)	Maintain dose level with LFTs** monitored per protocol
Grade 2 (> 1.5– 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then decrease 1 dose level
Grade 3 (> 3.0– 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Permanently discontinue patient from eribulin
Dose Modifications for eribulin	
Hepatic toxicity monitoring for patients with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only; the monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin, alkaline phosphatase. LFTs include albumin, ALT, AST, total bilirubin, alkaline phosphatase, and GGT - Cycle 1 and 2: every other week (if visit schedule allows more frequent monitoring, this should be considered) or more frequently if clinically indicated, especially for patients with borderline acceptable AST/ ALT/ bilirubin values - Cycle 3 and onward: monthly or more frequently if clinically indicated In case of any occurrence of ALT/AST/ bilirubin* increase ≥ grade 2, LFTs must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1. In case of any occurrence of ALT/ AST/ bilirubin* increase ≥ grade 3 LFTs must be monitored weekly or more frequently if clinically indicated until resolved to ≤ grade 1; thereafter, the monitoring should be continued every other week or more frequently if clinically indicated. until the end of treatment with study medication Patients who discontinued treatment with eribulin should be monitored weekly, including LFTs* or more frequently if clinically indicated until resolved to ≤ grade 1 or stabilization (no CTCAE grade change over 4 weeks).	
All other AEs	
Grade 1 or 2	Per physician discretion.
Grade 3	Omit dose until resolved to ≤ Grade 1, then decrease 1 dose level.
Grade 4	Permanently discontinue the patient from eribulin. Note: Omit dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal anti-emetic treatment.

Unanticipated Dose Interruptions

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record. Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with a re-challenge of grapiprant will be discontinued from trial treatment.

4.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the investigator's discretion in keeping with the community standards of medical care. Concomitant medication will be recorded as the standard of care in the subject's medical record.

Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the study.

- NSAIDs, COX-2 inhibitors.
- Any anti-cancer agents.
- Radiation therapy.

  Note: Radiation therapy to the symptomatic solitary lesion will be allowed. The treatment will be continued during the treatment.
- Live vaccines within 30 days before the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed. Any mRNA vaccines for COVID-19 approved under an Emergency Use Authorization will be allowed in any case.
- Subjects who, in the assessment by the investigator, require the use of any of the treatments mentioned above for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary. There are no prohibited therapies during the post-treatment follow-up phase.

Investigators should refer to the PI and associated addenda for complete details on the drug interaction potential of grapiprant. Highlights of drug interaction are summarized below.

- Grapiprant is a p-glycoprotein substrate, however, it is unknown if Grapiprant is a substrate of CYP450 enzymes. Use of strong inhibitors and inducers of CYP3A4 and p-glycoprotein have been restricted in prior studies with Grapiprant. In this study, participants taking strong CYP3A4 or P-

glycoprotein inhibitors or inducers are excluded from the study unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing.

- Concomitant use of drugs that are strong CYP3A inhibitors should be avoided (eg, aprepitant, clarithromycin, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, verapamil, and voriconazole).

- Concomitant use of drugs that are strong CYP3A inducers should be avoided (eg, phenytoin, rifampin, carbamazepine, St John's Wort, bosentan, modafinil, and nafcillin).

- Grapiprant is not an inhibitor of CYP450 enzymes, but it is unknown if Grapiprant is an inducer of CYP450 enzymes. The exposure of drugs that are CYP450 substrates may be reduced by concomitant use of Grapiprant.

- Concomitant use of drugs that are sensitive CYP450 substrates with a narrow therapeutic index should be avoided (e.g, warfarin, phenytoin, fentanyl).

- Strong CYP2C8 inhibitors (eg, gemfibrozil) should be used with caution with grapiprant.

Table 4: Examples of Narrow Therapeutic Index CYP450 Substrates

Narrow Therapeutic CYP substrate	**Examples**
CYP3A substrates	alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus,
CYP1A2 substrates	theophylline, tizanidine
CYP2C9 substrates	warfarin, phenytoin
CYP2C19	s-mephenytoin
CYP2D6 substrates	thioridazine

4.6 Rescue Medications & Supportive Care

There are no known rescue medications for the study treatments. Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events are outlined below. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to grapiprant or eribulin. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography to evaluate the event.

4.7 Subject Withdrawal/Discontinuation Criteria

In this study, grapiprant administration will continue until one of the following conditions is observed.

Disease progression [RECIST Criteria]

Disease progression is defined as the rapid growth of multiple measurable, non-measurable, or new lesions, or at least a 20% increase in the sum of diameters of target (measurable) lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Noncompliance:

If the patient cannot be compliant with the treatment schedule in the absence of toxicity, the study treatment should be discontinued.

Sustained side effects:

Study treatment will be discontinued for patients who have sustained toxic effects attributed to the study drug and require a dose interruption lasting more than 12 weeks.

Initiation of new anticancer treatment:

In patients for whom the investigator determines new treatment for breast cancer is warranted in their judgment, the study treatment may be discontinued.

Patient withdraws consent:

If a patient withdraws consent, the reason(s) for withdrawal must be documented. Patients must be informed that their participation in the study is voluntary and that they may choose not to take part in the study or to stop taking part at any time. If a patient chooses not to take part in the study or discontinue at any time, his/her future medical care or medical benefits will not be affected.

4.8 Study Stopping Rules

We may terminate this study at any time after informing the IND office. Conditions that may warrant termination of the study include, but are not limited to the following:

- Upon the emergence of an unexpected, serious, or unacceptable risk to the patients in the study.
- Grade 3/4 toxicity rate > 30% (See details in section 7. STATISTICAL ANALYSIS PLAN)
- Upon the observation of the inefficacy in the phase 2 part. The BOP2 design in the phase 2 part has an early stopping rule: if we observed less than 2 clical benefits in 12 patients, we will stop the study for futility.
- A decision on the part of the IKENA Oncology to suspend or discontinue testing, evaluation, or development of the grapiprant.

