Executive Summary

National Cancer Institute Gastrointestinal Steering Committee

Gastroesophageal Carcinoma Immuno-Oncology Clinical Trials Planning Meeting

May 21-22, 2018

Meeting Co-Chairs: Manish Shah M.D. and Tim Wang M.D.

Meeting Description

The National Cancer Institute (NCI) Gastrointestinal Steering Committee (GISC) convened a Clinical Trials Planning Meeting for Gastroesophageal Carcinoma Immuno-Oncology on May 21-22, 2018 in Rockville, MD. Meeting attendees included GISC members, members of the GISC Esophagogastric Task Force (EG TF), physicians, researchers, patient advocates, and NCI staff. The purpose of the meeting was to identify feasible strategies for the incorporation of immuno-oncology (IO) therapeutic approaches for gastric and esophageal cancer and to select clinical trial designs for maximal patient benefit. At the beginning of the meeting, the late Ms. Debbie Zelman was remembered as a patient and advocate who helped to raise awareness of these diseases.

Background

Current survival rates of gastric and esophageal cancer are low despite the use of various multimodality approaches (typically a combination of chemotherapy, radiation and surgery). Comprehensive molecular characterization of gastric and gastroesophageal junction tumors has revealed the presence of molecular subsets that show differences in immunobiology with potential implications for treatment[1]. For example, tumors that exhibit microsatellite instability high (MSI-H) or a high Epstein-Barr virus (EBV) burden may be the most amenable to checkpoint inhibition. Esophageal squamous cell carcinomas exhibit frequent amplification of driver oncogenes, including receptor tyrosine kinases, whereas esophageal adenocarcinomas are similar to chromosomally unstable gastric tumors, with less clear therapeutic implications[2]. Efforts to incorporate targeted therapy for HER2-positive tumors have met with some success and additional studies are ongoing. Tumor heterogeneity is thought to be the main reason why HER2-directed therapies are less successful in gastric and gastroesophageal junction cancers than in breast cancer[3,4]. Clinical trials for IO approaches such as checkpoint inhibitors have also had limited success and additional studies of various combinations are being conducted.

Inflammation is a key risk factor for gastric and esophageal cancers, and while the effects of chronic inflammation can include cancer growth and progression, it can also result in the inhibition of antitumor immunity and effects on the immune microenvironment. Most gastric and esophageal tumors are "cold" tumors, with limited infiltration of lymphocytes and an immune suppressive microenvironment. These inhibitory effects appear to be modulated by both myeloid derived suppressor cells (MDSCs) and regulatory T cells (T_{reg}), however the extent to which each inhibitory mechanism plays a dominant role is

unclear and is likely to depend on the disease subtype. The gastric microbiome, including infection with *H. pylori*, plays an important role in defining the immune microenvironment[5]. Efforts to overcome resistance to IO therapy and the incorporation of predictive biomarkers to select patients who are likely to respond to such therapies are required.

Consensus & Recommendations

There was a great deal discussion on the landscape of immunotherapy trials across the US and worldwide. Several international studies led by industry examine the role of IO therapy in the perioperative space for gastric cancer, pre-operative therapy for esophageal cancer, and first line chemotherapy combinations. Second line studies comparing IO therapy to chemotherapy alone have recently reported negative. This led to a discussion on the unique role NCTN can plan in drug development of IO therapies. There was specific discussion of a lack of fundamental knowledge of resistance mechanisms to anti PD-1 or anti PD-L1 based therapy across disease subtypes in both esophageal and gastric cancer. There was little enthusiasm for repeating or duplicating an industry sponsored study. However, there was enthusiasm for better developing a biologic understanding of the IO therapy in the context of the disease subtype, or of the combination IO therapy in the context of the specific gastroesophageal disease, understanding limitations of tissue acquisition from NCTN sites.

The meeting attendees discussed several ideas for potential clinical trials. The ideas were divided into three broad areas: combined radiation and IO, innate immune stimulators, and IO in MSI-H or EBV-positive patients. Given the uncertainties surrounding the modes of resistance to IO therapy, and the limited understanding of the implication of disease subtype on resistance, a consensus for specific IO clinical trials was not achieved at the meeting. However, the obstacles for IO therapies were well defined and a path forward to developing trials within the EG TF was delineated. There was consensus on two broad drug development strategies to be further developed with the EG TF – (1) a neoadjuvant trial, such as a window of opportunity study, to quickly delineate IO combination synergies but also to obtain tissue to better understand mechanisms of resistance, and (2) a 1st or 2nd line metastatic trial that may serve as a template for future IO combinations.

Clinical Trials: Challenges and Opportunities

- Optimization of IO combinations in refractory patients was agreed upon as a key goal but most of available supporting data is currently from animal models and in other diseases which may or may not be applicable to gastroesophageal cancers; thus, the collection of clinically annotated tissue specimens from patients is of the greatest importance. Tumor annotation regarding immune signature, genomic subtypes, and response to PD-1/PD-L1 agents is also key.
- Many of the participants believed that IO therapy in combination with chemotherapy would likely become standard therapy for gastroesophageal cancers in the near future, and thus future IO combinations may need to be tested on this backbone.
- Rational approaches to circumventing IO resistance mechanisms will require a greater understanding of the role of MDSCs, T_{reg} cells, and cytokine signaling.

