



HAL
open science

Combination of radiation therapy-immunotherapy for head and neck cancers: Promises kept?

Florence Huguet, Bénédicte Durand, Sarah Atallah, Coralie Prébet, Sandrine Richard, Bertrand Baujat

► To cite this version:

Florence Huguet, Bénédicte Durand, Sarah Atallah, Coralie Prébet, Sandrine Richard, et al.. Combination of radiation therapy-immunotherapy for head and neck cancers: Promises kept?. *Cancer/Radiothérapie*, 2021, 25 (8), pp.811-815. 10.1016/j.canrad.2021.08.018 . hal-03552062

HAL Id: hal-03552062

<https://hal.sorbonne-universite.fr/hal-03552062>

Submitted on 2 Feb 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

[Click here to view linked References](#)

1

**Combination of radiation therapy-immunotherapy for head and neck cancers: promises
kept?**

Florence Huguet ¹, Bénédicte Durand ¹, Sarah Atallah ², Coralie Prébet ³, Sandrine Richard ³,
Bertrand Baujat ²

¹ Service d'Oncologie Radiothérapie, ² Service d'Oto-Rhino-Laryngologie Chirurgie cervico-
faciale, ³ Service d'Oncologie Médicale, Hôpital Tenon, Sorbonne Université, AP-HP, Paris.

Corresponding author: Pr Florence HUGUET, Service d'Oncologie Radiothérapie, Hôpital
Tenon, 4 rue de la Chine, 75020 Paris ; tel 01 56 01 83 22 ; fax 01 56 01 64 00
florence.huguet@aphp.fr

French title: Combinaison radiothérapie-immunothérapie pour les cancers des voies aéro-
digestives supérieures: promesses tenues ?

Short title: Head and neck cancers: radiotherapy and immunotherapy.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Abstract

1
2 Chemoradiotherapy with concurrent cisplatin has been the standard treatment for locally
3
4 advanced head and neck squamous cell carcinoma (HNSCC) for over 20 years. Recently,
5
6 immunotherapy, a new therapeutic class, has emerged for patients with recurrent or
7
8 metastatic HNSCC and has significantly extended their survival. Will it bring the same benefit
9
10 to patients with localized tumors? There is a strong rationale for combining radiation
11
12 therapy and checkpoint inhibitors for HNSCC. Indeed, radiation therapy can have both
13
14 immunostimulatory and immunomodulatory effects. This is what explains the famous
15
16 abscopal effect. The aim of this review is to present the data available on the combination of
17
18 radiation therapy and immunotherapy for HNSCC.
19
20
21
22
23
24
25
26
27

28 **Keywords:** head and neck cancer; squamous cell carcinoma; radiotherapy;
29
30 chemoradiotherapy; cisplatin; immunotherapy; immune checkpoint inhibitors; PDL1, PD1;
31
32 abscopal effect.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Résumé

1
2 La chimioradiothérapie avec cisplatine est le traitement de référence des carcinomes
3
4 épidermoïdes des voies aéro-digestives supérieures (VADS) localement avancés depuis plus
5
6 de 20 ans. Récemment, l'immunothérapie, une nouvelle classe thérapeutique, a émergé
7
8 pour les patients ayant des cancers des VADS en rechute ou métastatique et permis
9
10 d'allonger significativement leur survie. Apportera-t-elle le même bénéfice aux patients avec
11
12 des tumeurs localisées? Il existe un rationnel solide pour combiner radiothérapie et
13
14 inhibiteurs de checkpoints pour les cancers des VADS. En effet, la radiothérapie peut avoir
15
16 des effets immunostimulateurs comme immunomodulateurs. C'est notamment ce qui
17
18 explique le fameux effet abscopal. Le but de cette revue est de faire le point sur les données
19
20 disponibles sur l'association radiothérapie et immunothérapie pour les cancers des VADS.
21
22
23
24
25
26
27
28
29
30

31 **Mots-clés** : cancers ORL; cancers des voies aéro-digestives supérieures; carcinome
32
33 épidermoïde; radiothérapie; chimioradiothérapie; cisplatine; immunothérapie; inhibiteurs de
34
35 checkpoint; PDL1, PD1; effet abscopal.
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1. Introduction

