A PHASE II, OPEN LABEL, MULTI-DOSE STUDY OF ^{89}ZR-DF-IAB22M2C (CD8 PET TRACER) FOR POSITRON EMISSION TOMOGRAPHY (PET/CT) IN PATIENTS WITH SELECTED ADVANCED OR METASTATIC SOLID MALIGNANCIES WHO ARE SCHEDULED TO RECEIVE STANDARD OF CARE IMMUNOTHERAPY ONLY, AS SINGLE AGENT OR IN COMBINATION.

Protocol Number:	**IAB-CD8-201**
Version Number:	**Version 3.1**
Version Date	**28 OCT 2020**
Development Phase:	**Phase II**
Investigational Compound:	**^{89}Zr-Df-IAB22M2C (CD8 PET Tracer)**
NCT Number:	**NCT03802123**
Sponsor:	ImaginAb Inc.

Name of Sponsor/Company: ImaginAb Inc.

Name of Study Product: ^{89}Zr-Df-IAB22M2C

Protocol Number: IAB-CD8-201	**Indication:** Patients with Selected Advanced and Metastatic Solid Tumors including Melanoma, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Squamous Cell Carcinoma of the Head and Neck, Colorectal Cancer-MSI high, Triple Negative Breast, Bladder, Cervical, and Esophagogastric Cancers

Title of Study:

A Phase II, Open Label, Multi-Dose Study Of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) For Positron Emission Tomography (PET/CT) In Patients With Selected Advanced Or Metastatic Solid Malignancies Who Are Scheduled To Receive Standard of Care Immunotherapy As Single Agent or In Combination.

Study Center: Up to 20 research sites in USA, Canada, Europe and Australia

Planned Number of Subjects:	**Study Development Phase:**
Approximately 47 Subjects	II

Objectives:

Primary Objectives:

- Evaluate safety of repeat doses of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer)
- Establish the relationship between ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) PET/CT lesion uptake with CD8+ cells by Immunohistochemical staining (IHC)

Secondary Objective:

- Assess ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake at Baseline and On-treatment in tumor lesions and reference tissues, including CD8+-cell rich reference tissues
- Measure potential change in ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake on PET in tumor lesions and reference tissues, including CD8+-cell rich tissues reference between baseline and On-treatment.
- Measure potential changes in ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake on $PET_{baseline}$ and PET_{Tx} scans compared to change in CD8+ cells in tumor lesions by IHC if the same lesion was biopsied at Baseline and On-Treatment visits
- Assess biodistribution for ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) on $PET_{baseline}$ and PET_{Tx} scans.

Exploratory Objectives:

- Explore visual and quantitative ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) PET measurements that best correlate with CD8+ cells as determined by IHC.
- Estimate positive predictive value, negative predictive value, sensitivity and specificity of ^{89}Zr-IAB22M2C (CD8 PET Tracer) PET for detecting CD8+ cells as determined by IHC.
- Explore the visual and quantitative ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) PET measurements with clinical outcomes.
- Evaluate the visual and quantitative ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) PET measurements with RECIST 1.1 radiology responses
- Evaluate the correlation of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake with immune infiltrates and other molecular biomarkers (such as CD4, CD8, PD-1 and PD-L1) expression by IHC
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Study Outcomes:

Primary Outcome Measure:

- The safety and tolerability of repeat doses of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) will be assessed by local and systemic signs and symptoms of infusion reactions, incidence of adverse events per CTCAE criteria, changes in laboratory test results, vital signs and 12-lead electrocardiogram (ECG) findings prior to and within 1 hour post injection.
- Correlation of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake in biopsied tumors as determined by SUV-based quantitative measures :SUVmax, SUVpeak, SUVmean, CD8 tumor volume (volume of tumor tissues with increased CD8 uptake with SUV > 40% SUVmax), and Tumor: Reference ratios with CD8+ cell measurements as determined by IHC from biopsy samples.

