Chapter 19
Update of Immune Therapies in Recurrent/ Metastatic Head and Neck Cancer

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Background: Prior to the Emergence of Immune Therapies

It is now over 30 years since single agent cisplatin was demonstrated to be active in recurrent/metastatic mucosal head and neck squamous cell carcinoma (R/M HNSCC) with trials suggesting improved survival [1, 2]. However, subsequent progress was slow, with the widely accepted use of platinum-based doublets shown to increase response rates without impacting on survival [3, 4]. The Extreme trial was a significant advance with the addition of the anti-EGFR monoclonal antibody, cetuximab to platinum and 5-Fluorouracil improving overall survival compared to chemotherapy alone [5]. The median overall survival improved from 7.4 months in the chemotherapy-alone arm to 10.1 months in the arm that received chemotherapy plus cetuximab (hazard ratio, 0.80; 95% confidence interval, 0.64 to 0.99; P = 0.04). Based on these results, the Extreme regimen was approved in many jurisdictions and became the standard of care for first-line treatment of R/M HNSCC. No treatment had been shown to improve survival in the second-line or beyond R/M HNSCC setting.

Emergence of Immune Therapies in HNSCC

Monoclonal antibodies directed against the PD-1 or PD-L1 receptors have transformed the treatment of many cancers, after initial success in melanoma. The first major report in R/M HNSCC was at the Annual Meeting of the American Society of

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Oncology in 2014 where the results of the head and neck cohort of Keynote 012 treated with the anti-PD1, pembrolizumab were reported. The key findings have held up over time: the response rate was 18%, responses were durable, similar activity was seen in patients with HPV positive and negative tumours and the response rate in patients with PD-L1 positive tumours was higher [6]. Over the last 5 years we have seen unprecedented clinical trial activity in HNSCC, with the role of immune checkpoint inhibitors as part of standard of care established.

Second-Line Randomised Trials of Immune Checkpoint Inhibitors

Three immune checkpoint inhibitors have been tested in randomised phase 3 trials. (see Table 19.1). The first trial was the Checkmate 141 that compared nivolumab 3 mg/kg 2-weekly to investigators choice of standard of care (methotrexate, docetaxel or cetuximab) in a 2:1 randomisation [7]. Eligibility included R/M HNSCC oral cavity, pharynx or larynx, progression <6 months after last dose of platinum and no limit on prior lines of therapy. The median overall survival (OS) improved from 5.1 months to 7.5 months with a hazard ratio of 0.68, P = 0.01. 2-year survival improved from 6.0% to 16.9% [8]. Nivolumab delayed time to deterioration in patient reported quality of life outcomes compared to standard of care [9]. Based on the results of this trial nivolumab was approved throughout the world for use in platinum refractory patients. In a similarly designed trial of pembrolizumab compared to standard of care, Keynote 040, median OS improved from 6.9 months to 8.4 months with a hazard ratio of 0.80 [10]. Pembrolizumab was initially approved in the US based on Keynote-012 and later in Europe based on Keynote-040 restricted to patients with PD-L1 Tumour Proportion Score (TPS) ≥ 50%. In contrast to the nivolumab and pembrolizumab trials, the anti-PD-L1 durvalumab did not meet its primary endpoint when compared to standard of care in a phase 3 trial [11].

Table 19.1 Randomised trials of immune checkpoint inhibitors in ≥2nd-line recurrent/metastatic HNSCC

Trial	Anti-PD1/ anti-PD-L1	Control arm	Hazard ratio (95%CI) Overall survival	2 year survival	Median OS (months)
Checkmate 141 [7, 8]	Nivolumab	Methotrexate, docetaxel or cetuximab	0.68 (0.54–0.86), P = 0.01	16.9% v 6.0%	7.5 v 5.1
Keynote-040 [10]	Pembrolizumab	Methotrexate, docetaxel or cetuximab	0.80 (0.65–0.98), nominal P = 0.016		8.4 v 6.9
Eagle[11]	Durvalumab	Methotrexate, taxane, fluoropyrimidine or cetuximab	0.88 (0.72–1.08), P = 0.20	18.4% v 10.3%	7.6 v 8.3