1
2 Head and neck squamous cell carcinoma (HNSCC) is the 6th leading cancer worldwide with
3
4
5 705,781 new cases and 358,140 deaths reported in 2018 (1). In France, 16853 new cases of
6
7 HNSCC have been diagnosed in 2018, responsible for 4772 deaths (2). Most patients present
8
9
10 with a locally advanced tumor at diagnosis. The risk of extension is mainly locoregional with
11
12 only 10% to 20% of patients presenting with distant metastasis. Therapeutic management
13
14 combines surgery, radiation therapy (RT), and chemotherapy based on the conclusions of a
15
16 multidisciplinary tumor board. For locally advanced tumors (stages III and IV), standard
17
18 treatment has been chemoradiotherapy (CRT) with concurrent cisplatin since the publication
19
20 of the results of MACH-NC meta-analysis by J.P. Pignon et al (3,4). In a recent update on 107
21
22 randomized trials and 19,805 patients, concurrent chemotherapy significantly increased the
23
24 rate of 5-year overall survival (OS) with an absolute benefit of 6.5% (HR=0.83; 95%CI 0.79;
25
26 0.86; p<0.0001) (5). For many years, researchers have tried to improve the efficacy of RT in
27
28 order to cure more patients. Concurrent chemotherapy, by increasing tumor's
29
30 radiosensitivity, is currently the most used. But other options are available such as
31
32 hyperfractionation or combination with cetuximab, an EGFR inhibitor (6,7). A new way to
33
34 explore is the combination of RT with immune checkpoint inhibitors. Indeed, these new
35
36 drugs are more efficient than classical chemotherapy to treat patients with recurrent and/or
37
38 metastatic HNSCC (8). The aim of this review is assess the potential benefit of these new
39
40 combinations for locally advanced HNSCC based on the available data.
41
42
43
44
45
46
47
48
49
50
51
52
53

2. Rational of radiation therapy and immunotherapy combination for HNSCC

54
55 The immune system plays a dual role in cancer development: it can not only suppress tumor
56
57 growth by destroying cancer cells or inhibiting their growth but also promote tumor
58
59
60
61
62
63
64
65

1 progression either by selecting for tumor cells that are more fit to survive in an
2 immunocompetent host or by establishing conditions within the tumor microenvironment
3 that facilitate tumor outgrowth. Schreiber et al have called this phenomenon "cancer
4 immunoediting" (9). The goal of immunotherapy is to tip the scales in the right direction,
5 towards tumor cells elimination rather than promotion. PD-1 (programmed cell death 1) is a
6 protein found on the surface of T cells and is a component of the PD-1 / programmed death-
7 ligand 1 (PD-L1) immune checkpoint. T cells can interact via PD-1 with a tumor cell
8 presenting PD-L1 on its surface. This interaction inactivates the T cell and therefore
9 inactivates one of the defense mechanisms of the immune system against tumor cells.
10 Therefore, the PD-1 / PD-L1 complex plays a central role in the immune system. Immune
11 checkpoint inhibitors are antibodies able to binding to PD-1 or PD-L1 and blocking them.
12 Blocking the immune checkpoint by preventing the interaction between PD-1 and PD-L1
13 activates the immune system (10).

14 For lung cancer, immune checkpoint inhibitors were more efficient in patients with a higher
15 number of somatic tumor mutations than those who had fewer (11). Tumor mutational
16 burden (TMB) is now a well known a genomic biomarker that predicts favorable responses
17 to immune checkpoint inhibitors (12). TMB in HNSCC is also quite high which suggests an
18 efficacy of immunotherapy (13).