- Promising targets for candidate IO combinations include anti-CD40, oncolytic viruses, and anti-CD73 (ADA-adenosine inhibitor).
- Various designs for future trials were debated including a scaffold design and a sequential design using a common template. The sequential design would move from one agent or combination to another as a "pipeline" where data collected is used to determine critical questions and future goals. The neoadjuvant setting can be helpful for data and tissue collection.
- Optimization and standardization of tissue collection and annotation, especially in the neoadjuvant and metastatic settings, will be required.
- Differential response to IO may be impacted by unique microbiota, which impact efficacy and toxicity via drug metabolism and inflammatory responses.

Biomarkers

- Potential predictive biomarkers for IO include PD-L1 immunohistochemistry, MSI status, tumor mutational burden, and immune cell gene expression profiling[6]. Other promising technologies include the cancer immunogram[7] and the immunoscore[8]. All such approaches would need to be validated in the context of gastric and esophageal cancer.
- Spatial and temporal heterogeneity in tumor phenotype and genotype at the single cell level, such as in circulating tumor cells, is another important factor in disease characterization. Assays such as high-definition single cell analysis (HD-SCA), liquid and solid biopsy, as well a single cell CNV, aim to probe these differences for diagnostic and prognostic purposes[9,10].
- The NCI-supported Cancer Immune Monitoring and Analysis Centers (CIMACs) and the Cancer Immunologic Data Commons (CIDC) provide resources and support for biomarker-related research conducted alongside IO trials. The infrastructure of the labs allows for sample collection and a systematic approach to support discovery and validation trials.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.

Anticipated Actions

The participants agreed on the importance of initiating a therapeutic study within the NCTN; however, the specific agent(s) and strategy have not yet been determined.

- The findings from the CTPM will be used as a basis for continued discussion within the EG TF to develop new therapeutic concepts.
- A white paper will be prepared for documentation of meeting outcomes and recommendations.

References

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10. Chalfin HJ, Glavaris SA, Malihi PD, et al. Prostate Cancer Disseminated Tumor Cells are Rarely Detected in the Bone Marrow of Patients with Localized Disease Undergoing Radical Prostatectomy across Multiple Rare Cell Detection Platforms. *J Urol.* 2018;199(6):1494-1501.

NCI Esophagogastric Task Force
Gastroesophageal Carcinoma Immuno-Oncology
Clinical Trials Planning Meeting
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AGENDA

Day 1

8:30 – 8:40 a.m.	Welcome/introductions/goals of the meeting	Manish Shah, Tim Wang
8:40 – 8:45	Tribute to Debbie Zelman	Jaffer Ajani

Gastric/Esophageal cancer landscape Moderator: Carmen Allegra

8:45 – 9:00 a.m.	Landscape for treatment in upper GI cancers – Localized disease	Jaffer Ajani
9:00 – 9:15	Gastric and Esophageal cancer therapy in metastatic disease	Heinz-Josef Lenz
9:15 – 9:35	Genomic landscape of esophagus and gastric cancers	Adam Bass
9:35 – 9:55	Current Immunotherapy trials in GI cancers	Dung Le

Break – 10 minutes

Tumor microenvironment Moderator: Tim Wang

10:05 – 10:25 a.m.	Role of Innate immunity in cancer development and tolerance	Tim Wang
10:25 – 10:45	Molecular mediators of I/O resistance for GI cancers	Jason Luke
10:45 – 11:05	Immune heterogeneity and therapeutic resistance in GI cancers	Greg Beatty
11:05 – 11:20	Gastric microbiome and the immune microenvironment	Manish Shah

Preliminary clinical trials presentation

11:20 – 12:00 p.m. Presenter: David Ilson

Lunch Break (on your own) – 1 hour

Biomarkers Moderator: Heinz-Josef Lenz

1:00 – 1:20 p.m.	Pathology – Biomarkers for immune therapy	Robert Anders
1:20 – 1:40	Tumor microenvironment in GI malignancies	Jerome Galon
1:40 – 2:00	Microbiome and immune checkpoint blockade	Romina Goldszmid
2:00 – 2:20	CTC/blood assessment	Peter Kuhn
2:20 – 2:30	CIMACs overview	Helen Chen

Break – 20 minutes

Brainstorming Session: clinical trial designs Moderators: Manish Shah, Syma Iqbal

2:50 – 5:00 p.m. All participants

Day 2

Novel agents/pathways and IO combinations Moderator: Lakshmi Rajdev

8:30 – 8:50 a.m.	New cancer agents in development	Chuck Drake
8:50 – 9:10	Novel immunotherapy combinations	Kohei Shitara
9:10 – 9:30	How cancer genomes influence immunotherapy efficacy	Nadeem Riaz
9:30 – 9:50	Radiation/IO combo	Chandan Guha
9:50 – 10:10	Chemo/IO combo	Ronan Kelly

Break – 10 minutes

Working group discussion on trial designs Moderator: Manish Shah

10:20 – 11:20 a.m. Carmen Allegra, Chandan Guha, Wayne Hofstetter, David Ilson, Syma Iqbal, Ronan Kelly, Lawrence Kleinberg, Heinz-Josef Lenz, Lakshmi Rajdev, Manish Shah, Tim Wang

Conclusions and Consensus Moderators: Manish Shah, Tim Wang

11:20 – 12:00 p.m. All Participants

Adjourn

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