First-Line Randomised Trials of Immune Checkpoint Inhibitors

The Keynote-048 trial evaluated the role of pembrolizumab alone (200 mg 3 weekly) or in combination with platinum-5-FU chemotherapy compared to the standard of care, the Extreme regimen of platinum, 5FU and cetuximab [12]. The rationale for combining chemotherapy with immunotherapy included possible disruption of the tumour architecture that might overcome tumour exclusion, enhancement of antigen shedding and more rapid control than immunotherapy alone. In both chemotherapy arms a maximum of 6 cycles of chemotherapy was administered, but patients could stay on pembrolizumab for up to 35 cycles and could continue with cetuximab. Key eligibility criteria included SCC of the oropharynx, oral cavity, hypopharynx and larynx, no prior systemic therapy for R/M disease, > 6 months since completing chemoradiation, ECOG performance status 0–1, tissue sample for PD-L1 assessment available and known p16 status if oropharyngeal primary.

The primary study endpoints were overall and progression-free survival (PFS) in the PD-L1 combined positive score (CPS) ≥ 20, CPS ≥ 1 and the total populations. Secondary endpoints included PFS at 6 and 12 months, response rate, quality of life and safety. Duration of response was an exploratory endpoint. The trial had a complex statistical design that allowed for several hypotheses about OS and PFS to be determined in parallel first either in the CPS ≥ 20 or total population. Subsequent testing in other populations e.g., CPS ≥ 1 only took place if the first hypothesis was positive. The pre-specified analysis plan allowed alpha from successful hypotheses to be passed to other hypotheses.

882 patients were randomised in <2 years from 206 sites in 37 countries. The arms were well balanced for baseline characteristics. The median age was approximately 61, > 80% were male, and 21% had p16 positive oropharyngeal cancer. With regard to PD-L1 status approximately 22% had TPS ≥ 50%. 40–45% had CPS ≥ 20, 85% had CPS ≥ 1.

Pembrolizumab when compared to Extreme improved OS in the CPS ≥ 20 and CPS ≥ 1 populations, and was non-inferior in the total population (Table 19.2). In the CPS ≥ 20 population the HR was 0.61 (95%CI 0.45–0.83, p = 0.0007), with medians of 14.9 versus 10.7 months and 2 year survival rates of 38.3% versus 22.1%. In the CPS ≥ 1 population the HR was 0.78 (95%CI 0.64–0.96, p = 0.0086), with medians of 12.3 versus 10.3 months and 2 year survival rates of 30.2% versus 18.6%. In the total population the HR was 0.83 (95%CI 0.70–0.99, p = 0.0199 which did not meet the superiority threshold for statistical significance), with medians of 11.5 versus 10.7 months and 2 year survival rates of 19.7% versus 10.0%. The progression-free survival curves crossed with more early progressions in the pembrolizumab arm. The response rate for the CPS ≥ 20 was 23.3% and for the CPS ≥ 1 it was 19.1%, while in the Extreme arm it was approximately 35%. The duration of response was markedly prolonged in the pembrolizumab arm, median 22.6 months versus 4.2 months. The safety profile was favourable for the pembrolizumab monotherapy arm when comparing treatment-related adverse events with

Table 19.2 Keynote-048: Overall Survival

		Hazard ratio (95% CI)	2 year survival (months) pembro arm versus Extreme	Median OS (months) pembro arm versus Extreme
Pembrolizumab versus Extreme[a]				
	PD-L1 CPS[b] ≥ 20	0.61 (0.45–0.83); p = 0.0007	38.3% v 22.1%	14.9 v 10.7
	PD-L1 CPS ≥ 1	0.78 (0.64–0.96), P = 0.0086	30.2% v 18.6%	12.3 v 10.3
	Total population	0.83 (0.70–0.99), P = 0.0199[c]	27.0% v 18.8%	11.5 v 10.7
Pembrolizumab + platinum/5FU Versus extreme				
	PD-L1 CPS ≥ 20	0.60 (0.45–0.80), P = 0.0004	35.4% v 19.4%	14.7 v 11.0
	PD-L1 CPS ≥ 1	0.65 (0.53–0.80), P < 0.0001	30.8% v 16.8%	13.6 v 10.4
	Total population	0.77(0.63–0.93), P = 0.0034	29.0% v 18.7%	13.0 v 10.7

