

**Adjuvant Durvalumab following Trimodality Therapy for Locally Advanced Esophageal
and Gastroesophageal Junction Adenocarcinoma**

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Short Title: Durvalumab for locally advanced esophagogastric adenocarcinoma

Abstract

Background: Concurrent chemoradiation (CRT) followed by esophagectomy is a standard of care for resectable locally advanced esophageal and gastroesophageal junction (GEJ) adenocarcinoma. The relapse rate is high among patients who do not achieve a pathologic complete response (pCR) following neoadjuvant CRT.

Methods: We conducted a phase II study of durvalumab in patients with locally advanced esophageal and GEJ adenocarcinoma who have undergone preoperative CRT followed by R0 resection with histologic evidence of persistent residual disease in the surgical specimen. Patients received durvalumab 1500 mg IV every four weeks for up to one year. The primary endpoint was 1-year relapse free survival (RFS).

Findings: Thirty-seven patients were enrolled. The majority (64.9%) had pathologically positive lymph nodes. One-year RFS was 73%, and median RFS was 21 months (95% CI, 14-40.4 months). Nineteen (51.4%) patients had PD-L1 CPS of $\geq 1\%$ and 7 (18.9%) had PD-L1 CPS of $\geq 10\%$. There was a numerical trend toward superior 1-year RFS among patients with PD-L1 positive disease compared to those with PD-L1 negative disease, using CPS of $\geq 10\%$ (100% vs 66.7%, $p=0.1551$) and $\geq 1\%$ (84.2% vs 61.1%, $p=0.1510$) cutoffs. The most common treatment related adverse events were fatigue (27%), diarrhea (18.9%), arthralgia (16.2%), nausea (16.2%), pruritus (16.2%), cough (10.8%), and increase in AST/ALT/bilirubin (10.8%). Three (8.1%) patients developed grade 3 immune mediated adverse events, including pneumonitis(1), colitis(1), and hepatitis(1).

Interpretation: Adjuvant durvalumab in patients with residual disease in the surgical specimen following trimodality therapy for locally advanced esophageal and GEJ adenocarcinoma led to clinically meaningful improvement in 1-year RFS compared to historical control rate. Higher PD-L1 expression may have a correlation with the efficacy of durvalumab in this setting.

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Introduction

Esophageal cancer is the 7th most common cancer and the 6th leading cause of cancer related deaths worldwide(1). While the incidence of squamous cell carcinoma (SCC) of the esophagus has declined in the US, adenocarcinoma (AC) incidence has been rising dramatically(2). Two-thirds of patients with esophageal AC present with locally advanced disease at the time of diagnosis(3). Trimodality therapy with neoadjuvant concurrent chemoradiation (CRT) followed by surgery, as established by the CROSS trial, is currently a standard of care approach for resectable locally advanced esophageal AC with 5-year overall survival (OS) of 43%(4). Approximately 23% of patients with AC achieve pathologic complete response (pCR) with neoadjuvant CRT(4). The relapse rate is high in patients who do not achieve pCR and those who have persistent disease in the resected lymph nodes, with 1-year relapse free survival (RFS) of approximately 50%(5-7). No post-operative therapy has been prospectively shown to improve survival in this patient population and there is a pressing need for novel therapies in this setting(8).

The programmed cell death 1 (PD-1) receptor/programmed cell death ligand 1 (PD-L1) is a well-established immune checkpoint pathway that is exploited by tumors to evade host immune system and has become an attractive target for therapeutic interventions in multiple solid tumors including PD-L1 expressing esophageal AC(9-15). Mounting evidence demonstrates that ionizing radiation, and to a certain extent chemotherapy, may enhance the infiltration of tumor-specific T cells and simultaneously upregulate PD-1/PD-L1 pathway in the tumor microenvironment by inducing DNA damage and promoting immunogenic cell death(16). This upregulation of PD-1/PD-L1 pathway provides a strong scientific rationale for the use of PD-1/PD-L1 inhibitors following CRT, as supported by the efficacy of consolidation durvalumab and pembrolizumab in unresectable stage III non-small cell lung cancer(17, 18).

Based on these data and the activity of immune checkpoint inhibitors (ICIs) in advanced esophageal AC, we designed a phase II trial to evaluate efficacy and safety of durvalumab following neoadjuvant CRT and surgery in patients with locally advanced esophageal and gastroesophageal junction (GEJ) AC who had pathologic evidence of residual disease in the surgical specimen.

