Real World Immuno-oncology Treatment Patterns and Outcomes in US Patients with Metastatic Head and Neck Cancer

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PURPOSE

- Immuno-oncology (I-O) agents have considerably changed the treatment of head and neck squamous cell carcinoma (HNSCC), offering durable antitumor activity and prolonged survival with acceptable safety.[1-3]
  - Programmed cell death protein 1 (PD-1) inhibitors pembrolizumab and nivolumab were approved for recurrent/metastatic (r/m) HNSCC with disease progression on or after platinum-containing chemotherapy by the US Food and Drug Administration (FDA) on August 5, 2016, and November 10, 2016, respectively.[4-7]
    - Median overall survival (OS) with pembrolizumab or nivolumab as second-line therapy (2L) or later was reported in clinical trials as 8.0 months and 7.5 months, respectively (no comparator in these clinical trials).[1,2]
  - Pembrolizumab is now approved by the FDA for the first-line (1L) treatment of patients with metastatic or with unresectable, recurrent HNSCC as either monotherapy (in patients whose tumors express programmed death-ligand 1 [PD-L1]) or combination therapy with platinum and fluorouracil.[4]
    - Treatment with pembrolizumab in combination with chemotherapy improved median OS versus cetuximab with chemotherapy (13.0 vs 10.7 months).[3]
- I-O agents offer promising improvements in OS for patients with r/m HNSCC, but ≈75–85% of patients show little or no response.[1,2,8]
- However, limited information on real-world (RW) clinical practice currently exists regarding I-O agents in patients with head and neck (HN) cancer, and questions remain unanswered around optimal duration of treatment and the potential for re-challenge with I-O agents after disease progression.

OBJECTIVES

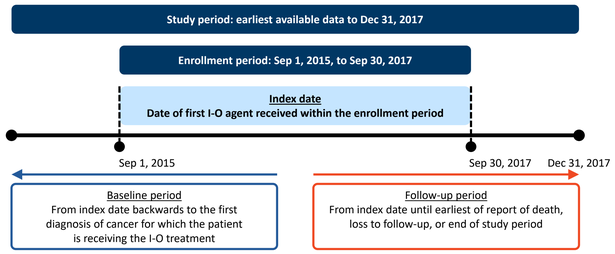
- To evaluate RW treatment patterns and outcomes of patients with HN cancer treated in the US community setting, including describing the use of I-O agents and examining RW progression-free survival (rwPFS) and RW OS (rwOS).

MATERIALS & METHODS

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 HN cancer.
  - The ION electronic medical record data warehouse captures data from 350 unique providers from 25 geographically diverse community practices and contains medical information for >650,000 patients in the form of standardized tables and electronically stored progress notes.
- Patient sample selection consisted of two phases:
  - **Phase 1** was a structured data review, with data captured through a combination of programmatic queries of standardized fields in health records.
  - **Phase 2** comprised electronic patient chart reviews conducted by clinical personnel including physicians and oncology nurses.
- Patients initiating nivolumab or pembrolizumab on or after September 1, 2015, were eligible for inclusion, and the first I-O agent received during the enrollment period was defined as index I-O (**Figure 1**).
- Completers were defined as patients with complete follow-up from the start of treatment with index I-O agent to discontinuation of index I-O agent.
- Data were descriptively summarized.

Figure 1. Study design



Eligibility criteria

- Patients were eligible for this analysis if they had a diagnosis of HN cancer (any histology) and initiated an I-O agent between September 1, 2015, and September 30, 2017.
- Exclusion criteria for each patient selection phase are summarized in **Table 1**.

