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A global perspective in second-line treatment patterns for patients with advanced esophageal squamous cell carcinoma

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Abstract

Background: Esophageal cancer is a highly prevalent cancer associated with low survival, especially among those with advanced disease. Second-line (2L) treatment patterns and related clinical outcomes of patients with advanced esophageal squamous cell carcinoma (advESCC) treated in routine clinical care were examined globally and regionally.

Methods: A retrospective, noninterventional study collected physician-provided chart data of patients aged ≥20 years receiving either 2L active systemic therapy or BSC following first-line active therapy for advESCC from 11 countries in Asian and Western regions (September–October 2018). Bivariate analyses examined treatment and outcomes by region.

Results: AdvESCC patients (Asia = 192; West = 195) were examined, of which 58.1% (Asia $n = 101$; West $n = 124$) received active systemic therapy. While regional differences in tumor classification and staging at diagnosis were observed with less advanced tumors in Asia, no regional differences for these characteristics at 2L initiation were reported. Both taxane- and nontaxane-based therapies were used as 2L therapy among Asian and Western patients, although more western than Asian patients received immuno- or targeted therapies (17.0% vs. 3.0%; $p = 0.001$). Alopecia (10.7%), neutropenia (9.3%), and fatigue (9.3%) were the most-commonly reported adverse events (AEs) in both regions. Significantly higher 2L AE-related emergency room visits (Asia = 22.5% vs. West = 8.0%; $p < 0.001$) and hospitalizations (Asia = 25.9 ± 31.2 vs. West = 4.7 ± 7.0, $p < 0.001$) were observed in Asian than in Western patients. No regional differences were reported for response to 2L treatment or the percent of patients who received third-line treatment/died.

Conclusions: While regional variations were observed throughout the course of a patient's advESCC journey, disease response and treatment outcomes were similar.

KEYWORDS
advanced ESCC, Esophageal cancer, healthcare resource utilization, second-line, treatment patterns

INTRODUCTION

Esophageal cancer (EC) is the seventh highest incident cancer and ranks sixth in cancer mortality worldwide.[1] Over the last few decades, the incidence of EC has continued to increase, with 604 100 new cases reported globally in 2020.[1–3] EC is often not recognized until advanced or metastasized stages, resulting in high morbidity and mortality.[4] The 5-year survival rate for EC is approximately 19% and 5% for metastatic or distant EC (US data).[5,6] Of the histological subtypes of EC, squamous cell carcinoma (SCC) and adenocarcinoma (AC), SCC is more common worldwide and in particular in East Asia, Africa, Central and Eastern Europe, and South America.[2,7,8] The prevalence of esophageal squamous cell carcinoma (ESCC) is higher among Asians compared with whites and Hispanic whites and

among men, and is associated with smoking and alcohol use.[2,9–11]

The European Society for Medical Oncology (ESMO) clinical practice guideline recommends different palliative treatment options for patients with metastatic EC depending on the clinical situation, which includes external radiotherapy, single-dose brachytherapy, or metal stent placement.[12] Chemotherapy is indicated for palliative treatment in selected patients, particularly for AC patients with good performance status. Best supportive care (BSC) or palliative monotherapy were recommended for ESCC patients, as the value of palliative combination chemotherapy was not substantially demonstrated.[12] Further, Pan-Asian adapted ESMO clinical practice guidelines recommends combination chemotherapy as the preferred option in clinical practice for fit patients and palliative monotherapy or BSC for unfit ESCC patients.[13] In a Cochrane database systematic review analyzing five randomized trials, the addition of systemic therapy to BSC was shown to improve quality of life and prolong survival in patients with advanced esophageal cancer.[14,15]

The short survival period and limited treatment strategies available for advanced ESCC (advESCC) has resulted in a significant unmet need in this patient population. Population-level data are minimal and studies are often subject to selection bias.[11,16,17] The effect of novel and neoadjuvant therapies, as well as that of other treatments including surgery, chemotherapy, and radiotherapy for the patient population with advESCC remains unknown. Further, real-world data on treatment patterns and healthcare resource use (HCRU) in 2L treatment of advESCC are scarce.[17–20]

As such, the aim of this global study was to collect real-world data to examine patient and their treating physician characteristics, treatment patterns, and related clinical outcomes of patients with advESCC who received 2L active systemic therapy or best supportive care (BSC) following 1L in routine clinical care. The study focused on understanding the similarities and differences by geographic region – Asian (China, Japan, Korea, and Taiwan) and Western (Canada, France, Germany Italy, Spain, United Kingdom **[UK], and United States [US]).**

METHODS

Study design

This was a retrospective, noninterventional study conducted among physicians in 11 different countries (Asia: Canada, Japan, Taiwan, Korea, and China; West: France, Germany, Italy, Spain, UK, and US) between September and October 2018. Physicians were recruited from Kantar's partner M3 and their respective partner panels, as per country specifications. Recruitment panels employed a stringent verification procedure for physicians that included submission of medical license and medical diploma verified against local medical council sites such as GMC (General Medical Council) in the UK and the ASIP Santé in France. Physician sampling was linked to a panel management system to ensure representative demographic cross section that accounted for population density and distribution, region (rural or urban), and practice type (hospital or office).

Anonymized physicians completed a web-based electronic case report form (eCRF) using medical record data for each patient. The eCRF was developed by consultants from different disciplines (i.e., primary research, health outcomes, and clinical oncology experts) and further confirmed by physicians with cognitive interviewing. Anonymized patient data were collected from these physicians using an email link and in accordance with each country's privacy laws. Physicians were recruited from physician panels if they meet the following inclusion criteria: completed medical oncology training, had at least 2 years of experience (or ≥ 5 years in China), had patients in whom they had completed or stopped 1L or 2L treatment for advanced or metastatic ESCC/EAC or BSC at either line, could provide informed consent and could provide data from at least two patient charts that fit within the study parameters. Physicians provided up to four of their most recent patients who met the following criteria: patients aged ≥20 years with advanced or metastatic ESCC or EAC, who had initiated 2L active systemic treatment for EC (ESCC or EAC), or who had initiated BSC during the specified 2 year study period and had a minimum of a 6 month follow-up period following treatment end or stopping (which may have included death). Data for patients diagnosed with adenosquamous cancer were excluded from this analysis. The current study focused mainly on patients who had 2L treatment for ESCC only.

The survey protocol and questionnaire received institutional review board exemption from Pearl IRB in accordance with FDA 21 CFR 56.104 and DHHS 45 CFR 46.101 (b) category 2, 4 (17-KANT-166).

Measures

Physician-level variables to define practice-related characteristics included specialty (oncology/gastroenterology/surgery), years in practice, and practice setting (university hospitals/private office, focus or hospital/ cancer center or specialized oncology hospital/non-university hospital, medical center, regional hospital or area hospital).

Patient-level demographic variables and health-related characteristics included age, sex, race, smoking/caffeine/alcohol consumption history, health history and status. Patient disease-related descriptors were reported at initial diagnosis, start of 1L, and start of 2L and included physician-reported Eastern Cooperative Oncology Group (ECOG) performance status (PS) (grades 0 through 4), tumor classification (de novo metastatic, recurrent, local/regional but patient is not amenable to curative therapy), staging based on TNM and tumor classification.

Treatment history were documented for neoadjuvant and adjuvant care (radiation/radiotherapy, chemotherapy, targeted therapy, immunotherapy), and active systemic and BSC for first- and second-lines of therapy. BSC was defined as palliative measures such as pain relief, monitoring and treatment of malnutrition, and treatment of other symptoms such as anorexia, fatigue, nausea/vomiting, and consistent with those found in the literature.[21] For 2L, treatment regimens were classified as taxanes, nontaxanes, immune-oncology, targeted and other therapy. Further subdivisions included mono, doublet and multiple therapy. Clinical outcomes were assessed for all patients who received 2L therapy and included physician-reported adverse events (AEs) (Grade 1 or 2/Grade 3 or 4), treatment and AE-related healthcare resource utilization (HCRU) (emergency room [ER] visits, days hospitalized), response to treatment based on RECIST 1.1.[22] (complete response, partial response, stable disease, disease progression, death) and outcomes following treatment (no further treatment, further line of treatment/clinical trial, death).