4.9 Criteria for Disease Control

This study aims to determine the safety and efficacy of grapiprant combination treatment in patients with mIBC. PI will be responsible for monitoring safety and disease control status. Detail of the adverse event and the evaluation of disease status will be documented and recorded in the study-specific database.

4.9.1. Definition of Treatment Response

We will perform imaging analysis by CT scan, bone scan, or PET-CT. If the patient had a locoregional disease, a mammogram and ultrasound would be considered. We will evaluate the treatment response in metastasis sites (and primary site, if it exists) and at the following time points: 1) baseline 2) after 2 cycles of proposed treatment (does not include window period) 3) every 3 cycles of proposed treatment. All imaging analysis will be performed based on RECIST criteria. The efficacy outcomes will be CBR, ORR, Time to progression (TTP), Progression-free survival (PFS), and overall survival (OS).

4.9.2. Response will not be considered evaluable in the following categories:

Patients have to receive at least 2 cycles of the combination of eribulin and grapiprant to be evaluated the response. The patients in the following categories are considered to be unevaluable for the response. Those patients who are not evaluable will be excluded from the response's statistical analysis and not be replaced.

Early Deaths:

Patients who die within the first 2 weeks of the initiation of proposed treatment. These cases will be considered treatment failures.

Lost to Follow-up:

Patients for whom there is inadequate information to judge tumor response because of loss of contact with our institution (> 2 months after a missed appointment) and referring physician despite repeated attempts to locate them. These cases will be considered treatment failures in the intent-to-treat analysis.

Major Protocol Violation:

Patients who significantly deviate from the treatment program by either adding or deleting another agent or another therapeutic maneuver or modifying the schedule substantially (delay treatment ≥ 7 days without administration reason) of the drug under evaluation. Patients who do not fulfill the requirements outlined under patient eligibility are also included in this category.

4.10 Follow Up after off treatment

30-day safety follow up

The mandatory Safety Follow-Up should be conducted approximately 30 days after the last dose of the proposed treatment or before initiating a new anti-cancer treatment, whichever comes first. All

AEs that occur before the safety follow-up visit should be recorded. Safety follow-up can be done in the clinic or by phone if the patient cannot visit the clinic for follow-up.

Patients who have an ongoing major study treatment related AE when the study treatment is completed or at discontinuation from the study will be followed up to 30 days until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

Survival Follow Up (yearly up to 5 years)

The survival follow-up can be performed yearly for up to 5 years; if the patient is unable to visit the clinic, the follow-up will be done by chart review or by phone.

4.11 Remote Procedures

In case of any unexpected incidents that patients can't come back to MD Anderson Cancer Center for study treatment and assessments, remote procedures can be applied for this trial conduction, including remote consent, remote toxicity assessment via phone calls, virtual visit, etc., with compliance with institutional policies. Patients can have lab work, scheduled scans, physical exams and receive treatment locally if applicable. Laboratory work done at an outside facility is to be forwarded to the subject's attending physician at MDACC or the PI of the study, who will date and sign off on the labs to verify the results were reviewed. If the patient's outside records are available to review in MDACC's EMR (i.e. EPIC 'Care Everywhere'), then it will be documented in either the physician's note and/or the study coordinator's note (attested by the physician) that the outside labs, infusions and other assessments were reviewed by the MDA attending physician. Remote monitoring can be applied as needed. Study drug may be mailed to the patient per institutional guidelines/approval.

4.12 Outside Physician Participation During Treatment

1. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to participate in the patient's care (see Local Site Documents in ePRTCL).

2. Protocol required evaluations outside MDACC will be obtained by 'Care Everywhere' in EPIC, fax, or email. Records obtained via fax or email will be and scanned into the patient's record.

3. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator or their representative prior to initiation and documented in the patient record.

4. MDACC investigators will perform all decisions regarding dose adjustments and treatment interruptions or re-initiation of treatment, grading and attribution of adverse events, and assessment of efficacy. The home physician will not make any decisions regarding dose adjustments and/or treatment interruptions or resumption of treatment, grading and/or attribution of adverse events, or assessing efficacy. These will all be done by the MDACC investigators.

5. Routine, standard-of-care laboratory assessments (and physical exam when/if needed) will be performed by the home physician.

6. A copy of the informed consent and treatment schema will be provided to the local physician.

7. Documentation to be provided by the local physician will include drug administration records, vital signs and progress notes, reports of the protocol required laboratory and diagnostic studies, and documentation of any hospitalizations. Laboratory work done at an outside facility is to be forwarded to the subject's attending physician at MDACC or the PI of the study, who will date and sign off on the labs to verify the results were reviewed.

8. The local physician will be requested to report to the MDACC physician investigator all life-threatening events within 24 hours of documented occurrence.

9. Eribulin will be administered on day 1 and day 8 of each cycle outpatient setting at MD Anderson or local clinic/hospital.

