Curr. Treat. Options in Oncol. (2019) 20: 65
DOI 10.1007/s11864-019-0664-z

Head and Neck Cancer (CP Rodriguez, Section Editor)

Approach to the Patient with Recurrent/Metastatic Disease

Joël Guigay, MD[*]
Esma Sâada-Bouzid, MD
Frédéric Peyrade, MD
Cécile Michel, MSc

Address
[*]Centre Antoine Lacassagne, Cancer research center, Medical Oncology Department, FHU Oncoage, University Côte d'Azur, 33 av. de Valombrose, 06189, Nice Cedex 2, France
Email: joel.guigay@nice.unicancer.fr

Published online: 25 June 2019

This article is part of the Topical Collection on *Head and Neck Cancer*

Keywords Recurrent/metastatic disease · Treatment · Standards · Advances · Review

Opinion statement

For most of patients with a recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), the treatment remains palliative: The main objective is to reduce the symptoms related to the locoregional relapse, prolong life while maintaining quality of life, which is a big challenge. The systemic treatment needs to be adapted to the performance status, comorbidities, and sequelae of patients. For fit patients, the combination of platinum-based chemotherapy and cetuximab (EXTREME) is the standard of care in first-line treatment since 2008, as no other targeted therapy has been approved in this setting until now. The replacement of 5-FU with a taxane (docetaxel) in the EXTREME regimen has been explored in the large randomized international study TPExtreme which results are awaited in a few months. Depending on the study results on survival, response rate, and tolerance, the TPEx regimen may become a treatment option for patients with R/M HNSCC. Unfit patients are usually treated with platinum-free combinations or with the monotherapies which are recommended in second-line setting (methotrexate, taxanes, cetuximab). However, the irruption of new immunotherapies (e.g., checkpoint inhibitors (CPI)) is changing the guidelines. The tolerance of anti-PD-1 CPI is better than that of chemotherapy, and they seem to be a good option for unfit patients. Anti-PD-1 nivolumab and pembrolizumab are now approved for platinum refractory patients, providing prolonged survival in the case of response, and improvement in quality of life. New options arise in first-line setting with pembrolizumab alone or combined with chemotherapy. Patients with a high PD-L1 biomarker level seem to benefit more from immunotherapy. Other situations

(e.g., PD-L1–low, PD-L1–negative, high tumor burden) may more likely to benefit from other combinations, such as cetuximab plus chemotherapy, to avoid local failures and life-threatening fast progression. In terms of perspectives, chemo-free and CPI-free approaches, using other immune oncology agents, should be the next steps.

Introduction

About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC) [1] that develop in the upper aerodigestive epithelium after exposure to carcinogens such as tobacco and alcohol. Human papillomavirus (HPV) associated with oropharyngeal carcinoma has also been strongly implicated as a causative agent in patients with no other classical risk factors, especially type 16 [2]. In R/M HNSCC, HPV/p16 positivity has been reported in a lower proportion of patients (approximately 10 to 20%) but implies a superior survival [3••, 4]. HPV types 18, 31, and 33 are also responsible for HNSCC, but less frequently. HNSCC is a heterogeneous group of disease with an incidence of > 700,000 cases worldwide and 358,144 deaths during 2018 [5].

Out of them, half of patients diagnosed with stage III-IVb disease will recur despite aggressive, site-specific multimodality therapy [6], with up to 60% risk of local failure and up to 30% risk of distant failure [7•]. Only 10% of patients have metastatic disease at diagnosis [8]. The presence of less than 5 synchronous metastases, known as oligometastatic state, seems to have a distinct biological behavior and outcome [9].

Patients with recurrent and/or metastatic (R/M) HNSCC who are not amenable to local therapy or surgery have poor prognosis with a median overall survival (OS) of less than 1 year [10]. In this context, the objective of the treatment is first to reduce the size of the tumor and thus the symptoms related to cancer (pain, swallowing, and speech disorders) to maintain a quality of life, while slowing the progression of the disease and prolonging survival. In the last 40 years, great efforts have been made to develop a more effective chemotherapy regimen, from the use of methotrexate alone to the combination of cisplatin and 5-fluorouracil (5FU) or paclitaxel.

EGFR has been observed to be overexpressed (38–47%) in HNSCC [11]. Cetuximab, an anti-EGFR monoclonal antibody, added to the cisplatin–5-FU doublet (EXTREME regimen) is currently the standard of care in first-line treatment for these patients [3••]. Since little progress has been made in long-term survival rates over the last decade, new management approaches are required. Novel combinations of chemotherapy with the replacement of 5FU by a taxane were recently explored [12, 13]. As immune evasion is one of the leading mechanisms explaining the recurrence and metastatic progression of HNSCC [14], immunotherapy using checkpoint inhibitors (CPI) has emerged as new options of treatment [15].

For the second line and beyond, equivalent options were weekly monotherapy (methotrexate, taxanes, cetuximab) or best supportive care, according to the performance status and toxicities [16–18]. Nivolumab and pembrolizumab are the first two CPIs able to prolong OS in the second-, later-line, and platinum-refractory setting, with tolerable toxicities.

This review summarizes the current state of the art and ongoing studies in R/M HNSCC systemic treatment options (Fig. 1).

Current gold standard for first-line treatment of patients with R/M disease

In 2008, based on the results of the phase III EXTREME trial [3••], the EXTREME regimen became the standard of care in the first-line R/M setting, as supported by international guidelines with a level of evidence and grade of recommendation of

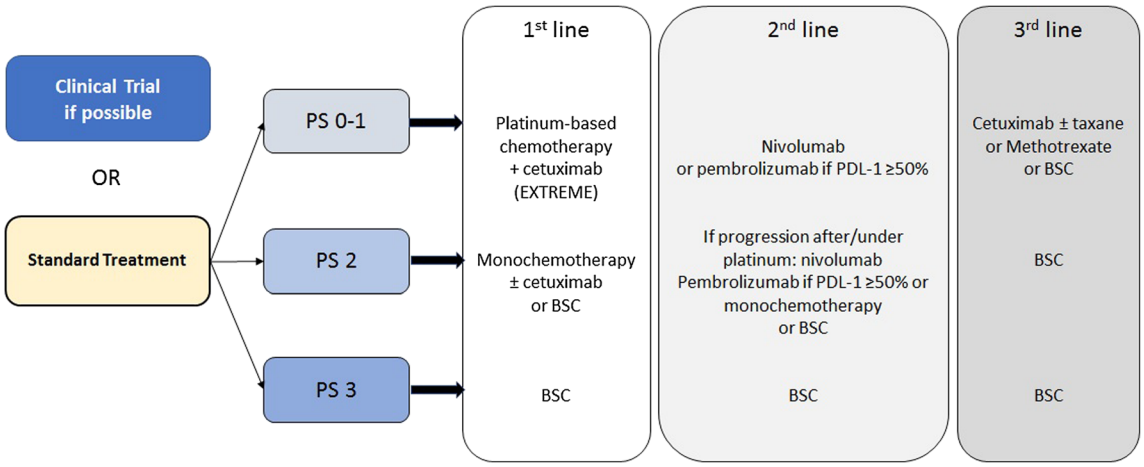

Fig. 1. Treatment of R/M HNSCC in the first quarter of 2019, according to current drug approvals.