19 Indeed, in patients with recurrent and/or metastatic HNSCC, immune checkpoint inhibitors
20 have shown efficacy and manageable safety. First, it has been shown that programmed cell
21 death 1 (PD-1) inhibitors pembrolizumab and nivolumab improved overall survival compared
22 with standard of care in patients with recurrent and/or metastatic HNSCC after a first line of
23 platinum-based chemotherapy (8,14). Secondly, in patients with untreated recurrent and/or
24 metastatic HNSCC, a polychemotherapy combining 5-fluorouracil (5-FU), platin, and

1 cetuximab (EXTREME regimen) has been compared to a monotherapy with pembrolizumab
2 or a combination of 5-FU, platin, and pembrolizumab in the phase III KEYNOTE-048 trial (8).
3
4 PD-L1 expression was characterized by the combined positive score (CPS), defined as the
5
6 number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the
7
8 total number of tumor cells \times 100. In patients with a CPS \geq 20 (40% to 45% of patients),
9
10 pembrolizumab monotherapy improved OS compared to EXTREME with a median OS of 13.6
11
12 months versus 10.4 months (HR=0.65; 95%CI 0.53–0.80; $p < 0.0001$). In patients with a CPS \geq
13
14 1 (40% to 45% of patients), chemotherapy plus pembrolizumab improved OS versus
15
16 EXTREME with a median OS of 14.9 months versus 10.7 months (HR=0.61; 95% CI 0.45–0.83;
17
18 $p = 0.0007$). These results changed the standard of care for these patients. Could immune
19
20 checkpoint inhibitors improve the outcome of patients with locally disease when combined
21
22 with radiation therapy?
23
24
25
26
27
28
29

30 Although ionizing radiations are known to induce tumor cell death via DNA damages, it has
31
32 been shown that ionizing radiations may also eliminate tumors via the activation of immune
33
34 response. For years, some teams have reported rare cases of patients with a cytotoxic effect
35
36 of radiation therapy outside of the radiation field, known as the abscopal effect. The
37
38 mechanism explaining this rare phenomenon has been elucidated recently: local radiation
39
40 produces systemic immune-mediated effects (15). Indeed, ionizing radiations can induce
41
42 immunological changes within the tumor microenvironment by facilitating tumor antigen
43
44 release, increasing T cell infiltration, and up-regulate MHC-1 molecule on tumor cells (16).
45
46
47 However, radiation can also attract immunosuppressive cells into the tumor
48
49 microenvironment. Combining RT with immune checkpoint inhibitors could reverse this
50
51 immunosuppressive effect in favor of immune system stimulation. Preclinical work
52
53 demonstrated synergy between RT and immunotherapy. In a HNSCC mouse model, Oweida
54
55
56
57
58
59
60
61
62
63
64
65

1 et al demonstrated enhanced tumor control and improved survival when combining 10 Gy
2 and a PD-L1 inhibitor (17). Tumor control was correlated with increased tumor T cell
3 infiltration. In another mouse model of HPV-positive HNSCC, the combination of RT and PD-1
4 inhibitor activated of B cells (18).
5
6
7
8
9

10 Current questions are: could the combination of RT and checkpoint inhibitors increase local
11 tumor control with additive or supra-additive effects? And can this combination induce
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

3. Do checkpoints inhibitors increase tumor radiosensitivity?

In order to improve local control and survival of patients with HNSCC, combining radiation therapy with immune checkpoint inhibitors appears like a promising option. Many trials assessing this new association have been launched during the last five years but few results are currently available.

First, the combination of RT and immune checkpoint inhibitors has been assessed in patients ineligible to cisplatin. In a phase II study, 29 patients received RT with 3 cycles of concurrent pembrolizumab followed by 3 more cycles of pembrolizumab (19). Toxicities were typical of RT. However, 59% of grade 3-4 lymphopenia were reported. The 1-year OS and DFS rates were 86% and 76%, respectively.