Statistical analysis

Baseline demographics, patient characteristics, and 2L treatment patterns were reported descriptively. Categorical data were expressed as frequencies and proportions and continuous data were expressed as means (standard deviations) and medians (ranges). Additionally, survey options included "do not know" and required responses to all survey questions in order to minimize missing values. No imputation strategy was employed for missing values. Differences between groups were examined in bivariate analyses using one-way ANOVAs or the median test for continuous variables and Chi-square or Fisher's exact tests for categorical variables. p-values <0.05 were considered statistically significant unless otherwise noted. No adjustments for multiplicity were performed. All statistical analyses were conducted using SPSS version 25 or in SAS version 9.4.

RESULTS

Data were collected from physicians from 11 countries who provided data for 387 ESCC patients treated at 2L with active therapy or BSC (Figure 1).

Physician characteristics

Of the 387 physicians, 192 (49.6%) were from Asia (Japan, Korea, Taiwan, and China) and 195 (50.4%) were from Western countries (US, Canada, Italy, Spain, France, Germany, UK). Detailed description of physician characteristics by Asian and Western geographies are illustrated in Table 1. Most physicians were male (76.0%) and had a mean age of 44.8 ± 10.0 years, although physicians from Asia

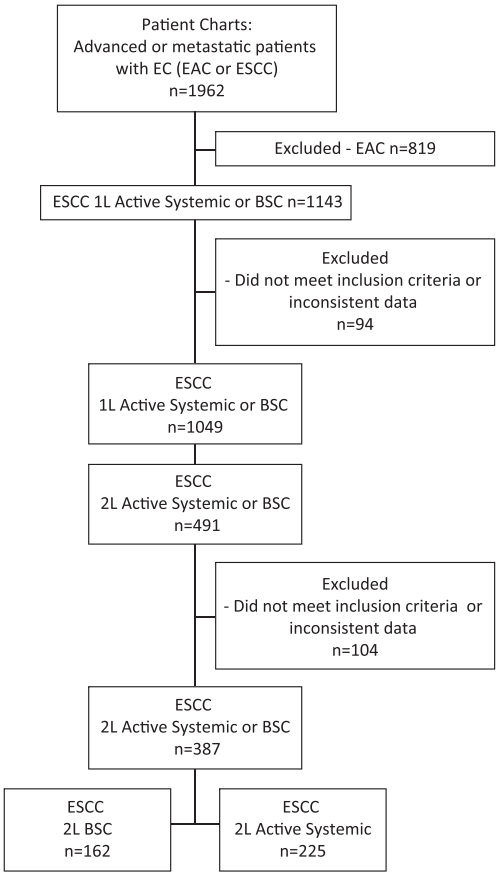

FIGURE 1 Study flow chart. Abbreviations: 1L, first-line; 2L, second-line; AE, adverse event; BSC, best supportive care; EAC, esophageal adenocarcinoma; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma

were significantly younger than the Western geographies (42.6 ± 9.1 years vs. 47.1 ± 10.4 years, respectively; $p < 0.001$). The majority of physicians specialized in oncology (59.4%), followed by gastroenterology (23.8%) and surgery (16.8%) and had an average 14.6 ± 6.8 years in practice. A significant regional group difference was seen in the practice settings ($p < 0.001$), with smaller number of physicians working at cancer center/specialized oncology hospital in Asia as compared with the Western countries.

Patient characteristics – overall cohort

Patients baseline demographic characteristics and behaviors were for the most part similar across geographies (Table 2). The mean age of the patients was 63.4 ± 10.6 years and 81.4% were male with no significant differences by geography. Smoking and alcohol use differed between Asian and Western geographies ($p \leq 0.002$). Among those who smoked, the mean number of packs of cigarettes smoked per week was 6.6 ± 5.5 in Asia compared to 8.9 ± 8.8 in the West ($p = 0.028$) and among those who drank alcohol, the mean number of alcoholic beverages consumed per week

TABLE 1 Physician characteristics by geography

	Total ($N = 387$)	Asia ($N = 192$)	West ($N = 195$)	p-value
Physician gender: Male, n (%)	294 (76.0)	150 (78.1)	144 (73.9)	0.325
Physician age, mean ± SD	44.8 ± 10.0	42.6 ± 9.1	47.1 ± 10.4	**<0.001**
Physician specialty, n (%)				**<0.001**
Oncology	230 (59.4)	77 (40.1)	153 (78.5)	
Gastroenterology	92 (23.8)	63 (32.8)	29 (14.9)	
Surgery	65 (16.8)	52 (27.1)	13 (6.7)	
Years in practice, mean ± SD	14.6 ± 6.8	14.7 ± 7.2	14.5 ± 6.4	0.783
Practice setting, n (%)				**<0.001**
University hospital	172 (44.4)	91 (47.4)	81 (41.5)	
Private office/private focus /private hospital	64 (16.5)	31 (16.2)	33 (16.9)	
Cancer centre/specialized oncology hospital	62 (16.0)	10 (5.2)	52 (26.7)	
Non-university hospital/medical center/regional hospital/ area hospital	89 (23.0)	60 (31.3)	29 (14.9)	

was 6.2 ± 6.7 in Asia compared to 9.5 ± 7.6 in the West ($p = 0.003$).

The mean body mass index (BMI) at diagnosis was 24.4 ± 12.8 kg/m.[2] Patients from Asian geographies (22.6 ± 3.5 kg/m^2) had significantly lower BMI at diagnosis than patients from the West (24.9 ± 4.1 kg/m^2; $p = 0.007$). Overall, history of gastroesophageal reflux disease was reported in 52.5% and Barrett's esophagus/dysplasia in 24.8% of the patients; no regional differences were observed ($p > 0.05$).

Overall, the most commonly reported comorbidities at diagnosis were hypertension (29.5%), diabetes (16.8%), and COPD (14.5%). The rates of some comorbidities were lower by approximately 2-fold in Asian compared to Western geographies (e.g., hypertension: 19.8% vs. 39.0% [$p < 0.001$]; COPD: 9.9% vs. 19.0% [$p = 0.011$]; hyperlipidemia: 8.9% vs. 19.5% [$p = 0.003$]).

At diagnosis, half the patients had locoregional disease (49.4%) and half had metastatic disease (48.1%). A significantly higher number of patients from Asia had locoregional disease (59.9%) while more patients from Western geographies had metastatic disease (58.5%) ($p < 0.001$). Approximately half of total patients (52.5%) had ECOG status of 1 at diagnosis with no significant group difference across geographies. Overall, a majority of the patients had stage 4 tumor at initial diagnosis (56.0%), specifically more patients from the West compared to those from Asia (62.3% vs. 49.4%).

The regional distribution of patients with ESCC who received treatment at 2L (active or BSC) is shown in Figure 2. No significant differences were noted in most of the demographic characteristics and health behaviors in those on BSC and active therapy, overall and in Asian and Western geographical regions (Table 2). Overall, a significantly higher percentage of patients in the BSC group had history of gastroesophageal reflux disease (GERD) compared with the active therapy group (55.9% vs. 50.0%; $p = 0.034$); a similar trend was observed in the Asian countries (56.0% vs. 40.6%; $p = 0.003$). The rates of some comorbidities significantly differed between the groups. For example, for the overall cohort, coronary artery disease (11.2% vs. 4.9%; $p = 0.030$), angina (8.1% vs. 3.1%; $p = 0.036$), and obesity (6.8% vs. 2.2%; $p = 0.036$) were significantly higher in the BSC than active systemic therapy groups. A similar trend for BSC and active systemic therapy was observed in the Asian region for coronary artery disease (8.8% vs. 2.0%; $p = 0.049$) and obesity (7.7% vs. 1.0%; $p = 0.028$) and in the Western region for angina (8.5% vs. 1.6%; $p = 0.028$), respectively. At initial diagnosis, a significantly higher percentage of patients in the BSC than active systemic therapy group had locoregional disease (57.8% vs. 43.4%; $p < 0.001$); this was also observed in the Asian region (68.1% vs. 52.5%; $p = 0.001$) and the Western region (45.1% vs. 35.5%; $p = 0.002$). Around half of the patients in the active therapy group in both the geographical regions had ECOG status 1 ($p = 0.035$ for Western countries; $p = 0.318$ for Asian countries).

