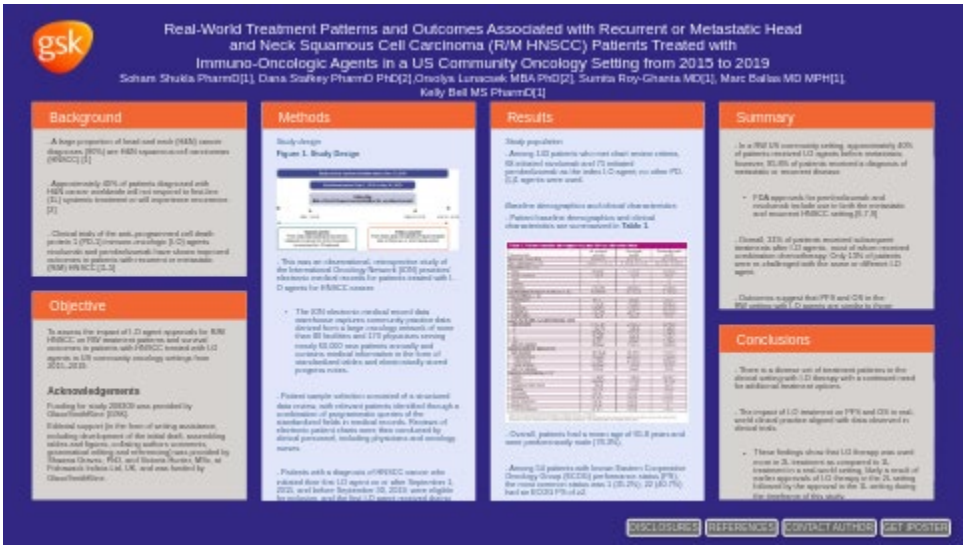
Real-World Treatment Patterns and Outcomes Associated with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) Patients Treated with Immuno-Oncologic Agents in a US Community Oncology Setting from 2015 to 2019



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BACKGROUND

- A large proportion of head and neck (H&N) cancer diagnoses (90%) are H&N squamous cell carcinomas (HNSCC).[1]

- Approximately 40% of patients diagnosed with H&N cancer worldwide will not respond to first-line (1L) systemic treatment or will experience recurrence.[2]

- Clinical trials of the anti–programmed cell death protein 1 (PD-1) immuno-oncologic (I-O) agents nivolumab and pembrolizumab have shown improved outcomes in patients with recurrent or metastatic (R/M) HNSCC.[3–5]

  - Pembrolizumab and nivolumab were approved by the US Food and Drug Administration (FDA) in August 2016 and November 2016, respectively for the treatment of R/M HNSCC with disease progression on or

after platinum-containing chemotherapy;[6,7] the pembrolizumab approval was conditional on established superiority of pembrolizumab over standard of care (SOC; KEYNOTE-040).[8]

- In June 2019, pembrolizumab was also approved by the FDA for 1L treatment of patients with R/M HNSCC as either monotherapy in patients with tumors that express programmed death-ligand 1 (PD-L1; combined positive score [CPS] ≥1) or as combination therapy with platinum and fluorouracil in all-comers.[9]

- Despite the improved overall survival (OS) outcomes achieved with checkpoint inhibitors in R/M HNSCC, approximately 75–85% of patients show little or no durable response.[1,4,5]

- Information on real-world (RW) clinical practice regarding I-O agents in R/M HNSCC cancer is limited, and questions remain unanswered around predictors of response and RW outcomes, optimal duration of treatments, and the potential for re-challenge with I-O agents after disease progression.[1,4,5,10–14]

OBJECTIVE

To assess the impact of I-O agent approvals for R/M HNSCC on RW treatment patterns and survival outcomes in patients with HNSCC treated with I-O agents in US community oncology settings from 2015–2019.