IIA [19]. It is composed of 6 cycles of chemotherapy (cisplatin/carboplatin–5-FU) associated with cetuximab delivered weekly. Following the chemotherapy phase, the anti-EGFR is administered alone as maintenance treatment until progressive disease (PD) or inacceptable toxicity. Median OS and progression-free survival (PFS) were significantly improved with the addition of cetuximab to chemotherapy (from 7.4 to 10.1 months and from 3.3 to 5.6 months, respectively). Similarly, objective response rate increased from 23 to 38.9% with the addition of anti-EGFR antibody to chemotherapy. The safety profile was consistent with that expected for the three drugs, including cardiac events related to 5-FU (7% grade ≥ 3), anorexia, and sepsis. The skin reactions related to cetuximab were estimated to be tolerable.

Since then, results of the EXTREME study have been confirmed in a large phase IV study (DIRECT study) [20] and in other prospective observational studies [21]. In the real-world setting, most of patients received 4 cycles out of 6 and nearly 50% of patients could start maintenance. This latter at 250 mg/m^2 weekly or 500 mg/m^2 every 2 weeks was tolerable and feasible. Long-term responses have been reported [22, 23], possibly related to the HPV tumor status and the duration of cetuximab administration and thus of the maintenance phase of the regimen [24].

For elderly fit patients eligible for chemotherapy, an adaptation of the EXTREME regimen (replacement of cisplatin by carboplatin) is currently tested in an ongoing dedicated Phase II trial (ELAN FIT, NCT01864772) [25]. Unfit patients (PS 2), until now, are treated by monotherapy, including, but not limited to, targeted therapeutics such as cetuximab or cytotoxic agents such as methotrexate, docetaxel, paclitaxel, carboplatin, 5-FU, and capecitabine [3••, 17, 19]. Another option may be the combination of cetuximab with a taxane for selected patients. Best supportive care (BSC) is always associated to treatment and sometimes remains the sole possible treatment for some unfit patients.

Current gold standard for second and further-line treatment of patients with R/M disease

Second-line setting

Over the past decade, patients with second-line R/M HNSCC received either chemotherapy with a single agent or BSC according to their PS and sequelae.

Available agents include methotrexate [26, 27], docetaxel, and paclitaxel, but taxanes, despite frequent use, have not demonstrated to be superior to other agents in this setting [17, 28]. Irinotecan has also shown very limited activity [10]. Combination therapy does not appear to yield better results than monotherapy [29] with a median OS of 5 months like BSC alone [30].

Cetuximab monotherapy demonstrated ORR of 10–13% and median OS between 5 and 6 months in phase II trials [10, 17, 18, 31]. It has been approved in USA in this setting.

Its association with taxane (paclitaxel or docetaxel) is also a palliative option in the second-line setting, reaching a median OS of 6.7–10.0 months [32–35].

Other trials with anti-EGFR therapies (panitumumab, gefitinib, erlotinib, lapatinib, afatinib) failed to demonstrate better efficacy results [26–28, 36, 37], with the exception of PFS with afatinib in the LUX-Head & Neck 1 trial [27].

Because the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR pathway is a signaling cascade downstream of the EGFR that stimulates cell growth, targeting this pathway is a potential option for overcoming resistance to anti-EGFR targeted therapy [38]. The results of phase II BERIL-1 study were encouraging with a median OS of 10.4 months with buparlisib, a pan-PI3K inhibitor, plus paclitaxel (vs 6.5 with paclitaxel alone), and needed to be confirmed in a phase III study which has not started yet [39].

In this context, the increased understanding of complex interactions between HNSCC and the host immune system as well as T cell regulatory mechanisms promoted the development of novel immunotherapies. Trials included patient selection for CPI according to PD-L1 and p16/HPV status. Table 1 summarizes trials exploring immune oncology (IO) agents.

The KEYNOTE-012 phase 1b trial [40, 48, 49] obtained first efficacy data with pembrolizumab, a monoclonal antibody to the receptor programmed cell death protein 1 (PD-1), firstly in pre-treated PD1 ligand (PD-L1) positive R/M HNSCC (initial cohort) and secondly in an expansion cohort irrespective of PD-L1 or HPV status. Pembrolizumab was further evaluated in the non-randomized phase II KEYNOTE-055 trial, in platin- and cetuximab-refractory patients [45] whatever PD-L1 or HPV status.

The CheckMate-141 trial evaluated nivolumab in pretreated patients, regardless of the number of previous treatment lines received, and was the first randomized positive trial demonstrating an advantage in OS compared to standard treatment (investigator's choice between weekly methotrexate, weekly cetuximab, weekly docetaxel 30 mg/m^2): Median OS was 7.5 vs 5.1 months ($p = 0.01$). Nivolumab delayed time to deterioration of patient-reported quality-of-life outcomes compared with standard therapy [50•]. The update of data after a median follow-up of 2 years confirmed the survival benefit as well as a favorable toxicity profile. The survival benefit was observed independent of tumor PD-L1 expression but was slightly better in PD-L1 ≥ 1% group (HR = 0.55; 95%CI 0.39–0.78 vs HR = 0.73, 95%CI 0.49–1.09 in PD-L1 < 1%) [41••, 42••].