In the randomized phase II GORTEC 2015-01 PEMBRORAD study, 133 patients were assigned to RT with cetuximab or to RT with pembrolizumab without maintenance treatment (20). Primary endpoint was the rate of locoregional control at 15 months. It was the same in the two arms (59% with cetuximab versus 60% with pembrolizumab, OR = 1.05, p=0.91). With a median follow-up of 25 months, the 2-year OS and DFS rates were also similar (OS: 55% versus 62%, respectively; PFS: 40% versus 42%). The compliance was very good with 92% of

1 patients receiving the planned dose of RT. Immunotherapy seems to have a better global
2 tolerance with 88% of patients receiving the planned dose of immunotherapy versus 75% of
3 patients who received the planned dose of cetuximab. The rates of grade3-4 mucositis and
4 dermatitis were significantly lower in the pembrolizumab arm but with a higher rate of
5 thyroid toxicity of any grade.
6
7
8
9

10
11
12 Concerning the combination of immune checkpoint inhibitors with RT and cisplatin, the first
13 results were presented at ASCO in 2017 by Powell et al (21). In a small phase IB study, 27
14 patients were treated with standard CRT (70 Gy with weekly cisplatin) with concurrent
15 pembrolizumab pursued after CRT for three months. The primary endpoint was the safety.
16
17
18
19
20
21
22
23 These first results were reassuring with a good compliance and a safety profile similar to that
24 of a CRT alone. This was confirmed in the publication of this study with a larger number of
25 patients (22). Among the 59 included patients, 98% completed the full planned RT dose and
26 88% of patients received at least 200 mg/m² of cisplatin. Toxicities were similar to the ones
27 usually reported, such as grade 3 dysphagia (44%) and mucositis (30%). At the end of the
28 treatment, 85% of HPV+ patients and 78% of HPV- had a complete response. For HPV+
29 patients, 2-year OS was 97%. For HPV-, 1-year OS was 86.5%. Adding pembrolizumab to CRT
30 seems safe with promising results.
31
32
33
34
35
36
37
38
39
40
41
42

43
44 In NRG-HN003 phase I study, patients with high-risk (ECS+ and/or R1) HPV- resected HNSCC
45 received adjuvant CRT (60 to 66 Gy with weekly cisplatin) with pembrolizumab (200 mg
46 every 3 weeks) for 8 doses in total, starting the week before CRT (23). Dose-limiting toxicity
47 (DLT) was defined as grade 3 or higher non-hematologic toxicity related to pembrolizumab,
48 immune-related toxicity requiring over two weeks of systemic steroids, or unacceptable RT
49 delay. Among the first 12 included patients, only one DLT was reported (grade 3 fever
50 requiring hospitalization). Twenty more patients were included in an expansion cohort with
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 3 more DLT (diverticulitis, wound infection, nausea). Overall, 94% of patients received the
2 planned dose of cisplatin and pembrolizumab and 85% the planned dose of RT. The 1-year
3 OS and DFS rates were 81% and 62%, respectively.
4

5
6
7 In another phase I study, RTOG 3504, nivolumab was combined with four different RT
8 regimens (10 patients/arm) with a 3-month maintenance: CRT with weekly cisplatin, CRT
9 with high dose cisplatin, RT with cetuximab, or RT alone (24). Administration of concurrent
10 nivolumab was safe with only 3 DLT among the 39 included patients. However, compliance
11 to maintenance nivolumab was very low after high-dose cisplatin or in patients unfit for
12 cisplatin.
13
14
15
16
17
18
19
20
21
22

23 In REACH phase III trial (NCT02999087), patients with locally advanced HNSCC were
24 randomized between an experimental arm combining RT with avelumab and cetuximab
25 followed by 12 months of adjuvant avelumab, versus either CRT with cisplatin for patients fit
26 for cisplatin or RT with cetuximab for unfit patients (20). Among the first 82 included
27 patients, tolerance was good with 99% patients receiving the planned dose of RT and 88%
28 receiving concurrent avelumab as planned. The rate of skin toxicity was not increased in the
29 experimental arm compared to the RT+ cetuximab arm. Results on efficacy are pending
30
31
32
33
34
35
36
37
38
39
40