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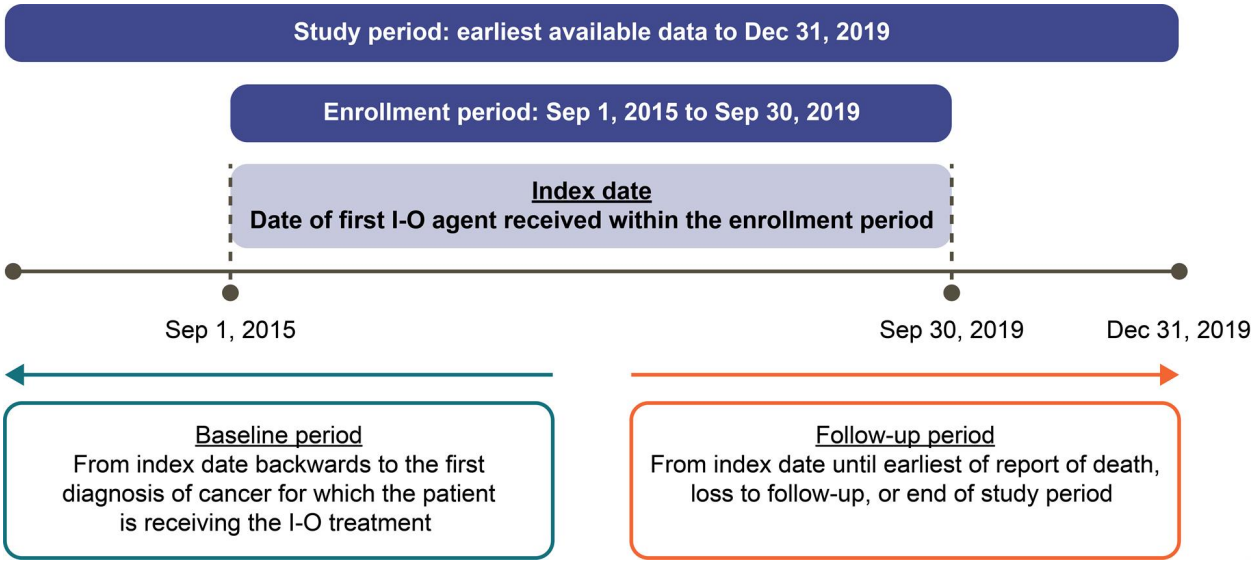
METHODS

Study design

Figure 1. Study Design



- This was an observational, retrospective study of the International Oncology Network (ION) practices' electronic medical records for patients treated with I-O agents for HNSCC cancer.

- The ION electronic medical record data warehouse captures community practice data derived from a large oncology network of more than 80 facilities and 170 physicians serving nearly 60,000 new patients annually and contains medical information in the form of standardized tables and electronically stored progress notes.

- Patient sample selection consisted of a structured data review, with relevant patients identified through a combination of programmatic queries of the standardized fields in medical records. Reviews of electronic patient charts were then conducted by clinical personnel, including physicians and oncology nurses.

- Patients with a diagnosis of HNSCC cancer who initiated their first I-O agent on or after September 1, 2015, and before September 30, 2019, were eligible for inclusion, and the first I-O agent received during the enrollment period was defined as the index I-O (**Figure 1**).

- The follow-up period for each patient included the time from index date until death, date of hospice, loss to follow-up, participation in a clinical trial, or study end date (December 31, 2019), whichever occurred first (**Figure 1**).

- Patient demographics and clinical characteristics, I-O treatment characteristics, and subsequent treatments were assessed descriptively. Real-world progression-free survival (rwPFS) and real-world overall survival (rwOS) were evaluated by line of therapy via Kaplan–Meier analyses.

Eligibility criteria

- Received an I-O agent on or after September 1, 2015 and before September 30, 2019
- Had a primary diagnosis of R/M HNSCC cancer
- No evidence of primary cancer other than R/M HNSCC during the enrollment period
- Aged ≥18 years at index I-O agent initiation
- Did not participate in a clinical trial during the baseline period or while receiving index I-O agent
- Had ≥30 days of follow-up after index I-O agent initiation
- Physician notes were available and complete

RESULTS

Study population

- Among 143 patients who met chart review criteria, 68 initiated nivolumab and 75 initiated pembrolizumab as the index I-O agent; no other PD-(L)1 agents were used.

