Nivolumab in Combination with Irinotecan and 5-Fluorouracil (FOLFIRI) for Refractory Advanced Gastroesophageal Cancer

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Keywords

Advanced gastric cancer · Nivolumab · Esophageal neoplasms · Irinotecan

Abstract

Introduction: Advanced unresectable gastroesophageal cancers continue to confer a dismal patient prognosis. Limited options remain once the cancer is refractory to cytotoxics/biologics (like irinotecan, taxane, and ramucirumab). Recently, anti-programmed death-1 (anti-PD-1) inhibitors have been used with limited efficacy in select patients with adenocarcinoma. Similarly, irinotecan-based therapy has marginal efficacy. We combined irinotecan plus a fluoropyrimidine with an anti-PD-1 antibody, nivolumab, with hopes of having a higher advantage for patients. **Objectives:** Primary objective was to assess safety judged by toxicities, dose delays, or dose reductions. Secondary endpoints included the assessment of response, overall survival (OS), and progression-free survival (PFS). **Methods:** We treated 15 patients with this combination during July 2017 to April 2019. Patients were included if they had follow-up at our institution. **Results:** Median doses given were nivolumab 240 mg + iri-

notecan 120 mg/m² + 5-FU 2,000 mg/m² over 46–48 h (or capecitabine 1,250 mg/m²/day; 7 days on, 7 days off) given every 2 weeks. Median age of the patients was 55 years, and all patients had an ECOG performance status of 0–1. The patients had a median of 1 prior therapy. Slightly over half of the patients had PD-L1 expression. The median number of cycles was 7. Five patients (33%) had a dose delay or dose adjustment. The most common reason for dose delay or adjustment was grade 2 fatigue. Disease control (response or stability) on first scan was 73.3% ($n = 11$). Median PFS and OS for the entire group was 7 and 13.3 months, respectively. **Conclusion:** In this small cohort of patients, we conclude that this combination is quite feasible and resulted in prolonged stability in some patients. Further development of this regimen is warranted.

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Introduction

Gastroesophageal cancers include gastric adenocarcinoma, gastroesophageal junction (GEJ) adenocarcinoma, distal esophageal adenocarcinoma, and esophageal squa-

mous cell carcinoma (SCC) [1, 2]. These tumors result in frequent cancer-related deaths, making them a global healthcare concern [1–3]. In Western countries, in which screening is not standard practice, patients often present with advanced disease without the option for a surgical curative approach [1]. Unresectable gastroesophageal cancers continue to carry a dismal prognosis plagued by symptomatic disease and, inevitably, patients will progress on standard therapy [4].

At the molecular level, gastroesophageal adenocarcinomas and esophageal SCCs differ greatly; however, in the advanced setting, treatment guidelines vary only minimally [1, 2, 5]. Standard front-line treatment is with a platinum (i.e., oxaliplatin or cisplatin) + a fluoropyrimidine (5-fluorouracil (5-FU) or capecitabine) [1, 2]. While second-line therapy recommendations include paclitaxel ± ramucirumab (ramucirumab is for adenocarcinoma histology only), irinotecan ± 5-FU, or docetaxel. Pembrolizumab, an anti-programmed death-1 (anti-PD-1) therapy, is available in the refractory setting for patients with microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR) (second-line) or those with programmed-death-ligand 1 expression (PD-L1) (second- or third-line for SCC; third-line for adenocarcinoma) [1, 2, 6]. A combined positive score (CPS) of ≥1 is required for adenocarcinoma histology, while a CPS score of ≥10 (second-line) or ≥1 (third-line) is required for SCC histology tumors dependent on line of therapy. Following these options, trifluridine-tipiracil is an option for adenocarcinoma [1, 2]. Although responses were seen with irinotecan or anti-PD-1 therapy, in majority of patients these agents fail. Hoping for an advantage over single-agent PD-1 inhibition, we combined nivolumab (anti-PD-1 therapy) + irinotecan + a fluoropyrimidine (5-FU or capecitabine).

