CT216

A Phase 0 Master Protocol Utilizing a Novel Intratumoral Microdosing Approach for Simultaneously Evaluating Multiple Drugs and Drug Combinations in Patients with Solid Tumors

K. Rajasekaran[1], J. G. Newman[1], R. G. Maki[2],T. J. Ow[3], V. Mehta[3], K. R. Gundle[4], D. R. Clayburgh[4], R. J. Li[4], M. Porosnicu[5], C. O. Nathan[6], A. Tang[7], B. A. Hatton[8], K. H. W. Sottero[8], G. Kung[8], M. O. Grenley[8], K. Anderson[8], and R. A. Klinghoffer[8]

[1]University of Pennsylvania Health System, Philadelphia, PA, [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, [3]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, [4]Oregon Health & Science University, Portland, OR, [5]Wake Forest School of Medicine, Winston-Salem, NC, [6]Louisiana State University Health, Shreveport, LA,[7]University of Cincinnati College of Medicine, Cincinnati, Ohio,[8]Presage Biosciences, Inc., Seattle, WA

INTRODUCTION

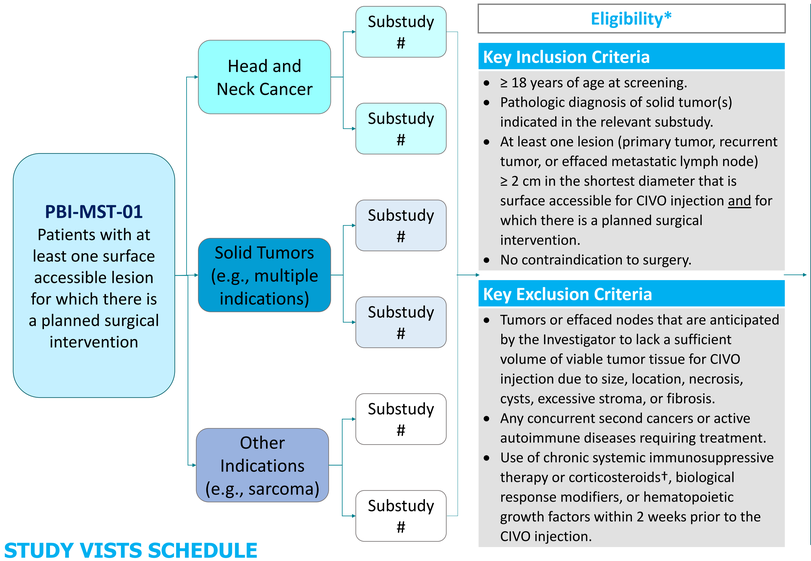
- Tumor responses to cancer treatments are highly context-specific and often involve complex interactions between the anti-cancer therapy, genetically diverse tumor cells, and a heterogeneous tumor microenvironment (TME).[1-4]
- The complexity of human tumors presents a challenge to the development of novel anti-cancer therapies, as all preclinical models fall short in capturing this complexity. This contributes to the high failure rates of investigational anti-cancer drugs entering Phase 1, with the likelihood of approval being as low as 6.7%.[1-5]
- CIVO (Comparative In Vivo Oncology) is an intratumoral microdose injection research tool intended to bridge the translational gap between preclinical and clinical studies by enabling *in situ* assessment of up to 8 oncology drugs or drug combinations simultaneously within a patient's tumor.[6]
- The CIVO Phase 0 model was established under FDA's exploratory IND guidelines for microdosing (Exploratory IND Studies, Guidance for Industry, Investigators, and Reviewers, CDER, January 2006). CIVO Phase 0 intratumoral microdosing studies can be conducted prior to completion of Phase 1 clinical safety trials and limit the toxicity associated with typical clinical exposures of these investigational agents.[7]
- As put forth by the 2018 FDA Guidance, Master Protocols have been utilized to build a single infrastructure, trial design, and protocol to simultaneously evaluate multiple drugs and/or disease populations in multiple substudies, allowing for flexibility and efficiency in drug development.
- A Master Protocol was thus developed for CIVO Phase 0 studies, enabling ongoing evaluation of multiple investigational drugs and combinations using the CIVO platform without a need for new stand-alone protocols. Each set of investigational drugs or combinations is added as a substudy of the Master Protocol, thus reducing administrative burden to clinical site staff and creating an infrastructure to ensure quality data and oversight of patient safety.

AIM

A Master Protocol to evaluate the localized pharmacodynamics (PD) of various anti-cancer therapies within the TME in multiple tumor types following intratumoral delivery of microdose quantities of drugs and drug combinations via the CIVO research tool in separate substudies.

STUDY DESIGN

PBI-MST-01 (NCT04541108) is a multi-center, non-randomized, open-label Phase 0 Master Protocol.



Eligibility*

Key Inclusion Criteria

- ≥ 18 years of age at screening.
- Pathologic diagnosis of solid tumor(s) indicated in the relevant substudy.
- At least one lesion (primary tumor, recurrent tumor, or effaced metastatic lymph node) ≥ 2 cm in the shortest diameter that is surface accessible for CIVO injection and for which there is a planned surgical intervention.
- No contraindication to surgery.