4.13 Study Calendar

Table 5. Study flow chart

a. Phase Ib

		Treatment Cycles (1 cycle = 21 days)						End of Treatment	Post-Treatment	
		Cycle 1			Cycle 2 and beyond					
	Screening /Baseline	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	If patient returns for follow up	30-days Safety F/U [g]	Survival Follow-Up [h]
Scheduling Window (Days):	Within 28 days	± 3	± 3	± 3	± 3	± 3	± 3	± 7	30 days after the last dose	Yearly, up to 5 years after off study
Informed Consent	x									
Inclusion/Exclusion Criteria	x									
Grapiprant Administration (*daily*)		x	x	x	x	x	x			
Eribulin Administration		x	x		x	x				
Physical Exam [a], PS [a]	x	x			x			x		
V/S	x	x	x		x	x		x		
Adverse Events [a]	x	x			x			x	x	
Pregnancy Test – Urine or Serum β-HCG (for women with childbearing potential) [j]	x									
Echo or MUGA[d]	x									
EKG[d]	x									
CBC (with diff) [a]	x	x	x		x	x		x		
CRP [b,]	x				x					
Biochemical Profiles [i, a]	x	x			x			x		
CT scan and bone scan, or PET-CT. Breast MRI, mammogram and/or ultrasound per SOC. [c]	x							x		
Research tumor tissue Collection (metastatic site or primary site [if available]) [e]	x				x					
Research Blood/Urine Collection [f]	x				x					
Survival Status [h]										x

a. Labs, PS and AEs will not be repeated if it was done within 8 (+/-3 days) days before starting treatment on Wk 1. PE at Wk 1 and day 1 of all subsequent cycles per physician discretion as clinically indicated
b. C-reactive protein (CRP) will be obtained at baseline and at C2D1 (prior to treatment).
c. As an evaluation of response, imaging analysis will be performed at baseline, after 2 cycles (C3) of proposed treatment (does not include window period), then at the end of every 3 cycles (C6, C9, C12, etc.). The other radiological evaluation may include ultrasound, bone scan, and X-rays, brain MRI, PET/CT, chest wall/breast photos as clinically indicated for a standard of care.
d. ECHO, MUGA and EKG will be performed at baseline and as clinically indicated thereafter.
e. Tumor tissue at the metastatic site or primary site (if available, exclude axillar lymph node) will be collected at baseline and C2D1 (prior to treatment). If the patient had both primary and distant metastasis sites, we would collect sample from the primary site only (excluding axillar lymph node). The biopsy will be done by core needle biopsy, but punch biopsy will be considered if the primary site was a superficial disease. CT-guided biopsy or ultrasonography-guided biopsy will be used based on the location of the metastasis site.
f. Peripheral blood and urine for correlative studies. Approximately 20 ml of blood (one 10 ml EDTA tube and one 10 ml Red top tube for the serum and PBMCs collection) will be drawn at baseline and after C2D1 (prior to treatment). . For the urine sample, we will collect 10 ml of sample in the urinalysis tube. Urine creatinine will be performed centrally at LabCorp from the frozen urine samples which will be shipped to them in batches.
g. The mandatory Safety Follow-Up should be conducted approximately 30 days after the last dose of the proposed treatment or before initiating a new anti-cancer treatment, whichever comes first. All AEs that occur before the safety follow-up visit should be recorded. Safety follow-up can be done in the clinic or by phone if the patient cannot come to the clinic for follow-up.
h. The survival follow-up will be performed yearly for survival status, up to 5 years, if the patient is unable to come to the clinic, the follow-up will be done by chart review or by phone.
i. Biochemical profiles/CMP (albumin, alkaline phosphatase, ALT, AST, LDH, GGT, uric acid, calcium, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, total protein, BUN, creatinine.
j. Screening Pregnancy test should be done within 7 days before the start of an initial regimen to be consistent with institutional policy CLN1114.

b. Phase II:

				Treatment Cycles (1 cycle = 21 days)						End of Treatment	Post-Treatment	
	Screening /Baseline	Window period		Cycle 1			Cycle 2 and beyond			If patient returns for follow up	30-day Safety F/U [g]	Survival Follow-Up [h]
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8			
Scheduling Window (Days):	Within 28 days	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	30 days after the last dose	Yearly, up to 5 years after off study
Informed Consent	x											
Inclusion/Exclusion Criteria	x											
Grapiprant Administration (*daily*)		x	x	x	x	x	x	x	x			
Eribulin Administration				x	x		x	x				
Physical Exam [a], PS [a]	x	x		x			x			x		
V/S	x			x	x		x	x		x		
Adverse Events [a]	x	x		x			x			x	x	
Pregnancy Test – Urine or Serum β-HCG (for women with childbearing potential) [j]	x											
Echo or MUGA[d]	x											
EKG [d]	x											
CBC (with diff) [a]	x	x		x	x		x	x		x		
CRP [b,]	x			X								
Biochemical Profiles [i, a]	x	x		x			x			x		
CT scan and bone scan, or PET-CT. Breast MRI, mammogram and/or ultrasound per SOC [c]	x									x		
Research tumor tissue Collection (metastatic site or primary site [if available]) [e]	x			x								
Research Blood/Urine Collection [f]	x			x								
Survival Status [h]												x