2L active systemic treatment patterns

Treatment patterns at 2L among patients with ESCC over different geographical regions are illustrated in Figure 3. Of the total 225 patients on 2L active therapy, 45.3% received taxanes (Asia = 48.5%; West = 42.8%; $p = 0.387$) whereas 44.0% received nontaxane-based (Asia 42.8%; West = 40.2%; $p = 0.218$) therapies. The proportion of patients who received either immunotherapy (Asia = 3.0%; West = 7.3%) or targeted therapy (Asia = 0.0%; West = 9.7%) as 2L treatment was higher in Western than Asian countries (immunotherapy + targeted therapy $p = 0.001$). Docetaxel was the most common taxane singlet therapy (Asia = 23.8%; West = 19.4%); the most common taxane doublet was cisplatin+docetaxel (8.9%) in Asia and carboplatin+paclitaxel (4.8%) in the West. Figure 4 and Supplemental Table S1 highlights the 1L treatment patterns of patients receiving

TABLE 2 Patient characteristics for patients with ESCC at 2L according to geography and therapy type (BSC vs. active systemic)

	Overall				Asia				West				Asia versus West
	Total ($N = 387$)	BSC ($N = 162$)	Active systemic ($N = 225$)	*p*-value	Total ($N = 192$)	BSC ($N = 91$)	Active systemic ($N = 101$)	*p*-value	Total ($N = 195$)	BSC ($N = 71$)	Active systemic ($N = 124$)	*p* value	*p* value
Demographic characteristics and health behaviors													
Age, years													
Mean ± SD	63.4 ± 10.6	63.3 ± 12.0	63.4 ± 9.4	0.915	63.1 ± 11.8	62.7 ± 13.0	63.6 ± 10.7	0.589	63.6 ± 9.2	63.9 ± 10.8	63.4 ± 8.3	0.696	0.701
Median (range)	65 (21.0–86.0)	66 (28.0–85.0)	65 (21.0–86.0)		66 (21.0–86.0)	65 (28.0–82.0)	66 (21.0–86.0)		65 (30.0–85.0)	67 (37.0–85.0)	64 (30.0–84.0)		
Male (%)	81.4%	79.5%	82.7%	0.419	83.3	81.3	85.2	0.477	79.5	77.5	80.6	0.713	0.331
Smoking status (%)				0.789				0.958				0.524	0.595
Ever	73.4%	71.6%	74.7%		71.9%	72.5%	71.3%		74.9%	70.4%	77.4%		
Never	23.0%	24.7%	21.8%		25.0%	24.2%	25.7%		21.0%	25.4%	18.5%		
Do not know	3.6%	3.7%	3.6%		3.1%	3.3%	3.0%		4.1%	4.2%	4.0%		
Average number of packs of cigarettes smoked per week among current/past smokers (Asia $n = 102$; West $n = 100$)				0.954				0.793				0.538	**0.028**
Mean ± SD	7.8 ± 7.4	7.7 ± 9.1	7.8 ± 6.0		6.6 ± 5.5	6.5 ± 5.4	6.8 ± 5.7		8.9 ± 8.8	9.7 ± 13.0	8.5 ± 6.1		
Median (range)	7.0 (1.0–60.0)	6.0 (1.0–60.0)	7.0 (1.0–40.0)		7.0 (1.0–40.0)	6.0 (1.0–30.0)	7.0 (1.0–40.0)		7.0 (1.0–60.0)	5.0 (1.0–60.0)	7.0 (1.0–30.0)		
Alcohol consumption (%)				0.912				0.481				0.875	0.406
Ever	71.8%	71.0%	72.4%		72.9%	71.4%	74.3%		70.8%	70.4%	71.0%		
Never	23.0%	23.5%	22.7%		23.4%	23.1%	23.8%		22.6%	23.9%	21.8%		
Do not know	5.2%	5.6%	4.9%		3.6%	5.5%	2.0%		6.7%	5.6%	7.3%		
Average number of alcoholic beverages consumed per week among current/past alcohol use (Asia $n = 97$; West $n = 75$)				0.135				0.106				0.335	**0.003**
Mean ± SD	7.7 ± 7.3	8.7 ± 9.3	7.0 ± 5.5		6.2 ± 6.7	7.5 ± 9.4	5.3 ± 2.8		9.5 ± 7.6	10.7 ± 8.8	8.9 ± 6.9		

(Continues)

TABLE 2 (Continued)

	Overall				Asia				West				Asia versus West
	Total ($N = 387$)	**BSC ($N = 162$)**	**Active systemic ($N = 225$)**	***p*-value**	**Total ($N = 192$)**	**BSC ($N = 91$)**	**Active systemic ($N = 101$)**	***p*-value**	**Total ($N = 195$)**	**BSC ($N = 71$)**	**Active systemic ($N = 124$)**	***p* value**	***p* value**
Median (range)	6.0 (1.0–50.0)	6.0 (1.0–50.0)	6.0 (1.0–30.0)		5.0 (1.0–50.0)	5.0 (1.0–50.0)	5.5 (1.0–14.0)		7.0 (1.0–40.0)	7.0 (2.0–40.0)	7.0 (1.0–30.0)		
Caffeinated consumption (%)				**0.015**				0.072				0.495	**<0.001**
Ever	50.1%	42.6%	55.6%		41.1%	34.1%	47.5%		59.0%	53.5%	62.1%		
Never	27.9%	35.2%	22.7%		39.1%	47.3%	31.7%		16.9%	19.7%	15.3%		
Do not know	22.0%	22.2%	21.8%		19.8%	18.7%	20.8%		24.1%	26.8%	22.6%		
Average number of caffeinated beverages consumed per week among current/past caffeine use (Asia $n = 50$; West $n = 51$)													
Mean ± SD	8.7 ± 6.5	8.8 ± 6.5	8.7 ± 6.5	0.914	6.8 ± 6.0	7.0 ± 6.6	6.7 ± 5.6	0.821	10.5 ± 6.5	11.4 ± 5.6	10.2 ± 6.9	0.559	**0.003**
Median (range)	7.0 (1.0–30.0)	7.0 (1.0–30.0)	7.0 (1.0–30.0)		5.5 (1.0–30.0)	5.0 (1.0–30.0)	6.0 (1.0–30.0)		8.0 (2.0–30.0)	10.0 (5.0–21.0)	7.0 (2.0–30.0)		
Health history and status													
BMI at diagnosis, kg/m^2													
Mean ± SD	23.8 ± 4.0	24.0 ± 4.7	23.6 ± 3.4	0.329	22.6 ± 3.5	22.9 ± 4.4	22.3 ± 2.5	0.188	24.9 ± 4.1	25.3 ± 4.8	24.6 ± 3.7	0.277	**<0.001**
Median (range)	23.4 (14.3–55.4)	23.3 (17.3–55.4)	23.4 (14.3–36.3)		22.5 (14.6–55.4)	22.8 (17.3–55.4)	22.1 (14.6–29.7)		24.5 (14.3–44.8)	24.6 (17.7–44.8)	24.5 (14.3–36.3)		
History of gastroesophageal reflux disease (%)				**0.034**				**0.003**				0.768	0.290
Yes	52.5	55.9	50.0		47.9	56.0	40.6		56.9	56.3	57.3		
No	41.6	35.4	46.0		46.9	35.2	57.4		36.4	35.2	37.1		
Do not know	5.9	8.7	4.0		5.2	8.8	2.0		6.7	8.5	5.6		
History of Barrett's esophagus and dysplasia (%)				0.794				0.836				0.849	0.543
Yes	24.8	26.7	23.5		26.6	28.6	24.8		23.1	25.4	21.8		
No	61.2	59.6	62.4		60.9	59.3	62.4		61.5	59.2	62.9		
Do not know	14.0	13.7	14.2		12.5	12.1	12.9		15.4	15.5	15.3		

(Continues)

TABLE 2 (Continued)

