

A Phase Ib/II Study of **Pembrolizumab** and **Monoclonal Antibody** Therapy in
Patients with Advanced Cancer (**PembroMab**)

Protocol ID: WG2014028 PembroMab

Site Tracking #: WG2014028

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I. Study Objectives

Primary Objective for phase Ib:

- Determine the recommended phase 2 dose (RP2D) of monoclonal antibody therapy (Mab) +/- eribulin in combination with pembrolizumab (pembro) in subjects with advanced cancer.

Primary Objective for phase II:

- Complete response by immune-related response criteria (irRECIST)¹

Secondary Objectives:

- Frequency of grade 3 or higher treatment-related adverse events by CTCAE 4.03
- Response rate by irRECIST and response evaluation criteria in solid tumors (RECIST) 1.1 criteria^{1,2}
- To determine the overall survival (OS) and progression-free survival (PFS)
- To characterize changes in circulating tumor DNA in patients enrolled on this study
- Textural changes identified on imaging that is done per routine practice

II. Background and Rationale

An estimated 585,000 individuals diagnosed with cancer will die from their disease in 2014³. While some may have long-term disease-free intervals, for most individuals that are diagnosed with metastatic disease, the survival rate is less than 5 years. For primary cancers such as squamous cell carcinoma of the head and neck (HNSCC), colorectal cancer (CRC), and HER2 overexpressed breast cancer, few individuals will live 3 years with metastatic disease. Patients with metastatic disease are usually treated with systemic chemotherapy, with the intent of prolonging survival and palliate symptoms (pain, weight loss and decrease in performance status). For the most common cancer types, there are defined recommendations for first- and/or second-line systemic therapy. Year after year, randomized trials are designed and launched to try and improve on median overall survival outcomes. In oncology, the success rate from phase I to FDA approval is a dismal 11%⁴. Even with the successful phase 3 clinical trials, the improvement in overall survival is modest, increasing the median by weeks to several months. For common non-hematologic cancers (and many rare cancers), there are no design strategies that are primarily seeking to attain complete (and hopefully durable) responses.

There have been promising results with antibody-based immunostimulatory therapy in melanoma, renal cell carcinoma, and non-small cell lung cancer^{5,6}. By irRECIST, some individuals may have long durable disease control. There have been recent clinical data on synergetic effects of chemotherapy and preclinical data on Mab given in combination with PD-1 immunostimulatory therapy^{7,8} (immunochemotherapy).

In this protocol, the phase Ib portion will allow inclusion of any advanced solid tumor patient that meets the eligibility criteria for the selected arm. Once the RP2D is determined for each arm, the phase II portion begins for that treatment arm. There will be one phase II cohort for pembro plus trastuzumab and eribulin⁹: patients with unresectable HER2 overexpressing metastatic breast cancer (MBC) for patients that have received prior trastuzumab. PD-1 has been reported to be overexpressed in this cancer type⁸. The pembro plus ado-trastuzumab emtansine phase II arm will be for patients with HER2 overexpressing MBC. There will be two phase II cohorts for pembro plus cetuximab: one cohort will be for

patients with HNSCC, the other cohort will be for patients with K-ras, B-raf, N-ras wildtype metastatic CRC. PD-1 has been reported to be expressed in HNSCC¹⁰ and CRC^{11,12}. We hypothesize that with optimal debulking of tumor with the combination of Mab +/- eribulin and immunostimulatory therapy, the response may be enhanced to achieve long durable complete responses. Each phase II arm is powered to at least 80% to address the primary objective.

III. Subject Eligibility

Inclusion criteria for Phase Ib and II:

1. Patient at least 18 years old and has definitive histologically or cytologically confirmed unresectable or metastatic solid tumor.
2. Patient has one or more tumor measurable as defined by RECIST 1.1 by CT scan (or PET/CT, if patient is allergic to CT contrast media). Tumor sites that are considered measureable must not have received prior radiation therapy. For metastatic tumors not measurable by CT and/or PET/CT, there needs to be tumor measuring at least 1cm in one dimension by digital calipers on physical exam.
3. Patients can be enrolled only on one of the treatment arms on this trial.
4. The investigator will select the appropriate treatment arm for the patient with the following requirements: (a) Patients cannot have had prior progression or intolerance to eribulin or ado-trastuzumab emtansine or cetuximab and then enrolled on the trastuzimab and eribulin or ado-trastuzumab emtansine or cetuximab arms plus pembro, respectively; (b) The systemic therapy on the arm selected must be considered standard of care or listed in the NCCN guidelines (www.nccn.org) for that cancer type. For example, a patient with K-ras, B-raf, N-ras wildtype CRC cannot be enrolled on the trastuzumab plus pembro arm, but can be enrolled on the cetuximab plus pembro arm.
5. Have recovered from acute toxicities of prior treatment:
 - a. ≥ 3 weeks must have elapsed since receiving any investigational agent.
 - b. ≥ 2 weeks must have elapsed since receiving any radiotherapy, or ≥ 3 weeks or 5 half-lives whichever is shorter for treatment with cytotoxic or biologic agents (≥ 6 weeks for mitomycin or nitrosoureas). Chronic treatment with non-investigational gonadotropin-releasing hormone analogs or other hormonal or supportive care is permitted.
6. Patient has adequate biological parameters as demonstrated by the following blood counts at time of screening:
7. Absolute neutrophil count (ANC) $\geq 1500 \text{ mm}^3$, platelet count $\geq 100 \times 10^9 \text{ L}$, hemoglobin $\geq 9 \text{ g/dL}$.
8. Serum creatinine ≤ 2.0 , total bilirubin $\leq 2 \text{ mg/dL}$, AST/ALT ≤ 5 times the upper limit of normal (ULN) range
9. Thyroid stimulating hormone (TSH) within institutional normal limits. If TSH is above the upper limit of normal range, then a free T4 within institutional normal limits is acceptable.
10. Persistent prior systemic therapy non-hematologic AE grade ≤ 2 (except alopecia or correctable electrolyte abnormality with supplementation)
11. Patient has a Karnofsky performance status (KPS) ≥ 70 .