Following these results, nivolumab was granted US Food and Drug Administration approval in 2016 in second-line treatment for use in patients who progress on or after platinum-based chemotherapy, with no PD-L1 testing requirement in place. A market authorization was granted to nivolumab in Europe in April 2017 by European Medicines Agency (EMA) and is reimbursed in France since June 2018 for patients refractory to

Table 1. Terminated and ongoing studies with immunotherapy in the R/M HNSCC setting

Terminated studies [ref]	No. of patients	Phase	Regimen	Subgroup	Median OS (months), *p*	Median PFS (months)	1-year OS (%)	ORR (%)
First-line setting								
KEYNOTE 048 [15]	882	III	A ($N = 301$): Pembrolizumab 200 mg q3w, 24 months	A vs B	Non-inferior	–	–	17.0 vs 36.0
				A vs B, PDL1 CPS ≥ 1				
			vs B ($N = 300$): EXTREME (standard doses, 6 cycles)	A vs B, PDL1 CPS ≥ 20	12.3 vs 10.3, $p = 0.0086$	–	–	19.0 vs 35.0
				C vs B, overall	14.9 vs 10.7, $p = 0.0007$	NS	–	23.0 vs 36.0
			vs C ($N = 281$): pembrolizumab 200 mg q3w, 24 months + cisplatin 100 mg/m^2 or carboplatin AUC5 q3w + 5-FU 1000 mg/m^2/day for 4 days q3w for 6 cycles		13.0 vs 10.7, $p = 0.0034$	NS	–	36.0 vs 36.0
						–	–	–
						–	–	–
EAGLE[a]		III	Durvalumab vs Durvalumab + tremelimumab vs EXTREME		NS	–	–	–
Second- or further-line setting								
KEYNOTE 012 [40]	192	Ib	Pembrolizumab 10 mg/kg q2w (initial cohort; $N = 60$) or 200 mg q3w (expansion cohort; $N = 132$)	Overall	8.0	2.1	38.0	18.0
				PDL1 CPS –	5.0	–	–	–
				PDL1 CPS +	10.0	–	–	–
CheckMate 141 [41••, 42••]	361	III	Nivolumab 3 mg/kg q2w ($N = 240$)	Overall	7.7 vs 5.1, $p = 0.01$	2.0 vs 2.3	36.0 vs 16.6	13.3 vs 5.8
			vs Investigator's choice (Methotrexate qw or cetuximab qw or docetaxel 30 mg/m^2 qw) ($N = 121$)	PDL1 < 1%	6.5 vs 5.5	–	–	–
				PDL1 ≥ 1%	8.2 vs 4.7	–	–	–
KEYNOTE 040 [43••]	495	III	Pembrolizumab 200 mg q3w ($N = 247$)	Overall	8.4 vs 6.9, p = 0.016	2.1 vs 2.3	37 vs 26.5	14.6 vs 10.1
			vs Investigator's choice (standard doses of methotrexate, docetaxel, or cetuximab) ($N = 248$)	PDL1 CPS < 1%	6.3 vs 7.0	–	–	–
				PDL1 CPS ≥ 1%	8.7 vs 7.1	–	–	–
				PDL1 TPS < 50%	6.5 vs 7.1	–	–	–
				PDL1 TPS ≥ 50%	11.6 vs 6.6	–	–	–
HAWK [44]	111	II	Durvalumab 10 mg/kg q2w for 12 months	PDL1 ≥ 25%	7.1	2.1	33.6	16.2
KEYNOTE 055 [45]	171	II	Pembrolizumab 200 mg q3w	Overall	8.0	2.1	–	16.0
				PDL1 CPS < 1%	–	–	–	12.0
				PDL1 CPS ≥ 1%	–	–	–	18.0
				PDL1 CPS < 50%	–	–	–	13.0

Table 1. (Continued)

				PDL1 CPS ≥ 50%	–	–	–	27.0
CONDOR [46]	267	II	Durvalumab 20 mg/kg + tremelimumab 1 mg/kg q4w, 4 cycles followed by durvalumab 10 mg/kg q2w (*N* = 129) vs Durvalumab 10 mg/kg q2w (*N* = 65) vs Tremelimumab 10 mg/kg q4w (7 doses), then q12w (2 doses) (*N* = 63)	Overall	7.6 vs 6.0 vs 5.5	2.0 vs 1.9 vs 1.9	37.0 vs 36.0 vs 24.0	7.8 vs 9.2 vs 1.6
Atezolizumab [47]	32	Ia	Atezolizumab q3w (16 cycles)	Overall	6.0	2.6	36.0	22.0
				PDL1 < 5%	–	–	–	14.0
				PDL1 ≥ 5%	–	–	–	24.0

Ongoing studies in first-line setting (NCT number)	**No. of patients**	**Phase**	**Regimen**	**Countries**	**Primary endpoint**	**Expected results**
CheckMate 651 (NCT02741570)	930	III	Nivolumab + Ipilimumab vs EXTREME	18 including USA	OS	2020
KESTREL (NCT02551159)	823	III	Durvalumab vs Durvalumab + tremelimumab vs EXTREME	23 including USA	OS	2020
ATHENA[b] (NCT03818061)	110	II	Atezolizumab 1200 mg + bevacizumab 15 mg/kg q3w	Europe	ORR	2022
NCT02643550	100	Ib/II	Monazilumab + cetuximab (400 mg/m^2 loading dose + weekly 250 mg/m^2)	2 countries	DLT (Ph. I) ORR (Ph II)	09/2020
KEYNOTE 137 (NCT02626000)	36	Ib	Pembrolizumab + TVEC 10^6 PFU/ml followed 3 weeks after by 10^8 PFU/ml q3w	11 including USA	DLT	March 2019

TPS Tumor Proportion Score, *CPS* Combined Positive Score, *DLT* dose-limiting toxicity, *NR* not reported, *NS* not significant, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *TVEC* talimogene laherparepvec, *qw* every week, *q2w* every 2 weeks, *q3w* every 3 weeks, *q12w* every 12 weeks

[a]First-line treatment + refractory patients results from a press release

[b]First- and second-line treatment

platin-based chemotherapy independently to PD-L1 status. It has replaced the cetuximab in USA and the methotrexate in Europe.

Since then, an update of the phase III randomized trial KEYNOTE-040 comparing pembrolizumab to investigator's choice (methotrexate, docetaxel, cetuximab) has been published [43••]. The stratification on PD-L1 expression (Tumor Proportion Score (TPS) ≥ 50% vs < 50%) and the limitation to second and further treatment lines may have contributed to the enrolment of better prognosis population than those of other trials with immune checkpoint inhibitor. In this trial, the median OS was superior in the pembrolizumab group (8.4 vs 6.9 months, $p = 0.0161$) and the survival benefit was due to a significantly higher proportion of long-term survivors in the group (37% vs 26.5%). In the subgroup of patients with a PD-L1 TPS of 50% or higher, median OS was 11.6 with pembrolizumab and 6.6 months with standard of care (HR = 0.53; $p = 0.0014$). A market approval has been obtained in Europe in this setting for this subgroup of R/M HNSCC progressing on or after platinum-containing chemotherapy.