Methods

Patients

We enrolled patients who were 18 years of age or older and had histologically confirmed locally advanced esophageal or GEJ AC (cTanyN1-3M0 based on AJCC 7th staging system) treated with preoperative CRT followed by R0 resection with histologic evidence of persistent residual disease in the surgical specimen (esophagus/GEJ or lymph node(s) or both). Eligibility also included an Eastern Cooperative Oncology Group performance status of 0 to 1 and adequate organ function as detailed in the protocol in the Supplementary Appendix. Patients were excluded if they had an active autoimmune disease or any other condition requiring chronic systemic corticosteroids or immunosuppressive agents, a history of primary immunodeficiency, or a history of interstitial lung disease or pneumonitis. Acceptable chemotherapy regimens used concurrently with standard dose of radiation included cisplatin and 5-fluorouracil or weekly carboplatin and paclitaxel. Documentation of PD-L1 expression was not required for the enrollment.

Study Design and Treatment

This was a single arm, multicenter, open label, phase II investigator-initiated trial

(ClinicalTrials.gov Identifier: NCT02639065 - Big Ten Cancer Research Consortium study BTCRC-ESO14-012). The primary endpoint was 1-year relapse free survival (RFS) with adjuvant durvalumab. Secondary endpoint was safety and tolerability of durvalumab following trimodality therapy. Exploratory endpoints included correlation of RFS with a variety of biomarkers including PD-L1 expression, HER-2 status, Immunoscore(19), and tumor infiltrating lymphocytes. Patients received flat dose durvalumab 1500 mg intravenously every four weeks, starting within one to three months following surgery. The treatment was administered for up to 12 months (total of 13 doses) or until unacceptable toxicities, disease relapse, or withdrawal of consent. Dose reductions were not allowed. Dose delays for toxicity were allowed for up to a maximum duration of 42 days. Study schema is shown in **Supplementary Figure 1**.

Assessments

Patients underwent baseline computed tomography (CT) scan of chest, abdomen, and pelvis within 28 days prior to enrollment on the study and every three months during treatment and follow-up for at least one year. History and physical examination were performed every four weeks during treatment, 30 days following treatment discontinuation, and every three months thereafter. Disease relapse was defined as any clinical or radiographic finding(s) that met the criteria for measurable or non-measurable lesions (confirmed by histology/cytology if solitary) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. RFS was defined as the time from the date of surgery until disease relapse or death from any cause. Patients who remained alive and relapse free were censored at their date of last disease evaluation. One-year RFS was defined as the percentage of patients who were alive and relapse-free at one year following surgery. OS was defined as time from study enrollment until death from any cause. Patients who remained alive were censored at their last date known alive. OS after relapse was defined as the time from the date of relapse until

death from any cause. Patients who remained alive were censored at their last date known alive. Toxicity was evaluated by the collection of adverse events (AEs), serious adverse events (SAEs), and immune related adverse events (irAEs) at every visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Patients who discontinued durvalumab prior to completion of one year of therapy for reasons other than disease relapse were followed every three months for one year from the time of treatment discontinuation for assessment of disease relapse, survival, and occurrence of any late AEs. Paired tissue samples from the time of initial diagnosis and surgery were collected and banked for analysis of PD-L1 expression, HER-2 expression, tumor infiltrating lymphocytes, Immunoscore, and next generation sequencing. Optional blood samples for circulating tumor cells (CTCs) analysis were collected immediately before the first dose of durvalumab, prior to cycle four, and at the time of disease relapse.

PD-L1 and HER-2 expressions on the tissue samples obtained at the time of diagnosis were assessed at Indiana University Pathology Laboratory following completion of the trial. Immunohistochemical (IHC) analysis of PD-L1 expression was performed using 22C3 pharmDx assay on formalin-fixed tumor samples obtained by core-needle biopsy at the time of diagnosis. Expression was categorized according to the combined positive score (CPS) (i.e., the ratio of the combining number of PD-L1 positive tumor cells and immune cells (lymphocytes, macrophages) by IHC staining to the total number of tumor cells)(15). HER-2 expression was analyzed by means of IHC using the HercepTest (Dako) and categorized as negative (IHC 0 or 1+), equivocal (IHC 2+), or positive (IHC 3+)(20).

Study Oversight

The study was designed by the lead investigators at Indiana University and funded by AstraZeneca. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by institutional review boards or relevant ethics committees at each of the participating sites. All patients provided written informed consent before screening and enrollment. Clinical data were generated by the investigators and research staff at the participating sites. Safety data were reviewed at regular intervals by study investigators, Indiana University Melvin and Bren Simon Comprehensive Cancer Center's Data and Safety Monitoring Committee, and the sponsor. Biostatisticians at Indiana University performed data analysis. All authors had full access to the data, reviewed the manuscript before it was submitted for publication, and provided input. The authors vouch for the accuracy and completeness of the data and analyses. The Big Ten Cancer Research Consortium provided administrative support for the study.

Statistical Analysis

Statistical analysis of this study was conducted by Biostatistics and Data Management Core at Indiana University Melvin and Bren Simon Comprehensive Cancer Center. Parameter estimates and relevant summary statistics are reported where appropriate. For continuous variables, summary statistics includes number of subjects, mean, median, standard deviation, minimum and maximum. Categorical endpoints are summarized using number of subjects, frequency, and percentages. Median RFS, OS, and OS after relapse and associated 95% confidence intervals (CI) were estimated using the Kaplan-Meier method. AEs were summarized by treatment relatedness and toxicity grade. Data analysis is performed in SAS Version 9.4.