Secondary Outcome Measures:

- Assessment of Baseline and On-Treatment ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake and distribution in tumors and lymphoid organs, and measurement of change between the paired observations, as determined by:
    - Tumor uptake analysis as described by visual scoring scales
    - Lymph node chain visibility defined as location and number of nodes in lymph node chains identified with elevated ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) activity.
- Assessment of Baseline and On-Treatment ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake and distribution in tumors and lymphoid organs and measurement of change between the paired observations, as determined by:
    - SUV-based quantitative analysis: SUVmax, SUVpeak, SUVmean, CD8 tumor volume (volume of tumor tissues with increased CD8 uptake with SUV > 40% SUVmax), and Tumor: Reference ratios
    - Visual and SUV-based quantitative analysis (SUVmax, SUVpeak, SUVmean) in tumor and reference tissues including lymph nodes, spleen and bone marrow.
- Measurement of change in ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake in biopsied tumors as determined by SUV-based quantitative analysis : SUVmax, SUVpeak, SUVmean, CD8 tumor volume (volume of tumor tissues with increase CD8 uptake with SUV > 40% SUVmax) and Tumor: Reference ratio from Baseline to On-Treatment PET scans and correlation with change in CD8+ cells as determined by IHC from biopsy samples obtained prior to and 4 to 7 weeks after the start of immunotherapy.
- Description of biodistribution patterns of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) on $PET_{baseline}$ and PET_{Tx} and any changes in biodistribution between baseline and On-Treatment.

Exploratory Outcome Measures:

- Correlation of visual and quantitative ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake in tumor lesions with change in CD8+ cells as determined by IHC from biopsy samples obtained prior to and 4 to 7 weeks after the start of immunotherapy.
- Estimation of positive predictive value, negative predictive value, sensitivity and specificity of ^{89}Zr-IAB22M2C (CD8 PET Tracer) PET for detecting CD8+ cells as determined by IHC.
- Correlation of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake with clinical outcomes (response rates, duration of response, disease stability rate and PFS) at defined intervals as determined by the local investigator.
- Correlation of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake with radiologic responses based upon:
    - Correlation of subject response by RECIST 1.1 compared to visual and quantitative SUV-based analysis
    - Correlation of RECIST 1.1 target lesion response as determined by best change in lesion diameter while on immunotherapy compared to visual and quantitative SUV-based analysis at baseline and On-treatment PET/CT scans.
- Correlation of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) tumor and lymph node uptake with immune infiltrates and other molecular biomarker (CD8) expression by IHC

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Name of Study Product: ^{89}Zr-Df-IAB22M2C	
Protocol Number: IAB-CD8-201	**Indication:** Patients with Selected Advanced and Metastatic Solid Tumors including Melanoma, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Squamous Cell Carcinoma of the Head and Neck, Colorectal Cancer-MSI high, Triple Negative Breast, Bladder, Cervical, and Esophagogastric Cancers

- Correlation of the ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake on a subset of $PET_{baseline}$ and PET_{tx} scans that have been virtually reconstructed with lower theoretical doses of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) with CD8+ cells from IHC analysis.

Safety Assessments:

- Incidence of Treatment-Emergent Adverse Events (AEs).
- Incidence of withdrawals due to AEs.
- Change/shifts in laboratory values.
- Change in vital signs.
- Change in Electrocardiogram (ECG) parameters.
- Anti-Drug Antibodies
- Serious Adverse Events (SAEs)

Trial Design:

- Eligible subjects who meet Inclusion/Exclusion criteria will receive ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) as an IV infusion within 1 week prior to the onset of immunotherapy, and 4 to 6 weeks after start of immunotherapy.
- Conventional CT Chest, Abdomen and Pelvis (including Neck for SCCHN subjects) or MRI or whole body ^{18}FDG-PET scan will be performed within 45 days prior to 1st infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer).
- Fresh tumor biopsy (Preferred3 to 5 core biopsies) will be performed at:
  - Baseline: within -28 to -7 days prior to 1st infusion or 0-6 days after 1st infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) ***and*** its associated PET/CT scan of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) at 24hrs post injection.
  - Within 2 weeks after 2nd infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) and its associated PET/CT scan at 24 hrs post injection.
  - Archival tumor biopsy tissues obtained within 2 months (60 days) prior to 1st infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) may be submitted in place of Baseline fresh biopsy, with approval from the Sponsor.
- PET/CT scans ($PET_{baseline}$ and PET_{Tx}) will be obtained at 24 ± 3 hours after each infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer).
- Anti-drug antibody (ADA) blood samples will be collected at the following time points: at Baseline, prior to receiving the 2nd infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer), and at End-of-Study safety follow-up visit.
- Safety follow-up: 4-6 weeks after the last dose of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer).
- Extended follow-up: collect Standard of Care (SOC) imaging only, up to 12 months after start of immunotherapy.