Third-line setting

No published controlled study has evaluated strictly third-line R/M HNSCC in our knowledge. Lala et al. in their review found 3 cohorts of third-line patients who progressed after platinum-cetuximab regimen in second-line trials [51]. In the first one, 53 patients were treated with a combination of platinum and cetuximab and without any objective response [18]. In the LUX-Head & Neck 1 trial, an ORR of 6% was observed with methotrexate [27]. Finally, the more recent one is the BERIL-1 trial using buparlisib associated to paclitaxel [39]. Results of the combination were encouraging in terms of survival (OS and PFS).

Although no standard of care exists, methotrexate, taxanes, or cetuximab is commonly used in this setting.

Alternative chemotherapy treatment for patients with R/M disease

Several alternative combinations have been evaluated in randomized studies [4, 52–54]. All failed to demonstrate any improvement in efficacy.

The replacement of 5-FU by a taxane (docetaxel or paclitaxel) in the EXTREME regimen continues to be heavily investigated. Pre-clinical data suggests a potential immunogenic and proapoptotic synergy between cetuximab and taxane [55, 56]. The immunostimulatory effects of both may cooperate towards and increase tumor cell killing [57]. The cetuximab and taxane chemotherapy combination has shown promising survival and response results in single arm studies [12, 58, 59]. However, studies testing the taxane-platinum-cetuximab combination differed in the population enrolled, taxane used, doses, and administration schedule, and are thus not comparable [12, 58–61]. Table 2 summarizes terminated and ongoing studies exploring taxane-based combinations.

The use of a taxane in place of 5-FU could be indicated in patients with contraindications to 5-FU or having DPD deficiency, and could potentially avoid cardiovascular events (angina, rhythm disturbances, and ischemic events). The combination of cetuximab and weekly paclitaxel is active and well

Table 2. Terminated and ongoing studies evaluating a taxane-platinum-cetuximab combination in first-line treatment of R/M HNSCC

Terminated study [ref]	No. of patients	Phase	Regimen	Median OS (months)	Median PFS (months)	ORR (%)
TPEx [12]	54	II	Docetaxel/cisplatin (75 mg/m^2) + G-CSF/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2): 4 cycles q3w + Maintenance cetuximab 500 mg/m^2 q2w	14.0	6.2	44.4
CSPOR-HN02 [59]	45	II	Paclitaxel (100 mg/m^2 Day 1, Day 8)/carboplatin (AUC 2.5 Day 1, Day 8)/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2): 6 cycles q3w + Maintenance cetuximab 250 mg/m^2 qw	14.7	5.2	40
CET-INT (B490) [60]	201	II	Cisplatin (100 mg/m^2)/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2): cycles q3w + Maintenance cetuximab 250 mg/m^2 qw vs paclitaxel (175 mg/m^2)/cisplatin (100 mg/m^2)/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2): cycles q3w + Maintenance cetuximab 250 mg/m^2 qw	13.0 vs 11.0 = (p = 0.117, HR 0.77)	6 vs 7	41.8 vs 51.7
CET-MET [61]	85	II	Paclitaxel (175 mg/m^2 qw)/carboplatin AUC 5/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2) + Maintenance cetuximab 500 mg/m^2 q2w vs cisplatin or carboplatin (100 mg/m^2/AUC5, respectively)/5-FU (1000 mg/m^2/24h for 4 days)/ cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2): cycles q3w + Maintenance cetuximab 500 mg/m^2 q2w	10.2 vs 8.4 (p = 0.166, HR 0.71)	6.5 vs 4.4 (p = 0.064, HR 0.65)	51.2 vs 47.6
CACTUX [58]	32	II	Cisplatin or carboplatin (75 mg/m^2 q3w/AUC5, respectively)/nab-paclitaxel (100 mg/m^2 qw)/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2) + Maintenance cetuximab 250 mg/m^2 + nab-paclitaxel 100 mg/m^2 qw	18.8[a]	6.8[a]	63.0[a]
Ongoing studies				**Countries**	**Primary endpoint**	**Expected results**
TPEXTREME (NCT02268695)	540[b]	II/III	Docetaxel/cisplatin (75 mg/m^2)/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2): 4 cycles q3w + maintenance cetuximab 500 mg/m^2 q2w vs EXTREME	France Germany Spain	OS	May 2019
LCCC1330 (NCT02124707)	38[b]	II	Paclitaxel (135 mg/m^2 qw)/carboplatin AUC 2/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2) + maintenance cetuximab 250 mg/m^2 qw	USA	OS	Feb 2020

Table 2. (Continued)

CACTUX (NCT02270814)	**40[c]**	**II**	**Cisplatin or carboplatin (75 mg/m^2 q3w/AUC5, respectively)/nab-paclitaxel (100 mg/m^2 qw)/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2) + maintenance cetuximab 250 mg/m^2 + nab-paclitaxel 100 mg/m^2 qw**	**USA**	**PFS**	**May 2021**
ENT0033 (NCT01437449)	**27[c]**	**II**	**Cisplatin (30 mg/m^2 qw)/docetaxel (30 mg/m^2 qw)/cetuximab (loading dose 400 mg/m^2 followed by weekly 250 mg/m^2) + maintenance: not specified**	**USA**	**ORR**	**Jan 2021**

AUC area under the curve, *nab-paclitaxel* albumin-bound paclitaxel, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *qw* every week, *q2w* every 2 weeks, *q3w* every 3 weeks

[a]Results from a planned interim analysis

[b]Either previously untreated or progressed on therapy in the locally advanced (LA) setting > 6 months ago

[c]Either previously untreated or progressed on therapy in the LA setting > 3–4 months ago

tolerated and may be an option for the treatment of medically unfit patients, particularly those for whom platinum is contraindicated, or those with poor prognosis or later-line setting [62].

Finally, from a patient's point of view, completing a chemotherapy course in 1 day [63, 64] and thus avoiding a 4-day continuous infusion are important in terms of fatigue, logistic, and potential complications.

Otherwise, long-term survivors having a sustained complete response with docetaxel-based chemotherapy regimen have been reported in several case reports [65–67].