We hypothesized that durvalumab will improve the relapse free survival rate at 1 year by 25% compared to historical rate. The null hypothesis was that 1-year RFS with adjuvant durvalumab in patients with disease in the surgical specimen following trimodality therapy is 50% or less. The alternative hypothesis was that 1-year RFS with adjuvant durvalumab in this patient population is 75% or greater. With a maximum acceptable type I error of 0.05, and acceptable type II error of 0.20, the calculated sample size was 23 evaluable patients. To improve accuracy for estimating the primary endpoint of 1-year RFS with a 95% CI, an additional 13 patients were planned to be enrolled for at least 34 patients evaluable for 1-year RFS and a target of maximum 39 patients to allow for approximately 10% unevaluable patients. With 34 evaluable patients, if the 1-year RFS is 75%, a 95% two-sided CI will have a half-width of 15% (using normal-approximation).

Results

Patients and Treatment

The study was initiated in April 2016 across five academic sites in the United States. Twenty-four patients were enrolled between April 2016 and January 2018. As noted above, the study was subsequently expanded to enroll additional 13 patients to a total of 37 patients to improve accuracy for estimating the primary endpoint of 1-year RFS. The enrollment concluded in September 2019 and the last patient completed one year of follow up in September 2020. Data cutoff for analysis was October 7, 2020. The patient characteristics were consistent with those seen in clinical practice in Western countries with 36 out of 37 patients being male and a median age of 61 years (range, 43-73 years). Eighteen patients (48.6%) had GEJ AC and the remaining had distal esophageal AC. The majority of patients (n=31, 83.8%) received weekly carboplatin and paclitaxel concurrently with radiation. Nearly two-thirds of patients (n=24, 64.9%) had pathologically positive lymph nodes at the time of surgery. The baseline characteristics are summarized in **Table 1**.

Median times from completion of surgery to initiation of durvalumab treatment was 2.4 months (95% CI=2.1-2.6 months). The median number of doses received was 12 (range, 1-13). Seventeen (45.9%) patients completed one year of durvalumab. The reasons for treatment discontinuation in the remaining 20 patients were disease relapse (n=11, 29.7%), AEs (n=8, 21.6%), and consent withdrawal (n=1, 2.7%).

Efficacy

At median follow-up time of 17.7 months (range, 1.7-24.3 months), 20 patients experienced disease relapse. Of these, ten relapses occurred within the first year after surgery with 1-year RFS of 73% (**Figure 1**). Two-year RFS was 50% with median RFS of 21 months (95% CI, 14-40.4 months). Post-hoc analysis of OS showed 1-year OS of 94%, 2-year OS of 64%, and median OS of 28.1 months (95% CI, 22.9-37.8 months) (**Figure 1**). Median OS after relapse was 11.1 months (95% CI, 0.8- 17 months). All ten relapses within the first year after surgery were systemic relapses. However, three of the later relapses were locoregional which were treated with repeat CRT. **Figure 2** summarizes the duration of treatment, disease relapse, and death based on pathologic lymph node stage. None of the patients received an ICI as a part of subsequent therapy for recurrent disease. Longer term follow-up data were available on 19 patients from the initial cohort of 24 patients. Of these, five did not experience disease relapse while two experienced locoregional relapse and received repeat CRT. All seven patients are alive and disease free at median of 47.8 months and 40 months following surgery and discontinuation of durvalumab, respectively. Five of these patients had positive lymph nodes at the time of surgery.

Of the 37 patients, 19 (51.4%) had PD-L1 CPS of $\geq 1\%$ and 7 (18.9%) had PD-L1 CPS of $\geq 10\%$. There was a numerical, yet statistically nonsignificant, trend toward superior 1-year RFS among

patients with PD-L1 positive disease compared to those with PD-L1 negative disease, using CPS of $\geq 10\%$ (100% vs 66.7%, $p=0.1551$) and $\geq 1\%$ (84.2% vs 61.1%, $p=0.1510$) cutoffs. Similarly, RFS and OS were numerically superior among patients with PD-L1 CPS $\geq 10\%$ compared to $<10\%$ (median RFS: not reached vs 16.8 months, $p=0.1825$; and median OS: not reached vs 28.1 months, $p=0.1370$). Using $\geq 1\%$ as a cutoff, patients with PD-L1 positive disease had numerically superior RFS (median RFS: 40.4 vs 15 months, $p=0.0727$), and superior OS that was clinically as well as statistically significant (median OS: 37.8 vs 22.9 months, $p=0.0109$). Overall, seven (18.9%) patients had HER-2 positive disease. A similar but much less pronounced numerical trend toward improved 1-year RFS and median RFS was observed in HER-2 positive patients (1-year RFS: 85.7% vs 70%, $p=0.6471$; median RFS: 40.4 vs 21 months, $p=0.5436$) (**Figure 3**).