12. Women of child-bearing potential (i.e., women who are pre-menopausal or not surgically sterile) must be willing to use an acceptable contraceptive method (abstinence, oral contraceptive or double barrier method) for the duration of the study and for 4 months following the last dose of pembrolizumab, 6 months for ado-trastuzumab emtansine, and 30 days for cetuximab, trastuzumab, and eribulin, and must have a negative urine or serum pregnancy test within 2 weeks prior to beginning treatment on this trial. Persons taking ado-trastuzumab emtansine must use at least one highly effective, non-hormonal method of contraception

Inclusion criteria for Phase II only:

1. Patients must have HER2 overexpressing MBC and received prior trastuzumab to be enrolled on the pembro plus trastuzumab and eribulin phase II portion.
2. Patients must have HER2 overexpressing MBC to be enrolled on pembro plus ado-trastuzumab emtansine phase II portion.
3. Patients must have HNSCC to be enrolled on Cohort 1 of the pembro plus cetuximab phase II portion.
4. Patients must have K-ras, B-raf, N-ras wildtype CRC to be enrolled on Cohort 2 of the pembro plus cetuximab phase II portion.

Exclusion Criteria for Phase Ib and II:

1. Active clinically serious infection > CTCAE (version 4.03) Grade 2.
2. Serious non-healing wound, ulcer, or bone fracture.
3. Patient has known brain metastases, unless previously treated and well-controlled for at least 1 month (defined as clinically stable, no edema, no steroids and stable in 2 scans at least 4 weeks apart).
4. Inability to complete informed consent process and adhere to the protocol treatment plan and follow-up requirements.
5. Patient has known active infection with HIV, hepatitis B, or hepatitis C (patients are NOT required to be tested for the presence of such viruses prior to therapy on this protocol).
6. Requiring daily corticosteroid dose ≥ 10 mg prednisone or equivalent per day. A brief (less than 2 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted (premedication for chemotherapy excluded).
7. Patient has undergone major surgery, other than diagnostic surgery (e.g., surgery done to obtain a biopsy for diagnosis without removal of an organ), within 4 weeks prior to Day 1 of treatment in this study.
8. Patient has a history of allergy or hypersensitivity to any of the study drugs or any of their excipients, or the patient exhibits any of the events outlined in the Contraindication or Special Warnings and Precautions sections of the product or comparator SmPC or Prescribing Information.
9. Patient has serious medical risk factors involving any of the major organ systems, or serious psychiatric disorders, which could compromise the patient's safety or the study data integrity.

10. Patient will be receiving any other anti-cancer therapy during participation in this trial, except concurrent hormonal therapy is allowed.
11. Prior treatment with pembro. Receipt of other PD-1 inhibitors or PD-L1 inhibitors is allowed.
12. Active or prior documented autoimmune disease requiring systemic treatment within the past 2 years.

Exclusion Criteria for phase II portion only:

1. Patients with a history of more than one primary cancer, with the exception of: a) curatively resected nonmelanomatous skin cancer; b) curatively treated cervical carcinoma in-situ; or c) other primary solid tumor treated with curative intent and no known active disease present and no treatment administered during the 2 years prior to enrollment.

IV. Subject Registration

A Subject Registration Form will be completed and retained by the clinical research department. Subjects must begin treatment within 28 days of all baseline studies. Follow **Table 1. Schedule of Study Procedures** in the Appendix.

V. Treatment Regimen

Patients will be evaluated for complete eligibility and enrollment.

Phase Ib portion for each treatment arm (will be analyzed separately for RP2D determination):

- Protocol visits and procedures will be scheduled per schedule of events in Table 1. Required and “as indicated” planned assessments and procedures are outlined in Table 1.

Dosing for pembro will be according to package insert:

- 2mg/kg administered intravenously over 30 minutes every 3 weeks. Pembro will be infused prior to the start of the assigned systemic therapy arm. There will be no dose reductions for pembro.

Dosing for the other systemic therapy arms will begin as follows:

Arm 1: Cycle length is 21 days. Intravenous (i.v.) trastuzumab 8 mg/kg on cycle 1 day 1, then each subsequent cycle will be i.v. trastuzumab 6 mg/kg on day 1 every 21 days. I.v. eribulin will be 1.4 mg/m² on days 1 and 8 every 21 days.

Arm 2: Cycle length is 21 days. i.v. ado-trastuzumab emtansine 3.6 mg/kg on day 1 every 21 days.

Arm 3: Cycle length is 21 days. i.v. cetuximab 400 mg/m² on cycle 1 day 1, then i.v. cetuximab 250 mg/m² on day 8. Each subsequent cycle will be i.v. cetuximab 250 mg/m² on days 1 and 8 every 21 days.

Initially, 3 patients will be enrolled onto each treatment arm, and beginning on Cycle 1 Day 1 will receive pembro 2 mg/kg followed by the other systemic therapy on that arm.

Patients will be followed for 21 days. If no-dose-limiting toxicities (DLTs) are observed, this dose will be the highest dose tested and it will be used for further phase II study (RP2D). Expansion of a cohort from 3 to 6 patients will occur if 1 of 3 patients experiences a DLT at a given dose. If this occurs, 3 more patients will be enrolled at that dose level. If 1 or more patients ($\geq 2/6$) exhibit a DLT again, the dose level will be designated to have exceeded the maximum tolerated dose (MTD) and the dose level below would be tested. To be declared the RP2D, that lower level would require no more than 1 of 6 patients with a DLT. Tables 2A-C list the dose levels for each systemic therapy arm that may be tested based on their toxicity profiles.

