LSTA1 Potentiates Complete Response in Metastatic Gastroesophageal Adenocarcinoma

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Abstract

Introduction: Gastroesophageal adenocarcinoma has an extremely poor prognosis and remains a major cause of cancer-related mortality worldwide. While chemotherapy remains the primary treatment for metastatic disease and improves survival overall, the prognosis for patients with gastroesophageal adenocarcinoma cancer remains poor; secondary to chemoresistance and limited targeted therapeutic approaches.

LSTA1 (certepetide) is a novel investigational drug designed to selectively target and enhance the uptake of anti-cancer drugs into solid tumours. Clinically, LSTA1 has demonstrated favourable safety, tolerability, and activity when added to gemcitabine and nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma. Given its mechanism of action, LSTA1 is thought to be agnostic to the modality of therapeutics with which it is combined and could bring significant advancement to the treatment outcomes in patients suffering from advanced solid tumours.

Case Presentation: This is a case report involving a subject with metastatic gastroesophageal adenocarcinoma with significant tumour burden. The subject underwent months of treatment with immunotherapy/chemotherapy and achieved a partial response. Upon addition of LSTA1 to their standard-of-care therapeutic regimen, the subject achieved a complete response confirmed radiographically and surgically.

Conclusion: Solid tumours are often inadequately treated with current treatment paradigms due to ineffective tumour targeting, insufficient tumour penetration, and/or a hostile Tumour Microenvironment (TME). Through its unique tumour targeting and penetration-enhancing capabilities, LSTA1, when added to the standard of care has demonstrated the ability to overcome such obstacles and improve treatment outcomes in a range of advanced solid tumours.

Keywords: Metastatic Gastroesophageal Adenocarcinoma • Complete response • Tumour targeting and penetration enhancing drug • LSTA1

Introduction

Gastroesophageal adenocarcinoma has an extremely poor prognosis and remains a major cause of cancer-related mortality worldwide. The incidence of gastroesophageal adenocarcinomas is increasing and thought to be secondary to Gastroesophageal Reflux Disease (GERD), Barrett's esophagus, obesity, and smoking and most patients present with advanced disease. Less than 50% of patients undergo curative treatment. For locally advanced esophageal cancer, chemotherapy and/or radiation in addition to surgery is considered the standard of care. While chemotherapy remains the primary treatment for metastatic disease and improves survival overall, the prognosis for patients with gastroesophageal adenocarcinoma cancer remains poor secondary to chemo-resistance and limited targeted therapeutic approaches. LSTA1 (certepetide) is a novel investigational drug designed to selectively target and enhance the uptake of anti-cancer drugs into solid tumours. Preclinically, LSTA1 has been shown to decrease the percentage of T-regulatory cells and increase the percentage of cancer-fighting cytotoxic CD8+ T cells thus making the tumour microenvironment less immunosuppressive. LSTA1 has also been shown to inhibit the metastatic cascade in highly fibrotic tumours. Clinically, LSTA1 has demonstrated favorable safety, tolerability, and activity when added to gemcitabine and nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma [1]. Given its novel mechanism of action, LSTA1 is completely agnostic to the modality of therapeutics with which it works including both cytotoxic agents and immunotherapies.

Case Presentation

This is a case report involving a subject with metastatic gastroesophageal adenocarcinoma who achieved a complete response when given LSTA1 in combination with standard-of-care therapy. Longitudinal patient records are reported including demographic data, diagnosis, interventions, imaging and surgical reports, and outcomes. Outcomes were assessed by a multi-disciplinary clinical team.

Subject NW is a 90 kg, 53-year-old Caucasian male who presented with mild dysphagia and weight loss. The subject underwent a gastroscopy on 1 June 2022 which revealed a tumour arising from the lesser curve and fundus of the stomach with involvement of the gastro-esophageal junction. Very large adjacent nodes directly invaded the oesophagus and pancreas. The biopsy revealed a poorly differentiated, large cell malignancy with necrosis. The subject was subsequently diagnosed with gastroesophageal adenocarcinoma on 2 June 2022.

A staging CT scan of the chest, abdomen and pelvis in early June 2022 revealed nodular thickening of the distal esophagus, consistent with the known malignancy, extending into the gastroesophageal junction and the adjacent fundus of the stomach. Additionally, there were small para-esophageal lymph nodes and grossly enlarged celiac axis and gastrohepatic nodes with the largest gastrohepatic node measuring 5 cm in short axis diameter consistent with metastasis. A PET scan confirmed the FDG-avid primary stomach tumour with large para-esophageal and upper abdominal nodal metastasis. An ultrasound and MRI of the liver confirmed there was no liver involvement.

On 22 June 2022, the subject commenced neoadjuvant chemotherapy and radiotherapy with FOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2, 5FU 100 mg/m^2, leucovorin 400 mg/m^2, and 5FU infusion 2,400 mg/m^2 over 48 hours) and pembrolizumab 135 mg IV every two weeks with the goal of potential resection pending significant tumour response.