Safety

Most patients ($n=30$, 81.1%) experienced at least one AE of any grade. The most common treatment related AEs occurring in $\geq 10\%$ of patients were fatigue (27%, $n=10$), diarrhea (18.9%, $n=7$), arthralgia (16.2%, $n=6$), nausea (16.2%, $n=6$), pruritus (16.2%, $n=6$), cough (10.8%, $n=4$), and increase in AST/ALT/bilirubin (10.8%, $n=4$) (**Table 2**). Ten (27%) patients experienced grade 3 AEs which were initially considered to be at least possibly related to durvalumab. Of these, three (hematuria, hypoglycemia, decreased platelet count) were later determined not to be treatment related and these patients completed one year of durvalumab. Two AEs (encephalopathy, increase in AST) were later attributed to disease progression rather than durvalumab. One patient with grade 3 elevation of AST, ALT, and CPK was found to have severe hypothyroidism. The laboratory abnormalities resolved with thyroid replacement therapy and the patient eventually completed one year of durvalumab. One patient developed grade 3 sick sinus syndrome and was taken off therapy. The remaining three patients developed grade 3 immune related adverse events (irAEs), including

pneumonitis (n=1), hepatitis (n=1), and colitis (n=1), that required treatment discontinuation. Two of these 3 patients are alive and disease free at 48 and 36 months from discontinuation of therapy, respectively. Four additional patients discontinued treatment because of grade 2 colitis, failure to thrive, creatinine elevation, and recurrent grade 2 AEs. No treatment-related deaths were observed.

Discussion

A standard of care treatment approach for resectable locally advanced esophageal and GEJ AC is concurrent CRT followed by surgical resection(4). As opposed to esophageal SCC, the majority of patients with AC do not achieve pCR following neoadjuvant CRT(4). These patients carry poor prognosis with a high risk of disease relapse within the first year following curative intent trimodality therapy. Lack of pCR in these patients indicates inherent resistance to chemotherapy and radiation, and therefore the lack of convincing data supporting the use of adjuvant chemotherapy in reducing the risk of relapse in these patients is not surprising. The upregulation of PD-1/PD-L1 pathway induced by radiation and possibly chemotherapy presents a unique opportunity to use immune checkpoint inhibition in this setting.

The results of our study indicate that adjuvant therapy with PD-L1 inhibitor durvalumab in patients who do not achieve pCR following trimodality therapy leads to improvement in 1-year RFS to 73% compared to historical rate of 50%. While the study failed to achieve its primary endpoint of 1-year RFS of 75% which is arguably quite optimistic, the 1-year RFS of 73% is encouraging and clinically meaningful since the majority of patients had pathologically positive lymph nodes, including 13 (35%) patients with pN2 or pN3 disease, who are at the highest risk of developing systemic disease recurrences shortly after surgery and have median OS of less than 10 months(5).

Adjuvant studies with ICIs are fraught with the notion that the microscopic burden of disease

associated with minimal neoantigen load may lead to suboptimal efficacy of an ICI. This did not appear to be the case in our study. These data also suggest that ICIs effective in advanced esophageal AC also demonstrate efficacy in the adjuvant setting. This is consistent with the promising activity of adjuvant ICIs reported in other diseases such as melanoma(21). Our data are in alignment with recently reported interim results of randomized CheckMate 577 trial comparing nivolumab with placebo following trimodality therapy for similar patient population showing superior disease free survival and a 31% reduction in the risk of recurrence or death with nivolumab (median disease free survival, 22.4 vs 11 months, HR 0.69; 95% CI, 0.56-0.86, $p=0.0003$)(22). With the caveat of cross trial comparison, the median RFS of 21 months (95% CI, 14-40.4 months) with PD-L1 inhibitor durvalumab in our study is similar to the reported median disease free survival of 22.4 months with PD-1 inhibitor nivolumab in CheckMate 577 trial which has now led to the incorporation of nivolumab in NCCN guidelines. In contrast to CheckMate 577 which included nearly 30% of patients with esophageal SCC, our study was restricted to patients with adenocarcinoma histology. It is relevant to outline this distinction given the fundamental genomic differences between SCC and AC, and the historically greater sensitivity of SCC to ICIs(23-26).