Maximum Tolerated Dose (MTD)

The MTD is defined as the highest dose at which ≤ 1 of 6 evaluable patients experience a DLT within the first 21 days of treatment (end of cycle 1). Evaluable patients must complete at least 75% of their planned doses, unless missed doses are due to AEs. The cohort may be expanded to better define the safety profile for confirmation of the MTD.

Dose-Limiting Toxicities (DLTs)

Standard AEs will be considered DLTs that count for the determination of the MTD of supplementation. A DLT is a drug-related toxicity that is observed to occur within the first 21 days of treatment (end of cycle 1) as defined below. Drug-related toxicities include any toxicity that is possibly, probably, or definitely drug-related. Toxicity grades will be defined by the NCI CTCAE v 4.03. DLTs are defined by the following:

- Non-hematologic toxicities
Any grade ≥ 3 non-hematologic toxicity, with the exception of self-limiting or medically controllable toxicities (e.g., nausea, vomiting, fatigue, electrolyte disturbances, hypersensitivity reactions) lasting < 3 days, and excluding alopecia.
- Hematologic toxicities
 - i. Febrile neutropenia not related to underlying disease (fever, $> 101^{\circ}\text{C}$; ANC < 500)
 - ii. Prolonged grade 4 neutropenia (> 7 days)
 - iii. Neutropenic infection: \geq grade 3 neutropenia with \geq grade 3 infection
 - iv. Thrombocytopenia \geq grade 3 with bleeding or grade 4 lasting ≥ 7 days
- Missed $\geq 25\%$ of planned doses over 21 days due to treatment-related AEs in the first cycle.

Dose delays or reductions will be implemented for patients who experience adverse drug reactions as indicated in Tables 3A-D.

Subjects will be replaced if they do not complete the planned dose on Cycle 1 Day 1 because of an infusion reaction, provided that the infusion reaction is not grade 3 or higher.

Initiation of phase II portion

The decision to proceed from the dose establishment portion of the study (Phase Ib) and to open the expansion cohorts (Phase II) will depend on establishing the RP2D is identified.

Protocol visits and procedures will be scheduled to coincide with routine clinic visits for treatment decision making +/- 2 days unless otherwise indicated. Required and “as indicated” planned assessments and procedures are outlined in Table 1.

Dose Delay or Reduction

Prior to administration of a subsequent dose of systemic treatment, a subject must meet the following criteria:

- Any clinically significant systemic treatment-related toxicity must return to baseline or at least grade 1
- In the event that the administration of systemic treatment was delayed for reasons of toxicity, the subject may receive subsequent administrations of systemic treatment at a reduced dose. The amount of dose reduction will be based on guidelines in Tables 2A-C in the Appendix.
- In the event of toxicity that necessitates a delay of more than 4 weeks or there is radiographic evidence of disease progression, systemic treatment will be discontinued.

The phase II portion of each treatment arm are designed to determine frequency of complete responses by irRECIST with immunochemotherapy

The irRECIST using unidimensional measurements is defined using this table, modified from Nishino et al.¹:

| | Unidimensional assessment |
|-----------------------------|---|
| Measurable lesions | ≥10 mm in the longest diameter |
| Measurement of each lesion | The longest diameter (cm) |
| The sum of the measurements | The sum of the longest diameters of all target lesions and new lesions if any |
| Response assessment | PD: ≥20% increase from the nadir PR: ≥30% decrease from baseline CR: Disappearance of all lesions |
| New lesions | The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements. |
| Confirmation | Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD |

Patients with metastatic solid tumors will be evaluated for complete eligibility and enrollment. Patients must have measurable disease by RECIST 1.1 at the time of enrollment and have no contraindications to receipt of pembro. Patients must meet all eligibility criteria and selection of treatment arm will be determined by slot availability and systemic therapy on the arm selected must be considered standard of care or listed in the NCCN guidelines for that cancer type.

Dose Delay or Reduction

Prior to administration of a subsequent dose of **pembro**, a subject must meet the following criteria:

- Any clinically significant treatment-related toxicity must return to baseline or at least grade 1, **AND** who are receiving less than 7.5 mg prednisone or equivalent per day

Discontinuation of Protocol Treatment Administration

Pembro treatment will be discontinued in the event of any of the following:

- *If there is continued progression by irRECIST or intolerable side effects from pembro, the patient will be removed from protocol, and additional systemic therapy may be initiated at the discretion of the treating provider.*
- Withdrawal of consent by the subject
- Lack of compliance by the subject
- Changes in the subject's medical condition that render further administration of pembro treatment unacceptable in the judgment of the Principal Investigator
- Termination of study by Western Regional Medical Center, Inc.

Removal of Subject from Study

Subjects will be removed from further follow-up for any of the following reasons:

- Request by the subject to no longer be followed
- Completion of all study required follow-up
- Death
- Termination of study by Western Regional Medical Center, Inc.

Use of Anti-emetics and Supportive Care

Based on safety and efficacy data from other clinical trials involving PD-1 and PD-L1 inhibitors, premedication on the day of chemotherapy infusion (Arm 1) with dexamethasone 12 mg intravenously will be allowed. The anti-emetic regimen will be dictated by Western Regional Medical Center guidelines for the level of emetogenic risk of the chemotherapy. Supportive measures should be used as dictated by current standard of care at Western Regional Medical Center.

Prohibited Concomitant Medications/Therapies

- No prophylactic use of G-CSF in cycle 1. G-CSF can be used as prophylaxis in subsequent cycles if patient meets criteria for use per ASCO guidelines¹³.
- Any other anti-cancer therapy including investigational therapies unless allowed at the time of study entry

VI. Study Drugs

Please see attached PDF files of package insert for pembro, trastuzumab, eribulin, ado-trastuzumab emtansine, and cetuximab.