Baseline demographics and clinical characteristics

- Patient baseline demographics and clinical characteristics are summarized in **Table 1**.

Table 1. Patient baseline demographics and clinical characteristics

Characteristic	All patients (n=143)	Nivolumab (n=68)	Pembrolizumab (n=75)
Mean age, years (SD)	65.8 (10.0)	65.2 (9.4)	66.3 (10.6)
Sex, male/female, n (%)	112 (78.3) / 31 (21.7)	57 (83.8) / 11 (16.2)	55 (73.3) / 20 (26.7)
Race/ethnicity, n (%)			
White	86 (95.6)	41 (97.6)	45 (93.8)
African American	4 (4.4)	1 (2.4)	3 (6.3)
Asian	0	0	0
Hispanic	0	0	0
Unknown	53 (37.1)	26 (38.2)	27 (36.0)
Southeastern US region of practice, n (%)	143 (100.0)	68 (100.0)	75 (100.0)
Type of HNSCC, n (%)			
Hypopharynx	11 (7.7)	6 (8.8)	5 (6.7)
Larynx	34 (23.8)	15 (22.1)	19 (25.3)
Oral cavity	42 (29.4)	17 (25.0)	25 (33.3)
Oropharynx	53 (37.1)	28 (41.2)	25 (33.3)
Multiple sites	3 (2.1)	2 (2.9)	1 (1.3)
ECOG PS at index I-O agent initiation, n (%)			
Data available	54 (37.8)	24 (35.3)	30 (40.0)
0	13 (24.1)	7 (29.2)	6 (20.0)
1	19 (35.2)	10 (41.7)	9 (30.0)
2	16 (29.6)	5 (20.8)	11 (36.7)
≥3	6 (11.1)	2 (8.3)	4 (13.3)
Data not available	89 (62.2)	44 (64.7)	45 (60.0)
Baseline smoking status, n (%)			
Data available	137 (95.8)	66 (97.1)	71 (94.7)
Current smoker	45 (32.8)	28 (42.4)	17 (23.9)
Past smoker	67 (48.9)	27 (40.9)	40 (56.3)
Never smoked	25 (18.2)	11 (16.7)	14 (19.7)
Data not available	6 (4.2)	2 (2.9)	4 (5.3)
Baseline comorbidities, n (%)[a]			
Anemia	37 (25.9)	17 (25.0)	20 (26.7)
COPD	26 (18.2)	13 (19.1)	13 (17.3)
Congestive heart failure	3 (2.1)	1 (1.5)	2 (2.7)
Diabetes	10 (7.0)	6 (8.8)	4 (5.3)
Neuropathy	6 (4.2)	5 (7.4)	1 (1.3)
Neutropenia	14 (9.8)	5 (7.4)	9 (12.0)
Renal impairment	6 (4.2)	2 (2.9)	4 (5.3)
Stroke or TIA	2 (1.4)	2 (2.9)	0
Thrombocytopenia	12 (8.4)	5 (7.4)	7 (9.3)

[a]Measured in the study period between first diagnosis of H&N cancer and start of I-O therapy.
COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; H&N, head and neck; HNSCC, head and neck squamous cell carcinoma; I-O, immuno-oncologic; PD-1/L1, programmed cell death protein/ligand 1; SD, standard deviation; TIA, transient ischemic attack

- Overall, patients had a mean age of 65.8 years and were predominantly male (78.3%).

- Among 54 patients with known Eastern Cooperative Oncology Group (ECOG) performance status (PS), the most common status was 1 (35.2%); 22 (40.7%) had an ECOG PS of ≥2.