From a safety perspective, it was feasible to initiate therapy with durvalumab within three months of esophagectomy, which is typically associated with significant post-operative morbidity. However, only 46% (n=17) of patients were able to complete the intended 12 months of therapy which is comparable to 43% treatment completion rate reported in CheckMate 577 as well as PACIFIC trial of durvalumab following concurrent CRT in unresectable stage III non-small cell lung cancer(17, 22). Similarly, in the MAGIC trial of perioperative chemotherapy and surgery versus surgery alone which included approximately 25% of patients with distal esophageal or GEJ

AC, only 55% of patients who were assigned to receive perioperative chemotherapy ended up receiving any postoperative chemotherapy(27). This finding raises a question of whether administration of ICI in a pre-operative setting, especially concurrently with CRT, may offer a greater benefit by obtaining maximum advantage of the synergy of ICI with CRT and the ability to deliver the desired amount of drug in the pre-operative setting. Eight (21.6%) patients discontinued durvalumab due to AEs, which is slightly higher than 15.4% reported in PACIFIC trial. Two of the three patients who experienced irAE leading to early discontinuation of durvalumab had significantly longer RFS, corroborating with the emerging body of evidence suggesting greater efficacy of ICIs in patients who develop irAE(28).

Clinical trials utilizing ICIs in metastatic gastroesophageal AC have shown positive correlation between therapeutic efficacy of immunotherapy and PD-L1 expression(15, 26, 29). However, a well-defined cutoff for PD-L1 expression and other biomarkers of response to immunotherapy to guide optimum patient selection are lacking. Our study showed a trend toward improved RFS and OS in patients with PD-L1 positive disease. While both traditionally used PD-L1 expression cutoffs to define positivity, $\geq 1\%$ and $\geq 10\%$, seemed to correlate with efficacy of durvalumab in post-trimodality setting, the trend was more pronounced among patients with PD-L1 $\geq 10\%$ disease, with all seven patients being relapse free at one year. Except for the difference in median OS among patients with PD-L1 $\geq 1\%$ versus $< 1\%$, none of the other comparisons were statistically significant. This is at least in part explained by very small sample size in each subgroup. Moreover, retrospective evaluation of PD-L1 expression by IHC in banked tissue samples could have been affected by the duration and mode of tissue storage as described in the literature(30, 31). Nevertheless, these findings are hypothesis generating and may imply that PD-L1 expression is a relevant biomarker of the efficacy of adjuvant durvalumab following trimodality therapy in locally

advanced disease. There was a trend toward improved RFS in HER-2 positive disease with durvalumab, which was limited by a small sample size. With the emerging data showing synergistic activity between PD-1/PD-L1 inhibitors and HER-2 targeting treatments in metastatic gastroesophageal cancer, a combination strategy in the adjuvant setting will be intriguing(32).

Our study is limited by its small sample size and non-randomized design. The historical control rate for 1-year RFS of patients who did not obtain a pCR with neoadjuvant CRT was largely derived from retrospective studies as this is not reported by prospective trials(6, 7). Additionally, it is debatable whether the endpoint of 1-year RFS with an adjuvant therapy given for one year is an acceptable surrogate endpoint of long-term benefit. It remains unclear if durvalumab in the adjuvant setting is merely delaying the disease relapse rather than eliminating micrometastatic disease. Nevertheless, longer term follow-up of the first 24 patients enrolled on the study indicate that a subset of patients (n=7) did derive durable benefit from durvalumab and have remained relapse free for nearly 3-5 years following discontinuation of therapy. Interestingly, while many relapses in our study were systemic, a small subset of patients who experienced late relapses following discontinuation of durvalumab had locoregional disease that was amenable to curative intent therapy. None of the patients who experienced systemic disease relapse in our study received subsequent ICI, either because the relapses occurred soon after discontinuation of durvalumab or occurred prior to FDA approval of ICI for metastatic esophageal AC. The OS results from CheckMate 577 may elucidate the effect of post-relapse therapies on OS in the post-ICI approval era.

In conclusion, adjuvant durvalumab in patients with residual disease in the surgical specimen following trimodality therapy for locally advanced esophageal and GEJ AC led to a clinically meaningful improvement in 1-year RFS compared to historical control rate. The safety profile of

durvalumab was consistent with what has been previously reported, however, less than 50% of patients were able to complete intended duration of therapy. Higher PD-L1 expression may have a correlation with the efficacy of durvalumab in this setting. The ongoing biomarker analysis of the study including next generation sequencing of paired tissue samples and Immunoscore may identify additional potential predictive biomarkers of efficacy of adjuvant ICI following trimodality therapy.