VII. REGULATORY AND REPORTING REQUIREMENTS

The study will be conducted according to the principles of the Declaration of Helsinki (as Scotland 2000, as clarified in 2002), the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects. Adverse event reporting will be as per the current NCI criteria.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (<http://ctep.cancer.gov/reporting/ctc.html>).

VIII. Institutional Review Board (IRB)/Ethics Committee (EC)

Approval of this study will be obtained from an IRB/EC prior to enrolling subjects on study.

IX. Public Trial Registry

This study will be listed on a Public Trial Registry such as ClinicalTrials.gov shortly after IRB approval.

X. Written Informed Consent

Consent forms must be in a language fully comprehensible to the prospective subject, otherwise the document must be translated into the subject's native language per institutional policy. Written, dated informed consent for the study must be obtained from all subjects before the start of any protocol specified procedures.

XI. Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subject's individual identifying information will be kept as confidential as possible under local, state, and federal law. Data generated as a result of this study are to be available for inspection on request by the following:

- Government agencies including the Food and Drug Administration (FDA)
- Western Regional Medical Center designated research personnel,
- or the Western Institutional Review Board.

Western Regional Medical Center may retain in its files copies of subject medical information required for auditing of case report forms (CRFs).

Individual subject identities will not be disclosed in any report or publication related to the study.

XII. Financial Disclosure

Investigators must be in compliance with the current FDA guidelines and regulations concerning financial disclosure.

XIII. Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use Good Clinical Practices (GCP) guidelines regarding clinical data management practices and procedures.

XIV. Control of the Study Materials

The Principal Investigator or their representative will account for all study materials. All study materials will be kept under lock in an inaccessible location while in storage. The

Principal Investigator shall maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects.

XV. Adverse Events

Adverse Event (AE) Definition (using CTCAE version 4.03)

An AE is any untoward medical event that occurs to a subject following the start of study drug administration, whether or not the event is considered drug-related. Pre-existing conditions are not considered an AE unless the condition worsens by at least one grade following the start of study drug(s) administration.

Death due to disease progression occurring 31 days or more from the day of last pembro or systemic therapy administration as part of this protocol will not be reported as an AE or SAE.

Any drug related AE of grade 3 or higher should be followed for resolution until either 1) subsequent anti-cancer therapy or 2) death.

Serious Adverse Event (SAE) Definition

An SAE is any AE that results in any of the following outcomes:

- Death
- A life-threatening experience
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

An event that is not listed above but that requires intervention to prevent one of the outcomes listed above is also considered an SAE.

Elective hospitalizations that are not in response to an AE will not be considered an SAE.

Serious Adverse Event Reporting

All SAEs must be reported to Western Regional Medical Center's Institutional Review Board (IRB) within 24 hours of the Investigator becoming aware of the SAE.

To report an SAE, sites will complete an SAE Report and email or FAX the SAE report to Western Regional Medical Center's IRB.

Site must report all SAEs that occur within 30 days after the last dose of **pembro or systemic therapy** treatment while on this study or until the subject receives additional cancer therapy.

Relationship to pembro or systemic therapy on this study

The relationship of an AE or SAE to **pembro or systemic therapy** on this study will be classified using the following four (4) categories:

- Definitely related
- Likely related

- Unlikely related
- Definitely not related

XVI. STATISTICAL AND ANALYTICAL CONSIDERATIONS

Analysis Datasets

The definitions of the analysis datasets are as follows:

- The Evaluable for Safety Population will consist of all subjects who receive at least one dose of pembro
- The Evaluable for Efficacy Population will consist of all subjects who receive at least one dose of pembro and who have had at least one post-baseline disease assessment

Subject Disposition

Data tabulations will summarize the following subject numbers, per dose group:

- Enrolled
- Received treatment
- Evaluable for safety and efficacy
- Who violate the protocol
- Who complete the protocol
- Who withdraw because of 1) adverse event(s), 2) disease progression, 3) physician's recommendation, or 4) withdrawal of consent

Subject Characteristics

Demographic characteristics of subjects will be summarized using descriptive statistics:

- Age
- Sex
- Ethnicity
- Performance status
- Tumor type
- Prior cancer treatment
- Smoking history

Efficacy Analysis

The primary objective of the Phase Ib is to determine the RP2D of pembro with Mab +/- eribulin.

The primary objective of the Phase II study is designed to determine frequency of complete responses by irRECIST in each of the treatment arms.

For each of the following arms, a complete response to the systemic therapy would be expected to be no more than the following % based on the following pivotal trial references:

Arm 1: 6% for trastuzumab and eribulin⁹ plus pembro

Arm 2: 1% for ado-trastuzumab emtansine^{14,15} plus pembro

Arm 3 Cohort 1: <1% for cetuximab¹⁶ plus pembro

Arm 3 Cohort 2: <1% for cetuximab¹⁷ plus pembro

For Arm 1, assuming a complete response rate of up to 6% in this setting with trastuzumab and eribulin and a rate of 29% for those subjects treated with trastuzumab and eribulin plus pembro, a sample size of 12 subjects will be required based on power of 80% and a one-sided alpha of 0.05.

For Arm 2, and Arm 3, assuming a complete response rate of up to 1% in this setting with Mab and a rate of 14.5% for those subjects treated with Mab plus pembro, a sample size of 12 subjects in each arm will be required based on power of 80% and a one-sided alpha of 0.05.