Results of the randomized TPEXTREME study, which is investigating the clinical benefits of the TPEx regimen as described in the GORTEC 2008-03 study [12] vs EXTREME, are eagerly awaited to confirm the activity of taxane-based chemotherapy. Depending on the results, the TPEx regimen may become a treatment option for fit patients with R/M HNSCC. More generally, it may open the way for new taxane-based combinations.

Treatment of oligometastatic patients

The standard of care in the case of oligometastatic disease is systemic chemotherapy [7•, 19, 68•]. More aggressive approaches combining chemotherapy and locoregional treatment (including surgery and radiotherapy) demonstrated prolonged survival in some patients [69]. The analysis of small retrospective studies showed that there is a potential benefit from loco-ablative approaches combined with systemic treatment in disease-free survival or 5-year OS [70–73] despite a heterogeneous population with different histological subtypes, not allowing generalization. A prospective Phase II trial is currently ongoing comparing stereotactic radiotherapy associated to EXTREME regimen to stereotactic radiotherapy alone (NCT03070366).

Alternative immunotherapy treatment for patients with R/M disease

The landscape in the R/M HNSCC setting is evolving, and the first-line standard of care is becoming fragmented due to newly available treatment options. The advent of CPIs has brought about a paradigm shift in the landscape.

Cancer immunotherapy with immune checkpoint blockade is based on the inhibition of the tumor-mediated suppression of anticancer immune responses, in contrast with therapeutic strategies that exert direct cytotoxic effects on tumor cells [74–77]. CPIs include, among others, monoclonal antibodies to the receptor cytotoxic T lymphocyte antigen-4 (CTLA-4) and PD-1 expressed on T cells, or PD-L1, which is expressed by a variety of cell types, including some tumor cells.

Several studies evaluated various CPIs as monotherapy treatment or in combination (Table 1).

After the CheckMate-141 and KEYNOTE-040 reference studies [41••, 42••, 43••, 45, 48, 49] that led to the approval of anti-PD1 nivolumab and pembrolizumab, anti-PD-L1 were tested. In monotherapy in second-line treatment, the Phase II HAWK trial [44] tested durvalumab in PD-L1 positive R/M HNSCC, and atezolizumab was tested in a small Phase Ia trial of 32 patients

[47]. Both studies showed similar results than those obtained with anti-PD1, encouraging to do further studies.

With the view to affect multiple aspects of the immune response and potentiate anti-cancer immunity, combinations of anti-CTLA-4 and anti-PD-1 antibodies were assessed [46]. Blockade of CTLA-4 induces a proliferative signature in T cells, whereas PD-1 blockade leads to modification of genes that are involved in T cell or NK functions [78]. Furthermore, anti-CTLA-4 antibodies seem more capable of inducing antibody-dependent cell-mediated cytotoxicity (ADCC) than PD-1 antibodies, as demonstrated in melanoma [79].

The Phase II CONDOR evaluated durvalumab monotherapy, tremelimumab monotherapy, and combination of durvalumab + tremelimumab in pre-treated R/M HNSCC [46]. A key eligibility criteria was the PD-L1-low/negative status defined as tumor cells < 25%. The combination demonstrated a median OS superior to monotherapy arms (6.0 vs 5.5 vs 7.6 months). Median PFS was not different between arms.

However, the first results of randomized trials seem disappointing. KESTREL and EAGLE are two parallel phase III trials designed to evaluate durvalumab alone or associated with tremelimumab compared with EXTREME regimen in first-line setting (KESTREL, NCT02551159) or in platinum refractory disease (EAGLE, NCT02369874). The phase III EAGLE trial results have not yet been published, but a press release mentioned that the trial was negative: Durvalumab monotherapy and durvalumab + tremelimumab did not improve OS compared to standard-of-care chemotherapy. KESTREL's results are awaited for 2019.

The Phase III Checkmate 651 trial (NCT02741570) compares nivolumab in combination with ipilimumab with EXTREME regimen in frontline setting. The primary endpoint is OS. No preliminary results are available at this point.

Three Phase Ib or II trials are evaluating other combinations with CPI: ATHENA (NCT03818061) with atezolizumab + bevacizumab, KEYNOTE-137 (NCT02643550) with pembrolizumab + talimogene laherparepvec (TVEC), and one with monazilumab + cetuximab (NCT02643550). Preliminary data of KEYNOTE-137 were presented at 2018 ASCO Annual congress, showing low response rates.

Immune checkpoint inhibitors combined with conventional cancer treatments

Chemo-induced immune modulation is based on several mechanisms, like cisplatin which undermines tumorigenic activities of tumor-associated macrophages [80]. On the other hand, cisplatin enhances T cell-mediated immune responses.

The Phase III KEYNOTE-048 trial compared 3 arms: pembrolizumab monotherapy (A), EXTREME regimen (B), and pembrolizumab + cisplatin (or carboplatin) + 5-FU (C) [15] in the first-line setting. Stratification was performed on PD-L1 expression (TPS ≥ 50 vs < 50), p16 status for oropharyngeal tumors (positive vs negative), and performance status (0 vs 1). Two hypotheses were scheduled: the first one related to arm A vs B and the second one to B vs C. First results presented at 2018 ESMO annual congress were positive: Arm A was superior in OS to the standard B for PD-L1 overexpressed tumors with a better safety profile; arm C superior to arm B whatever PD-L1 expression level. Data are presented in Table 1.

This trial is the first one with an anti-PD1 demonstrating a superior OS over the standard of care in first-line setting. This study established PD-L1 combined positive score (CPS) as a valid marker to select patients that potentially would benefit from pembrolizumab monotherapy. Complete results are awaited. Patients with PD-L1-low and PD-L1-negative tumors and those with high tumor burden may more likely to benefit from other chemotherapy-based combination.

Perspectives for the treatment of R/M HNSCC

Besides anti-PD-1 and anti-PD-L1 CPIs, alone or combined with an anti-CTLA-4 agent, chemotherapy or cetuximab, there are other ways which are currently explored.

The combinations of anti-PD(L)-1 with another IO agent

Despite first promising studies testing indoleamine 2,3 dioxygenase (IDO) inhibitor (anti-IDO1, epacadostat), the randomized trials planned in HNSCC testing this new agent in different combinations have been abandoned after the disappointing results of a randomized study in melanoma.