An FDG PET scan and CT chest, abdomen, and pelvis with contrast performed on 9 August 2022 revealed a good partial metabolic response with less wall thickening of the previous distal esophageal tumour and significantly reduced FDG activity in this region. The previously noted large lymph nodes in the gastrohepatic ligament had reduced in size and activity, although these nodes remained active peripherally.

For cycles 7-9, commencing 12 September 2022, LSTA1 at 3.2mg/kg IV push was added to the subject's FOLFIRINOX/pembrolizumab regimen as part of the Australia Special Access Scheme (SAS). For cycles 10-14, LSTA1 was not given in combination with the FOLFIRINOX/pembrolizumab regimen due to a temporary drug shortage of LSTA1.

Another FDG PET scan and CT chest, abdomen, and pelvis with contrast performed on 29 September 2022 revealed a complete metabolic response at the lower esophageal tumour with good partial metabolic response at the upper abdominal nodal metastases. More specifically, the scan demonstrated only low grade (within normal limits) linear FDG activity at the site of the initial FDG-avid distal esophageal tumour. The gastrohepatic ligament node remained intensely FDG-avid and enlarged but was smaller than previously measured, 24 mm in short axis diameter (previously 34 mm).

On 7 December 2022, a restaging FDG PET scan and CT chest, abdomen, and pelvis with contrast was performed revealing a persistent complete metabolic response in the distal esophageal tumour with further partial metabolic and structural response in the upper abdominal node (gastrohepatic ligament) although FDG activity persisted. More specifically, no residual mass or abnormal FDG uptake was seen in the distal esophagus and the prominent gastric node in the gastrohepatic ligament was smaller (17 mm) and less active.

On 12 December 2022, (Cycle 12) the subject ceased taking oxaliplatin after experiencing the adverse event of peripheral sensory neuropathy. Prior to ceasing oxaliplatin, the oxaliplatin dose was reduced by 25% for cycle 10, further reduced by 25% for cycle 12, and eventually ceased for cycle 13.

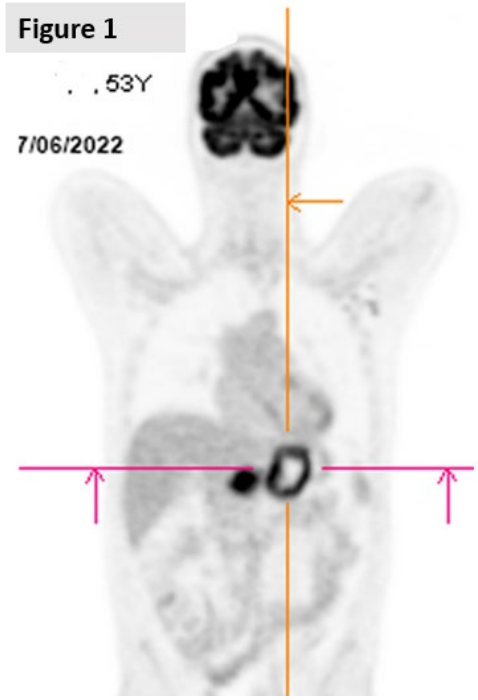
On 24 January 2023, the subject underwent an FDG PET scan and CT chest, abdomen, and pelvis with contrast revealing a persistent complete metabolic response in the distal esophageal tumour with continued partial metabolic and structural response in the gastrohepatic ligament lymph node.

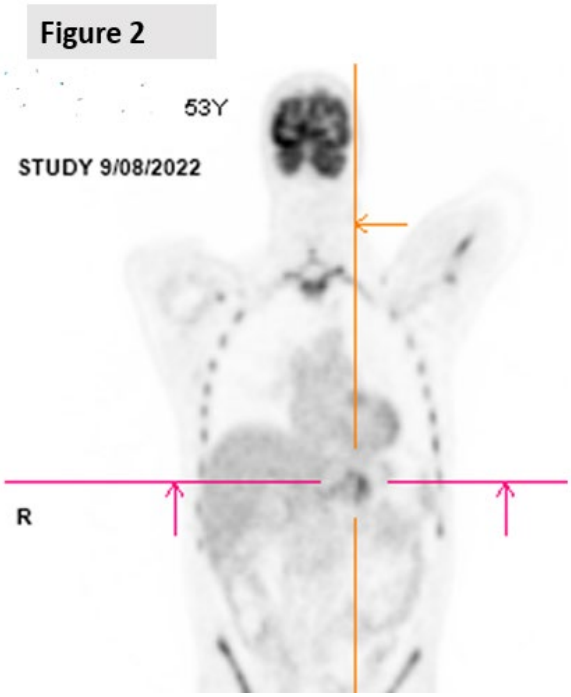
On 30 January 2023 (Cycle 15) the subject commenced treatment with LSTA1 at 3.2 mg/kg in combination with FOLFIRINOX (without oxaliplatin) and pembrolizumab. This regimen continued for cycles 16 and 17.