The calculations for statistical power and sample size using percentage complete response were computed using this: <http://www.stat.ubc.ca/~rollin/stats/ssize/b1.html> and confirmed using averages/one sample with this: <https://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/statisticalpowercalculators.aspx>

Note that the cohort that determines the RP2D will be counted towards the number required to be included in the statistical analysis calculations for the primary objective of the Phase II portion above, IF the subjects in that cohort have the cancer type to be assessed in the Phase II portion. For example, for cetuximab plus pembro (Arm 3), if 6 patients were required to reach the RP2D and 2 of those patients had HNSCC and 4 had K-ras, B-raf, N-ras wildtype CRC, then 10 additional patients with HNSCC and 8 additional patients with K-ras, B-raf, N-ras wildtype CRC will be required to complete the primary objective for the Phase II portion for Arm 3 Cohort 1 and Cohort 2, respectively.

The statistical analysis will be mainly descriptive. Continuous variables will be summarized using descriptive statistics: N, mean, standard deviation, median, minimum and maximum. Categorical variables will be presented using frequencies and percentages. Time-to-event variables will be described by N, median, range, number censored, and Kaplan-Meier plots.

All data collected on the CRF will be listed. There will be no imputations for missing data other than dates. A statistical analysis plan will be finalized prior to analysis. Any deviations from the statistical methods given in the protocol will be described and fully justified in the statistical analysis plan and/or in the final report as appropriate.

The primary reason for discontinuation in the study will be summarized for all patients.

Baseline characteristics and demographic data will be summarized for all patients who receive at least one treatment dose.

Results for the secondary objectives will be presented descriptively and with percentages where applicable.

Definitions:

- Tumor Response: Subjects will be assigned one of the following categories based on the response criteria outlined in irRECIST and RECIST 1.1 as appropriate for each tumor

type: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease. An objective response will be defined as either a CR or PR.

- DFS is defined as the period of time from the date of surgical resection to the date that the subject is determined to have disease relapse/recurrence or death due to any cause.
- OS is defined as the period of time from the date of enrollment to the date of death due to any cause.

Criteria response evaluation and overall response rates will be summarized by proportions together with exact binomial 95% confidence intervals for each dose group. Durations (DFS and OS) will be summarized by Kaplan- Meier methods. Median survival with 95% confidence intervals will be calculated and survival graphs will be presented for all Kaplan-Meier analyses.

Safety Analysis

All subjects who receive any amount of **pembro** (Safety Population) will be included in the final summaries and listings of safety data.

Frequencies of subjects experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: description of the event, duration, whether the AE was serious, relationship to study drug, action taken, clinical outcome, and whether or not it was a DLT. Severity of the AEs will be graded according to the CTCAE version 4.03. Emphasis in the analysis will be placed on AEs classified as dose limiting.

Summary tables will present the number of subjects observed with any grade AEs and corresponding percentages. The denominator used to calculate incidence percentages consists of subjects receiving at least one dose of study drug for each dose group. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event severity and relationship to study drug.

Deaths and other SAEs will be tabulated.

XVII. Pharmacodynamic analysis

Circulating tumor DNA in plasma provides a minimally invasive and potentially highly sensitive assay to meet this end. This methodology quantifies circulating tumor DNA in plasma and where available, matched tumor in specimens from cancer patients. It is hoped that this approach may provide valuable clinical decision-making information over the current treatment paradigm that involves periodic imaging for disease restaging.

Procedures for tumor DNA analysis:

Tissue processing. MACRODISSECTION OF TISSUES.

The referring pathologist should mark an area of >70% tumor cells on an H&E or immune-stained slide that must be sent with the material for testing. 5 freshly-cut serial sections of the tumor FFPE tissue, each with a thickness of 10 µm per slice will be prepared. For ≥ 250 square-mm surface area: combine 2 x 5 sections, each with a thickness of 10 µm into two empty Eppendorf tubes (5 sections per tube, total 10 sections). For ≤250 square-mm surface

area: combine 3 x 5 sections, each with a thickness of 10 μm in three empty Eppendorf tubes (5 sections per tube, total 15 sections). When preparing pathological material for DNA analysis, please ensure the equipment (especially the microtome blade and water bath) is completely clean between cases to prevent cross contamination. This can be achieved by wiping the microtome blade and any other surfaces with ethanol until they are free of any debris from earlier cases.

Blood collection, processing, and shipping:

Peripheral blood from a suitable vein or from an indwelling catheter (after blood collected for routine clinical care) is collected in two pre-labeled purple top K2-EDTA tubes (no heparin, BD or BCT). Once collected:

1) Gently invert tubes 8-10 times.

2) Store vacutainer tubes upright at 4°C until centrifugation. Wait ~10mins for EDTA clotting.

3) Centrifuge at 1,100-1,300g max, at 4°C, no break on centrifuge to avoid hemolysis.

4) Collect plasma and aliquot into sterile tubes.

*Aliquot in amounts of 500 μl (at least 4 tubes) and 1000 μl

**Stop aliquoting plasma when the total volume of plasma remaining is less than 500 μl .

5) Centrifuge plasma aliquots in a bench top centrifuge at 16,000-20,000g (max speed) for 10 minutes to pellet any remaining cellular debris.

6) Each tube will be labeled with a unique patient code, and log the date and time of blood draw.

7) Snap-freeze after separation in liquid nitrogen.

(From blood collection to aliquoting aim for less than 1 hour, preferably less than 45 minutes)

The samples will be batched and collected by TGen personnel or shipped to TGen at 445 N 5th St, Phoenix, AZ 85004.

Blood collections for circulating tumor DNA and proteomics correlates will be collected at up to 4 time points (starting with amendment 3, including the phase 1b portion): (1) 20 mL blood draw at baseline will be performed after informed consent but prior to initiation of C1D1, (2) after the first imaging assessment, and where applicable: (3) after imaging/exam confirms a complete response by irRECIST and/or (4) after imaging/exam confirmed disease progression by irRECIST.