	Overall				Asia				West				Asia versus West
	Total ($N = 387$)	BSC ($N = 162$)	Active systemic ($N = 225$)	*p*-value	Total ($N = 192$)	BSC ($N = 91$)	Active systemic ($N = 101$)	*p*-value	Total ($N = 195$)	BSC ($N = 71$)	Active systemic ($N = 124$)	*p* value	*p* value
Comorbidities (% yes)[a]													
Hypertension	29.5	29.8	29.2	0.910	19.8	22.0	17.8	0.470	39.0	39.4	38.7	1.000	**<0.001**
Diabetes	16.8	17.4	16.4	0.890	15.1	13.2	16.8	0.481	18.5	22.5	16.1	0.338	0.377
Chronic obstructive pulmonary disease	14.5	11.2	16.8	0.143	9.9	11.0	8.9	0.630	19.0	11.3	23.4	0.057	**0.011**
Dysphagia	14.2	14.3	14.2	0.542	16.1	13.2	18.8	0.290	12.3	16.9	9.7	0.174	0.280
Hyperlipidemia	14.2	16.8	12.4	0.240	8.9	11.0	6.9	0.323	19.5	23.9	16.9	0.262	**0.003**
Coronary artery disease	7.5	11.2	4.9	**0.030**	5.2	8.8	2.0	**0.049**	9.7	14.1	7.3	0.137	0.090
Peptic ulcer disease	5.7	6.8	4.9	0.505	7.8	9.9	5.9	0.309	3.6	2.8	4.0	0.719	0.073
Angina	5.2	8.1	3.1	**0.036**	6.3	7.7	4.9	0.433	4.1	8.5	1.6	**0.028**	0.340
Kidney disease	4.7	3.7	5.3	0.626	3.6	2.2	4.9	0.449	5.6	5.6	5.6	1.000	0.351
Atherosclerosis	4.7	3.7	5.3	0.626	5.2	5.5	4.9	1.000	4.1	1.4	5.6	0.262	0.606
Cardiac arrhythmias	4.7	5.6	4.0	0.473	5.2	6.6	4.0	0.522	4.1	4.2	4.0	1.000	0.606
Asthma	4.4	5.0	4.0	0.802	2.1	3.3	1.0	0.347	6.7	7.0	6.5	1.000	**0.028**
Obesity	4.1	6.8	2.2	**0.036**	4.2	7.7	1.0	**0.028**	4.1	5.6	3.2	0.465	0.975
Cirrhosis	3.9	5.0	3.1	0.426	3.1	5.5	1.0	0.103	4.6	4.2	4.8	1.000	0.448
Liver disease	3.1	0.6	4.9	**0.033**	3.1	1.1	4.9	0.215	3.1	0.0	4.8	0.088	0.987
Do not know	3.1	5.0	1.8	0.083	2.6	5.5	0.0	**0.023**	3.6	4.2	3.2	1.000	0.576
ESCC characteristics at diagnosis and surgery to treat tumor													
Tumor characteristics at initial diagnosis (%)				**<0.001**				**0.001**				**0.002**	**<0.001**
Locoregional	49.4	57.8	43.4		59.9	68.1	52.5		39.0	45.1	35.5		
Metastatic	48.1	36.0	56.6		37.5	26.4	47.5		58.5	47.9	64.5		
Do not know	2.6	6.2	0.0		2.6	5.5	0.0		2.6	7.0	0.0		
Tumor staging at initial diagnosis (%)				0.547				0.637				0.831	**0.004**
Stage 1	4.4	3.8	4.8		4.2	2.8	5.3		4.6	5.1	4.3		

(Continues)

TABLE 2 (Continued)

	Overall				Asia				West				Asia versus West
	Total ($N = 387$)	**BSC ($N = 162$)**	**Active systemic ($N = 225$)**	***p*-value**	**Total ($N = 192$)**	**BSC ($N = 91$)**	**Active systemic ($N = 101$)**	***p*-value**	**Total ($N = 195$)**	**BSC ($N = 71$)**	**Active systemic ($N = 124$)**	***p* value**	***p* value**
Stage 2	14.4	15.3	13.8		15.7	18.1	13.8		13.1	11.9	13.8		
Stage 3	25.2	29.0	22.9		30.7	33.3	28.7		20.0	23.7	18.1		
Stage 4	56.0	51.9	58.6		49.4	45.8	52.1		62.3	59.3	63.8		
PS ECOG at diagnosis (%)				0.276				0.318				**0.035**	0.146
Grade 0	24.0	21.7	25.7		26.6	28.6	24.8		21.5	12.7	26.6		
Grade 1	52.5	49.7	54.4		49.0	41.8	55.5		55.9	60.6	53.2		
Grade 2	17.3	19.3	15.9		17.2	20.9	13.9		17.4	16.9	17.7		
Grade 3	4.7	6.8	3.1		5.2	5.5	5.0		4.1	8.5	1.6		
Grade 4	1.0	1.9	0.4		2.1	3.3	1.0		0.0	0.0	0.0		
Do not know	0.5	0.6	0.4		0.0	0.0	0.0		1.0	1.4	0.8		
Tumor size at initial diagnosis, cm													
n	315	132	183		176	83	93		139	49	90		
Mean ± SD	4.3 ± 1.9	4.1 ± 1.9	4.4 ± 1.9	0.178	4.2 ± 1.9	4.1 ± 1.9	4.3 ± 1.9	0.442	4.4 ± 1.9	4.2 ± 1.9	4.5 ± 1.9	0.331	0.178
Median (range)	4.0 (1.0–10.0)	4.0 (1.0–10.0)	4.0 (1.0–10.0)		4.0 (1.0–10.0)	4.0 (1.0–9.0)	4.0 (1.0–10.0)		4.0 (1.0–10.0)	4.0 (1.0–10.0)	4.0 (1.0–10.0)		
Treatment with surgery (% yes)[b]	23.5	28.6	19.9	0.052	29.2	33.0	25.7	0.271	17.9	23.9	14.5	0.121	**0.002**
n	61	31	30		56	30	26		35	17	18		
Neoadjuvant/adjuvant systemic therapy (% yes)[c]	67.0	67.4	66.7	1.000	66.1	70.0	61.5	0.505	68.6	64.7	72.2	0.725	0.805
Neoadjuvant/adjuvant radiation/ radiotherapy (% yes)[c]	28.6	30.4	26.7	0.817	21.4	26.7	15.4	0.305	40.0	35.3	44.4	0.733	0.056
Neoadjuvant/adjuvant chemotherapy (% yes)[c]	41.8	39.1	44.4	0.673	35.7	36.7	34.6	0.873	51.4	47.1	55.6	0.740	0.139
Neoadjuvant/adjuvant targeted therapy (% yes)[c]	9.9	8.7	11.1	0.739	10.7	10.0	11.5	1.000	8.6	5.9	11.1	1.000	1.000

(Continues)

TABLE 2 (Continued)

	Overall				Asia				West				Asia versus West
	Total ($N = 387$)	**BSC ($N = 162$)**	**Active systemic ($N = 225$)**	***p*-value**	**Total ($N = 192$)**	**BSC ($N = 91$)**	**Active systemic ($N = 101$)**	***p*-value**	**Total ($N = 195$)**	**BSC ($N = 71$)**	**Active systemic ($N = 124$)**	***p* value**	***p* value**
Neoadjuvant/adjuvant immunotherapy (% yes)[c]	5.5	6.5	4.4	1.000	8.9	10.0	7.7	1.000	0.0	0.0	0.0	na[d]	0
Time to recurrence, months													
n	89	46	43		56	30	26		33	18	17		
Mean ± SD	7.1 ± 8.4	6.1 ± 3.8	8.3 ± 11.4	0.221	6.2 ± 8.3	5.4 ± 3.4	7.0 ± 11.7	0.485	8.8 ± 8.5	7.3 ± 4.5	10.2 ± 11.0	0.331	0.160
Median (range)	6.0 (0–60.0)	6.0 (0–18.0)	5.0 (1.0–60.0)		4.0 (0–60.0)	5.0 (0–12.0)	3.0 (1.0–60.0)		6.0 (0–48.0)	6.0 (0–18.0)	5.0 (2.0–48.0)		
Time to surgery, months[b]													
n	80	42	38		53	28	25		27	14	13		
Mean ± SD	3.0 ± 5.0	3.2 ± 6.0	2.8 ± 3.6	0.703	2.6 ± 3.4	2.8 ± 3.1	2.4 ± 3.9	0.716	3.8 ± 7.1	4.1 ± 9.6	3.5 ± 3.0	0.828	0.313
Median (range)	2.0 (0–37.0)	2.0 (0–37.0)	1.5 (0–19.0)		1.0 (0–19.0)	2.0 (0–15.0)	1.0 (0–19.0)		2.0 (0–37.0)	2.0 (0–37.0)	1.5 (0–12.0)		

Abbreviations: 2L, second-line; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; SD, standard deviation; na, not applicable.