However, other combinations of new IO agent with anti-PD(L)-1 are currently explored. First results of early phase trials have been presented at the last ESMO congress. Despite any activity of these new agents in monotherapy, the combinations of STAT3 inhibitor or M7824 anti-TGF beta trap with anti-PDL-1 durvalumab have shown first promising results [81, 82].

Intratumoral administration of a new drugs is also explored, such as SD01, a TLR9 agonist in combination with anti-PD1 (pembrolizumab) [83].

Chemo-free and anti-PD(L)-1 free combinations seem possible, and several trials are ongoing to explore this new approach.

A trial testing the monalizumab (anti-NKG2A drug) and cetuximab combination showed promising results with 27% ORR and 10 months OS in platinum refractory patients [84].

A randomized clinical trial that investigates CDK4/6 inhibitors combined with cetuximab vs cetuximab alone in platinum-resistant HPV-negative HNSCC is ongoing (NCT02499120), after the first promising results of the phase II (ORR 39%, median OS 9.5 months).

Vaccines

In HPV-positive HNSSC, vaccine strategies are under investigation. Encouraging results from a phase II trial evaluating the efficacy of nivolumab + vaccine ISA101 in patients with HPV-related tumors including 22 oropharyngeal HNSCC have been reported [85]. The ORR in OPC was 36% with a good tolerance and prolonged responses. A randomized trial has been programmed.

Conclusion

These new combinations could be the next options in the therapeutic armamentarium for HNSCC, either in first-line or after anti-PD1 treatment, challenging the question of the best sequence of this therapies. Increasing our

knowledge of mechanisms of oncogenesis and useful biomarkers should help to define the patients who benefit from these new agents and to determine the best sequence of treatment for R/M HNSCC patients.

Compliance with Ethical Standards

Conflict of Interest

Joel Guigay has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, Innate Pharma, and Merck KGaA, and has received research grants from GlaxoSmithKline, Bristol-Myers Squibb, Chugaï, and Merck KGaA.
Esma Sâada-Bouzid declares that she has no conflict of interest.
Frédéric Peyrade declares that he has no conflict of interest.
Cécile Michel declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2008;83:489–501.
2. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000;92:709–20.
3.•• Vermorken JB, Mesia R, Rivera F, et al. Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer. N Engl J Med. 2008;359:1116–27.
Reference article establishing the current first line treatment in R/M HNSCC.
4. Vermorken JB, Stöhlmacher-Williams J, Davidenko I, et al. Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): an open-label phase 3 randomized trial. Lancet Oncol. 2013;14:697–710.
5. Organization WH. The globocan project. Geneva; 2018. Available from http://globocan.iarc.fr/. Accessed 04 Dec 2018.
6. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. Lancet. 2008;371:1695–709.
7.• Sacco AG, Cohen EE. Current Treatment Options for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2015;33:3305–13.
Reference publication on R/M HNSCC.
8. Leon X, Quer M, Orus C, et al. Distant metastases in head and neck cancer patients who achieved loco-regional control. Head Neck. 2000;22:680–6.
9. Sun XS, Michel C, Babin E, et al. Approach to oligometastatic disease in head and neck cancer, on behalf of the GORTEC. Future Oncol. 2018;14(9):877–89.
10. Price KR, Cohen E. Current Treatment Options for Metastatic Head and Neck Cancer. Curr Treat Options in Oncol. 2012;13:35–46.
11. Kalyankrishna S, Grandis JR. Epidermal growth factor receptor biology in head and neck cancer. J Clin Oncol. 2006;24:2666–72.
12. Guigay J, Fayette J, Dillies AF, et al. Cetuximab, docetaxel, and cisplatin as first-line treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma: a multicenter, phase II GORTEC study. Ann Oncol. 2015;26:1941–7.
13. Guigay J, Keilholz U, Mesia R, et al. PO-091: TPExtreme randomized trial: Docetaxel-Platinum(P)-Cetuximab(C) versus 5FU-P-C in recurrent/metastatic HNSCC. Radiother Oncol. 114:46.
14. Ferris RL. Immunology and Immunotherapy of Head and Neck Cancer. J Clin Oncol. 2015;33:3293–304.