- PD-L1 status was known for only five patients (3.5%). One patient was tested for PD-L1 status after the June 2019 FDA approval of pembrolizumab in 1L for R/M HNSCC with a CPS ≥1.[9]

- Among 88 patients (61.5%) with a known human papillomavirus (HPV) status, 37 (42.0%) were positive.

  - Of the 53 patients with cancer of the oropharynx, 20 (37.7%) were HPV positive.

Index I-O treatment characteristics

- Index I-O treatment characteristics are summarized in **Table 2**.

Table 2. Index I-O treatment characteristics

	All patients (n=143)	Nivolumab (n=68)	Pembrolizumab (n=75)
Monotherapy/combination therapy, n (%)	138 (96.5) / 5 (3.5)	68 (100.0) / 0	70 (93.3) / 5 (6.7)
Metastatic/recurrent disease diagnosis, n (%)	137 (95.8)	63 (92.6)	74 (98.7)
Line of therapy index I-O agent was received, n (%)			
Non-metastatic[a]	57 (39.9)	29 (42.6)	28 (37.3)
Metastatic	86 (60.1)	39 (57.4)	47 (62.7)
1L metastatic	50 (58.1)	23 (59.0)	27 (57.5)
2L metastatic	30 (34.9)	14 (35.9)	16 (34.0)
3L+ metastatic	6 (7.0)	2 (5.1)	4 (8.5)
Mean time from metastatic/recurrent diagnosis to index I-O agent initiation, months (SD)[b]	9.8 (19.2)	9.6 (18.4)	9.9 (19.9)
Mean duration of index I-O treatment, months (SD)	6.7 (7.9)	6.6 (8.1)	6.8 (7.8)
Mean duration of index I-O treatment among completers[c] (n=114[d]), months (SD)	5.3 (6.2)	5.7 (6.9)	5.0 (5.4)

[a]Patients who received index I-O agent before metastasis; [b]Patients who received index I-O agent before metastasis/recurrence (n=6) are not included in this calculation; [c]Patients who discontinued I-O therapy for some reason and were not lost to follow-up while receiving I-O therapy; [d]Nivolumab n=58 and pembrolizumab n=56.
1L, first-line; 2L second-line; 3L+, third or later line (up to 6 lines); I-O, immuno-oncologic; SD, standard deviation.

- The mean time from I-O treatment initiation to end of follow-up was 10.4 months (standard deviation [SD], 10.0) for all patients, 11.2 months (SD, 11.0) for patients who received nivolumab, and 9.8 months (SD, 8.9) for patients who received pembrolizumab.

- Index I-O treatment increased until 2017 and remained stable thereafter; 83.2% of patients received index I-O treatment from 2017 to 2019.

- Index I-O treatment was initiated prior to a metastatic diagnosis in 39.9% of patients overall, and in 42.6% of patients receiving nivolumab and 37.3% of those receiving pembrolizumab. Most patients (95.8%) had a diagnosis of metastatic or recurrent disease.

- In the metastatic setting (n=86), index I-O treatment was most frequently initiated as 1L therapy (58.1%), with 34.9% and 7.0% of patients receiving it as second-line (2L) or third-line or later (3L+) therapy, respectively.

- Nivolumab and pembrolizumab were both initiated most frequently as 1L therapy in the metastatic setting (59.0% and 57.5%, respectively).

- The mean time from metastatic/recurrent diagnosis to initiation of index I-O treatment was 9.8 months (SD, 59.0) and was similar for both agents.

- The most common reasons for discontinuation of index I-O treatment were disease progression (36.4%), end of progress notes (20.3%), death (11.2%), moved to hospice (8.4%), and agent toxicity/intolerability (5.6%).

Subsequent treatments and time-to-next treatment

- Subsequent treatment patterns, including re-challenge with the same or different I-O-agent, and time-to-next treatment (TTNT) data are summarized in **Table 3**.