41 However, one phase III trial failed to show an improvement in survival. In this study, 697
42 patients were randomly assigned to CRT (70 Gy with high dose cisplatin) with placebo or
43 with avelumab, an anti-PDL1 antibody (25). Avelumab was administered at a dose of 10
44 mg/kg every two weeks starting two weeks before CRT and continued for up to one year.
45
46
47
48
49
50
51 Primary endpoint was PFS. At interim analysis, HR for PFS and overall OS were 1.21 (95% CI:
52 0.93-1.57; p=0.92) and 1.31 (95% CI: 0.93-1.85; p=0.94), respectively. Median PFS was not
53 reached. The response rate was similar in the two arms (74% versus 75%). Tolerance was
54 about the same in the two groups. However, more grade 3-4 adverse events were reported
55
56
57
58
59
60
61
62
63
64
65

1 in the avelumab arm with 80% versus 74% (25). Interestingly, it seems that the subgroup of
2 patients with a level of expression of PDL1 superior to 25% at baseline could benefit of the
3 addition of avelumab.
4
5

6
7 In this context, the results of the KEYNOTE-412 phase III study are eagerly awaited (26). In
8 this study, 780 HNSCC patients are randomized between CRT (70 Gy with high dose cisplatin)
9 + placebo or CRT + pembrolizumab (200 mg every 3 weeks up to one year). Primary endpoint
10 is event free survival (NCT03040999).
11
12

13
14 The combination of RT and immune checkpoint inhibitors has also been evaluated in the
15 adjuvant setting. For example, in ongoing NIVOPOSTOP phase III trial, patients with resected
16 tumors with high risk factors of relapse are randomized between adjuvant CRT with cisplatin
17 versus the same treatment combined with nivolumab (NCT03576417).
18
19

20 All these published data are rather disappointing. While the tolerance seems good,
21 combination of immune checkpoint inhibitors with RT or CRT does not seem to improve its
22 efficacy. In patients ineligible to cisplatin, it could be an alternative to cetuximab with a
23 better tolerance.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 **4. Abscopal effect: an urban legend?**

42 In metastatic HNSCC, use of RT and immunotherapy has drawn interest in order to induce
43 abscopal effect defined as a reduction in metastatic disease burden outside of the targeted
44 treatment area. RT is known to have a dual effect on the immune system:
45 immunosuppressive with lymphopenia or increase of regulatory immune cells in tumor
46 microenvironment but also immunogenic effect with liberation of neoantigens in particular
47 when a high dose of radiation is used. Radiation induced neoantigens can boost
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 immunogenic effect through the activation of antigen-presenting cells and then CD8+ T cell
2 priming able to recognize both the primary tumor and the metastatic sites (27).
3

4 For metastatic non small cell lung carcinomas, the pooled analysis of PEMBRO-RT and
5 MDACC trials has shown a significant increase in response rate for unirradiated lesions when
6 pembrolizumab is associated to RT compared to pembrolizumab alone (41.7% versus 19.7%,
7 OR=2.96, $p= 0.004$). Median OS was also significantly longer (19.2 months versus 8.7
8 months, $p= 0.0004$).
9

10 For HNSCC, several cases have already been described. For example, abscopal effect was
11 observed in a patient with metastatic sinonasal squamous cell carcinoma treated with
12 nivolumab 480 mg every 4 weeks after stereotactic body radiation (SBRT) at a dose of 30 Gy
13 in 5 fractions to a single metastasis (28). Another case described an abscopal effect with a
14 complete response of all lesions in a patient with poorly differentiated carcinoma treated
15 with pembrolizumab after SBRT at a dose of 24 Gy in 3 fractions (29).
16

17 However, a single-center phase II trial found that the addition of SBRT to nivolumab did not
18 improve the objective response rate of non irradiated lesions compared to nivolumab alone
19 (30). In this study, 62 patients with metastatic HNSCC were randomly assigned to nivolumab
20 at 3 mg/kg every 2 weeks with or without SBRT at a dose of 9 Gy in 3 fractions to one lesion.
21 Objective response rates in non irradiated lesions were 29% with SBRT and 34.5% without
22 ($p=0.86$). Overall survival was 14.2 months versus 13.9 months ($p= 0.75$). Toxicity was not
23 statistically different in the two groups.
24