Key Exclusion Criteria

- Tumors or effaced nodes that are anticipated by the Investigator to lack a sufficient volume of viable tumor tissue for CIVO injection due to size, location, necrosis, cysts, excessive stroma, or fibrosis.
- Any concurrent second cancers or active autoimmune diseases requiring treatment.
- Use of chronic systemic immunosuppressive therapy or corticosteroids†, biological response modifiers, or hematopoietic growth factors within 2 weeks prior to the CIVO injection.

Common CIVO Research Platform

Simultaneous intratumoral microdose injections of up to 8 drugs/drug combinations followed by ex vivo biomarker analysis of tumor response via IHC, ISH, or gene expression analyses

CIVO Injection Procedure

Drug compounding and loading at the site pharmacy

Injection in the outpatient setting

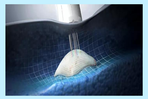
CIVO Microdose Injection Device + **CIVO GLO**

Fluorescent tracking microspheres co-injected to enable visualization of injection sites throughout study procedures

CIVO GLO is visualized after injection

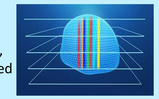
Timepoint

CIVO injects multiple columns of drugs simultaneously in microdose quantities directly into a patient's tumor

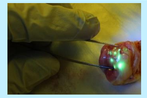


Drugs interact with the tumor while within the patient

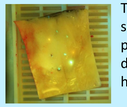
4 hours to up to 7 days after injection, the tumor is resected



Surgery/Site Sample Processing

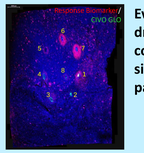


CIVO GLO is visualized and enables sample resection and tissue orientation



Tissues are gross sectioned perpendicularly to the drug columns for histological processing

Biomarker Analysis at Presage



Evaluating multiple drugs and drug combinations simultaneously in the patient tumor

STUDY VISTS SCHEDULE

Visit 1 Day 0	Informed Consent; Screen; Enroll	→	Visit 2 Day 1	CIVO Microdose Injection	→	Visit 3 Day 1-5*	Tumor Resection; Sample Processing	→	Visit 4 Day 6-14*	Safety Monitoring	→	Visit 5 Day 28	Safety Monitoring; End of Study (phone or in-person)

*Eligibility criteria and timepoints will be specified in each substudy. †Prednisone or equivalent exceeding a total dose of 140 mg over the last 14 days. Intranasal, inhaled, topical, or local corticosteroid injections or steroids as premedication for hypersensitivity reactions are exceptions to this criterion.

STUDY STATUS

There are currently two active, recruiting substudies under PBI-MST-01.

Substudy ID	MST01-TAK-02	MST01-MSD-03
Study Drugs	TAK-676, Carboplatin, Paclitaxel, Fluorouracil	MK-0482, MK-4830, Pembrolizumab
Indication(s)	HNSCC	HNSCC or STS
Timepoint	4-96 Hours	48-96 Hours
Minimum Lesion Size	2.0 cm in shortest diameter	3.0 cm in shortest diameter
Enrollment Began	May 2021	October 2021

HNSCC = head and neck squamous cell carcinoma; ILT = immunoglobulin-like transcript; PD-1 = programmed death-1; STING = stimulator of interferon genes; STS = soft tissue sarcoma.

Presage Biosciences, Inc. is the Sponsor for this study. This study is also financially supported by Takeda Development Center Americas and Merck Sharp & Dohme Corp.

REFERENCES

1 **Gould SE et al**. Translational value of mouse models in oncology drug development. *Nat Med 2015;21:431-439.*

2 **Letai A.** Functional precision cancer medicine - moving beyond pure genomics. *Nat Med 2017;23:1028-1035.*

3 **Liu Z et al**. Lessons learned from two decades of anticancer drugs. *Trends Pharmacol Sci 2017;38:852-872.*

4 *Cancer Moonshot Blue Ribbon Panel Report (Oct. 2016).*

5 **Hay M et al**. Clinical development success rates for investigational drugs. *Nat Biotechnol 2014;32:40-51.*

6 **Klinghoffer RA et al**. A technology platform to assess multiple cancer agents simultaneously within a patient's tumor. *Sci Transl Med 2015;7:284ra58.*

7 **Moreno-Gonzalez A et al**. Predicting responses to chemotherapy in the context that matters – the patient. *Mol Cell Oncol 2015;3:e1057315.*

SUMMARY

The CIVO Phase 0 Master Protocol (NCT04541108) was established to efficiently add substudies and accommodate evaluation of a wider repertoire of new agents in order to continually inform and de-risk drug development.

Each substudy allows intratumoral administration of microdoses of up to 8 oncology drugs or combinations simultaneously within a patient's tumor to safely and efficiently evaluate TME impact, immune profiles, PD biomarkers, drug combination potential, and responder hypotheses.