Blood Processing and analysis along with and tumor samples (where applicable) will occur at TGen. All samples given to TGen will be devoid of patient identifiers and the results provided by TGen to the investigators will be kept in a secure database in the Western Regional Medical Center research offices. At no time will TGen have access to any patient related identifiers.

Quantitative Texture Analysis (QTA) will utilize standard imaging obtained from baseline and for the duration of subject participation on protocol. QTA can be performed on all types of imaging scans (CT or MRI and PET/CT scans). QTA is a novel analysis platform that measures tumor morphology and density on a pixel-by-pixel basis and provides a quantitative

read out tumor heterogeneity. Tumor heterogeneity is an important feature of tumor behavior and is driven by underlying biologic changes in tumor perfusion, oxygenation, proliferation and extracellular architecture¹⁸. QTA can help to provide biologic, predictive and prognostic information about tumor behavior, mutation status, hormone receptor status and early indicators of response. QTA may be performed from standard of care images, such as CT scans, and has been shown to be more predictive of response in renal cell carcinoma to TKI agents¹⁹. Given this novel approach of tumor analysis, QTA will be applied to image studies obtained in this trial and analyzed for associations with primary and secondary endpoints.

XVIII. Financial Responsibility

Pembro is commercially available, and will be provided at no cost to enrolled subjects (unless during the course of the study it receives a FDA label for a patient with the cancer being treated under study—in that situation the patient would be informed before proceeding with treatment on study). Patients will be enrolled onto a treatment arm where the other systemic therapy is billed to the patient's health plan or insurance company since it is commercially available and standard of care or listed in NCCN guidelines for treatment of their cancer. Research-related blood collection and QTA analysis will not be charged to enrolled subjects. The cost of treating cancer with any other treatments received (including imaging and supportive care medicines), the cost of standard of care blood work, and the cost of treating any side effects from such treatments will be billed to the patient's health plan or insurance company. If medical care is needed as a result of injury while being in this study, medical care will be provided to the patient and the insurance company will be billed.

XIX. References

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Appendix
Table 1. Schedule of Study Procedures

| Parameter | Baseline | Cycle 1 | | | Cycle 2 | | | Cycle 3 | | | Cycle 4+ | | | End of Study |
|---|-----------|---------|-------|----|---------|-------|----|---------|-------|----|----------|-------|----|--------------|
| | -28 to -1 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | |
| Day of study | -28 to -1 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | |
| Informed consent | X | | | | | | | | | | | | | |
| Complete medical history, height | X | | | | | | | | | | | | | |
| Complete physical exam | X | X | | | X | | | X | | | X | | | |
| Symptom directed exam | | | (X) | | | (X) | | | (X) | | | (X) | | (X) |
| Karnofsky performance status (KPS) | X | X | (X) | | X | (X) | | X | (X) | | X | (X) | | X |
| Vital signs (BP, HR, RR, temp, pain) and weight | X | X | (X) | | X | (X) | | X | (X) | | X | (X) | | X |
| Review con meds, AEs | X | X | (X) | | X | (X) | | X | (X) | | X | (X) | | X |
| ECG | X | | | | | | | | | | | | | |
| 2D echocardiogram q3months* (except for cetuximab arm) | X* | | | | | | | | | | X* | | | (X) |
| Disease status (baseline, preC4 and then q12 +/- 1 week) | X | | | | | | | | | | X | | | (X) |
| Pregnancy test | (X) | | | | | | | | | | | | | |
| CBC with differential | X | X | (X)** | | X | (X)** | | X | (X)** | | X | (X)** | | X |
| Serum chemistries | X | X | (X)** | | X | (X)** | | X | (X)** | | X | (X)** | | X |
| TSH (or free T4 if baseline TSH is above the upper limit of normal range) | X | | | | X | | | X | | | X | | | X |
| Tumor marker(s) | X | | | | (X) | | | (X) | | | (X) | | | (X) |

| | | | | | | | | | | | | | |
|--|---|------|-------|--|---|-------|--|---|-------|---|---|-------|-----|
| Pharmacodynamic studies | X | | | | | | | | | X | | | (X) |
| Survival assessment | | | | | | | | | | | | | X |
| Other systemic therapy administration (d1 +/- d8 depending on the arm)** | | X | (X)** | | X | (X)** | | X | (X)** | | X | (X)** | |
| Pembro administration | | X*** | | | X | | | X | | | X | | |

General

- Blood draws and vital signs are performed prior to dosing of pembro
- Except for Cycle 1, study visits and procedures may occur +/- 2 days of the day
- There is no clinical value to repeat Cycle 1 Day 1 laboratory testing, IF screening laboratory tests were performed within two calendar days AND those screening laboratory tests are acceptable for enrollment and dosing.
- X – required event
- (X) – as indicated, visits/assessments on day 8 are required if treatment arm includes day 8 dosing.
- *: 2D echocardiogram to be done at baseline (unless there is one available within 60 days of cycle 1 day 1), and then q3 months +/- 21 days for patients enrolled and receiving treatment on the trastuzumab and eribulin plus pembro or ado-trastuzumab emtansine plus pembro arms.
- **: Based on other systemic therapy assigned arm. See dose and schedule for each arm in Tables 2A-C. If the other systemic therapy therapy schedule includes day 8 dosing, then CBC with differential and serum chemistries will be performed and verified within acceptable limited for dosing prior to administration of other systemic therapy on day 8.
- X***: **Pembro**—Dosing will be according to package insert – 2mg/kg administered IV over 30 minutes every 3 weeks. CBC with differential and serum chemistries will be repeated on Cycle 1 Day 1 and confirmed to be within dosing parameters (inclusion #7 and 8) prior to dosing

End of Study Visit—This assessment can occur +/- 30 days of last dose of treatment on protocol if patient is removed from protocol for disease progression or intolerable toxicity.