The detailed study schedule and assessments in each visit are provided in Section **Error! Reference source not found.** of the protocol.

Tumor Biopsy:

- Fresh tumor biopsy from a RECIST 1.1 measurable lesion (excluding cutaneous lesions) within -28 to -7 days prior to 1st infusion immunotherapy or 1 to 6 days after 1st infusion of ^{89}Zr-Df-IAB22M2C (CD8

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PET Tracer) and its associated PET/CT scan; and within 2 weeks after 2nd infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) and its associated PET/CT scan.

- If biopsy will be performed after the PET/CT scan (either Baseline or On-treatment), image guided biopsy will be the preferred method, where the lesion is chosen based on CD8+ PET signal on the CD8 PET/CT scan.
- The need for the Baseline biopsy will be considered on a case by case basis following discussion with the Sponsor.
- If a patient has had a diagnostic biopsy within 2 months (60 days) prior to the 1st infusion of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer), the archival tissue can be submitted for IHC analysis, with approval of the Sponsor, provided the specimen is of adequate quality and the biopsy was obtained from a lesion that is RECIST 1.1 measurable and remains visible on conventional imaging with CT/MRI. If these conditions are met, then the patient can be exempt from the Baseline biopsy.
- Archival tumor tissue must have been obtained after last systemic therapy. The lesion from which the archival tissue is obtained should not have received radiation post-biopsy.
- For the 2nd biopsy (within 2 weeks after 2nd infusion of ^{89}Zr-Df-IAB22M2C [CD8 PET Tracer] and PET/CT scan), optional surgical resection may be performed in place of biopsy if investigator determines the tumor as resectable.
- Assuming a correlation between Tumor SUVmax to SUVmean Aorta reference tissues and CD8+ cell measurements by IHC of 0.65, 47 patients will be needed to obtain a width of 0.30. The 95% confidence interval is 0.47-0.78, which would be in the range of a good correlation.

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Inclusion Criteria:

Subjects will be eligible for enrollment in the study only if they meet ALL of the following criteria:

1. Patients with advanced or metastatic solid tumors including Melanoma, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Squamous Cell Carcinoma of the Head and Neck, Colorectal Cancer (MSI-High) Triple Negative Breast, Bladder, Cervical and Esophagogastric cancers selected to receive standard-of-care immunotherapy only, as single agent or in combination.
2. Patients with at least one non-irradiated lesion:
    - At least 1 non-irradiated measurable lesion documented on CT, MRI (per RECIST criteria 1.1) or are FDG-avid on FDG-PET within 45 days prior to first ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) infusion.
    - At least 1 non-cutaneous and non-bone lesion that is accessible, per investigator's assessment, and eligible for biopsy. If only a single RECIST 1.1 measurable lesion is present, investigator to determine if the tumor biopsy could interfere with RECIST 1.1 assessments of response.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
4. Meeting all clinical safety lab values per institution's standard of care, or Investigator's discretion, for patients receiving cancer treatment.
5. Age ≥ 18 years.
6. Ability to understand the purposes and risks of the trial and has signed an IRB-approved informed consent form.
7. Willingness and ability to comply with all protocol required procedures.
8. For men and women of child-producing potential, use of effective double barrier contraceptive methods during the study, up to 30 days after the last administration of the investigational product.

Exclusion Criteria:

Subjects will NOT be eligible for enrollment in the study if they meet ANY of the following criteria:

1. Serious nonmalignant disease or conditions that in the opinion of the Investigator and/or ImaginAb could compromise protocol objectives.
2. Patients with a single RECIST 1.1 measurable lesion for biopsy of which, per Investigator's assessment, is likely to interfere with RECIST 1.1 assessments of response.
3. Patients who have any splenic disorders, or had splenectomy, that in the opinion of the Investigator and/or ImaginAb could compromise protocol objectives.
4. Pregnant women or nursing mothers.
5. Life expectancy < 6 months

Statistical Considerations:

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® for Windows, version 9.4 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for continuous variables. Frequencies and percentages will be presented for categorical variables.