[a]Comorbidities are listed for those with a prevalence of ≥3% in the overall ESCC 2L population.

[b]Surgery was defined as undergoing local excision, esophagectomy, endoscopic mucosal resection, endoscopic submucosal dissection, or ablation.

[c]Percentages are out of the total number of patients who underwent surgery to remove the tumor.

[d]Statistical testing was not performed.

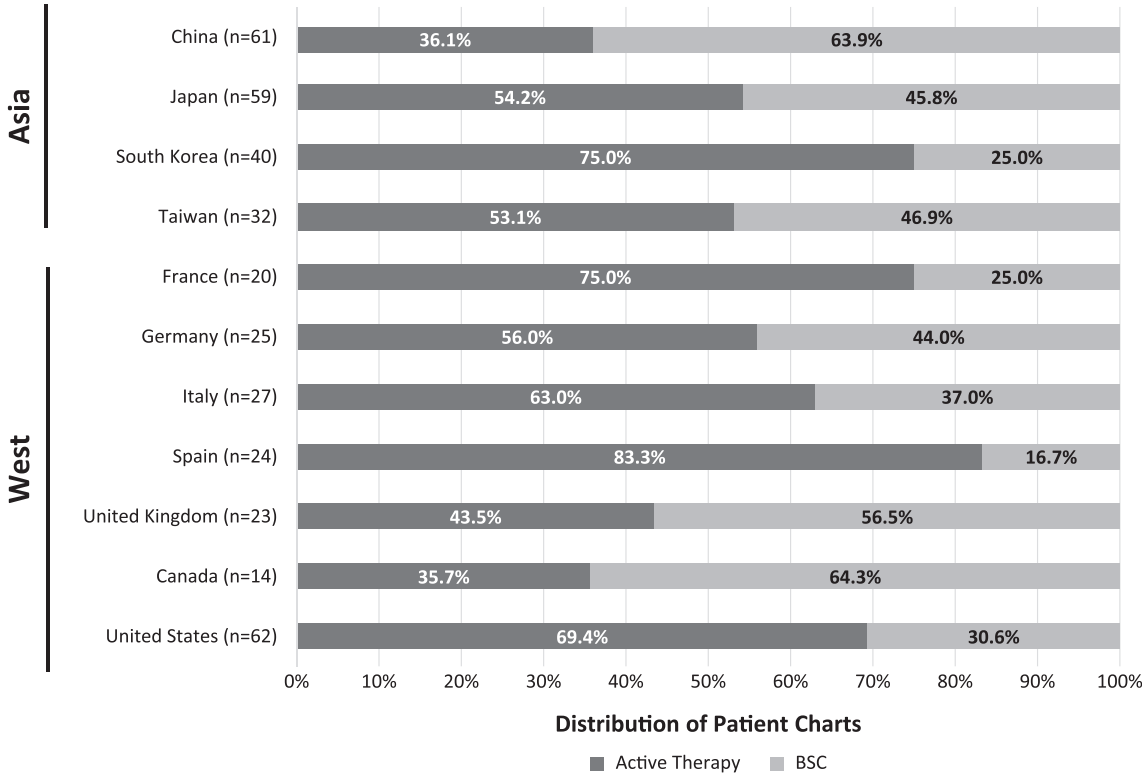

FIGURE 2 Regional distribution of sample patients with ESCC who received treatment at 2L. Abbreviations: 2L, second-line; BSC, best supportive care; ESCC, esophageal squamous cell carcinoma. Note: Active treatment in Asia was 52.6% and in Western countries was 63.6%

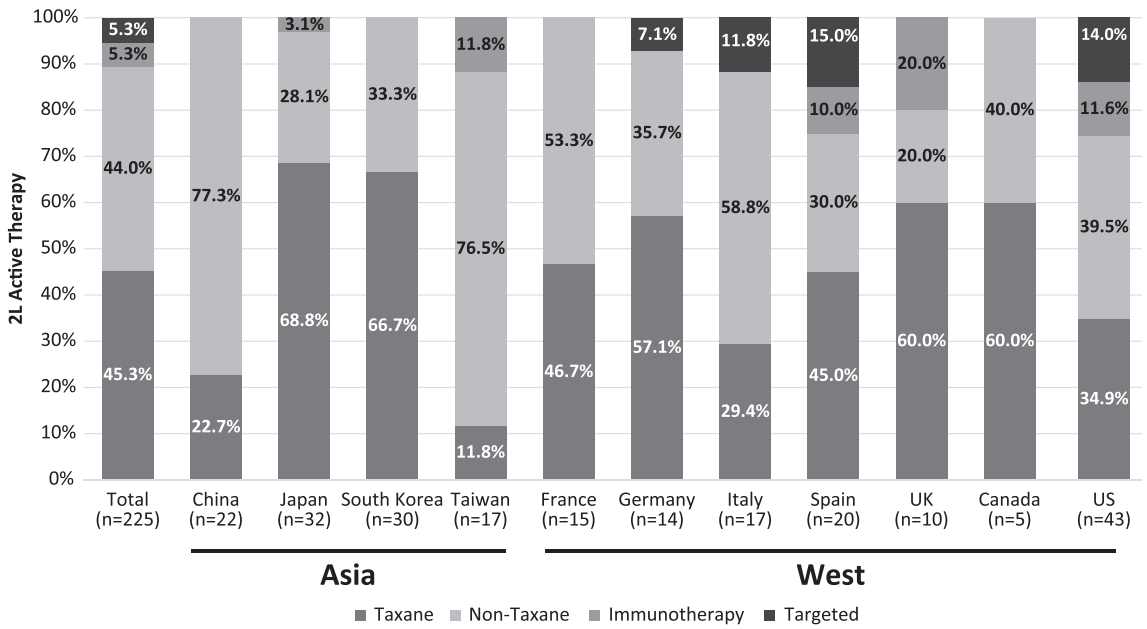

FIGURE 3 2L treatments for patients with ESCC. Abbreviations: 2L, second-line; BSC, best supportive care; ESCC, esophageal squamous cell carcinoma. Note: Active therapy for Asia: taxane = 48.5%, nontaxane = 48.5%, immunotherapy = 3.0%, and targeted therapy = 0.0% and for the West: taxane = 42.7%, nontaxane = 40.3%, immunotherapy = 7.3%, and targeted therapy = 9.7%

2L active systemic treatment in Asian and western countries. Specifically, most patients who received a taxane at 2L received a CT doublet at 1L. For both regions, those who received non-taxane treatments at 2L had varying 1L CT active systemic therapy (singlet, doublet, and triplet).