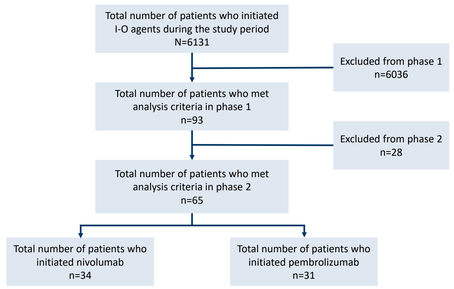
Table 1. Exclusion criteria by patient selection phase

Phase 1	Phase 2
• Received an I-O agent before September 1, 2015 • Evidence of ≥1 primary cancer during the enrollment period • <18 years of age at index I-O agent initiation • Participated 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	• Did not have a primary diagnosis of HN cancer • Diagnosis of any other malignancy • Diagnosed/treated for their primary cancer outside of the ION network • Participated in a clinical trial during the baseline period or while receiving index I-O agent • Incomplete/missing physician notes

RESULTS

- The study population is shown in **Figure 2**.
- The majority (n=6036) of the 6131 patients who initiated I-O agents during the study period were excluded due to one or more of the phase 1 criteria detailed in **Table 1** or did not have an HN cancer diagnosis; 93 patients were included in the phase 2 selection process.
  - 28 patients were excluded from phase 2, most commonly because a primary HN cancer diagnosis was not identified (n=7), they had incomplete/missing physician notes (n=7), or they had a diagnosis of any other malignancy (n=6).
  - Of 65 patients who met chart review criteria, 34 initiated nivolumab as index I-O agent and 31 initiated pembrolizumab as index I-O agent; no other PD-(L)1 agents were used.

Figure 2. Flow diagram showing analysis profile



Baseline demographics and clinical characteristics

- Patients included in the study had a mean age of 62.3 years and were predominantly male (76.9%) (**Table 2**).
- The most common Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 1 (60.7%).
- Five (7.7%) patients had known PD-(L)1 status.

Table 2. Patient baseline demographics and clinical characteristics*

	All patients (N=65)	Nivolumab (n=34)	Pembrolizumab (n=31)
Mean age, years (SD)	62.3 (12.2)	63.2 (10.9)	61.3 (13.6)
Sex, n (%), female/male	15 (23.1) / 50 (76.9)	7 (20.6) / 27 (79.4)	8 (25.8) / 23 (74.2)
Prior diagnosis of metastatic disease, n (%)	63 (96.9)	34 (100.0)	29 (93.5)
ECOG PS at index I-O agent initiation, n (%)			
Data available	28 (43.1)	18 (52.9)	10 (32.5)
0	4 (14.3)	2 (11.1)	2 (20.0)
1	17 (60.7)	10 (55.6)	7 (70.0)
2	5 (17.9)	4 (22.2)	1 (10.0)
≥3	2 (7.1)	2 (11.1)	0 (0.0)
Data not available	37 (56.9)	16 (47.1)	21 (67.7)
Baseline smoking status, n (%)			
Data available	60 (92.3)	31 (91.2)	29 (93.5)
Current smoker	8 (13.3)	5 (16.1)	3 (10.3)
Past smoker	30 (50.0)	19 (61.3)	11 (37.9)
Never smoked	22 (36.7)	7 (22.6)	15 (51.7)
Data not available	5 (7.7)	3 (8.8)	2 (6.5)
Baseline comorbidities, n (%)†			
Anemia	28 (43.1)	18 (52.9)	10 (32.3)
COPD	4 (6.2)	1 (2.9)	3 (9.7)
Congestive heart failure	3 (4.6)	1 (2.9)	2 (6.5)
Diabetes	10 (15.4)	6 (17.6)	4 (12.9)
Neuropathy	13 (20.0)	8 (23.5)	5 (16.1)
Neutropenia	17 (26.2)	10 (29.4)	7 (22.6)
Renal impairment	7 (10.8)	6 (17.6)	1 (3.2)
Stroke or TIA	1 (1.5)	0 (0.0)	1 (3.2)
Thrombocytopenia	13 (20.0)	10 (29.4)	3 (9.7)

*Baseline characteristics are measured in the study period between the first diagnosis of HN cancer and the start of treatment with I-O agent; †baseline comorbidities are not mutually exclusive and a patient may have had more than one comorbidity in the baseline period.
COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

