

Creating a Cancer-free World. One Person, One Discovery at a Time.

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An Update on Gastroesophageal Cancer Research in Radiation Oncology at OSU

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The Burden of Gastroesophageal Cancer

- The majority of patients with esophagus/gastroesophageal junction (GEJ)/gastric cancer present with advanced stage disease (≥T2 or with tumor spread to lymph nodes).
- The treatment course for patients with this cancer is arduous.
 - May involve chemotherapy, radiation therapy, and surgery.
 - Many patients are hospitalized at multiple points during treatment.
- For patients who complete this therapy, the overall survival at 5 years remains around 50%.





The Role of Radiation Therapy in Gastroesophageal Cancer

- For esophageal and GEJ cancer, most patients receive treatment with chemotherapy and radiation therapy prior to surgery.
- For gastric cancer, when radiation is delivered, it is typically delivered with chemotherapy following surgery.
 - Challenges with delivering radiation therapy following surgery:
 - Delays in recovery from surgery.
 - Challenges in defining targets for treatment.
 - Larger radiation fields are used resulting in more dose to surrounding normal organs.
 - Poor tolerance of therapy.



Treatment Delivery





Research Focus Areas

- Accurate staging of disease and assessment of treatment response.
 - Digital PET imaging.
- Development of more effective therapies.
 - Novel therapies:
 - Addition of radiosensitizer, adavosertib, to radiation therapy for esophagus/GEJ cancer.
 - Total neoadjuvant therapy for gastric cancer.
- Mitigation of acute and long term treatment toxicity.
 - Cardiotoxicity.



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Digital PET Imaging - Wright Center of Innovation in Biomedical Imaging



Dr. Michael Knopp



Dr. Chadwick Wright



Dr. Katherine Binzel



Accurate Staging of Disease

- Accurate staging is vitally important for esophageal/GEJ/gastric cancer given the morbidity and mortality associated with curative therapy.
 - Current imaging approaches are not always sufficient to detect occult metastatic disease.
 - We need imaging that is sensitive enough to ensure that patients who are planned for curative surgery, do not have metastatic disease.







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Assessment of Treatment Response





Images provided courtesy of Dr. Michael Knopp, MD, PhD, Dr. Chadwick Wright, MD, PhD, Dr. Katherine Binzel, PhD



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Addition of Adavosertib (AZD1775) to Radiation Therapy for Esophagus/GEJ Cancer – Study Team



Dr. Eric Miller Radiation Oncology



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Dr. Sajid Jalil Gastroenterology



Dr. John Hays Medical Oncology



Dr. Lai Wei Biostatistics



High Level of TP53 Mutations in Esophageal Cancer



71% TP53 mutation rate

91% TP53 mutation rate



TCGA, Nature 2017;541:169

Targeting Cell Cycle Checkpoints to Improve Chemoradiation Efficacy



Aleem et al. Front in Cell/Developmental Biology 2015;3:1-22. Gray et al. JCO 2017;35;e20. Oza et al. JCO 2015;33;5506.

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AZD1775 Significantly Sensitizes Esophageal Cancer Cells to Radiation *In Vivo*





Yang, L. et al. Clin Cancer Res, 2020.

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Study Rationale

- For patients with inoperable or metastatic esophageal cancer, radiation therapy (RT) is an established treatment for relieving swallowing difficulty due to the tumor and improving quality of life.
 - For patients with localized disease who are not eligible for systemic therapy, RT alone is unlikely to provide sustained locoregional control.¹
 - Local recurrence or progression following palliative RT may result in problems swallowing and bleeding.
- For patients with metastatic disease, the development of more effective systemic therapies including targeted agents and immunotherapy has made durable control of the primary tumor a higher priority.^{2,3}
 - Aggressive control of the primary tumor in patients with metastatic disease has been associated with improved survival.⁴
 ¹Zhu LL et al PLoS One 2015 10(6): p. e0128616

¹Zhu, L.L., et al. PLoS One, 2015. **10**(6): p. e0128616.
²Bang, Y.J., et al. Lancet, 2010. **376**(9742): p. 687-97.
³Shah, M.A., et al. JAMA Oncol, 2018.
⁴Guttmann, D.M., et al. J Thorac Oncol, 2017. **12**(7): p. 1131-1142.