Follow-up and survival assessment –Survival assessment should occur 4-6 weeks after end of study and can occur via phone, email, review of medical records, and then at a minimum of 3 months thereafter until 12 months after study arm patient is on has completed enrollment.

Disease status –All subjects should have their disease status monitored with at least a CT with po and iv contrast of the chest, abdomen, and pelvis (or PET/CT if iv contrast is contraindicated).

CBC with differential – WBC, ANC, RBC, HGB, HCT, platelets, MCV, and differential.

Serum chemistries – Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin.

Tumor markers: As indicated for tumor type, such as CEA, CA15-3, CA27.29 – if baseline is elevated above the upper limit of normal, then it will be repeated per schedule of events where marked (X).

Pharmacodynamic studies: Blood collections for circulating tumor DNA, and correlates for PD-1 if available, will be collected at up to 4 time points (starting with amendment 3, including the phase 1b portion): (1) 20 mL blood draw at baseline will be performed after informed consent but prior to initiation of C1D1, (2) after the first imaging assessment, and where applicable: (3) after imaging/exam confirms a complete response by irRECIST and/or (4) after imaging/exam confirmed disease progression by irRECIST. Archival tumor tissue will be collected, where available.

Infusion times for the standard of care drugs below is per package insert. Premedications per institutional guidelines.

Table 2A. Arm 1: Trastuzumab and eribulin

| Dose level | Trastuzumab dose level for C1D1 | Trastuzumab dose level for C2D1 and beyond | Eribulin dose level for all cycles |
|------------|---|--|---|
| 1 | 8 mg/kg on day 1 of cycle 1 every 21 days | 6 mg/kg on day 1 every 21 days | 1.4 mg/m ² on days 1 and 8 every 21 days |
| -1 | 6 mg/kg on day 1 of cycle 1 every 21 days | 4 mg/kg on day 1 every 21 days | 1.1 mg/m ² on days 1 and 8 every 21 days |
| -2 | 4 mg/kg on day 1 of cycle 1 every 21 days | 2 mg/kg on day 1 every 21 days | 0.7 mg/m ² on days 1 and 8 every 21 days |

Table 2B. Arm 2: Ado-trastuzumab emtansine

| Dose level | Ado-trastuzumab emtansine dose |
|------------|----------------------------------|
| 1 | 3.6 mg/kg on day 1 every 21 days |
| -1 | 3 mg/kg on day 1 every 21 days |
| -2 | 2.4 mg/kg on day 1 every 21 days |

Table 2C. Arm 3: Cetuximab

| Dose level | Cetuximab dose level for C1D1 | For patients on study at C2D1 and beyond |
|------------|---|--|
| 1 | 400 mg/m ² on day 1 of cycle 1, then 250 mg/m ² on day 8 of cycle 1 | 250 mg/m ² on day 1 and day 8 every 21 days |
| -1 | 250 mg/m ² on day 1 and day 8 every 21 days | 200 mg/m ² on day 1 and day 8 every 21 days |
| -2 | 200 mg/m ² on day 1 and day 8 every 21 days | 150 mg/m ² on day 1 and day 8 every 21 days |

Table 3A. Dose Delay and Intervention Guidelines for Pembro

| |
|---|
| Grade 1 immune related adverse reaction: No action. Provide symptomatic treatment |
| |
| Grade 2 immune related adverse reaction*: May withhold pembro. Consider systemic corticosteroids in addition to appropriate symptomatic treatment |
| |
| Grade 3 and Grade 4 immune related immune adverse reaction*: Withhold pembro. Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisolone equivalent within 12 weeks of toxicity. Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisolone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks |
| |
| |
| * Other systemic therapy may be continued as long as there are no contraindications. |

Severe or life-threatening adverse reactions, including any of the following:

- Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times the upper limit of normal or total bilirubin >3 times the upper limit of normal
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
- Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
- Severe immune-mediated reactions involving any organ system (eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

Table 3B. Dose Delay and Reduction Guidelines for Arm 1: Trastuzumab and eribulin plus Pembro

For trastuzumab:

| ABSOLUTE GRANULOCYTE COUNT (X 10 ⁶ /L) | | PLATELET COUNT (X 10 ⁶ /L) | % OF FULL DOSE |
|---|-----|---------------------------------------|----------------|
| ≥ 500 | And | ≥ 50,000 | 100 |
| < 500 | Or | < 50,000 | Hold |

When trastuzumab requires holding because of hematologic toxicity, reduce by 1 dose level in subsequent cycles. Discontinue the trastuzumab after 2 dose reductions.

Dose Modifications For Non-Hematologic Adverse Reactions

Permanently discontinue trastuzumab for any of the following

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-Uremic Syndrome
- Capillary Leak Syndrome
- Withhold for ≥ 16% absolute decrease in left ventricular ejection fraction (LVEF) from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values

For eribulin:

| ABSOLUTE GRANULOCYTE COUNT (X 10 ⁶ /L) | | PLATELET COUNT (X 10 ⁶ /L) | % OF FULL DOSE |
|---|-----|---------------------------------------|----------------|
| At least 1,500 | And | ≥ 100,000 | 100 |
| <1,500 | Or | 50,000-99,999 | Hold |

When eribulin requires holding because of hematologic toxicity, reduce by 1 dose level in subsequent cycles. Discontinue eribulin after 2 dose reductions.