Index I-O treatment characteristics

- Index I-O treatment characteristics are summarized in **Table 3**.
  - Index IO-treatment was initiated in 2015 or 2016 for 70.8% of patients .
  - Overall, 36.9% of patients initiated index I-O treatment as 1L metastatic, 40.0% as (2L) metastatic, and 20.0% as third-line or later (3L+) metastatic.
  - The mean time from metastatic diagnosis to initiation of index I-O treatment was 7.5 months (standard deviation [SD]: 8.7 months) and was similar for both agents.
  - Nivolumab was most commonly initiated as 2L metastatic therapy (50.0%) and pembrolizumab was most commonly initiated as 1L metastatic therapy (48.4%).
- The most common reasons for discontinuation of index I-O treatment were disease progression (58.5%), end of progress notes (21.5%), and death (13.8%).

Table 3. Index I-O treatment characteristics

	All patients (N=65)	Nivolumab (n=34)	Pembrolizumab (n=31)
Year of index I-O agent initiation, n (%)			
2015	5 (7.7)	3 (8.8)	2 (6.5)
2016	41 (63.1)	20 (58.8)	21 (67.7)
2017	19 (29.2)	11 (32.4)	8 (25.8)
Line of therapy index I-O agent was received, n (%)			
Non-metastatic*	2 (3.1)	0 (0.0)	2 (6.5)
1L metastatic	24 (36.9)	9 (26.5)	15 (48.4)
2L metastatic	26 (40.0)	17 (50.0)	9 (29.0)
3L+ metastatic	13 (20.0)	8 (23.5)	5 (16.1)
Mean time from metastatic diagnosis to initiation of index I-O agent, months (SD)†	7.5 (8.7)	7.3 (6.5)	7.7 (10.8)
Monotherapy, n (%)	65 (100.0)	34 (100.0)	31 (100.0)
Mean duration of index I-O treatment, months (SD)	3.9 (4.6)	4.7 (5.7)	3.1 (2.7)
Mean duration of index I-O treatment among completers (n=51), days (SD)	3.1 (3.4)	3.5 (4.1)	2.6 (2.5)

*Patients who received index I-O agent before metastasis; †patients who received index I-O agent before metastasis (n=5) are not included in this calculation.

Subsequent treatments

- Subsequent treatment patterns, including the percentage of patients who were re-challenged with the same or different I-O agent in any later line, are summarized in **Table 4**.
  - In total, 23.1% of patients received subsequent treatments.
  - Chemotherapy, either as monotherapy or in combination with other chemotherapies, was the most commonly received subsequent treatment (16.9%).

Table 4. Subsequent treatments received after index I-O agent discontinuation*

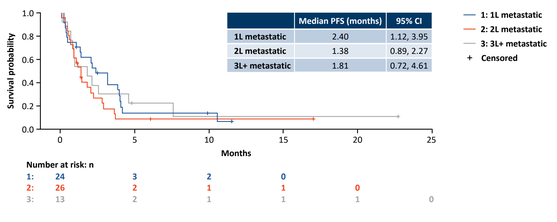
	All patients (N=65)	Nivolumab (n=34)	Pembrolizumab (n=31)
Mean TTNT, days (SD)†	23.2 (18.8)	21.9 (18.3)	28.3 (24.0)
Patients with subsequent treatment, n (%)	15 (23.1)	12 (35.3)	3 (9.7)
Subsequent regimen among those with subsequent treatment, n (%)			
Chemotherapy only (mono or combo)‡	11 (73.3)	8 (66.7)	3 (100.0)
Cetuximab-cisplatin-docetaxel	1 (6.7)	1 (8.3)	0 (0.0)
Investigational I-O drug	1 (6.7)	1 (8.3)	0 (0.0)
Everolimus	1 (6.7)	1 (8.3)	0 (0.0)
Cetuximab	1 (6.7)	1 (8.3)	0 (0.0)
Patients who were re-challenged with the same or different I-O agent, n (%)§	1 (1.5)	1 (2.9)	0 (0.0)