a. Labs, PS and AEs will not be repeated if it was done within 8 (+/-3 days) days before starting treatment on C1D1. PE per physician discretion as clinically indicated at C1D1 and day 1 of all subsequent cycles.
b. C-reactive protein (CRP) will be obtained at baseline and after the window period of proposed treatment.
c. As an evaluation of response, imaging analysis will be performed at baseline, after 2 cycles (C3) of proposed treatment, then at the end of every 3 cycles (C6, C9,C12 etc). The other radiological evaluation may include ultrasound, bone scan, and X-rays, brain MRI. PET/CT, chest wall/breast photos as clinically indicated for a standard of care
d. ECHO, MUGA and EKG will be performed at baseline and as clinically indicated thereafter.
e. Tumor tissue at the metastatic site or primary site (if available, exclude axillar lymph node) will be collected at baseline and after the window peroid (prior to C1D1 treatment). If the patient had both primary and distant metastasis sites, we would collect sample from the primary site only (excluding axillar lymph node). The biopsy will be done by core needle biopsy, but punch biopsy will be considered if the primary site was a superficial disease. CT-guided biopsy or ultrasonography-guided biopsy will be used based on the location of the metastasis site.
f. Peripheral blood and urine for correlative studies. Approximately 20 ml of blood (one 10 ml EDTA tube and one 10 ml Red top tube for the serum and PBMCs collection) will be drawn at baseline and after window peroid (prior to C1D1 treatment). . For the urine sample, we will collect 10 ml of sample in the urinalysis tube. Urine creatinine will be performed centrally at LabCorp from the frozen urine samples which will be shipped to them in batches.
g. The mandatory Safety Follow-Up should be conducted approximately 30 days after the last dose of the proposed treatment or before initiating a new anti-cancer treatment, whichever comes first. All AEs that occur before the safety follow-up visit should be recorded. Safety follow-up can be done in the clinic or by phone if the patient is unable to come to the clinic for follow up.
h. The survival follow-up will be performed yearly up to 5 years for survival status, if the patient is unable to come to the clinic, the follow-up will be done by chart review or by phone.
i. Biochemical profiles/CMP (albumin, alkaline phosphatase, ALT, AST, LDH, GGT, uric acid, calcium, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, total protein, BUN, creatinine.
j. Screening Pregnancy test should be done within 7 days before the start of an initial regimen to be consistent with institutional policy CLN1114.

5.0 OTHER STUDY PROCEDURES

5.1 Informed Consent/Patient Registration

The study will be discussed with the patient, and any patient wishing to participate must give informed consent. A signed Institutional Review Board (IRB) approved, informed consent must be obtained from patients before any study-specific procedures or registration for study treatment can occur. All patients will be registered in the Clinical Oncology Research (CORe) system.

5.2 Biomarker assessments

In the phase Ib and II part, we will perform a correlative study to determine 1) change in the tumor microenvironment after grapiprant treatment by focusing on the immune cell population, PD-1/PD-L1 expression, and ALDH expression in tumor cells. 2) the role of urine prostaglandin E2 metabolite as a biomarker for grapiprant treatment. A description of each assay is described below.

Tumor Samples

Collection

Tumor tissue at the metastatic site or primary site (if available, exclude axillar lymph node) will be collected before therapy and after completing cycle 1 (phase Ib) and window period (phase II). If the patient had both primary and distant metastasis sites, we would collect sample from the primary site only (excluding axillar lymph node). The biopsy will be done by core needle biopsy, but punch biopsy will be considered if the primary site was a superficial disease. CT-guided biopsy or ultrasonography-guided biopsy will be used based on the location of the metastasis site. We will also collect urine and blood samples before therapy and after the completion of the window period. To ensure the obtained tissue samples include the highest possible proportion of tumor content, we will obtain 4 to 6 cores from the most representative lesions. Those tissues will be preserved by the formalin-fixed and paraffin-embedded (FFPE) form. The pre- and post-biopsy are mandatory both in phase Ib and II part (if applicable). Residual sample materials will be archived at the IBC lab and be available after completion of the designated assays. It may be used in the future for the identification of additional predictive markers or to enhance understanding of disease biology. In that case, we will obtain IRB approval before conducting additional assays. If biomarker samples are drawn but the study drug is not administered, samples will be retained.

Evaluation

We will determine the change in the tumor microenvironment that responds to the proposed treatment by multiplex staining. We will evaluate a population of immune cells (CD8+ T cell, CD4+ T-cell, B cell, Treg, Dendritic cell, and Macrophage [M1/M2]). Expression of PD-L1, PD-1, and ALDH1 on tumor and immune cells are also evaluated.

Urine samples

Collection

In the phase Ib and phase II part, we will collect a urine sample (phase Ib, before and after cycle 1 treatment; phase II before and after window period). Urine collection is mandatory. The sample collection and processing will be as follows:

- A midstream urine sample should be collected in the clinic by having the patient void the first part into the toilet, then bringing the urine collection cup into the "midstream" to collect the urine sample.

- The remainder of the urine may be voided directly into the toilet.

- No part of the interior of the collection cup should be touched with the hands or any other part of the body.

- Place urine sample on ice and prepare an aliquot from the urine sample immediately after the collection (no later than 30 minutes post-collection) to avoid any potential degradation.

- Using a pipette, transfer at least 1mL of urine from the Urine collection cup into one (1) 10 mL Urine Transport tube (white cap).

- Immediately place transport tube on ice.

- The urine transport tube should then be transferred from ice to frozen at ultra-low (-70 degrees Celsius +/- 10 degrees Celsius) as soon as possible.

- Urine creatinine will be performed centrally at LabCorp from the frozen urine sample shipped to them in batches. Discard the urine collection cup according to site regulations once the creatinine aliquot has been obtained.

- Ship one (1) urine transport tube to Labcorp :

  ATTN: BioA Sample Management
  9211 Scicor Dr.
  Suite B, Door 19
  Indianapolis, IN 46214

Blood samples

Collection

We will collect 20 ml of blood before cycle 1 treatment and after completing the window period (both mandatory). The blood sample will be obtained in one 10 ml EDTA tube and one 10 ml Red top tube for preserving serum and PBMCs. In the event a 10 ml EDTA or 10 ml red top is unavailable, the tubes may be substituted per institutional guidelines. The blood samples will be archived for future research related to this study. The future research will be a predictive biomarker investigation which includes comprehensive cytokine/chemokine analysis by serum and multiple immunoassays by PBMCs. Samples will be stored in IBC lab for 10 years, minimum.

Assays

We will investigate the immunological change in the tumor microenvironment to determine the immunomodulatory effect of grapiprant treatment.