15. Burtness B, Harrington KJ, Greil R, et al. KEYNOTE-048: Phase 3 study of first-line pembrolizumab for recurrent/metastatic head and neck squamous cell carnicoma. Oral Present Abstr #LBA8-PR ESMO, 2018.
16. Guardiola E, Peyrade F, Chaigneau L, et al. Results of a randomized phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer. 2004;40:2071–6.
17. Peyrade F, Cupissol D, Geoffrois L, et al. Systemic treatment and medical management of metastatic squamous cell carcinoma of the head and neck: Review of the literature and proposal for management changes. Oral Oncol. 2013;49:482–91.
18. Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol. 2007;25:2171–7.
19. Grégoire V, Lefebvre J-L, Licitra L, et al. Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21:v184–6.
20. Guigay J, Peyrade F, Petre-Lazar B, et al. Cetuximab relative dose intensity (RDI) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): First observational prospective study in unselected patients (DIRECT trial). Ann Oncol. 2014;25.
21. Le Tourneau C, Ghiani M, Cau MC, et al. The observational ENCORE study: cetuximab + platinum-based therapy (PBT) for first-line (1 L) treatment of patients with recurrent/metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). Ann Oncol. 2017;28.
22. Linares J, Rullan A, Taberna M, et al. Emergence of long-term surviving patients with the introduction of Cetuximab in recurrent/metastatic disease of squamous cell carcinoma of head and neck. Oral Oncol. 2016;55:e4.
23. Vermorken JB, Remenar E, Hitt R, et al. Platinum-based chemotherapy (CT) plus cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck cancer (R/M-SCCHN): 5-year follow-up data for the EXTREME trial. ASCO Annu Meet Proc, 2014; 32(15_suppl): 6021.
24. Castet F, Brenes J, Taberna M, Mesia R. The emergence of long-term survivors in recurrent and metastatic quamous cell head and neck cancer. Curr Opin Oncol. 2019;31(3):160–168. https://doi.org/10.1097/CCO.0000000000000530.
25. Guigay J, Le Caer H, Mertens C, et al. Elderly Head and Neck Cancer (ELAN) study: personalized treatment according to geriatric assessment in patients age 70 or older: first prospective trials in patients with squamous cell cancer of the head and neck (SCCHN) unsuitable for surgery. J Clin Oncol. 2014;32(15_suppl):abstract TPS6099.
26. Kushwaha VS, Gupta S, Husain N, et al. Gefitinib, Methotrexate and Methotrexate plus 5-Fluorouracil as palliative treatment in recurrent head and neck squamous cell carcinoma. Cancer Biol Ther. 2015;16:346–51.
27. Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomized phase 3 trial. Lancet Oncol. 2015;16:583–94.
28. Argiris A, Ghebremichael M, Gilbert J, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an eastern cooperative oncology group trial. J Clin Oncol. 2013;31:1405–14.
29. Argiris A, Buchanan A, Brockstein B, et al. Docetaxel and irinotecan in recurrent or metastatic head and neck cancer: a phase 2 trial of the Eastern Cooperative Oncology Group. Cancer. 2009;115:4504–13.
30. Machiels J-P, Subramanian S, Ruzsa A, et al. Zalutumumab plus best supportive care versus best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomized phase 3 trial. Lancet Oncol. 2011;12:333–43.
31. Vermorken JB, Herbst RS, Leon X, et al. Overview of the efficacy of cetuximab in recurrent and/or metastatic squamous cell carcinoma of the head and neck in patients who previously failed platinum-based therapies. Cancer. 2008;112:2710–9.
32. Jimenez B, Trigo JM, Pajares BI, et al. Efficacy and safety of weekly paclitaxel combined with cetuximab in the treatment of pretreated recurrent/metastatic head and neck cancer patients. Oral Oncol. 2013;49:182–5.
33. Knoedler M, Gauler TC, Gruenwald V, et al. Phase II study of cetuximab in combination with docetaxel in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck after platinum-containing therapy: a multicenter study of the Arbeitsgemeinschaft Internistische Onkologie. Oncology. 2013;84:284–9.
34. Peron J, Poupart M, Ceruse P, et al. Efficacy and safety of capecitabine in heavily pretreated recurrent/metastatic head and neck squamous cell carcinoma. Anti-Cancer Drugs. 2012;23:1107–11.
35. Sosa AE, Grau JJ, Feliz L, et al. Outcome of patients treated with palliative weekly paclitaxel plus cetuximab in recurrent head and neck cancer after failure of platinum-based therapy. Eur Arch Otorhinolaryngol. 2014;271:373–8.
36. Rischin D, Spigel DR, Adkins D, et al. PRISM: phase 2 trial with panitumumab monotherapy as second-line treatment in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Head Neck. 2016;38(Suppl 1):E1756–61.

37. Seiwert TY, Fayette J, Cupissol D, et al. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. Ann Oncol. 2014;25:1813–20.
38. Simpson DR, Mell LK, Cohen EE. Targeting the PI3K/AKT/mTOR pathway in squamous cell carcinoma of the head and neck. Oral Oncol. 2015;51:291–8.
39. Soulieres D, Faivre S, Mesia R, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomized, double-blind, placebo-controlled phase 2 trial. Lancet Oncol. 2017;18:323–35.
40. Mehra R, Seiwert TY, Gupta S, et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M SCCHN): pooled analyses after long-term follow-up in KEYNOTE-012. Br J Cancer. 2018;119(2):153–9.
41.•• Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncol. 2018;81:45–51.
Results having lead to nivolumab approval grant by US Food and Drug Administration and European Medicines Agency in second-line treatment.
42.•• Ferris RL, Blumenschein GR, Fayette J, et al. Further evaluations of nivolumab (nivo) versus investigator's choice (IC) chemotherapy for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Checkmate 141. J Clin Oncol. 2016;34(suppl):abstr 6009.
Results having lead to nivolumab approval grant by US Food and Drug Administration and European Medicines Agency in second-line treatment.
43.•• Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomized, open-label, phase 3 study. Lancet. 2019;393:156–67.
Results having lead to market aproval in Europe of pembrolizumab for R/M patients progressing on or after platinum-containing chemotherapy.
44. Zandberg DP, Algazi AP, Jimeno A, et al. Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: results from a single-arm, phase II study in patients with >/=25% tumor cell PD-L1 expression who have progressed on platinum-based chemotherapy. Eur J Cancer. 2019;107:142–52.
45. Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: results from a single-arm, phase II study. J Clin Oncol. 2017:JCO2016701524.
46. Siu LL, Even C, Mesia R, et al. Safety and efficacy of durvalumab with or without tremelimumab in patients with PD-L1-low/negative recurrent or metastatic HNSCC: The Phase 2 CONDOR Randomized Clinical Trial. JAMA Oncol. 2018.
47. Colevas AD, Bahleda R, Braiteh F, et al. Safety and clinical activity of atezolizumab in head and neck cancer: results from a phase I trial. Ann Oncol. 2018;29:2247–53.
48. Chow LQ, Haddad R, Gupta S, et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol. 2016.
49. Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016;17:956–65.
50.• Harrington KJ, Ferris RL, Blumenschein G Jr, et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomized, phase 3 trial. Lancet Oncol. 2017;18:1104–15.
Article showing that nivolumab delay time to deterioration of patient quality of life compared to standard treatment.
51. Lala M, Chirovsky D, Cheng JD, Mayawala K. Clinical outcomes with therapies for previously treated recurrent/metastatic head-and-neck squamous cell carcinoma (R/M HNSCC): a systematic literature review. Oral Oncol. 2018;84:108–20.
52. Machiels JP, Kaminsky MC, Keller U, et al. Phase Ib trial of the Toll-like receptor 9 agonist IMO-2055 in combination with 5-fluorouracil, cisplatin, and cetuximab as first-line palliative treatment in patients with recurrent/metastatic squamous cell carcinoma of the head and neck. Investig New Drugs. 2013;31:1207–16.
53. Vermorken JB, Licitra L, Stöhlmacher-Williams J, et al. Phase II study of pemetrexed in combination with cisplatin and cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck. Eur J Cancer. 2013;49:2877–83.
54. Vermorken JB, Peyrade F, Krauss J, et al. Cisplatin, 5-fluorouracil, and cetuximab (PFE) with or without cilengitide in recurrent/metastatic squamous cell carcinoma of the head and neck: results of the randomized phase I/II ADVANTAGE trial (phase II part). Ann Oncol. 2014;25:682–8.
55. Morelli MP, Cascone T, Troiani T, et al. Sequence-dependent antiproliferative effects of cytotoxic drugs and epidermal growth factor receptor inhibitors. Ann Oncol. 2005;16(Suppl 4):iv61–8.
56. Rose WC, Wild R. Therapeutic synergy of oral taxane BMS-275183 and cetuximab versus human tumor xenografts. Clin Cancer Res. 2004;10:7413–7.
57. Garnett CT, Schlom J, Hodge JW. Combination of docetaxel and recombinant vaccine enhances T cell responses and antitumor activity: effects of docetaxel on immune enhancement. Clin Cancer Res. 2008;14:3536–44.