Table 3. Subsequent treatments[a] received after index I-O agent discontinuation and TTNT

	All patients (n=143)	Nivolumab (n=68)	Pembrolizumab (n=75)
Patients with subsequent treatment, n (%)	45 (31.5)	22 (32.4)	23 (30.7)
Mean TTNT, days (SD)[b]	46.5 (60.6)	52.2 (74.3)	41.0 (44.9)
Subsequent regimen among those with subsequent treatment, n (%)	**(n=45)**	**(n=22)**	**(n=23)**
Investigational drug	3 (6.7)	1 (4.5)	2 (8.7)
Single-agent chemotherapy/other targeted therapy[c]	11 (24.4)	5 (22.7)	6 (26.1)
Combination chemotherapy[d]	17 (37.8)	9 (40.9)	8 (34.8)
Nivolumab	5 (11.1)	5 (22.7)	0
Pembrolizumab	8 (17.8)	2 (9.1)	6 (26.1)
Pembrolizumab with chemotherapy	1 (2.2)	0	1 (4.3)
Patients who were re-challenged with the same or different I-O agent, n (%)[e]	18 (12.6)	9 (13.2)	9 (12.0)

[a]Subsequent treatments were captured as the next treatment initiated after discontinuation of index I-O; [b]TTNT was the time interval between discontinuation of the index I-O treatment and first date of administration of the next line of therapy; [c]Single-agent chemotherapies were carboplatin, docetaxel, paclitaxel, and targeted therapy was cetuximab; [d]Combination chemotherapy regimens were carboplatin + cetuximab, carboplatin + cetuximab + fluorouracil, carboplatin + docetaxel, carboplatin + paclitaxel, cetuximab + cisplatin, cisplatin + fluorouracil, cisplatin + paclitaxel, gemcitabine + methotrexate; [e]Patients were considered to have been re-challenged if they progressed on their index I-O agent and received the same or different I-O agent in any later line.
I-O, immuno-oncologic; SD, standard deviation; TTNT, time-to-next treatment.

- In total, 45 patients (31.5%) received subsequent treatments, most commonly chemotherapy or other targeted therapy (cetuximab), either as a monotherapy or in combination with other chemotherapies (n=28; 62.2%).

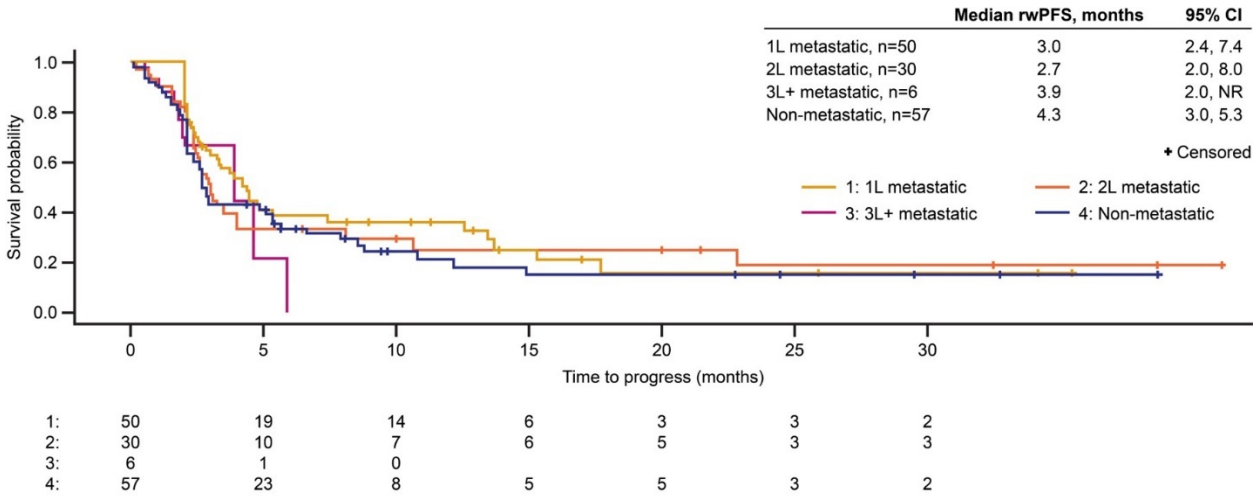
- Only 12.6% of patients were re-challenged with the same or a different I-O agent during follow-up.