[a]Extreme—cisplatin or carboplatin, 5-Fluorouracil and cetuximab
[b]CPS—combined positive score
[c]non-inferior but did not meet superiority threshold

incidence ≥15% in the total population: any grade 58.3% v 96.9%, grade 3–5 16.7% v 69.0%, led to death 1.0% v 2.8%, and led to discontinuation 4.7% v 19.9%. Subgroup analyses for OS revealed that the pembrolizumab arm was favoured in most comparisons.

Pembrolizumab + chemotherapy when compared to Extreme improved OS in the CPS ≥ 20, CPS ≥ 1 and in the total population (Table 19.2). In the CPS ≥ 20 population the HR was 0.60 (95%CI 0.45–0.82, p = 0.0004), with medians of 14.7 versus 11.0 months and 2 year survival rates of 35.4% versus 19.4%. In the CPS ≥ 1 population the HR was 0.65 (95%CI 0.53–0.80, p = 0.0086), with medians of 13.6 versus 10.4 months and 2 year survival rates of 30.8% versus 16.8%. In the total population the HR was 0.77 (95%CI 0.63–0.93, p = 0.0034), with medians of 13.0 versus 10.7 months and 2 year survival rates of 29.0% versus 18.7%. The progression-free survival curves favoured the pembrolizumab arm but did not reach the designated superiority threshold. Unlike the monotherapy arm, there was no increase in early progression in the pembrolizumab-chemotherapy arm relative to Extreme. The response rate for the CPS ≥ 20 was 42.9% versus 38.2%, and for the CPS ≥ 1 it was 36.4% versus 35.7%, in the pembrolizumab-chemotherapy and Extreme arms respectively. The duration of response was prolonged in the pembrolizumab-chemotherapy arm e.g., in the CPS ≥ 20 median was 7.1 months (range 2.1+ − 39.0+) versus 4.9 months (1.2+ − 31.5+). The safety profile was similar in terms of number

of adverse events, grade 3–5 events, deaths due to adverse events and adverse events that led to discontinuation.

Based on the results of Keynote-048 both pembrolizumab monotherapy and pembrolizumab and chemotherapy have been established as new first-line therapies for R/M HNSCC, and have been approved in many jurisdictions. In the US, the FDA approved pembrolizumab monotherapy for patients whose tumours express PD-L1 CPS $\geq$ 1, and the pembrolizumab-chemotherapy combination for all patients. In Europe, the EMA has approved monotherapy and the combination in patients with CPS $\geq$ 1. The pre-specified analysis plan did not permit evaluation of efficacy in the CPS 1–19 and CPS < 1 subgroups separately, though these exploratory analyses will be presented at a later date. However, there is sufficient information available to suggest that pembrolizumab monotherapy would not be recommended in the CPS < 1 population.

Overall, the results do not suggest synergy between platinum/5FU and pembrolizumab with similar numbers of longer-term survivors in the combination and monotherapy arms. The combination offers the benefit of more rapid response and less risk of early progression than monotherapy. Patient selection will be important with the combination favoured for patients with high symptom burden and/or rapidly progressive disease and/or disease with imminent risk of complications e.g., airway compromise. On the other hand, patients who do not have these features could be treated with monotherapy that is associated with a much more favourable toxicity profile. Although the response rate is higher with Extreme than monotherapy, the durability of pembrolizumab responses has translated into a major survival advantage in the CPS $\geq$ 20 and $\geq$ 1 populations. The long-term survival benefit in the pembrolizumab arms appears to be greater than can be explained by the long term responders alone. It is possible that exposure to an immune checkpoint inhibitor alters the tumour microenvironment and in turn changes the natural history of R/M HNSCC and the response to subsequent therapies. The Extreme regimen or platinum/taxane-cetuximab combinations [13] will continue to have a role in the CPS <1 population and in patients with a contraindication to immunotherapy. The role of cetuximab/chemotherapy regimens for 2nd-line R/M HNSCC is worthy of study.