Materials and Methods

We conducted a retrospective evaluation of advanced gastric adenocarcinoma, GEJ adenocarcinoma, distal esophageal adenocarcinoma, and esophageal SCC patients who received nivolumab + irinotecan + a fluoropyrimidine during July 2017 to April 2019. Patients were excluded if they received this therapy or had tumor assessments in their local community. No other selection criteria were implemented. All diagnostic imaging was performed at our institution every 8–10 weeks. The primary objective was to determine safety. Safety was evaluated through collecting the number of patients that required a dose delay or dose adjustment. Reasons for these delays or adjustments were also collected. Common Terminology Criteria for Adverse Effects (CTCAE) version 4.0 [7] was utilized to determine adverse effect grade retrospectively. Secondary objectives were overall survival (OS), progression-free survival

Table 1. Patient demographics

Age, years	
Median	55
Range	35–84
Sex	
Male	10 (66.7%)
Female	5 (33.3%)
Ethnicity	
White	8 (53.3%)
Asian	2 (13.3%)
Arabic	2 (13.3%)
Hispanic	1 (6.7%)
South African	1 (6.7%)
NR	1 (6.7%)
ECOG performance status	
0	3 (20%)
1	12 (80%)
Primary tumor location	
Gastric adenocarcinoma	11 (73.3%)
Gastroesophageal junction adenocarcinoma	2 (13.3%)
Esophageal squamous cell carcinoma	2 (13.3%)
Line of treatment	
First	3 (20%)
Second	7 (46.7%)
Third	4 (26.7%)
Fourth	1 (6.7%)
Metastatic disease sites	
One organ involved	8 (53.3%)
Two or more organs involved	7 (46.7%)
MSI-H/dMMR	
Yes	0 (0%)
No	11 (73.3%)
Unknown	4 (26.7%)
PD-L1 expression	
Yes	8 (53.3%)
No	6 (40%)
Unknown	1 (6.7%)

Data are reported as *n* (%) unless indicated otherwise. MSI-H/dMMR, microsatellite instability-high/deficient mismatch repair; PD-L1, programmed-death-ligand 1 expression.

(PFS), and first restaging scan response. OS was measured from regimen start date to death or last follow-up. PFS was from regimen start date to progression, death, or last follow-up. Response was classified as disease control (any response + stable disease) versus progression on the first scan.

Data collection included baseline demographics (age, sex, and ethnicity), Eastern Cooperative Oncology Group (ECOG) performance status, primary site of disease and histology (gastric, GEJ, distal esophageal, or esophageal SCC), and number of metastatic disease sites. Relevant molecular information was collected including MSI-H/dMMR-positive status and PD-L1 expression. Treatment and outcome data consisted of line of therapy, nivolumab + irinotecan + 5-FU/capecitabine start date, starting doses, dose delays or adjustments, progression date, death date, and last follow-up date.

Table 2. Safety outcomes (with reasons) and efficacy outcomes (with results)

<i>Safety Outcomes</i>	
Patient with dose delay or adjustment (<i>n</i> = 5)	
Patient 1	Grade 2 fatigue
Patient 2	Grade 2 hypothyroidism
Patient 3	Grade 3 liver function elevation; grade 1 fatigue
Patient 4	Grade 2 fatigue; febrile neutropenia on admission
Patient 5	Grade 2 mucositis; grade 2 fatigue
<i>Efficacy Outcomes</i>	
First scan response	
Disease control, <i>n</i> (%)	11 (73.3%)
Progression, <i>n</i> (%)	4 (26.7%)
Median overall survival, months (95% CI)	13.3 (9.54, NA)
Median progression-free survival, months (95% CI)	7 (3.5, NA)

Statistical Analysis

Summary statistics using categorical and continuous variables were performed for baseline demographics. The Kaplan-Meier method was used to estimate median OS and median PFS. Response and toxicity were summarized with frequency and percentages. Log-rank test was applied to explore the difference in OS or PFS among subgroups.