Dose Modifications For Non-Hematologic Adverse Reactions

Permanently discontinue eribulin for any of the following

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-Uremic Syndrome
- Capillary Leak Syndrome
- Posterior reversible encephalopathy syndrome

Withhold trastuzumab and/or eribulin or reduce each dose by 1 dose level for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

Table 3C. Dose Delay and Reduction Guidelines for Arm 2: Ado-trastuzumab emtansine plus Pembro

Tables imported from package insert

Note: KADCYLA is ade-trastuzumab emtansine

49 **Table 1 Recommended Dose Reduction Schedule for Adverse Events**

| Dose Reduction Schedule | Dose Level |
|--|-----------------------|
| Starting dose | 3.6 mg/kg |
| First dose reduction | 3 mg/kg |
| Second dose reduction | 2.4 mg/kg |
| Requirement for further dose reduction | Discontinue treatment |

50

51 *Hepatotoxicity [see Warnings and Precautions (5.1)]*

52 A reduction in the dose of KADCYLA is recommended in the case of hepatotoxicity exhibited as
53 increases in serum transaminases and/or hyperbilirubinemia (see Tables 2 and 3).

54 **Table 2 Dose Modification Guidelines for Increased Serum Transaminases (AST/ALT)**

| Grade 2 (> 2.5 to $\leq 5 \times$ ULN) | Grade 3 (> 5 to $\leq 20 \times$ ULN) | Grade 4 ($> 20 \times$ ULN) |
|--|--|----------------------------------|
| Treat at same dose level. | Do not administer KADCYLA until AST/ALT recovers to Grade ≤ 2 , and then reduce one dose level. | Permanently discontinue KADCYLA. |

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.

55

56 **Table 3 Dose Modification Guidelines for Hyperbilirubinemia**

| Grade 2 (> 1.5 to $\leq 3 \times$ ULN) | Grade 3 (> 3 to $\leq 10 \times$ ULN) | Grade 4 ($> 10 \times$ ULN) |
|---|--|----------------------------------|
| Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1 , and then treat at same dose level. | Do not administer KADCYLA until total bilirubin recovers to Grade ≤ 1 , and then reduce one dose level. | Permanently discontinue KADCYLA. |

57

58 Permanently discontinue KADCYLA treatment in patients with serum transaminases $> 3 \times$ ULN
59 and concomitant total bilirubin $> 2 \times$ ULN.

60 Permanently discontinue KADCYLA in patients diagnosed with nodular regenerative
61 hyperplasia (NRH).

62

67 *Left Ventricular Dysfunction [see Warnings and Precautions (5.2)]*

68 **Table 4 Dose Modifications for Left Ventricular Dysfunction**

| Symptomatic CHF | LVEF < 40% | LVEF 40% to ≤ 45% and decrease is ≥ 10% points from baseline | LVEF 40% to ≤ 45% and decrease is < 10% points from baseline | LVEF > 45% |
|---------------------|---|---|--|----------------------------------|
| Discontinue KADCYLA | Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks. If LVEF < 40% is confirmed, discontinue KADCYLA. | Do not administer KADCYLA. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from baseline, discontinue KADCYLA. | Continue treatment with KADCYLA. Repeat LVEF assessment within 3 weeks. | Continue treatment with KADCYLA. |

69 CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

70

71 *Thrombocytopenia [see Warnings and Precautions (5.6)]*

72 A reduction in dose is recommended in the case of Grade 4 thrombocytopenia
73 (platelets < 25,000/mm³) (see Table 5).

74 **Table 5 Dose Modification Guidelines for Thrombocytopenia**

| Grade 3 PLT 25,000/mm ³ to < 50,000/mm ³ | Grade 4 PLT < 25,000/mm ³ |
|--|---|
| Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm ³), and then treat at same dose level. | Do not administer KADCYLA until platelet count recovers to ≤ Grade 1 (≥ 75,000/mm ³), and then reduce one dose level. |

PLT = Platelets

75

76 *Pulmonary Toxicity [see Warnings and Precautions (5.4)]*

77 KADCYLA should be permanently discontinued in patients diagnosed with interstitial lung
78 disease (ILD) or pneumonitis.

79 *Peripheral Neuropathy [see Warnings and Precautions (5.7)]*

80 KADCYLA should be temporarily discontinued in patients experiencing Grade 3 or 4 peripheral
81 neuropathy until resolution to ≤ Grade 2.

All other grade 3 or 4 non-hematologic toxicities: withhold ado-trastuzumab emtansine or reduce each dose by 1 dose level for other severe (Grade 3 or 4) until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

Table 3D. Dose Delay and Reduction Guidelines for Arm 3: Cetuximab plus Pembro

| ABSOLUTE GRANULOCYTE COUNT (X 10 ⁶ /L) | | PLATELET COUNT (X 10 ⁶ /L) | % OF FULL DOSE |
|---|-----|---------------------------------------|----------------|
| ≥ 500 | And | ≥ 50,000 | 100 |
| < 500 | Or | < 50,000 | Hold |

When cetuximab requires holding because of hematologic toxicity, reduce by 1 dose level in subsequent cycles. Discontinue the cetuximab agent after 2 dose reductions.

Table below imported from package insert

Note: ERBITUX is cetuximab

Dose Modifications For Non-Hematologic Adverse Reactions

Table 4: ERBITUX Dose Modification Guidelines

| Severe Acneform Rash | ERBITUX | Outcome | ERBITUX Dose Modification |
|----------------------|-----------------------------|----------------|--------------------------------------|
| 1st occurrence | Delay infusion 1 to 2 weeks | Improvement | Continue at 250 mg/m ² |
| | | No Improvement | Discontinue ERBITUX |
| 2nd occurrence | Delay infusion 1 to 2 weeks | Improvement | Reduce dose to 200 mg/m ² |
| | | No Improvement | Discontinue ERBITUX |
| 3rd occurrence | Delay infusion 1 to 2 weeks | Improvement | Reduce dose to 150 mg/m ² |
| | | No Improvement | Discontinue ERBITUX |
| 4th occurrence | Discontinue ERBITUX | | |

Permanently discontinue cetuximab for any of the following

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-Uremic Syndrome
- Capillary Leak Syndrome

Withhold cetuximab or reduce dose by one dose level for other severe (Grade 3 or 4) non-hematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.