Combination of Other Treatments with Anti-PD1 or PD-L1 Agents

As the role of anti-PD1 and anti-PD-L1 agents have become established in many cancers, there has been increasing focus on combinations with other agents. There has been a rapid expansion in the number of combination immunotherapy trials since 2011. It has been increasing significantly year on year, with 467 new trials in 2017 [14]. HNSCC was the sixth most common tumour type targeted for combination immunotherapy trials. Across all tumour types the most common strategy being

tested in trials was combination with anti-CTLA-4 agents, followed by chemotherapy and radiotherapy [15]. There are many rational combination strategies including agents involved in a) T cell priming e.g., anti-CTLA4, vaccines, oncolytic viruses, b) T cell activation and homing e.g., anti-OX40, TIM3/LAG3 inhibitors, targeted therapies, c) Tumour antigen release e.g., chemotherapy, radiotherapy, oncolytic virus, targeted therapy and d) Improving the tumour microenvironment e.g., TGF beta inhibitor, adenosine antagonist [16]. The sheer number of potential strategies, agents and combinations poses a major drug development challenge. Detailed discussion of combination strategies and development pathways for combinations is beyond the scope of this chapter. The focus will be on combinations that have yielded promising results in R/M HNSCC and in particular on combinations investigated in randomised trials.

Anti-PD1/PD-L1 with Anti-CTLA4 Combinations

The combination of the anti- cytotoxic T-lymphocyte-associated protein (CTLA4), ipilimumab with nivolumab is well established as the standard of care in melanoma [17]. This has led to investigation of this combination in several other malignancies. In R/M HNSCC two anti-CTLA 4 agents have been studied, ipilimumab and tremelimumab. Two trials combining tremelimumab with durvalumab have failed to show benefit for the combination over single agent durvalumab or when compared to chemotherapy. In the Condor randomised phase 2 trial, in patients deemed to have low or no PD-L1 expression, the response rate for durvalumab was 9.2%, durvalumab + tremelimumab 7.8% and for tremelimumab monotherapy 1.6% [18]. In the Eagle phase 3 trial neither the durvalumab monotherapy arm nor the durvalumab + tremelimumab arm improved OS compared to single agent chemotherapy [11]. The durvalumab + tremelimumab combination did not appear to be any better than durvalumab monotherapy, though the trial was not designed to conduct this comparison.

Ipilimumab and nivolumab was compared to nivolumab alone in the randomised phase 2 Checkmate 714 trial in 1st-line R/M HNSCC. There has been a press release that it did not meet its primary endpoints (https://news.bms.com/press-release/corporatefinancial-news/bristol-myers-squibb-reports-first-quarter-financial-results-1).

Two phase 3 trials in the 1st-line R/M HNSCC setting are awaited. The Checkmate 651 trial that is comparing ipilimumab and nivolumab to Extreme, and the Kestrel trial comparing durvalumab +/− tremilumumab versus Extreme.

Other Combinations

There has been considerable interest in combining VEGF inhibitors with immune checkpoint inhibitors. Anti-angiogenic agents may decrease immunosuppression and increase CD8 infiltration when combined with immune checkpoint inhibitors.

Lenvatinib is a multikinase inhibitor of VEGFR1, VEGFR2 and VEGFR3 that is widely used in recurrent/metastatic papillary thyroid cancer. In endometrial cancer the combination with pembrolizumab achieved a response rate of 40% leading to accelerated approval by the FDA [19]. Preliminary results from an expansion cohort of the phase 1 trial of lenvatinib and pembrolizumab in R/M HNSCC reported responses in 8/22 patients (36%) [20]. A phase 3 trial in R/M HNSCC is planned.