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Table 1: Baseline Patient and Disease Characteristics

Characteristic	Value
Patients Enrolled	37
Sex	
Female	1
Male	36
Age, y	
Median (range)	61 (43 – 73)
Enrolling Site	
Indiana University	25
University of Michigan	7
University of Iowa	5
Site of Disease	
GEJ	18
Distal Esophagus	19
Chemotherapy Regimen	
Cisplatin + 5-fluorouracil	6
Carboplatin + paclitaxel	31
Pathologic Lymph Node Stage	
N3	3
N2	10
N1	11
N0	13
T3	8
T2	2
T1	2
T0	1

Table 2: Treatment Related Adverse Events Occurring in $\geq 10\%$ of Patients*

Adverse Event	Any Grade, No. (%)	Grade 1-2, No. (%)	Grade 3, N0. (%)	Grade ≥ 4, N0. (%)
Fatigue	10 (27%)	10 (27%)	0 (0·0)	0 (0·0)
Diarrhea	7 (18·9%)	6 (16·2%)	1 (2·7%)	0 (0·0)
Arthralgia	6 (16·2%)	6 (16·2%)	0 (0·0)	0 (0·0)
Nausea	6 (16·2%)	6 (16·2%)	0 (0·0)	0 (0·0)
Pruritus	6 (16·2%)	6 (16·2%)	0 (0·0)	0 (0·0)
Cough	4 (10·8%)	3 (8·1%)	1 (2·7%)	0 (0·0)

*Excluding increase in AST/ALT/Bilirubin (reported in Table 3)

Table 3: Possible Immune-related Adverse Events

Adverse Event	Any Grade, No. (%)	Grade 1-2, No. (%)	Grade 3, N0. (%)	Grade ≥ 4, N0. (%)
Diarrhea	7 (18·9%)	6 (16·2%)	1 (2·7%)	0 (0·0)
Elevated AST	4 (10·8%)	1 (2·7%)	3 (8·1%)	0 (0·0)
Elevated ALT	4 (10·8%)	3 (8·1%)	1 (2·7%)	0 (0·0)
Elevated Bilirubin	4 (10·8%)	3 (8·1%)	1 (2·7%)	0 (0·0)
Hyperthyroidism	3 (8·1%)	3 (8·1%)	0 (0·0)	0 (0·0)
Colitis	2 (5·4%)	2 (5·4%)	0 (0·0)	0 (0·0)
Skin Rash	2 (5·4%)	2 (5·4%)	0 (0·0)	0 (0·0)
Adrenal Insufficiency	1 (2·7%)	1 (2·7%)	0 (0·0)	0 (0·0)
Hypothyroidism	1 (2·7%)	1 (2·7%)	0 (0·0)	0 (0·0)
Pneumonitis	1 (2·7%)	0 (0·0)	1 (2·7%)	0 (0·0)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase