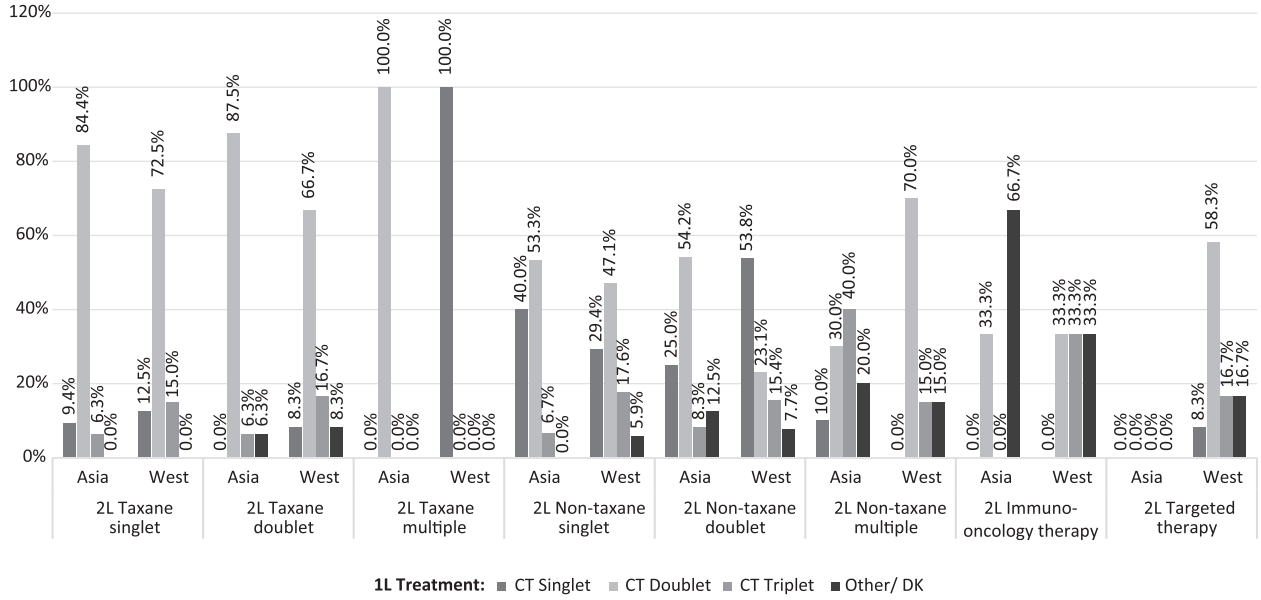

FIGURE 4 1L treatment of patients with ESCC receiving 2L according to geography. Abbreviations: 1L, first-line; 2L, second-line; CT, chemotherapy; ESCC, esophageal squamous cell carcinoma

The similarities and differences in the natural course of the disease between 2L active systemic therapy treated patients in Asian ($N = 101$) and western patients ($N = 124$) were further examined (Table 3). Asian patients were less likely to be diagnosed as metastatic (47.5% vs. 64.5%; $p = 0.010$) and more likely to receive surgery in the curative setting (25.7% vs. 14.6%; $p = 0.037$). Time to initiation of radiotherapy was longer for Asian than western patients (mean months: 8.3 vs. 2.8; $p = 0.039$), although radiotherapy did not appear to be used at a high level in either region (overall 5.3%; Asia = 4.0% vs. West = 6.5%; $p = 0.554$). The vast majority of patients had PS ECOG 0–1 at diagnosis with no differences by region (Asia = 80.2% vs. West = 80.5; $p = 0.957$). Most patients were diagnosed with advanced disease (stage III/IV) (Asia = 81.7% vs. West = 81.9%). However, there were less stage 4 in Asia than in the West (52.7% vs. 63.8%) (Table 3).

At initiation of active systemic 1L therapy, 54.7% of patients presented with de novo metastatic tumors and 18.7% with recurrent tumors, 75.6% had PS ECOG 0–1, and had a mean time from diagnosis of 4.3 ± 9.8 months. Patients from Asia were more likely to have recurrent tumors (29.7% vs. 9.7%; overall $p = 0.001$) and fewer PS ECOG 0–1 (68.3% vs. 81.5%; $p = 0.023$); staging and time from diagnosis to 1L were similar across regions.

At initiation of active systemic 2L therapy, 42.2% of patients had de novo metastatic tumors and 42.7% had recurrent tumors (Table 3). Over half the patients had a PS of ECOG 0–1 (57.3%). No difference in time from initial diagnosis to initiation of second-line treatment was observed by region (mean months: 11.6 vs. 11.2 months; $p = 0.091$).

2L active systemic therapy-related adverse events

The most commonly reported grade 3 or grade 4 adverse events related to 2L active systemic therapy were alopecia (10.7%), neutropenia (9.3%) and fatigue (9.3%) (Table 4). A significantly higher percentage of patients in Asian compared to Western countries had treatment-related adverse events of neutropenia, nausea, diarrhea, anorexia, vomiting, adrenal insufficiency, rash and hand-foot syndrome (all $p < 0.05$).

2L active systemic therapy outcomes

Less than one-sixth of patients had AE-related ER visits (14.7%) or AE-related hospitalizations (13.3%) (Table 6). AE-related ER visits were significantly higher in Asian than in Western countries (22.5% vs. 8.0%; $p < 0.001$), while no regional differences were observed for AE-related hospitalizations (22.5% vs. 5.3%; $p = 0.118$). Further, the number of days of hospitalization during 2L treatment was significantly higher in patients in Asian than in Western countries (25.9 ± 31.2 vs. 4.7 ± 7.0, $p < 0.001$), while no regional differences were observed for ER visits (1.5 ± 5.6 vs. 0.8 ± 1.7; $p = 0.279$).

Based on physician-reported RECIST v1.1., approximately 32.0% of patients receiving 2L active systemic treatment showed disease progression and 31.5% showed complete/partial response (Table 5). Response to treatment was similar between Asian and Western countries ($p = 0.663$), with comparable frequencies observed for complete or partial response (33.7% vs. 29.8%), disease stability (19.8% vs. 21.8%), progression (28.7% vs. 34.7%), and death (17.8% vs. 13.7%).

TABLE 3 Diagnostic and treatment characteristics among patients with ESCC who received 2L active systemic therapy according to geography

Variables		Overall N (% or M ± SD)	Asia N (% or M ± SD)	West N (% or M ± SD)	*p*-value[a]
	Total actively treated patients	225 (58.1)	101 (52.6)	124 (63.6)	
At Initial diagnosis	Tumor classification				**0.010**
	Local regional disease	97 (43.1)	53 (52.5)	44 (35.5)	
	Metastatic disease	128 (56.9)	48 (47.5)	80 (64.5)	
	Staging	209	93	116	0.286
	Stage 1 disease	9 (4.3)	4 (4.3)	5 (4.3)	
	Stage 2 disease	29 (13.9)	13 (14.0)	16 (13.8)	
	Stage 3 disease	48 (23.0)	27 (29.0)	21 (18.1)	
	Stage 4 disease	123 (58.9)	49 (52.7)	74 (63.8)	
	PS ECOG[b]				0.957
	0–1	180 (80.0)	81 (80.2)	99 (79.8)	
	2–4	44 (19.6)	20 (19.8)	24 (19.4)	
	Tumor size (cm)	183 (4.4 ± 1.9)	94 (4.3 ± 1.9)	90 (4.5 ± 1.9)	0.370
	Treatment with surgery[c]	44 (19.6)	26 (25.7)	18 (14.6)	0.0
	Time to surgery, months				
	n	38	25	13	
	Mean ± SD	2.8 ± 3.6	2.4 ± 3.9	3.5 ± 3.0	0.396
	Median	1.5	1.0	3.0	**0.001**
	Neo/adjuvant modality-radiation or radiotherapy	12 (5.3)	4 (4.0)	8 (6.5)	0.554
	Timing of initiating radiation or radiotherapy since diagnosis, months)				
	n	9	4	5	
	Mean ± SD	5.2 ± 4.1	8.3 ± 3.4	2.8 ± 3.0	**0.039**
	Median	5.0	7.5	1.0	**0.001**
	Time to recurrence (months)	43 (8.3 ± 11.4)	26 (7.0 ± 11.7)	17 (10.2 ± 11.0)	0.377
At Initiation of 1 L of Treatment	Tumor classification				**0.001**
	De novo metastatic	123 (54.7)	43 (42.6)	80 (64.5)	
	Recurrent	42 (18.7)	30 (29.7)	12 (9.7)	
	Local/regional, but patient is not amenable to curative therapy	53 (23.6)	25 (24.8)	28 (22.6)	
	Do not know	7 (3.1)	3 (3.0)	4 (3.2)	
	Staging[d]	207	96	111	0.905
	Stage 1 disease	5 (2.4)	3 (3.1)	2 (1.8)	
	Stage 2 disease	17 (8.2)	8 (8.3)	9 (8.1)	
	Stage 3 disease	41 (19.8)	20 (20.8)	21 (18.9)	
	Stage 4 disease	144 (69.6)	65 (67.7)	79 (71.2)	
	PS ECOG[b]				**0.023**
	0–1	170 (75.6)	69 (68.3)	101 (81.5)	
	2–4	55 (24.4)	32 (31.4)	23 (18.5)	
	Time from diagnosis to 1L (months)				
	Mean ± SD	4.3 ± 9.8	5.3 ± 12.9	3.5 ± 6.4	0.169
	Median	1.0	1.0	1.0	0.157
At Initiation of 2 L of Treatment	Tumor classification				0.349
	De novo metastatic	95 (42.2)	39 (38.6)	56 (45.2)	
	Recurrent	96 (42.7)	42 (41.6)	54 (43.5)	
		29 (12.9)	17 (16.8)	12 (9.7)	