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NCI #10389: A Phase 1 Trial Combining WEE1 Inhibitor Adavosertib (AZD1775) with Radiation Therapy for Metastatic or Inoperable and Ineligible for Definitive Chemoradiation Esophageal and Gastroesophageal Junction Cancer

Phase I Trial

Registration		Treatment	Week 1	Week 2	Week 3	
		AZD1775 administered	V		V	Weeks 4-6
		escalation level	~		X	Break/Toxicity evaluation
		Radiation therapy (37.5 Gy in 15 fractions)	Х	Х	Х	

Following the phase I trial, there will be a 12 patient expansion cohort to confirm safety and verify target engagement.



Objectives

Primary Objective:

To identify the maximally tolerated dose of AZD1775 to be used in combination with radiation therapy in patients that are metastatic or inoperable and not eligible for definitive chemoradiation.

Secondary Objectives:

- To evaluate the efficacy of AZD1775 when administered in combination with radiation therapy by assessing:
 - improvement in swallowing difficulty following treatment.
 - time to second intervention for difficulty swallowing.
 - overall survival.
- To identify biomarkers that are predictive of response to experimental therapy.



Inclusion criteria

- Biopsy-confirmed esophageal cancer (either squamous cell or adenocarcinoma), including Siewert gastroesophageal junction adenocarcinomas Types 1 and 2.
- Patients must be inoperable and not eligible for definitive chemoradiation after multidisciplinary review or have pathologically confirmed or imaging consistent with metastatic disease.
- Patients ≥18 years of age.
- ECOG Performance Status 0-1.
- Adequate organ function including leukocytes ≥ 3,000/µL; ANC ≥ 1,500/µL; hemoglobin ≥ 9 g/dL; platelets ≥ 100,000/µL; bilirubin ≤ 1.5 x upper limit of normal; AST/ALT ≤ 3 x upper limit of normal; serum creatinine ≤ 1.5 x upper limit of normal or calculated creatinine clearance ≥ 60 mL/min calculated by the Cockcroft-Gault formula.
- Patients must be non-pregnant and non-nursing. Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 1 week of registration.
- Willing to and capable of signing informed consent.
- Able to swallow whole capsules.
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible.

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Exclusion criteria

- Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study.
- Patients who have not recovered from adverse events due to prior anti-cancer therapy (with residual toxicities > Grade 1) with the exception of hair loss.
- Prior thoracic or abdominal radiation therapy for cancer.
- Pregnant women are excluded from this study.
- Patients with certain heart issues.
- Active use of certain medications which may interact with AZD1775.



AZD1775 Dose Escalation Schedule

	Dose			
Dose Level	AZD1775	Radiation Therapy		
	(mg)	(Gy)		
Level -1	150 mg QD on Days 3 and 5 of weeks 1 and 3	37.5 Gy/15 fractions		
Level 1*	150 mg QD on Days 1, 3, and 5 of weeks 1 and 3	37.5 Gy/15 fractions		
Level 2	200 mg QD on Days 1, 3, and 5 of weeks 1 and 3	37.5 Gy/15 fractions		
Level 3	200 mg QD on Days 1-5 of weeks 1 and 3	37.5 Gy/15 fractions		

* Starting dose

This trial is currently under development and will likely be open in Fall 2020.