On 28 February 2023, a complete response was achieved. The subject underwent another FDG PET scan and CT chest, abdomen, and pelvis with contrast revealing a persistent complete metabolic response in the gastroesophageal tumour with no residual mass or increased FDG activity. Furthermore, the prominent left gastric node reduced in size and activity suggestive of an almost complete metabolic response in nodal disease, with no evidence of lymphadenopathy elsewhere above or below the diaphragm (table 1) (figures 1 and 2).

Table 1. Objective response to treatment over time

Date of FDG PET scan and CT scan	Measurable disease	Treatment
2 June 2022	Lymph node 5 cm	Pembrolizumab + FOLFIRINOX
29 September 2022	Lymph node 2.4 cm	Pembrolizumab + FOLFIRINOX + LSTA1
7 December 2022	Lymph node 1.7 cm	Pembrolizumab + FOLFIRINOX + LSTA1
28 February 2023	Complete response	Pembrolizumab + FOLFIRI + LSTA1





Figures 1 and 2. PET scan images shown in Figures 1 and 2 below from June 2022 and September 2022 demonstrate reduction in FDG activity with the addition of LSTA1 to pembrolizumab and FOLFIRINOX therapies.

The subject continued LSTA1, pembrolizumab, and FOLFIRI every two weeks from cycle 18 onward. Cycle 29 occurred on 14 August with the plan to continue for an additional 2 years.

Given the significant tumour response, an exploratory laparoscopy for potential surgical resection occurred for this subject in August 2023. The operative report noted a scar at the site of the lymph node on the surface of the pancreas which was unable to be resected without distal pancreatectomy. No other disease was present.

Conclusion

Gastroesophageal adenocarcinoma has an extremely poor prognosis and remains a major cause of cancer-related mortality worldwide. The incidence of gastroesophageal adenocarcinomas is increasing and thought to be secondary to Gastroesophageal Reflux Disease (GERD), Barrett's esophagus, obesity, and smoking and the majority of patients present with

advanced disease. Less than 50% of patients undergo curative treatment. For locally advanced esophageal cancer, chemotherapy and/or radiation in addition to surgery is considered the standard of care. While chemotherapy remains the primary treatment for metastatic disease and improves survival overall, the prognosis for patients with gastroesophageal adenocarcinoma cancer remains poor, secondary to chemoresistance and limited targeted therapeutic approaches, including anti-HER2 and Anti-Vascular Endothelial Growth Factor (VEGF) drugs [2].

This case represents a complete response in a patient with metastatic gastroesophageal adenocarcinoma who received the standard chemotherapy/immunotherapy regimen along with LSTA1. LSTA1, is a novel investigational drug that actuates the CendR active transport mechanism while also having the potential to modify the Tumour Microenvironment (TME) and make it less immunosuppressive. LSTA1 targets tumour vascular endothelial cells as well as tumour cells themselves based on its affinity for alpha-v, beta-3, and beta-5 integrins that are upregulated on these cells, but not healthy tissue. LSTA1 is a nine-amino acid cyclic internalizing RGD peptide that, once bound to these integrins, is cleaved by proteases expressed in the TME to release a peptide fragment, called a CendR fragment. The CendR fragment then has a high affinity for and binds to an adjacent receptor, called neuropilin-1, also upregulated on tumour endothelial and tumour cells to activate the C-end Rule active transport pathway and ferry anti-cancer drugs more efficiently into solid tumours. LSTA1 has been shown in a range of preclinical models to modify the TME making it less hostile to immune cells. Specifically, LSTA1 has been shown in highly fibrotic tumours to deplete immunosuppressive T cells, enhance cytotoxic T regulatory cells, and inhibit the metastasis cascade. LSTA1 is the subject of over 300 scientific publications including non-clinical data demonstrating enhanced delivery of a range of emerging anti-cancer therapies, including immunotherapies and RNA-based therapeutics. Clinically, LSTA1 has demonstrated favourable safety, tolerability, and activity when added to gemcitabine and nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma.2 The safety and efficacy of LSTA1 administered in combination with standard of care regimens is currently being explored in clinical trials involving multiple solid tumour types.

Through its unique tumour targeting and penetration enhancing capabilities, LSTA1 may bring significant advancement to the treatment outcomes in patients suffering with advanced solid tumours.

References

1. Dean, A., et al. "Dual αV-integrin and neuropilin-1 targeting peptide CEND-1 plus nab-paclitaxel and gemcitabine for the treatment of metastatic pancreatic ductal adenocarcinoma: A first-in-human, open-label, multicentre, phase 1 study." *Lancet Gastroenterol Hepatol* 7.10 (2022): 943-951.

2. Greally, M., et al. "Optimal management of gastroesophageal junction cancer." *Cancer* 125.12 (2019): 1990-2001.

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