Figure 1: Relapse free survival and overall survival

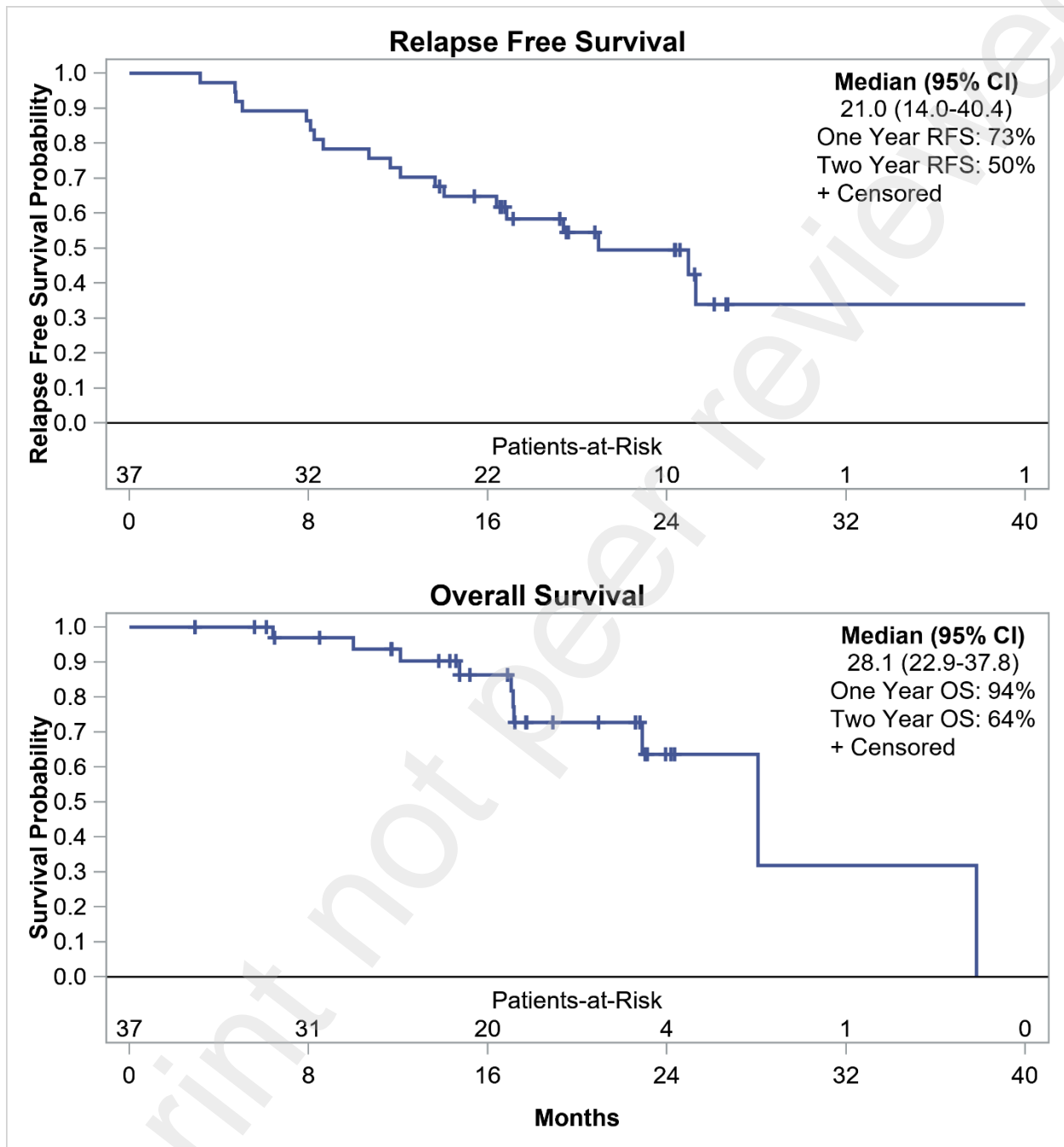


Figure 2: Treatment duration, disease relapse, and follow up based on pathologic lymph node status