Results

Fifteen patients were included in the analysis. The baseline demographics are summarized in Table 1. Median age was 55 years, with a mainly Caucasian and male population. All patients had an EGOG performance status of 0–1. The median number of prior therapies was 1 (range: 1–3 prior therapies). Most patients had gastric adenocarcinoma. A little over half of our population (53%) had PD-L1 expression by CPS, while no patients were identified as having MSI-H/dMMR status. Half of the patients with PD-L1 expression (*n* = 4) had CPS scores reported as ≥1, while the remaining 4 patients had CPS scores reported as 20, 15, 5, and 3 (*n* = 1 each). The median follow-up time was 7.5 months (range 2.5–23.3 months). The median number of cycles was 7. Two patients were on treatment beyond 1 year. The median doses were nivolumab 240 mg (200–240 mg) + irinotecan 120 mg/m² (range 120–150 mg/m²) + 5-FU 2,000 mg/m² (2,000–2,400 mg/m²) over 46–48 h repeated every 2 weeks. Thirteen patients received 5-FU as the fluoropyrimidine portion of their regimen, while 2 patients received capecitabine dosed at 1,250 mg/m²/day for 7 days then off 7 days.

Most patients (*n* = 10; 66.7%) were able to receive therapy without modification or delay. Five patients required

a dose adjustment or delay. Delays or adjustments were correlated to one adverse effect or multiple dependent on the patient. One patient was admitted for febrile neutropenia, and 1 patient had grade 3 liver function enzyme elevation; however, the liver function elevation was attributed to that patient's underlying disease. Most patients with dose delays or modifications had adverse effects of grade ≤2. The most common reason for adjustments was grade 2 fatigue. These events are listed in Table 2. Eleven patients (73%) had disease control on first scan. Median OS was 13.3 months (95% CI: 9.54, NA), and median PFS was 7 months (95% CI: 3.5, NA) (Figs. 1 and 2). One-year survival rate was 54% (95% CI: 0.3–0.95), and 1-year PFS rate was 53% (95% CI: 0.32–0.86). No differences between PD-L1 expression, gender, primary tumor location/histology, and number of metastatic sites were identified. Two patients have yet to progress on therapy at the time of data collection. Outcome data is included in Tables 2 and 3.

Discussion/Conclusion

Nivolumab in combination with irinotecan and capecitabine (CAPIRI) was evaluated in a Phase Ib/II study in metastatic colorectal and pancreatic adenocarcinoma patients [8]. In an abstract, the authors reported on 12 patients. No dose-limiting toxicities or study-related serious adverse events were discovered. The authors recommended a dosing scheme of nivolumab 3 mg/kg days 1 and 15 + irinotecan at 175 mg/m² day 1 and 15 with capecitabine 1,000 mg p.o. twice daily 5 days on and 2 days off every week for the phase 2 portion. In addition, two trials are currently being planned looking at nivolu-

Fig. 1. Our total population's median overall survival (OS) on nivolumab plus FOLFIRI was 13.3 months (95% CI: 9.54, NA).

Fig. 2. Our total population's median progression-free survival (PFS) on nivolumab plus FOLFIRI was 7 months (95% CI: 3.5, NA).

Table 3. Overall survival (OS) and progression-free survival (PFS) per subgroup analysis