The multiplex immunostaining imaging and cytokine/chemokine assay (tumor tissue)

We will use multiplex immunostaining imaging (Akoya Biosciences) of FFPE or fresh samples for multiplex imaging analysis conducted routinely in our laboratory. In detail, we will quantify the following markers, which are known to be involved in tumor progression and therapeutic response: pan macrophage marker CD68; M2 markers CD163; T lymphocyte markers CD3 and CD8 regulatory T cell (Treg) markers FOXP3. The expression of PD-L1, PD-1, and ALDH1 on tumor cells will also be evaluated. Dr. Jangsoon Lee will perform the multiplex imaging analysis in the IBC lab.

Urine prostaglandin E2 metabolite (PGEM, urine)

We will determine the association between treatment response and the change in urine PGEM as a predictive biomarker. The assay will be performed at the laboratory in IKENA oncology.

5.3 Safety Monitoring and Reporting

5.3.1 Adverse Event

An Adverse Event is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study. Adverse events will be captured from the time of the first protocol-specific intervention until 30 days after the last dose.

Adverse events will be assessed according to the CTCAE version 5.0. All study patients who have received any dose of grapiprant will be evaluated for safety. Unexpected adverse events, including laboratory adverse events, deemed clinically significant by the investigator will be graded and recorded.

Adverse Events Recording

Adverse events will be captured in the study database REDCap.

For Phase Ib and Phase II AEs ≥ 2 non-hematological and ≥ 3 hematological AEs occurring from the first dose of study treatment until 30 days after the last dose (or before initiating a new anti-cancer treatment, whichever comes first) observed by the investigator or reported by the subject (whether attributed to an investigational product) will be documented in the medical record and recorded in RedCap database. Baseline toxicities will be captured as part of the patient's medical history, in the medical record/RedCap database. Abnormal laboratory values will not be reported as AEs; however, the abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study
- Requires treatment, modification/interruption of study treatment dose, or any other therapeutic intervention
- Is judged to be of significant clinical importance
- If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the eCRF. If the

abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Events not included in the NCI CTCAE will be scored as follows:

General grading:

- **Grade 1:** Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- **Grade 2:** Moderate: discomfort present with some disruption of daily activity, require treatment.
- **Grade 3:** Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- **Grade 4:** Life Threatening: discomfort that represents immediate risk of death

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

5.3.2 Serious Adverse Event Reporting (SAE)

5.3.2.1 Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsored Single Site IND Protocols

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

- Death
- A life-threatening adverse event
- 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 a serious adverse drug experience 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug unless the participant withdraws consent.

- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution**.**

- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.

- All events reported to the supporting company must also be reported to the IND Office

5.3.2.2 Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

  It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

5.3.2.3 Investigator Communication with Supporting Companies:

The MDACC Internal SAE Report Form will be used for reporting to the IKENA oncology office (email: IITSafety@Ikenaoncology.com, FAX: 617-904-1802), and reporting timeline is as below:

- Deaths that are unanticipated and definitely, probably, or possibly related to study intervention that occurs during and within 30 days after the last day of active study intervention will be reported to the IKENA oncology office within 24 working hours.

- All other SAEs that are serious, unanticipated, and definitely, or possibly related to study drugs will be reported to the IKENA oncology office within 2 working days.

  .

- All SAEs and/or ECIs (events of clinical interest) from the time of treatment through 30 days following cessation of study treatment must be reported by the investigator and forwarded to Ikena periodically.

- Pregnancy and Lactation

  Although pregnancy and lactation are not considered adverse events, investigators or their designees must report any pregnancy or lactation in a subject during the trial or within 120 days of the study drug's last dose. Pregnancy outcomes of spontaneous abortion missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (the infant's health) must also be reported. Pregnancy report submission is to be done via eSAE application as "Other Important Medical Event".

5.3.3 Evaluating Adverse Events

An investigator or a designee will evaluate and record adverse events according to the NCI-CTCAE version 5.0 as standard practice per institution guidelines.

Attribution - the determination of whether an adverse event is related to a medical treatment or procedure.

- **Definite** - the adverse event is clearly related to the investigational agent(s).
- **Probable** - the adverse event is likely related to the investigational agent(s).
- **Possible** - the adverse event may be related to the investigational agent(s).
- **Unlikely** - The adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s).

6.0 DRUG INFORMATION

6.1 *Grapiprant*

Adverse reactions

Liver Function Test Abnormalities

In the 2 phase I oncology studies, ARYS-001 and ARYS-002, treatment-emergent adverse events (TEAEs) of the liver > grade 2, including increased ALT, AST, transaminases, abnormal liver results, and hepatitis (elevated liver function tests), have occurred in 14/57 (25%) subjects on the study (10 in ARYS-001 and 4 in ARYS-002) and have resulted in 7/57 (12.3%) subjects withdrawing from study treatment as a result of hepatic AEs. These events were all monitorable and resolved when study treatment was withheld. Other safety events continue to be assessed.

GI Events
There have been 2 GI events of colitis (3.5% of all subjects) reported as related to study treatment in the two ongoing Phase I oncology studies (ARYS-001 and ARYS-002) by patients receiving 300 mg BID doses of grapiprant and 200 mg of pembrolizumab. Pembrolizumab is known to have colitis as a reported AE in approximately 3% of patients (Pembrolizumab package insert); however, grapiprant may also contribute to the frequency or severity of these events and thus will continue to be monitored.

Cardiac Events
In the ARYS-002 study, 1 subject with a diagnosis of NSCLC treated at 300 mg BID had a TEAE arrhythmia. This subject had a prior history of Intermittent Junctional Tachycardia that started at the initial diagnosis of the NSCLC. Two occurrences of junctional arrhythmia occurred on study within hours of taking grapiprant; the first on cycle 1, day 1 resulting in delayed grapiprant dosing and hospitalization for 24-hour observation with full recovery without pharmacologic intervention, and again on cycle 1, day 4 (second dose of grapiprant), with full recovery within hours without pharmacologic intervention. Both occurrences resulting in no change in blood pressure, no change in ECG interval lengths for PR, QRS, or QT segments and were deemed not life-threatening but prompted discontinuation by the investigator, who later deemed the event to be related to grapiprant.

