USE OF PD-1 AND PD-L1 INHIBITORS AFTER FIRST-LINE THERAPY IN ESOPHAGEAL CANCER PATIENTS IN THE US

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INTRODUCTION

- Esophageal cancer (EC), which includes esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), makes up only 3.2% of all cancers but ranks as the seventh most common cancer and sixth among cancer-related deaths worldwide[1].
  - The incidence of EC in the US has risen over the last 20 years, with an estimated 18,440 new cases and 16,170 deaths in 2020[2].
- The direct economic burden of EC in the US was estimated at $1.7 billion in 2018, and patient-specific costs vary widely by histology, stage, and treatment[3,4].
- For early stage disease, standard first-line nonsurgical treatments include chemotherapy, radiation therapy, or a combination of chemotherapy plus radiation (chemoradiation).
- Several immunotherapies are in clinical development or have been approved to treat patients with EC, especially refractory disease.
  - These include inhibitors of the programmed cell death protein-1 (PD-1) receptor such as pembrolizumab and nivolumab and inhibitors of the programmed death-ligand 1 (PD-L1) such as atezolizumab, durvalumab and avelumab.
  - In the following, we will use the term PD(L)1 inhibitors to categorize both, inhibitors of the receptor and its ligand.
  - Few studies have examined the real-world usage of PD(L)1 inhibitors in EC patients.
- Consequently, the overarching objective of this real-world claims analysis was to determine the use of PD(L)1 inhibitors following first-line therapy in EC patients.
  - The analysis also sought to determine the proportion of EC patients that switch to PD(L)1 inhibitors after receiving first-line therapy and to examine which specific PD(L)1 inhibitors are utilized in these patients.

MATERIALS

Data Source and Cohort Creation

- Newly-diagnosed EC (including both adenocarcinoma and squamous cell carcinoma) patients were identified in the IBM MarketScan Commercial and Medicare Supplemental databases during the study period of May 1, 2015 (approval of first PD(L)1 inhibitors in the US) through October 31, 2019.
- Eligible patients met the following criteria:
  - At least one claim for EC (ICD-9-CM: 150.x; ICD-10-CM: c15.3, c15.4, c15.5, c15.8, c15.9) during the study period.
  - No previous EC claim prior to study period.
  - Continuous enrollment at least 60 days prior to and 60 days after first EC claim.
  - Began EC treatment with a first-line therapy.
- Newly diagnosed patients were assigned to one of four patient cohorts based on the first-line therapy they received: chemotherapy only, radiation only, chemoradiation, or esophageal transhiatal/ transthoracic surgery.
- After first-line therapy, the database was searched for the first claim for a PD(L)1 inhibitor (i.e., pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab-rwlc).

Key Variables and Analytic Approach

- Descriptive analyses examined demographic characteristics such as age and sex.
- Time in days from initial diagnosis to first-line therapy (Time to First-Line) as well as time from first-line therapy to initiation of a PD(L)1 inhibitor (Time to PD(L)1 inhibitor) were both examined.
- Differences between cohorts were tested using chi-square for categorical variables. Parametric tests were used for normally distributed continuous variables while non-parametric tests were used for non-normally distributed continuous variables.

RESULTS

- A total of 6,077 newly diagnosed EC patients starting first-line therapy were identified.
- Overall, the average age of patients at date of diagnosis was 62.6 years (standard deviation [SD] = 11.4) and 23.1% of patients were female.

First-Line Therapy

- Table 1 provides the patient characteristics of the four cohorts.
- The radiation only cohort was significantly older (at 64.2 years old) than the other three cohorts (ranging from 60.6 to 62.6) and the chemoradiation cohort was also significantly older than the chemotherapy only cohort.
- The median number of days between first diagnosis and initiation of first-line therapy was significantly different between all the cohorts, with the exception of chemotherapy only and radiation only. The surgery cohort experienced the longest duration to initiation of first-line therapy.

Table 1. Characteristics of EC Patients by First-Line Therapy Cohort (N = 6,077)

Patient Characteristic	Full Sample (n = 6,077)	Chemotherapy Only (n = 2,065)	Radiation Only (n = 2,807)	Chemo-radiation (n = 995)	Surgery (n = 210)	p
Age years, mean (SD)	62.6 (11.4)	60.6 (10.9)	64.2 (11.6)	62.2 (11.5)	61.6 (10.4)	< 0.05
Female, n (%)	1,402 (23.1)	499 (24.2)	640 (22.8)	216 (21.7)	47 (22.4)	> 0.05
Time to First-Line, days						
Median	23.0	23.0	23.0	21.0	48.5	
Mean (SD)	55.7 (137.1)	45.8 (111.4)	73.0 (173.3)	25.7 (35.4)	64.4 (75.0)	< 0.05

EC: esophageal cancer; SD: standard deviation.