*Subsequent treatments were captured as the next treatment initiated immediately after discontinuation of index I-O; †TTNT was the time interval between start of index I-O treatment and first date of administration of the next line of therapy; ‡chemotherapy regimens were carboplatin + gemcitabine, carboplatin + paclitaxel, docetaxel, methotrexate, and vinorelbine; §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.
Combo, combination therapy; mono, monotherapy; TTNT, time to next treatment.

rwPFS and rwOS

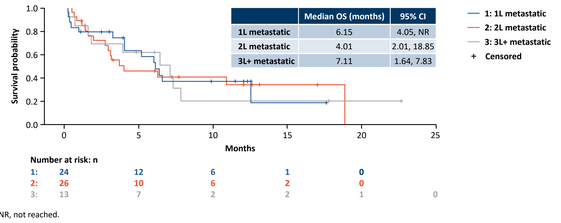
- rwPFS after first I-O agent by line of therapy is shown in **Figure 3**.

Figure 3. Kaplan–Meier estimate of rwPFS after first I-O agent by line of therapy



- rwOS after first I-O agent by line of therapy is shown in **Figure 4**.

Figure 4. Kaplan–Meier estimate of rwOS after first I-O agent by line of therapy



NR, not reached.

SUMMARY

- In the RW community setting, I-O agents were used largely in line with their FDA approvals for use in r/m HNSCC with disease progression on or after platinum-containing chemotherapy; however, they were also utilized off-label, which included:
  - Use in patients with HN cancer before their initial 2016 FDA approval (7.7%).
  - Considerable use in the 1L setting (36.9%), which may have included some off-label use before data release from randomized clinical trials in 2019.[8]
- The percentage of patients receiving subsequent treatments overall was 23.1%.
  - Patients who received nivolumab as index I-O agent more commonly received subsequent treatment (35.3%) than patients who received pembrolizumab as index I-O agent (9.7%).
  - The majority of patients received chemotherapy as their subsequent treatment (16.9%).
  - Only one patient was re-challenged with the same or different I-O agent.
- Both median rwPFS and rwOS outcomes were lower than those observed in I-O agent clinical trials.[1,2,8]
  - The patient population in this study had a similar age (median 62.3 years) to clinical trial participants but likely had poorer performance status, as 10.8% of all patients had an ECOG PS of ≥2 and patients with ECOG PS of ≥2 were excluded from the clinical trials.[1,2,8] Some characteristics commonly reported for clinical trial participants, e.g. PD-(L)1 status, were not available for the majority of patients in this study.

Limitations and future research

- Although the patients included in this study had a diagnosis of HN cancer, rather than a specific diagnosis of metastatic HNSCC, 90% of patients with HN have HNSCC[8] and both pembrolizumab and nivolumab were indicated specifically for the treatment of metastatic HNSCC.[4,5]
- As PD-(L)1 status data were not available for the majority of patients, PD-(L)1 status could not be analyzed as a predictor of response, which was likely a reflection of the lack of a PD-(L)1 expression-dependent indication for both pembrolizumab and nivolumab during the study enrollment period.[4,5]
  - PD-L1 testing is now required by the FDA for use of pembrolizumab as a 1L monotherapy (PD-L1 combined positive score ≥1).[8]
- Safety data were not collected in this RW study.

CONCLUSIONS

- This study evaluated the use of I-O agents in the RW, which has a more varied patient population than clinical trials.
- Additional research is required to identify subpopulations of patients with HNSCC who are more likely to benefit from treatment with I-O agents, such as those with high PD-L1 expression.

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DISCLOSURES

- **KFB** is an employee of GSK and Humana (I) and owns stock and other ownership interests in CVS (I). **ASB** is an employee of Bayer and owns stocks and other ownership interests in AmerisourceBergen and Bristol-Myers Squibb. **DS-M** and **SM** are employees of Xcenda. **MSB** is an employee of GSK and holds stock in GSK, Bristol-Myers Squibb, Abbott, and Novartis.

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