A review of the safety databases across clinical development programs for grapiprant (ARY007) of MedDRA preferred terms of supraventricular tachycardia at that time (August 2019) revealed a total of 0 events reported in subjects treated to date with grapiprant up to 300 mg BID. A review of all potentially treatment-related cardiac events revealed a total of 9 events: 1 episode of sinus bradycardia; 1 episode of cardiac flutter; 2 episodes of palpitations; 2 episodes of vasodilation; 2 episodes of prolonged QT interval, and 1 episode of ST-T change on ECG. As a result of these findings, blood pressure will continue to be monitored for early phase studies, and patients with a significant cardiac history will be excluded from enrollment.

Events of Clinical Interest
In addition to the events noted previously, one event of thrombosis, deemed by the investigator not to be related to study treatment, was reported as an event of clinical interest. The event was grade 3 and resolved without sequelae.
See the investigator brochure for detail on events of clinical interest defined for grapiprant .

6.2 *Eribulin*

The most common adverse reactions (≥ 25%) reported in patients receiving eribulin were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving eribulin were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of eribulin was peripheral neuropathy (5%). The adverse reactions described in Table 2 were identified in 750 patients treated in the previous clinical trial (EMBRACE trial). In the study, patients were randomized (2:1) to receive either eribulin (1.4 mg/m^2 on days 1 and 8 of a 21-day cycle) or single-agent treatment chosen by their physician (control group). A total of 503 patients received eribulin and 247 patients in the control group received therapy consisting of chemotherapy (total 97%

[anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, other chemotherapies 10%]) or hormonal therapy (3%). The median duration of exposure was 118 days for patients receiving eribulin and 63 days for patients receiving control therapy. **Table 6** reports the most common adverse reactions occurring in at least 10% of patients in either group.

Adverse reactions

Cytopenias

Grade 3 neutropenia occurred in 28% (143/503) of patients who received eribulin in the EMBRACE trial, and 29% (144/503) of patients experienced grade 4 neutropenia. Febrile neutropenia occurred in 5% (23/503) of patients; two patients (0.4%) died from complications of febrile neutropenia. Dose reduction due to neutropenia was required in 12% (62/503) of patients, and discontinuation was required in <1% of patients. The mean time to nadir was 13 days, and the meantime to recovery from severe neutropenia (<500/mm^3) was 8 days. Grade 3 or greater thrombocytopenia occurred in 1% (7/503) of patients. G-CSF (granulocyte colony-stimulating factor) or GM-CSF (granulocyte-macrophage colony-stimulating factor) was used in 19% of patients who received eribulin.

Peripheral Neuropathy

In the EMBRACE trial, 17% of enrolled patients had grade 1 peripheral neuropathy, and 3% of patients had grade 2 peripheral neuropathy at baseline. Dose reduction due to peripheral neuropathy was required by 3% (14/503) of patients who received eribulin. Four percent (20/503) of patients experienced peripheral motor neuropathy of any grade, and 2% (8/503) of patients developed grade 3 peripheral motor neuropathy.

Liver Function Test Abnormalities

Among patients with grade 0 or 1 ALT levels at baseline, 18% of eribulin-treated patients experienced grade 2 or greater ALT elevation. One eribulin-treated patient without documented liver metastases had concomitant grade 2 elevations in bilirubin and ALT; these abnormalities resolved and did not recur with re-exposure to eribulin.

Less Common Adverse Reactions

The following additional adverse reactions were reported in ≥ 5% to < 10% of the eribulin-treated group:

- Eye disorders: increased lacrimation
- Gastrointestinal disorders: dyspepsia, abdominal pain, stomatitis, dry mouth
- General disorders and administration site conditions: peripheral edema
- Infections and infestations: upper respiratory tract infection
- Metabolism and nutrition disorders: hypokalemia
- Musculoskeletal and connective tissue disorders: muscle spasms, muscular weakness
- Nervous system disorders: dysgeusia, dizziness
- Psychiatric disorders: insomnia, depression
- Skin and subcutaneous tissue disorders: rash

Table 6. Adverse reactions with a per-patient incidence of at least 10% in the study

Adverse Reactions	HALAVEN n=503		Control Group n=247	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Blood and lymphatic system disorders[b]				
Neutropenia	82%	57%	53%	23%
Anemia	58%	2%	55%	4%
Nervous system disorders				
Peripheral neuropathy[c]	35%	8%	16%	2%
Headache	19%	<1%	12%	<1%
General disorders				
Asthenia/Fatigue	54%	10%	40%	11%
Pyrexia	21%	<1%	13%	<1%
Mucosal inflammation	9%	1%	10%	2%
Gastrointestinal disorders				
Nausea	35%	1%	28%	3%
Constipation	25%	1%	21%	1%
Vomiting	18%	1%	18%	1%
Diarrhea	18%	0	18%	0
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	22%	<1%	12%	1%
Back pain	16%	1%	7%	2%
Bone pain	12%	2%	9%	2%
Pain in extremity	11%	1%	10%	1%
Metabolism and nutrition disorders				
Decreased weight	21%	1%	14%	<1%
Anorexia	20%	1%	13%	1%
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	16%	4%	13%	4%
Cough	14%	0	9%	0
Skin and subcutaneous tissue disorders				
Alopecia	45%	NA[d]	10%	NA[d]
Infections				
Urinary Tract Infection	10%	1%	5%	0

[a] adverse reactions were graded per National Cancer Institute Criteria for Adverse Events version 4.0.
[b] based upon laboratory data.
[c] includes peripheral neuropathy, peripheral sensorimotor neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, and paraesthesia.
[d] not applicable; (grading system does not specify > Grade 2 for alopecia).