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Total Neoadjuvant Therapy for the Treatment of Gastroesophageal Junction (GEJ) and Gastric Cancers



Dr. Ning Jin Medical Oncology



Dr. Dayssy A. Diaz Radiation Oncology



Dr. Jordan Cloyd Surgical Oncology



Dr. Michael Knopp Radiology



Dr. Chadwick Wright Radiology



Background

- The adequate treatment approach for gastric cancer has not been elucidated.
- Postoperative chemoradiation has been found to improve overall survival compared to surgery alone.
- Multiple studies have shown improved outcomes with the use of chemotherapy prior to surgery.
- The use of digital PET imaging to adapt treatment volumes has the potential to decrease toxicity.
- The resident microbiome has a role in the response of several cancer treatments. Its role in gastric cancer will be tested.



Objectives

- Primary Objective
 - To evaluate the feasibility of delivering tailored targeted chemotherapy followed by chemoradiation prior to surgery in patients with GEJ and gastric cancer.
- Secondary objectives
 - To identify the resident microbiota (bacterial) species associated with higher response to the combination therapy.
 - To evaluate the role of PET perfusion imaging using digital PET in the treatment of gastric cancer during treatment.



Trial diagram



*stool samples will be obtained at several timepoints to evaluate microbiome



Inclusion criteria

- Patients with histologically proven, cT2N0-T4aN3M0 (TNM 8th edition), gastric or GEJ adenocarcinoma.
- Evaluation with EUS and staging laparoscopy prior to enrollment is strongly recommended.
- Patients should be ≥18 years old.
- ECOG performance status ≤ 2 .
- Patients must have adequate blood, kidney, and liver function.



 Please consider enrollment in this trial if you were recently diagnosed with locally advanced gastric cancer



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Cardiotoxicity in Patients Receiving Thoracic Radiation Therapy



Dr. Daniel Addison Cardio-Oncology



Dr. Eric Miller Radiation Oncology



Dr. Terence Williams Radiation Oncology



Cardiotoxicity in Gastroesophageal Cancer





- With modern treatment, the median survival of patients with localized esophagus/GEJ cancer has nearly doubled.
 - While delayed treatment side effects were previously not a concern due to early mortality, advances in therapy have resulted in long-term survivors who must live with potential delayed morbidity from treatment.
 - Excess radiation to the heart has been associated with increased cardiac morbidity and mortality, and presents a primary source of long-term morbidity and mortality in patients treated with thoracic radiation therapy.

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Cardiotoxicity in Gastroesophageal Cancer



 As the majority of esophageal cancers are located in the lower thoracic esophagus, this patient population may be especially vulnerable to the cardiac effects of radiation therapy.



Cardiotoxicity in Gastroesophageal Cancer

- Retrospective review of 208 consecutive patients with localized esophageal or GEJ cancer treated definitively at OSU between 2007-2017.
 - Identify patient and treatment factors associated with major adverse cardiovascular events (MACE).
- Results:
 - 40% of patients experienced a MACE event.
 - Patients with pre-existing cardiovascular disease have a significant risk for severe cardiac events, but more advanced radiation therapy planning may help to protect against these events.
 - Further research into mechanisms and preventative strategies against cardiovascular disease for this patient population are needed.

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Future Strategies for Detection, Prevention, and Mitigation of Cardiotoxicity in Treatment of Gastroesophageal Cancer

- Develop innovative strategies for detection:
 - Cardiac-MRI
 - PET
 - Blood biomarkers
- Develop preventative strategies:
 - Pharmacologic
 - More advanced radiation therapy planning and delivery (proton beam therapy)
- Develop novel therapies for mitigation:
 - Anti-inflammatory
 - Anti-fibrotic



Conclusions

- The treatment of gastroesophageal cancer is complex and difficult with less than optimal outcomes.
- OSU Radiation Oncology is focused on three research areas:
 - Accurate staging of disease and assessment of treatment response through digital PET imaging.
 - Development of more effective therapies.
 - Adding the radiosensitizer, adavosertib (AZD1775), to radiation therapy for esophagus/GEJ cancer.
 - Total neoadjuvant therapy for gastric cancer.
 - Mitigation of acute and long term toxicity of treatment focusing on cardiotoxicity.



Thank You!

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