Progression-free survival and overall survival

- The median rwPFS was 3.4 months (95% confidence interval [CI]: 2.8, 4.4) overall; rwPFS by line of therapy is presented in **Figure 2**.

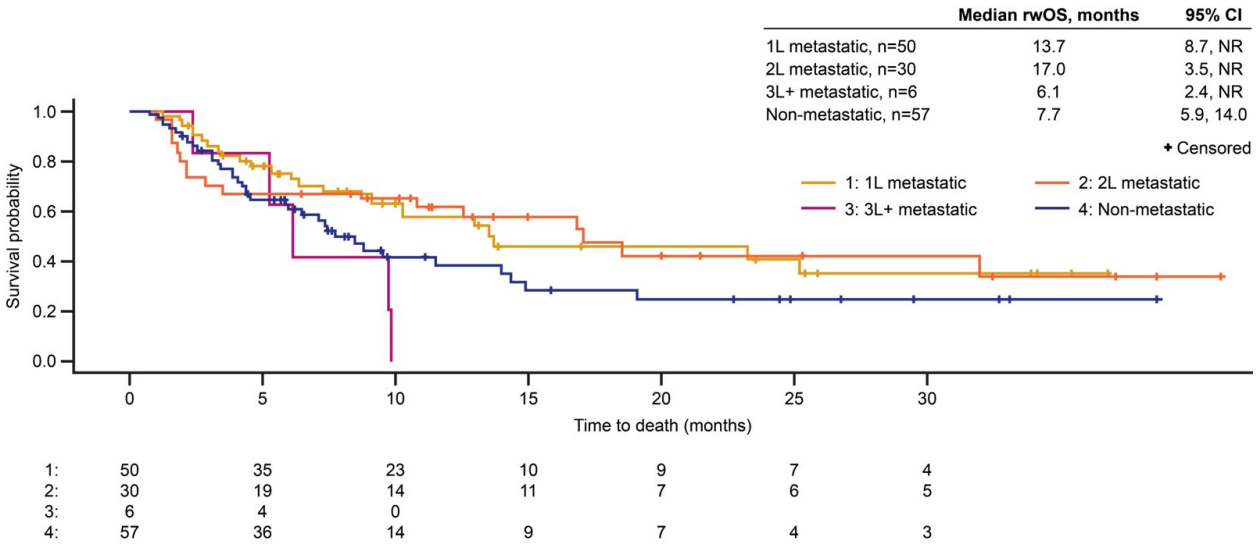
- The median rwOS was 11.5 months (95% CI: 8.5, 14.8) overall. Median rwOS was longest for patients receiving index I-O agent as 2L metastatic therapy (17.0 months), followed by those receiving 1L metastatic therapy (13.7 months, **Figure 3**).

Figure 2. rwPFS[a] by line of therapy



[a]Progression defined as first progression of disease, admission into hospice, or death, whichever comes first after initiation of I-O.
1L, first-line, 2L, second-line, 3L, third or later line (up to 6 lines); CI, confidence interval; I-O, immuno-oncologic; NR, not reached; rwPFS, real-world progression-free survival.

Figure 3. rwOS[a] by line of therapy



[a]rwOS defined as no admission to hospice or death, after index I-O.
1L, first-line, 2L, second-line, 3L, third or later line (up to 6 lines); CI, confidence interval; I-O, immuno-oncologic; rwOS, real-world overall survival.

SUMMARY

- In a RW US community setting, approximately 40% of patients received I-O agents before metastasis; however, 95.8% of patients received a diagnosis of metastatic or recurrent disease.

  - FDA approvals for pembrolizumab and nivolumab include use in both the metastatic and recurrent HNSCC setting.[6,7,9]

- Overall, 31% of patients received subsequent treatments after I-O agents, most of whom received combination chemotherapy. Only 13% of patients were re-challenged with the same or different I-O agent.