Characteristic	N	Events, <i>n</i>	Survival (95% CI)			<i>p</i> value
			median	at 6 months	at 1 year	
OS						
PD-L1 expression						
Yes	8	2	NA (10–NA)	0.88 (0.69–1)	0.66 (0.35–1)	0.1549
No	6	4	9.54 (8.36–NA)	0.83 (0.58–1)	0.42 (0.15–1)	
Gender						
Male	10	6	10 (8.36–NA)	0.8 (0.59–1)	0.46 (0.22–0.93)	0.1957
Female	5	0	NA	1	1	
Primary tumor site						
Gastric adenocarcinoma	11	4	10 (8.36–NA)	0.8 (0.59–1)	0.4 (0.14–1)	0.3619
Gastroesophageal junction adenocarcinoma	2	2	11.39 (9.54–NA)	1	0.5 (0.13–1)	
Esophageal squamous cell carcinoma	2	0	NA	1	1	
Metastatic sites						
One organ involved	8	3	13.25 (9.54–NA)	0.86 (0.63–1)	0.57 (0.24–1)	0.7388
Two or more organs involved	7	3	NA (8.36–NA)	0.86 (0.63–1)	0.51 (0.24–1)	
PFS						
PD-L1 expression						
Yes	8	7	7 (5.61–NA)	0.6 (0.33–1)	0.15 (0.02–0.91)	0.5311
No	6	5	7.48 (3.5–NA)	0.5 (0.22–1)	0.25 (0.05–1)	
Gender						
Male	10	10	6.02 (2.11–NA)	0.5 (0.27–0.93)	0.2 (0.06–0.69)	0.9983
Female	5	3	7.5 (5.61–NA)	0.53 (0.21–1)		
Primary tumor site						
Gastric adenocarcinoma	11	9	5.61 (2.5–NA)	0.44 (0.22–0.87)		0.1009
Gastroesophageal junction adenocarcinoma	2	2	9.04 (5.04–NA)	0.5 (0.13–1)	0.5 (0.13–1)	
Esophageal squamous cell carcinoma	2	2	11.21 (9.93–NA)	1	0.5 (0.13–1)	
Metastatic sites						
One organ involved	8	6	6.27 (3.5–NA)	0.5 (0.25–1)	0.25 (0.05–1)	0.8161
Two or more organs involved	7	7	7 (2.11–NA)	0.57 (0.3–1)	0.14 (0.02–0.88)	

mab in combination with irinotecan-based regimens, one trial in small cell lung cancer (a phase 1 with nivolumab + irinotecan) and one trial in colorectal cancer (a phase 2 with nivolumab + irinotecan + oxaliplatin + 5-FU + bevacizumab) [9, 10]. Of interest to patients with advanced gastroesophageal cancer, a combination of anti-PD-L1 therapy plus FOLFIRI ± anti-cytotoxic t-lymphocyte-associated protein 4 therapy is currently recruiting for second-line therapy [11].

Until results are reported of the above-mentioned studies, our analysis adds 15 additional patients treated with an anti-PD-1 therapy plus FOLFIRI or CAPIRI. No unexpected toxicities were found when these agents were combined, while our results suggest promising efficacy with the combination regardless of PD-L1 expression. FOLFIRI alone in the second-line refractory gastroesophageal setting has shown responses of approximately 20% with median OS of 5–6 months [1, 2, 4]. Compared to best supportive care, irinotecan alone in the second-line setting showed a median PFS of 2.6 months (95% CI: 1.7–4.3 months) [12]. While anti-PD-1 therapy dependent on tumor location and histology along with PD-L1 expression and CPS score showed responses of approximately 11–22% [1, 2, 13, 14]. In the second-line setting compared to paclitaxel, pembrolizumab had a reported median PFS of 1.5 months (95% CI: 1.4–2 months) [13]. Combination therapy with nivolumab + irinotecan + a fluoropyrimidine in our small cohort showed a median PFS of 7 months.

As mentioned previously, anti-PD-1 therapy in the USA currently holds approval for those with MSI-H/dMMR-positive disease or PD-L1 expression. In Japan, nivolumab holds approval in the refractory setting regardless of PD-L1 expression based on the results of the ATTRACTION 2 phase III trial (Asian population) which showed nivolumab compared to placebo had higher 1-year OS rates (nivolumab 26.2% vs. placebo 10.9%) [1, 2]. Our 1-year OS rate was 54%. Over the next few years, prospective data will continue to emerge with regard to the role of checkpoint inhibitors in localized and metastatic gastroesophageal cancer. Until more is known, our analysis showed 7 patients (47%) achieved a PFS of >6 months with nivolumab + FOLFIRI or CAPIRI with 2 patients achieving a PFS beyond 1-year; thus, showing long-term durable efficacy could be achieved. The regimen was safe to administer as seen in colorectal and pancreatic cancer patients. We encourage continued exploration of combined checkpoint inhibition with standard of care refractory chemotherapy agents. Along with the investigation of novel agents, we feel these approaches will hopefully improve clinical outcomes.