Initiation of PD(L)1 Inhibitor Therapy

- Of the total 6,077 EC patients that began first-line therapy, 379 subsequently began therapy with a PD(L)1 inhibitor (Table 2).
  - 54.1% (205/379) received chemotherapy alone as their first-line treatment. 118/379 (31.1%) received radiation only as first-line treatment. 14.8% (56/379) received chemoradiation.
  - No patients identified who had surgery in the first line setting received subsequent therapy with a PD(L)1 inhibitor.
- The median time from the start of first-line therapy to initiation of a PD(L)1 inhibitor was 259 days.

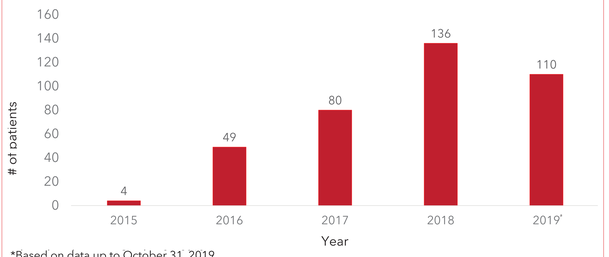
Table 2. Characteristics of EC Patients Receiving a PD(L)1 inhibitor by First-Line Therapy Cohort (n = 379)

Patient Characteristic	All Patients	Chemotherapy Only	Radiation Only	Chemoradiation	p
Number of patients (%)	379	205 (54)	118 (31.1)	56 (14.8)	< 0.05
Age years, mean (SD)	59.9 (10.7)	58.3 (9.5)	64.4 (10.7)	62.8 (13.7)	< 0.05
Female Gender, n (%)	87 (23.0)	51 (24.9)	23 (23.1)	13 (23.2)	> 0.05
Time to PD(L)1, days					
Median	259	240.0	295.0	312.0	> 0.05
Mean (SD)	324.9 (283.8)	290.3 (257.6)	348.7 (276)	401.7 (354.9)	

EC: esophageal cancer; SD: standard deviation.

- The use of PD(L)1 inhibitors increased over the five years of the study period (Figure 1).

Figure 1. Number of Patients Prescribed a PD(L)1 Inhibitor over the Study Period



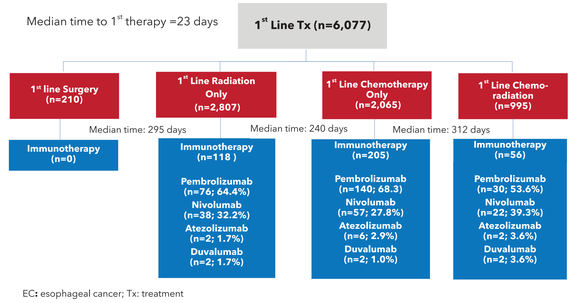
*Based on data up to October 31, 2019

- The specific PD(L)1 inhibitors that were utilized in each of the cohorts are presented in Figure 2.
- Pembrolizumab (64.9%) was used most frequently across the three cohorts followed by nivolumab (30.9%), atezolizumab (2.6%), and durvalumab (1.6%). Of the PD(L)1 inhibitor treatments searched, no patients received avelumab or cemiplimab-rwlc.

DISCUSSION

- The current study represents one of the first attempts to examine real-world patterns of PD(L)1 inhibitor utilization using US administrative claims data.
- The results of these analyses suggest that PD(L)1 inhibitors are increasingly used in EC after first-line therapies, especially among patients that initially received chemotherapy only (54.1%).
- Of the patients who received PD(L)1 inhibitors, a lower proportion received radiation only or combination chemoradiation as first-line therapy (31.1% and 14.8%, respectively).
- The main limitation of this study is the lack of clinical detail which is inherent in studies using retrospective administrative claims.
- The findings of this study also suggest a growth in the use of PD(L)1 inhibitors over the past five years reflecting an increasing acknowledgment of their effectiveness.
  - Over 65% of the PD(L)1 inhibitor utilization occurred in the last two years.

Figure 2. Frequencies of EC Patients Receiving a PD(L)1 inhibitor by First-Line Therapy Cohort (n = 379)



EC: esophageal cancer; Tx: treatment

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DISCLOSURE

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