7.0 STATISTICAL ANALYSIS PLAN

The design of the present study is phase Ib/II. Previous phase I clinical trial conducted in colorectal cancer and non-small cell lung cancer has established P2RD as 300 mg BID when grapiprant was combined with an immune checkpoint inhibitor. DLT was not observed in the group with 300 mg BID, and the most frequent adverse event was the elevation of liver enzymes. We expect that even if grapiprant was combined with eribulin, the combination treatment will be safely administered; however, we will start the combination from the phase Ib part to ensure safety. The decision of de-escalation is described in **Figure 2**. The maximum sample size of this study is **25 patients**.

In the phase Ib part, a safety lead-in to the phase II part, the three enrolled patients will initially start grapiprant with 300 mg BID every day and eribulin (1.4 mg/m^2, day 1 and day 8 of every cycle). We will monitor DLT during the 1st cycle of the treatment. If we observe < 2/3 DLT, we will enroll 3 more patients. If we observe 0 or 1/6 DLT, we will start phase II in that dose and roll over the patients to phase II. If we observe DLT ≥ 2/3 or 2/6 patients, we will de-escalate the dosing to 200 mg BID. In de-escalation (200 mg cohort), if we observe < 2/3 DLT, enroll 3 more patients. If we observe 0 or 1/6 DLT, we will start phase II in that dose and roll over the patients to phase II. If we observe DLT ≥ 2/3 or 2/6 patients, we will stop the safety trial.

For phase II, the same toxicities that are defined as DLT in phase Ib will be continuously monitored during the first cycle of treatment using the following safety rule: After the first 9 patients (including the first 6 patient rolled over from phase Ib part), if the grade 3/4 toxicity rate >30%, the investigators will inspect the totality of the safety data and potentially terminate the trial for safety.

Phase II adopts the Bayesian optimal phase II (BOP2) design with the null hypothesis H0: CBR = 10% versus the alternative hypothesis H1: CBR = 30%. If the phase II part starts with 300 mg dosing, we will enroll 6 patients and evaluate the clinical benefit in 12 patients (including 6 patients from the phase Ib cohort). For the purpose of futility monitoring, the assessment window for CBR is 24 weeks. If we observed 2 or more clinical benefits in 12 patients, we will proceed to enroll 13 patients and claim the study promising if we observed 5 or more clinical benefits in 25 patients. This design yields the power of 86% with the type I error of 10%.

If the phase II part starts with 200 mg dosing, we will enroll 5 patients and evaluate the clinical benefit in 11 patients (including 6 patients from the phase Ib cohort). If we observed 2 or more clinical benefits in 11 patients, we will proceed to stage 2. For stage 2, (a) if 3 patients treated at 300mg, we will enroll additional 11 patients, and we claim the study promising if we observed 4 or more clinical benefit in 22 (or 19) patients; and (b) if 6 patients treated at 300mg, we will enroll additional 8 patients and we claim the study promising if we observed 4 or more clinical benefit in 19 patients. The power of the design is 86% and 82%, respectively in case (a) and (b), given the type I error of 10%. The operating characteristics for the phase II portion of the trial are summarized in the **Table 7** below:

Table 7: **The Operating Characteristics for Phase II**

Scenario	Clinical Benefit Rate	Early Stopping (%)	Claim Promising (%)	Average Number of Patients (%)
1	0.1	65.9	8.3	16.4
2	0.2	27.5	52.0	21.4
3	0.3	8.5	86.4	23.9

Scenario	Clinical Benefit Rate	Early Stopping (%)	Claim Promising (%)	Average Number of Patients (%)
4	0.4	2.0	97.5	24.7
5	0.5	0.3	99.7	25.0