58. Adkins D, Ley J, Atiq OT et al. Multicenter phase II trial of carbo- or cisplatin, nanoparticle album bound (nab)-paclitaxel, and CeTUXimab as first line therapy for recurrent/metastatic HNSCC: the CACTUX trial. Multidisciplinary Head and Neck Cancers Symposium 2018; LBA9.
59. Tahara M, Kiyota N, Yokota T, et al. Phase II trial of combination treatment with paclitaxel, carboplatin and cetuximab (PCE) as first-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CSPOR-HN02). Ann Oncol. 2018;29:1004–9.
60. Bossi P, Miceli R, Locati LD, et al. A randomized, phase 2 study of cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2017;28:2820–6.
61. Friesland S, Tsakonas G, Kristensen C, et al. Randomized phase II study with cetuximab in combinaton with 5-FU and cisplatin or carboplatin versus cetuximab in combination with paclitaxel and carboplatin for treatment of patients with relapsed or metastatic squamous cell carcinoma of the head and neck (CETMET trial). J Clin Oncol. 2018;36(suppl):abstr 6032.
62. Hitt R, Irigoyen A, Cortes-Funes H, et al. Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Ann Oncol. 2012;23:1016–22.
63. Peron J, Ceruse P, Lavergne E, et al. Paclitaxel and cetuximab combination efficiency after the failure of a platinum-based chemotherapy in recurrent/metastatic head and neck squamous cell carcinoma. Anti-Cancer Drugs. 2012;23:996–1001.
64. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf. 2009;8:191–202.
65. Guigay J, Even C, Mayache-Badis L, et al. Long-term response in patient with recurrent oropharyngeal carcinoma treated with cetuximab, docetaxel and cisplatin (TPEx) as first-line treatment followed by cetuximab maintenance. Oral Oncol. 2017.
66. Perri F, Longo F, Della Vittoria Scarpati G, et al. Metastatic HPV-related oropharyngeal carcinoma cured with chemoradiotherapy: importance of pretherapy biomolecular assessment. Clin Case Rep. 2018;6:56–62.
67. Szturz P, Specenier P, Van Laer C, et al. Long-term remission of locally recurrent oropharyngeal cancer after docetaxel-based chemotherapy plus cetuximab. Eur Arch Otorhinolaryngol. 2016;273:1629–36.
68.• Argiris A, Harrington KJ, Tahara M, et al. Evidence-based treatment options in recurrent and/or metastatic squamous cell carcinoma of the head and neck. Front Oncol. 2017;7:72.

Review giving evidence-based treatment options in R/M HNSCC.

69. Leeman JE, Li JG, Pei X, et al. Patterns of treatment failure and postrecurrence outcomes among patients with locally advanced head and neck squamous cell carcinoma after chemoradiotherapy using modern radiation techniques. JAMA Oncol. 2017.
70. Haro A, Yano T, Yoshida T, et al. Results of a surgical resection of pulmonary metastasis from malignant head and neck tumor. Interact Cardiovasc Thorac Surg. 2010;10:700–3.
71. Leeman JE, Rimner A, Montecalvo J, et al. Histologic subtype in core lung biopsies of early-stage lung adenocarcinoma is a prognostic factor for treatment response and failure patterns after stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys. 2017;97:138–45.
72. Miyazaki T, Hasegawa Y, Hanai N, et al. Survival impact of pulmonary metastasectomy for patients with head and neck cancer. Head Neck. 2013;35:1745–51.
73. Shiono S, Kawamura M, Sato T, et al. Pulmonary metastasectomy for pulmonary metastases of head and neck squamous cell carcinomas. Ann Thorac Surg. 2009;88:856–60.
74. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. Annu Rev Immunol. 1996;14:233–58.
75. Nishino M, Jagannathan JP, Krajewski KM, et al. Personalized tumor response assessment in the era of molecular medicine: cancer-specific and therapy-specific response criteria to complement pitfalls of RECIST. AJR Am J Roentgenol. 2012;198:737–45.
76. Nishino M, Tirumani SH, Ramaiya NH, Hodi FS. Cancer immunotherapy and immune-related response assessment: the role of radiologists in the new arena of cancer treatment. Eur J Radiol. 2015;84:1259–68.
77. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. Clin Cancer Res. 2013;19:5300–9.
78. Das R, Verma R, Sznol M, et al. Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. J Immunol. 2015;194:950–9.
79. Somasundaram R, Herlyn M. Nivolumab in combination with ipilimumab for the treatment of melanoma. Expert Rev Anticancer Ther. 2015;15:1135–41.
80. Potapov SL, Korman DB, Shamaev VI, et al. Sensitivity of clonogenic cells of human ovarian ascitic cancer to antitumor drugs. Arch Geschwulstforsch. 1988;58:99–104.
81. Cho BC, Daste A, Ravaud A, et al. M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF in patients with advanced SCCHN: results from a phase 1 cohort. Ann Oncol. 2018;29(suppl_8):viii372–99.
82. Cohen EEW, Harrington KJ, Hong DS, et al. A phase 1b/2 study (SCORES) of durvalumab (D) plus danvatirsen (DAN; AZD9150) or AZD5069 (CX2i) in advanced solid malignancies and recurrent/metastatic HNSCC. Ann Oncol. 2018;29(suppl_8):viii372–99.

83. Cohen EEW, Algazi A, Laux D, et al. Phase 1b/2 open label, multicenter study of intratumoral SD-101 in combination with pembrolizumab in anti-PD-1 treatment naïve patients with recurrent/metastatic HNSCC. Ann Oncol. 2018;29(suppl_8):viii372–99.
84. Fayette J, et al. Results of a phase II study evaluating monalizumab in combination with cetuximab in previously treated recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). ESMO annual meeting 2018; Abstr.1249PD.
85. Massarelli E, William W, Johnson F, et al. Combining immune checkpoint blockade and tumor-specific vaccine for patients with incurable human papillomavirus 16-related cancer: a phase 2 clinical trial. JAMA Oncol. 2019;5:67–73.

Publisher's Note