(Continues)

TABLE 3 (Continued)

Variables	Overall N (% or M ± SD)	Asia N (% or M ± SD)	West N (% or M ± SD)	*p*-value[a]
Local/regional, but patient is not amenable to curative therapy				
Do not know	5 (2.2)	3 (3.0)	2 (1.6)	
Staging[d]	213	96	117	0.287
Stage 1 disease	0 (0.0)	0 (0.0)	0 (0.0)	
Stage 2 disease	7 (3.3)	4 (4.2)	3 (2.6)	
Stage 3 disease	22 (10.3)	13 (13.5)	9 (7.7)	
Stage 4 disease	184 (86.4)	79 (82.3)	105 (89.7)	
PS ECOG[b]				0.061
0–1	129 (57.3)	51 (50.5)	78 (62.9)	
2–4	96 (42.7)	50 (49.5)	46 (37.1)	
Time from diagnosis to 2L (months)				
Mean ± SD	11.4 ± 1	11.6 ± 15.2	11.2 ± 7.8	0.825
Median	1.8 9.0	8.0	9.0	0.091

Abbreviations: 1L, first-line; 2L, second-line; CT, chemotherapy; DK, do not know; ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; PS, performance status.
[a]Median test was performed for time variables.
[b]ECOG score was unknown for $n = 1$.
[c]Surgery was defined as undergoing local excision, esophagectomy, endoscopic mucosal resection, endoscopic submucosal dissection, or ablation.
[d]Staging was based on TNM and tumor classification. Tumor staging was not available for $n = 16$ patients at diagnosis; $n = 18$ patients at 1L; $n = 12$ patients at 2L.

TABLE 4 Adverse events (grades 3 or 4) related to 2L active systemic therapy of patients with ESCC according to geography

AE grade 3 or 4	Overall ($N = 225$) N (%)	Asia ($N = 101$) N (%)	West ($N = 124$) (%)	*p*-value[a]
Alopecia	24 (10.7)	12 (11.9)	12 (9.7)	0.594
Neutropenia	21 (9.3)	15 (14.9)	6 (4.8)	**0.010**
Fatigue	21 (9.3)	11 (10.9)	10 (8.1)	0.468
Nausea	18 (8.0)	15 (14.9)	3 (2.4)	**<0.001**
Diarrhea	17 (7.6)	12 (11.9)	5 (4.0)	**0.027**
Anorexia	17 (7.6)	12 (11.9)	5 (4.0)	**0.027**
Vomiting	13 (5.8)	11 (10.9)	2 (1.6)	**0.003**
Adrenal insufficiency	10 (4.4)	8 (7.9)	2 (1.6)	**0.046**
Febrile neutropenia	9 (4.0)	6 (5.9)	3 (2.4)	0.305
Rash	9 (4.0)	8 (7.9)	1 (0.8)	**0.012**
Anemia	8 (3.6)	6 (5.9)	2 (1.6)	0.144
Thyroiditis	7 (3.1)	5 (5.0)	2 (1.6)	0.248
Hand-foot syndrome	6 (2.7)	6 (5.9)	0 (0.0)	**0.008**
Vitiligo	6 (2.7)	5 (5.0)	1 (0.8)	0.092
Hemorrhage	6 (2.7)	5 (5.0)	1 (0.8)	0.092
Pruritus	5 (2.2)	4 (4.0)	1 (0.8)	0.176
Hypertension	5 (2.2)	4 (4.0)	1 (0.8)	0.176
Neuropathy	3 (1.3)	3 (3.0)	0 (0.0)	0.089
Hypophysitis	3 (1.3)	3 (3.0)	0 (0.0)	0.089
Other	1 (0.4)	0 (0.0)	1 (0.8)	na

Abbreviations: 2L, second-line; AE, adverse event; ESCC, esophageal squamous cell carcinoma; na, not applicable.
[a]Chi-square or Fisher's exact tests were used to assess group differences, in bold, $p < 0.05$.

TABLE 5 Outcomes following 2L active systemic therapy in patients with ESCC

	Overall (*N* = 225)	Asia (*N* = 101)	West (*N* = 124)	
	N (% or M ± SD)	N (% or M ± SD)	N (% or M ± SD)	*p*-value[a]
Any AE (% yes)	211 (93.8)	98 (97.0)	113 (91.1)	0.068
Any AE grade 3 or 4 (% yes)	71 (31.6)	45 (44.6)	26 (21.0)	**<0.001**
AE-related ER visit (% yes)[c]	31 (14.7)	22 (22.5)	9 (8.0)	**<0.001**[b]
AE-related hospitalization (% yes)[c]	28 (13.3)	22 (22.5)	6 (5.3)	0.118[b]
ER visits	145 (1.2 ± 4.4)	81 (1.5 ± 5.6)	44 (0.8 ± 1.7)	0.279
Hospitalizations	157 (17.0 ± 26.3)	91 (25.9 ± 31.2)	66 (4.7 ± 7.0)	**<0.001**
ECOG PS				0.061
0–1	129 (57.3)	51 (50.5)	78 (62.9)	
2–4	96 (42.7)	50 (49.5)	46 (37.1)	
Response[d]				0.663
Complete or partial response	71 (31.5)	34 (33.7)	37 (29.8)	
Stable disease	47 (20.9)	20 (19.8)	27 (21.8)	
Disease progression	72 (32.0)	29 (28.7)	43 (34.7)	
Death	35 (15.6)	18 (17.8)	17 (13.7)	
2L outcome				0.933
Died before receiving 3L	73 (32.4)	32 (31.7)	41 (33.1)	
Alive but did not receive 3L	124 (55.1)	57 (56.4)	67 (54.0)	
Received 3L	28 (12.4)	12 (11.9)	16 (12.9)	

Abbreviations: 1L, first-line; 2L, second-line; 3L, third line; CT, chemotherapy; DK, do not know; ECOG, Eastern Cooperative Oncology Group; ER, emergency room; ESCC, esophageal squamous cell carcinoma; PS, performance status.

[a]Chi-square or Fisher's exact tests were used to assess group differences, in bold, $p < 0.05$.

[b]Number out of the total with an AE $n = 211$.

[c]Median test.

[d]Response was based on physician-reported RECIST v1.1.

A majority of the patients survived following 2L active systemic therapy but did not progress to 3L treatment (55.1%), including 32.4% of the patients who died before receiving 3L treatment (Table 5). The outcomes following 2L active systemic therapy were similar between Asian compared to Western countries ($p = 0.933$), with regard to the proportion of patients who received 3L (11.9% vs. 12.9%), were alive but did not progress to 3L treatment (56.4% vs. 54.0%), and died before receiving 3L (31.7% vs. 33.1%).

DISCUSSION

The current study examined regional similarities and differences in 387 advESCC patients treated systemically or with BSC at 2L in Asian and Western countries. Regional differences were noted for patient characteristics, tumor characteristics, treatment patterns, and AEs-related to active systemic care; however, outcomes including PS, response, and prognosis following this treatment were similar.