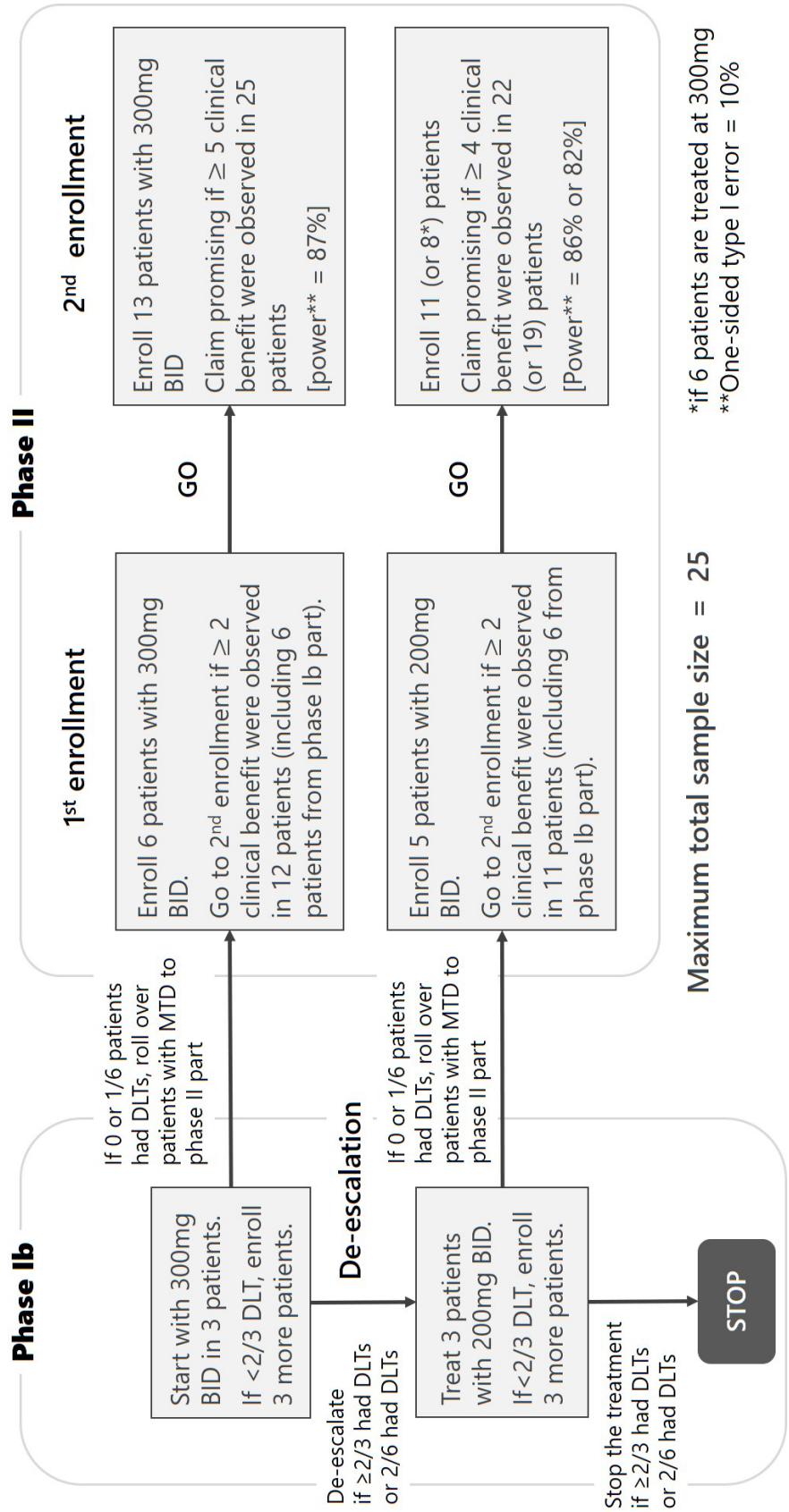


Figure 2. Trial design for phase Ib/II of grapiprant and eribulin treatment

The CBR and ORR will be summarized by frequency and percentage with 95% exact confidence intervals for all patients and by doses. Time to progression (TTP), progression-free survival (PFS), and overall survival (OS) will be summarized using the Kaplan-Meier method, including median with 95% confidence intervals.

For each exploratory outcome measure (see 6.2, Biomarker Assessments), samples will be acquired pre- and post-treatment. Change associated with treatment will be assessed by t-test and regression models with relation to treatment time, with adjustment for relevant demographic and baseline covariates. A logistic regression model will be used to assess the association between objective response status and change in exploratory outcomes. A proportional hazard model will be used to assess the association between TTP, PFS, and OS with the change in urine prostaglandin E2 metabolite. Additional statistical methods may be used.

The Investigator is responsible for completing an efficacy/safety summary report and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval.

Phase1b:
After the first 3 evaluable patients complete 1 cycle of study treatment, and every 3 patients thereafter. IND Office approval must be obtained, prior to expanding/changing dose levels.

Phase II:
Toxicity summary will be submitted after the first 9 evaluable patients (including the 6 patients treated at MTD), then every 6 evaluable patients complete 1 cycle of treatment.

Efficacy summary:
If the MTD is 300mg, summary will be submitted after 12 evaluable patients (including the 6 patients treated at MTD), complete 24 weeks of treatment and after the 25 evaluable patients complete 24 weeks cycles of treatment.

If the MTD is 200 mg, Summary will be submitted after 11 evaluable patients (including the 6 patients treated at MTD), complete 24 weeks of treatment, and after 25 evaluable patients complete 24 cycles of treatment.

A copy of the safety summary report should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.0 LABELING, PACKAGING, STORAGE, AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product per the protocol and any applicable laws and regulations. Clinical Supplies will be provided by IKENA oncology as summarized in **Table 7**.

Table 8. Product Descriptions

Product Name & Potency	Dosage Form
Grapiprant (100 mg)	Oral Solid Dose Tablet, 50 count bottle

8.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label per regulatory requirements.

8.3 Clinical Supplies Disclosure

This trial is an open-label; therefore, the subject, the trial site personnel, the designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. An authorized person must record receipt and dispensing of trial medication at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from IKENA oncology or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational products will be destroyed at the site per institutional policy. The Investigator's responsibility is to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.0 DATA MANAGEMENT

9.1 Data collection plan

Data collected from the study will be entered in RedCap/Prometheus. The Principal Investigator is responsible for assuring that the data entered into the database are complete and accurate and that data entry is performed promptly.

Data collection for this study including:

i. demographic information (sex, race, and date of birth).

ii. physical information (weight and height)

iii. date of initial breast cancer diagnosis, pathology report of primary breast cancer, biomarker status, and date and location of distant metastases.

iv. date of disease progression, death.

v. history of breast cancer surgery and radiation therapy, if applicable.

vi. date and type of endocrine therapy, chemotherapy, and immunotherapy for metastatic disease.

vii. all AEs will be collected; however, only ≥ 2 non-hematologic AEs and ≥ 3 hematological AEs will be recorded. Other abnormal laboratory values will not be reported as AEs; however, any clinical consequences of abnormality should be reported as AEs.

viii. Concomitant medication will be recorded per standard of care in the clinic database and not recorded in the study database.

9.2 Data confidentiality plan

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity will be possible only after accessing a password-protected database. Access to the database will be available only to individuals directly involved in the study. Information gathered for this study will not be reused or disclosed to any other person or entity or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point, they will be destroyed.

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