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Statement of Ethics

The study protocol has been approved by the research institute's Committee on Human Research. Our study was approved by the Institutional Review Board and a waiver of consent was granted due to the retrospective evaluation and patients lost to follow-up, no longer at the institution, or expired.

Disclosure Statement

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Author Contributions

Jane E. Rogers: conceptualization, formal analysis, data curation, investigation, methodology, resources, supervision, writing of original draft, writing of review and editing, final approval. Li-anchun Xiao: conceptualization, formal analysis, writing of original draft, writing of review and editing, final approval. Allison Trail: conceptualization, resources, provision of patients, writing of original draft, writing of review and editing. Mariela Blum Murphy and Melissa Palmer: conceptualization, resources, provision of patients, writing of original draft, writing of review and editing, final approval. Jaffer A. Ajani: conceptualization, investigation, resources, provision of patients, methodology, supervision, writing of original draft, writing of review and editing, final approval.

References

- 1 National Comprehensive Cancer Network (NCCN). Gastric cancer, version 3.2019. November 18, 2019. [cited 2019 Nov 26]. Available from: <https://www.nccn.org/>
- 2 National Comprehensive Cancer Network (NCCN). Esophageal and esophagogastric junction cancers, version 3.2019. November 18, 2019. [cited 2019 Nov 26]. Available from: <https://www.nccn.org/>
- 3 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394–424.

- 4 Ghosn M, Tabchi S, Kourie HR, Tehfe M. Metastatic gastric cancer treatment: second line and beyond. *World J Gastroenterol*. 2016 Mar 21;22(11):3069–77.
- 5 The Cancer Genome Atlas Research Network. Integrated genomic characterization of oesophageal carcinoma. *Nature*. 2017;541: 169–75.
- 6 Keytruda (pembrolizumab) package insert. Whitehouse Station: Merck and Company; 2019 Sept. [cited 2019 Nov 26].
- 7 National Cancer Institute: Diversion of Cancer Treatment and Diagnosis. Common terminology criteria for adverse events (CTCAE) v4.0. [cited 2019 Nov 26]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
- 8 Khemka V, Haire P, Waypa J, Weiss G. Phase Ib/II study of nivolumab plus CAPIRI: initial results of metastatic colon cancer and pancreatic adenocarcinoma patients. *Ann Oncol*. 2016 Jun;27(Suppl 2):ii80–ii81.
- 9 Clinicaltrials.gov. Nivolumab plus FOLFOX-IRI/bevacizumab in first line chemotherapy of advanced colorectal cancer RASm/BRAFm patients (NIVACOR). NCT04072198. [cited 2019 Nov 26]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04072198>
- 10 Clinicaltrials.gov. Feasibility and safety study of nivolumab with irinotecan for small cell lung cancer. NCT04173325. [cited 2019 Nov 26]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04173325>
- 11 Clinicaltrials.gov. Clinical trial evaluating FOLFIRI + durvalumab vs. FOLFIRI + durvalumab and tremelimumab in second-line treatment of patients with advanced gastric or gastro-oesophageal junction adenocarcinoma. NCT03959293. [cited 2019 Nov 26]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03959293>
- 12 Thuss-Patience PC, Kretzschmar AR, Bichev D, Deist T, Hinke A, Breihaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer*. 2011 Oct; 47(15):2306–14.
- 13 Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2018 Jul 14;392(10142):123–33.
- 14 Harada K, Lopez A, Shanbhag N, Badgwell B, Baba H, Ajani J. Recent advances in the management of gastric adenocarcinoma patients. *F1000Res*. 2018 Aug 30;7.