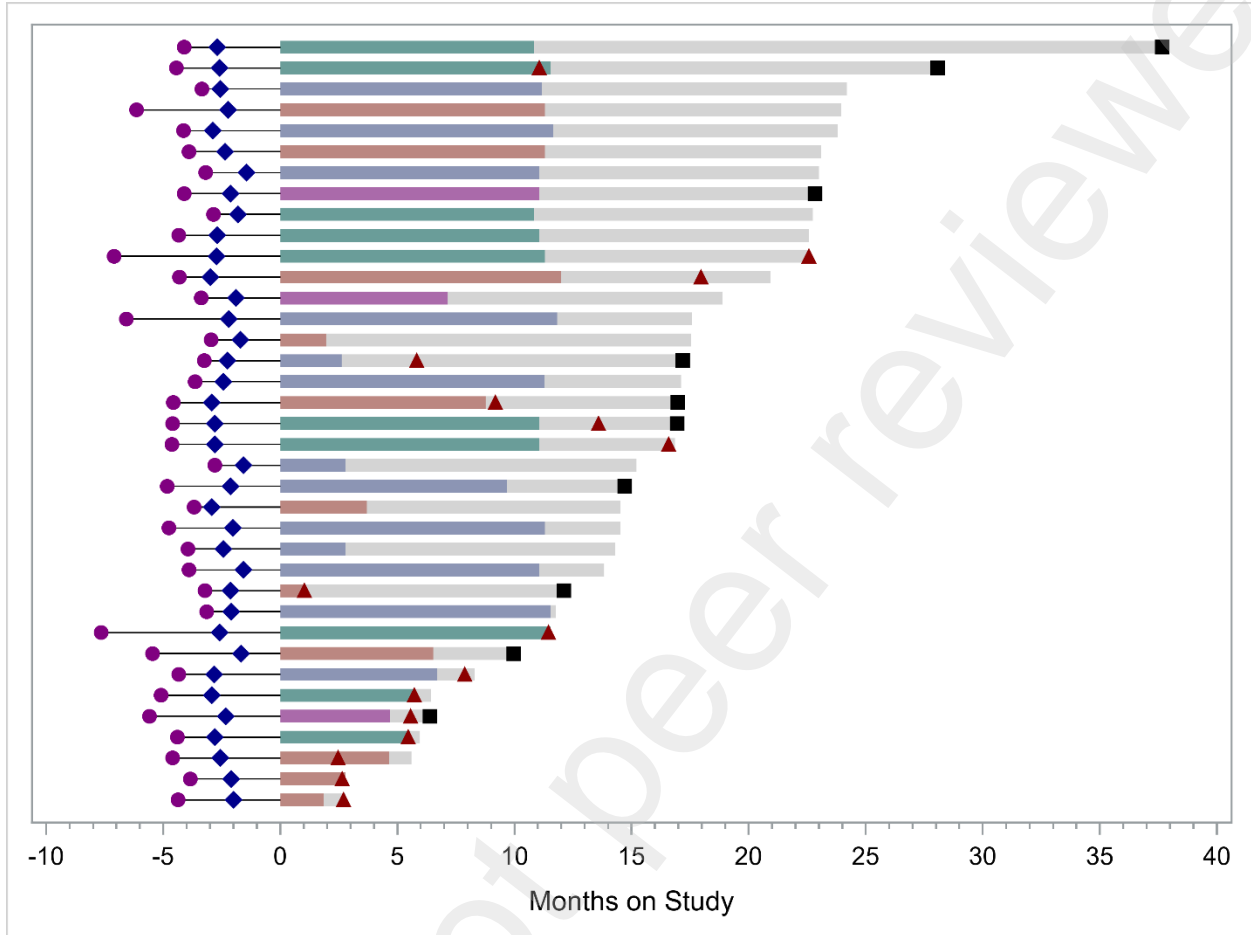
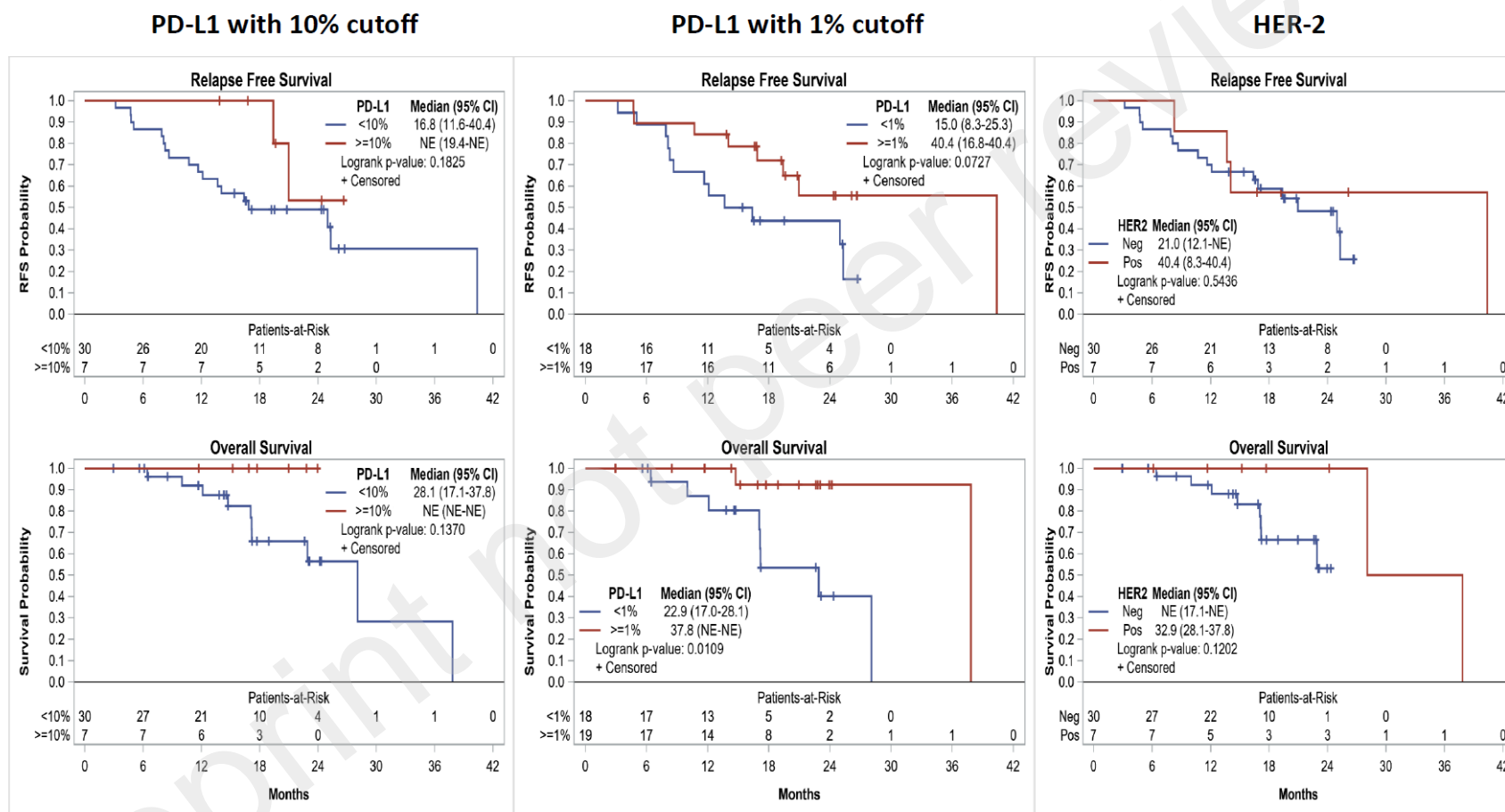


Figure Legend

- Treatment Duration with N0
- Treatment Duration with N1
- Treatment Duration with N2
- Treatment Duration with N3
- Follow-up Duration
- End of Chemoradiation
- ◆ Surgery
- ▲ Relapse
- Death

Figure 3: Relapse free survival and overall survival based on PD-L1 expression and HER-2 status



Supplementary Figure 1: Study Schema

A Phase II Study Evaluating Safety and Efficacy of Durvalumab Following Multi-modality Therapy in Esophageal Cancer:
Big Ten Cancer Research Consortium BTCRC-ESO14-012