The patient cohort identified, while differed somewhat by region, was comparable to the sociodemographic and clinical profile of 2L ESCC patients previously reported using different study design settings.[17,32–35] We note that previous research analyzing treatment outcomes in ESCC patients were predominantly from Asian populations[32,35,36] unlike the current findings, where almost equal number of patients were included from both Asian and Western regions. This study found that smoking and alcohol consumption differed significantly between regions, although were high and are consistent with the these factors increasing the risk of ESCC in a dose-dependent manner.[37] In past studies, most patients presented with better performance status (ECOG 0 or 1) at different stages of disease[20,32,35,38]; likewise, we also found that PS ECOG 0 or 1 was well-represented in our study, with no significant difference between regions at initial diagnosis or at initiation of 2L treatment. Previous RCTs have reported 21%–58% of patients undergoing surgery[35,36,39] whereas in the present analysis, overall, 23.5% of ESCC patients underwent surgery, although patients receiving BSC at 2L were more likely to have undergone surgery than those on systemic therapy. This latter finding might be attributable to the older population of patients more prevalent in our analysis compared to other studies.[17,36,38]

Treatment of 2L patients varied by country and geography with docetaxel and other taxanes used most often and aligning with evidence of the effectiveness of these treatments.[20,34,36] The recent GENERATE study, a retrospective

TABLE 6 Review of current real-world evidence of 2L active systemic therapy in patients with ESCC

Study	Country	Treatment regimen	Number of patients	Findings
Asia				
Mizota et al. 2011[23]	Japan	Docetaxel and Paclitaxel	124 EC patients (86 docetaxel and 38 paclitaxel) — ~95% ESCC patients	mOS: 6.1 (docetaxel) — 7.2 (paclitaxel) months
Chen et al. 2013[24]	China	Docetaxel, paclitaxel, or methotrexate	113 ESCC patients (13 docetaxel, 76 paclitaxel, and 24 methotrexate)	mOS: 8.5 months.11.5 (docetaxel) — 8.9 (paclitaxel) — 5.6 (methotrexate) months
Moriwaki et al. 2014[25]	Japan	Docetaxel and best supportive care (BSC)	Docetaxel: 66 EC patients (63 ESCC) BSC: 45 EC patients (44 ESCC)	mPPS: 5.4 (docetaxel) — 3.3 (BSC) months
Sakamoto 2014[26]	Japan	Paclitaxel	13 ESCC patients	mOS: 7.3 months
Shirakawa et al. 2014[27]	Japan	Docetaxel and Paclitaxel	163 ESCC patients (132 docetaxel and 31 paclitaxel)	mOS: 5.5 (docetaxel) — 6.1 (paclitaxel) months
Song et al. 2014[28]	China	Docetaxel	85 ESCC patients	mPFS: 3.5 months mOS: 5.5 months
Tsushima 2015[29]	Japan	Docetaxel/ Paclitaxel	24 ESCC patients	mOS: 6.4 months
Nakatsumi et al. 2016[30]	Japan	Docetaxel and Paclitaxel	39 EC patients (25 docetaxel and 14 paclitaxel)— ~ 89% ESCC patients	mOS: 5.29 (docetaxel) — 8.61 (paclitaxel) months
Yao et al. 2021[31]	China	Camrelizumab monotherapy (200 mg), Camrelizumab/ chemoradiotherapy, Camrelizumab/chemotherapy, and Camrelizumab/ chemotherapy/antiangiogenic therapy	63 ESCC patients (8 camrelizumab monotherapy, 22 camrelizumab/ chemoradiotherapy combination therapy, 26 camrelizumab/ chemotherapy combination therapy, and 7 camrelizumab/ chemotherapy/antiangiogenic therapy combination therapy)	mPFS: 6.33 months
West				
Abraham et al. 2020[20]	US	Taxane therapy and nontaxane therapy	86 ESCC patients (37 taxane therapy and 49 nontaxane therapy)	mOS: 6.7 months 7.3 (taxane therapy) — 5.1 (nontaxane therapy) months

Abbreviations: BSC, best supportive care; EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; mOS, median overall survival; mPFS, median progression-free survival; mPPS, median post-progression survival; SEER, surveillance, epidemiology, and end results; PPS, post-progression survival.

chart survey in Australia, Canada, Italy and UK, reported that monotherapy and combination therapies were both equally used to treat at 2L for patients with ESCC, with variations between and within therapy groupings by country (e.g., monotherapy use 45% in Italy and 63% in UK).[17,33,36,38,39] In contrast to the present findings that most 2L patients received doublet chemotherapy at 1L, in the GENERATE study, while most patients received combination therapy, triplet therapy was predominant.[17] Use of immune-oncology and other targeted therapies (i.e., ramucirumab + paclitaxel) were low in this study, although treatment was more prevalent in Western countries. Several RCTs have reported promising efficacy outcomes in ESCC with PD-1 and PD-1L-targeted immune-oncology drugs, mainly nivolumab and pembrolizumab in 2L and subsequent treatment lines.[40–43] Of note, ramucirumab is available as monotherapy or in combination with chemotherapy in the 2L setting in unresectable locally advanced or metastatic EAC.[44] Nonetheless, the survival rates still remain low and there is a continuous demand for further targeted therapies[45] and immunotherapy.[44]

In the current study, any Grade 3 or 4 AEs following 2L active systemic therapy were more than 2-fold higher among patients from Asian compared with Western countries. Specifically, neutropenia, nausea, diarrhea, anorexia, vomiting, adrenal insufficiency, and rash and hand-foot syndrome were significantly higher in the former. Resource use related to 2L treatment and specific to AEs were also higher among Asians compared with Western countries. Thus, while ESCC patients often visit hospitals for chemotherapy infusion as well as management of cancer-related symptoms,[46,47] differential utilization might be attributed in part to the preferred use of neoadjuvant or definitive chemoradiotherapy in Western countries.[48]Practical implications of higher HCRU among these patients complement the findings from other real-world studies further highlighting the burden of this disease on the patient and healthcare system.[17,46,47,49,50]

The similarity in patient outcomes for 2L therapy across regions demonstrated in this study align with results from other real-world studies and clinical trials of fairly similar outcomes, such as overall survival of patients with advESCC regardless of geographic location (Table 6).[20,48] In a

randomized phase III KEYNOTE-181 trial, pembrolizumab showed significant improvement in OS compared with chemotherapy in ESCC patients with PD-L1 CPS ≥ 10 patients (median OS 9.3 vs. 6.7 months).[51] Similarly, in the ATTRACTION-3 trial, nivolumab demonstrated significant benefit in the OS compared with chemotherapy (median OS 10.9 vs. 8.4 months) in the treatment of advESCC.[43] Another PD-L1 inhibitor, camrelizumab significantly improved OS compared with chemotherapy (median OS 8.3 vs. 6.2 months) in patients with advESCC in China.[52] The results of the aforementioned studies supported the use of PD-L1 inhibitors as a second-line treatment option for patients with advESCC in Asia, Europe and US.[43,51]

There are several strengths associated with our analysis, first and foremost being the extensive assessment of treatment patterns across varying population groups, healthcare systems, and geographies. The study design was uniform which made analysis comparable across countries aiding better understanding of the healthcare outcomes related to ESCC treatment. A holistic and longitudinal picture of treatment and HRCU during 2L therapy was possible since we have included a large sample of treating physicians per country each with two to three patients which expected to provide variability across each population and healthcare system. The study limitations are primarily related to the study design. The study is a retrospective chart review, which may be associated with systematic bias or under-recording or omission of some data on the clinical charts at random. As such, physician inclusion criteria were designed to minimize the potential for patient records with missing data. The assessment was based exclusively on the estimation by the treating physician which may have been influenced by local practice standards. Furthermore, there might be a selection bias as the study data were collected from physician panels of mainly larger oncology practices may limit generalizability of the outcomes in fairly smaller clinical practices existing within each country. Finally, physicians were asked to identify patients with a minimum of approximately 6 months of follow-up; this may have minimized recall bias. However, we note that the follow-up time may have been insufficient for patients to progress or die and limited our ability to calculate overall survival.

In conclusion, currently, there is no international consensus to improve outcomes in 2L ESCC patients given the high rate of adverse event-related healthcare resource utilization, disease progression, and mortality. This real-world study provides insights on patient characteristics, treatment patterns, HCRU and clinical outcomes in 2L ESCC patients across prominent geographies of Asian and Western countries. Taxanes either as monotherapy or in combination represent the most commonly used chemotherapy, although targeted and immunotherapies are less prescribed across Asia and the West. Differences in patient characteristics and treatment throughout the patient journey differed between regions; however, the patient profile at 2L and response to treatment and outcomes following 2L active systemic therapy were similar. Further studies with large sample size and recent data are needed to further examine the determinants of 2L therapy in ESCC.

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CONFLICT OF INTEREST

JG is an employee of Bristol-Myers Squibb. DHJ, MD, and MDS are employed at Cerner Enviza, which was paid by Bristol-Myers Squibb to conduct the study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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