- Outcomes suggest that PFS and OS in the RW setting with I-O agents are similar to those observed in clinical trials,[3,5,8] despite a slightly older (mean age of 66 years) population with generally poorer performance status, with 41% having an ECOG PS of ≥2 (patients with ECOG PS of ≥2 were excluded from the clinical trials).[3–5]

  - The median rwOS was 11.5 months. In the KEYNOTE-048 trial, median OS was 11.6 and 13.0 months, respectively, for pembrolizumab alone and pembrolizumab in combination with a platinum-based chemotherapy in the 1L setting.[3] The median OS was 8.4 months with pembrolizumab monotherapy in the 2L+ setting in the KEYNOTE-040 trial.[8] Nivolumab alone demonstrated a median OS of 7.5 months in the 2L+ setting in the Checkmate-141 trial.[5]

  - The median rwPFS was 3.4 months. In the KEYNOTE-048 trial, the median PFS was 2.3 months with pembrolizumab alone in the 1L setting and 4.9 months with pembrolizumab in combination with a platinum-based chemotherapy.[3] The median PFS was 2.1 months with pembrolizumab monotherapy in the 2L+ setting in the KEYNOTE-040 trial.[8] Nivolumab alone demonstrated a median PFS of 2.0 months in the 2L+ setting in the Checkmate-141 trial.[5]

  - The majority of patients (96.5%) in this study received index I-O agent as monotherapy, which may account for differences in the reported median rwPFS and rwOS.

- Patient characteristics, including disease-related features and underlying pathological factors, may play a role in predicting which patients are most likely to benefit from immunotherapy, including HPV status.[15,16]

  - This analysis included patients heterogenous for HPV status. PD-L1 status was rarely tested as the timeframe of this study was prior to routine PD-L1 testing to guide use of anti-PD-(L)1 agents. The influences of these factors on real-world patient outcomes warrant further investigation.

Limitations

- A majority of the study population (95.6%) were white, and all patients resided in the Southeastern region of the US; therefore, results may not be generalizable to all populations.

- Data from the ION warehouse are subject to coding errors of omission and commission.[17,18] Problems with inadequate or inaccurate documentation in the databases may therefore have introduced some level of misclassification bias of certain diagnoses, events, or procedures of interest in the study.

- The reason for treatment selection was not captured during this analysis; thus, factors that led to the use of I-O agents in this study population cannot be discerned.

- The timeframe of the study was relatively long and the emergence of new data, clinical trials, and FDA approvals (e.g., pembrolizumab for 1L treatment in R/M HNSCC) during this time may have led to heterogeneous treatment patterns over time.

CONCLUSIONS

- There is a diverse set of treatment patterns in the clinical setting with I-O therapy with a continued need for additional treatment options.

- The impact of I-O treatment on PFS and OS in real-world clinical practice aligned with data observed in clinical trials.

    - These findings show that I-O therapy was used more in 2L treatment as compared to 1L treatment in a real-world setting, likely a result of earlier approvals of I-O therapy in the 2L setting followed by the approval in the 1L setting during the timeframe of this study.

- Further investigation into the optimal sequencing of treatments in these patients is warranted as newly approved therapies become more established.

- Future studies are needed to further define patient subpopulations most likely to benefit from I-O therapies.

DISCLOSURES

SS is an employee of GlaxoSmithKline (GSK). **DS** and **OL** are employees of Xcenda. **SR-G** is an employee of GSK, holds stock in and has received research funding from GSK, and has received travel/accommodation/expenses from GSK. **MB** is an employee of GSK, has received travel funds and research funding from and held leadership roles at GSK, holds stock in GSK, Bristol-Myers Squibb, and Moderna, has patents/royalties/intellectual property in GSK and AstraZeneca, and has an immediate family member with conflicts of interest of other nature with Abbvie. **KB** is an employee of and holds stock in GSK, and an immediate family member is an employee of Humana and holds stock in CVS.

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