Sample Size Determination and Rationale

The sample size calculation is based on the co-primary outcome measure of correlation of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer) uptake as determined by Tumor SUVmax to SUVmean Aorta reference tissue with CD8+ cell measurement as determined by IHC from biopsied lesions. Since there are no validated comparator studies or imaging scans that can serve as reference values scans for CD8+ cell count, the objective of this study is to estimate the correlation between CD8+ cells and quantitative uptake by PET with sufficient precision.

The objective is to estimate the Spearman's correlation coefficient with a 0.30 width (width of the 95% confidence interval calculated based on Bonett and Wright (2000) method). The sample size is adjusted for intra-patient correlation assuming two observations per patient (baseline and on-treatment) and a moderate intra-patient correlation of 0.30 (plausible as patients will receive treatment between the two observations). Assuming a correlation between Tumor SUVmax to SUVmean Aorta reference tissue and CD8+ cell measurements of 0.65, 47 patients will be needed to obtain a width of 0.30. The 95% confidence interval is 0.47-0.78, which would be in the range of a good correlation. If the estimated correlation is 0.75, the 95% confidence interval becomes 0.61-0.85 (width = 0.24). If the estimated correlation is 0.50, the 95% confidence interval becomes 0.29-0.66 (width = 0.37).

Analysis Populations

Efficacy population

The efficacy population is defined as all subjects who have received at least one dose of study imaging agent and have at least one CD8 PET scan of adequate quality and corresponding core biopsy samples of adequate quality from at least one location.

For correlating treatment-related change in PET signal with change in CD8+ cell measurements on IHC: Efficacy population is defined as all subjects who have paired Baseline and On-treatment CD8 PET scans and corresponding paired biopsy samples.

Per Protocol (PP) Population

The Per Protocol (PP) population is defined as the set of subjects who meet the efficacy population requirements and were not associated with a major protocol violation. This population will be identified before the database lock.

Safety Population

The Safety population is defined as all subjects receiving at least one dose of the study imaging agent.

Analysis Methods:

The primary analysis of the primary and secondary outcome measures will be conducted using the PP population. Analyses of safety outcomes will be conducted using safety population.

Safety Analysis:

Analyses of safety outcomes will be conducted using the safety population.

Adverse events will be coded using MedDRA. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by treatment group and by stage of the study, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment.

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In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

The first co-primary objective is the evaluation of the safety of repeat doses of ^{89}Zr-Df-IAB22M2C (CD8 PET Tracer). Adverse events will be graded using CTCAEv5. All grades will be tabulated overall and by injection number (1st injection vs 2nd injection). Considering that the safety profile of one dose has been established before, no severe (grade ≥3) events are expected, but safety will be closely monitored and safety data will be reviewed by a data safety committee.

In addition, all the data from physical examination, 12-Lead ECG, Serum chemistry, hematology, and vital signs will also be descriptively summarized.

Efficacy Analysis:

The primary analysis of the primary and secondary outcome measures will be conducted using the PP population.

For the efficacy outcome measures, the data will be summarized and compared according to the variable type.

Continuous data summaries will include:

- Descriptive summary of number of observations, mean, standard deviation, median, 1st and 3rd quartile and minimum and maximum values.
- Inferential statistics include:
    - Pearson correlations
    - T-test or ANCOVA using the baseline value as a covariate, if the Normality assumption is met
    - non-parametric or rank based analysis, if the Normality assumption is not met.

Categorical data summaries will include:

- Frequency counts and percentages.
- Chi square test or Logit model for inferential statistics.

To establish the relationship of the PET/CT uptake with CD8+ cells (the second co-primary objective), the main analysis will be the Spearman's correlation coefficient between Tumor SUVmax to Aorta reference tissue and CD8+ cells value at all times (baseline and post-treatment). The correlation will then be estimated using SUVpeak, SUVmean, CD8 tumor volume (defined as the volume of tumor tissue with SUV > 40% of SUVmax), and other tumor: reference ratio. The correlation will be given with a two-sided 95% confidence interval accounting for clustering with subjects as clusters (as most subjects will have measurements at 2 times). Those analyses will be repeated separately at baseline and post-treatment as exploratory analyses.

The first 15 to 20 patients might be described during the study in order to check the technical quality of the data and the imaging. This description will not allow for stopping the trial, no statistical inference will be done, and therefore no type-I error is spent at this stage.