The inducible T-cell co-stimulatory receptor (ICOS) is highly upregulated upon T-cell receptor stimulation and expressed on tumour infiltrating lymphocytes. HNSCC has high ICOS expression. The inducible T-cell co-stimulatory receptor agonist, GSK3359609 has been combined with pembrolizumab. In a HNSCC expansion cohort of the phase I trial, there were responses in 8/34 patients (24%), and the toxicity profile was similar to pembrolizumab monotherapy [21]. The combination of GSK3359609 with pembrolizumab, platinum and 5FU has also been tested and found to be safe. Induce 3 is a randomised phase 2/3 trial of pembrolizumab +/− GSK3359609 in 1st line R/M HNSCC. Induce 4 is a planned randomised trial of pembrolizumab, platinum and 5FU +/− GSK3359609.

SD-101 is a synthetic cytidine-phospho-guanosine (CpG) oligonucleotide agonist of Toll-Like Receptor 9. It stimulates dendritic cells to release interferon-alpha and mature into antigen presenting cells, in turn activating T-cell anti-tumour responses. In a phase 2 trial of intra-tumoural SD-101 in combination with pembrolizumab in immune checkpoint inhibitor naïve R/M HNSCC, responses were observed in 12/50 patients (24%) [22]. Responses were seen in injected and non-injected lesions and in 'cold' tumours. Treatment was reported to be well tolerated.

The NKG2A receptor is expressed on natural killer (NK) cells and some CD8+ tumour infiltrating lymphocytes. HLA-E, the NKG2A ligand, is upregulated in many cancers including HNSCC. NKG2A blockade with monalizumab promotes innate anti-tumour immunity mediated by NK and $CD8^+$ T cells and enhances human NK cell antibody-dependent cell-mediated cytotoxicity (ADCC) induced by cetuximab [23]. In a phase 2 trial of monalizumab and cetuximab, responses were seen in 11/40 (28%), with 36% response rate in immune checkpoint inhibitor naïve patients and 17% in patients previously treated with an immune checkpoint inhibitor [24]. The median duration of response was 5.6 months and the median overall survival was 8.3 months. A phase 3 trial is planned.

Finally, there are strategies targeting the human papillomavirus (HPV), which is now the predominant cause of oropharyngeal cancer in many countries. There are several HPV therapeutic vaccines under development. Results have been reported for the ISA 101 HPV 16 vaccine targeting E6 and E7 given in combination with nivolumab [25]. 24 patients were treated (22 had oropharyngeal cancer). The response rate was 33%, with median duration of response of 10.3 months and median OS of 17.5 months [25]. There is also considerable interest in developing cellular therapies for HPV associated cancers. In a preliminary report of T-cell receptor gene therapy for HPV associated cancers, autologous genetically engineered T cells expressing a T-cell receptor directed against HPV 16 E6 was administered to patients, and there was evidence of anti-cancer activity [26]. In addition, tumour-infiltrating lymphocyte therapy for HPV associated cancers has been

studied. With this adoptive T cell therapy TIL cultures from resected metastasis were selected for HPV E6/E7 reactivity and administered to patients [27]. Responses were observed in 7/29 patients (24%).

Conclusion

Immune checkpoint inhibitors have had a major impact on the management of R/M HNSCC. Based on Keynote-048, pembrolizumab +/− chemotherapy in HNSCC represents the new first-line standard of care for the majority of patients with R/M HNSCC. Many rational combinations of agents with immune checkpoint inhibitors are under investigation, but it is difficult to evaluate single arm trials of combinations, and the selection of the best combinations for study in randomised trials remains very challenging. In a rapidly evolving area the awaited results of completed trials of immune therapies in earlier stages of HNSCC may ultimately affect the optimal management options for R/M HNSCC.

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