25 Another phase I-II trial is currently ongoing. It includes patients with extracranial metastatic
26 HNSCC that received durvalumab, an anti-PDL1 antibody, at a dose of 1500 mg every
27 4 weeks, and tremelimumab, an anti-CTLA4, at a dose of 75 mg every 4 weeks, for 4 cycles
28 with SBRT to a maximum of 5 sites (31). The first results seem to suggest a good tolerance, in
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 particular SBRT did not seem to add toxicity compared to the combination of
2 immunotherapies. The response rate seems encouraging with an estimated median PFS of
3
4
5 7.2 months.
6

7 In conclusions, abscopal effect has been described in a minority of patients treated with
8
9
10 immunotherapy and SBRT for metastatic HNSCC but failed to show outcome improvement in
11
12
13 one phase II trial. However, more studies should be done to define the best therapeutic
14
15
16 sequence when combining RT and immunotherapy in order to obtain an abscopal effect.
17
18
19

20 **5. Perspectives**

21
22
23 Even if these first results are disappointing, many questions are still unanswered, mainly
24
25
26 about the optimal therapeutic sequence and the selection of patients. Indeed, in these first
27
28
29 trials, immune checkpoint inhibitors have been used as if their action mechanisms were the
30
31
32 same than a classical chemotherapy. They have been administered concurrently with
33
34
35 radiation therapy and chemotherapy, mainly with cisplatin, and most often with a
36
37
38 maintenance treatment ranging from 3 months to 1 year. Is it the best way to combine
39
40
41 them? CRT may contribute to a severe immunosuppression status. Let's remember that the
42
43
44 benefit of this combination has been proven in non small cell lung cancer first, with the
45
46
47 results of PACIFIC trial (32). In this study, patients received a sequential treatment with a
48
49
50 CRT followed by durvalumab, an anti-PDL1 antibody, every 2 weeks for 12 months starting 1
51
52
53 to 42 days after the completion of CRT. For HNSCC, two trials explore the question of the
54
55
56 sequence: one NCI phase II randomized trial comparing a CRT (70 Gy with cisplatin) followed
57
58
59 by pembrolizumab from week 10 to 31 versus the same CRT with concurrent pembrolizumab
60
61
62 from week 1 to 22. In IMvoke010 phase III trial, patients with HNSCC with high risk of relapse
63
64
65 are randomized after CRT between a sequential treatment with atezolizumab, an anti-PD1

antibody, for one year versus placebo (NCT03452137). Primary endpoint is overall survival.

Of note, adjuvant treatment should start between 2 and 3 months after the end of CRT, a longer free interval than in PACIFIC trial.

Combining CRT with concurrent immunotherapy does not seem to be synergistic. One explanation of this lack of efficacy could be the immunosuppressive effect of large cervical lymph node areas irradiation. Indeed, Dammeijer et al showed that tumor-draining lymph nodes (TDLNs) play an important role in anti-tumor immune response induced by PD-L1 inhibitor in mouse models (33). In REWRITE phase II trial, patients non eligible to cisplatin with only homolateral involved lymph nodes receive RT at a dose of 70 Gy with concurrent durvalumab followed by adjuvant durvalumab for 6 months (NCT03726775). The originality of this study is that patients do not have contralateral elective node irradiation in order to protect TDLNs. The primary endpoint is non-irradiated neck nodal control rate.

Another related question is the necessity and duration of maintenance treatment. The PACIFIC trial has shown the benefit of an adjuvant treatment for non small cell lung cancer but HNSCC is a different disease with a minor risk to develop distant metastasis. Maintenance (or adjuvant) treatment has been proposed for HNSCC based on the results of studies for recurrent/metastatic tumors but we do not have solid data showing its efficacy for locally advanced tumors. Its length varies from 3 to 12 months without a strong rational.

Another approach is to use immunotherapy as neoadjuvant treatment. Uppaluri et al reported 44% of patients with pathological tumor necrosis after one cycle of neoadjuvant pembrolizumab followed 2 to 3 weeks later by surgery (34). In the ongoing KEYNOTE-689 phase III trial, patients with a resectable tumor are randomized between upfront surgery versus two cycles of pembrolizumab followed by surgery and adjuvant pembrolizumab. In

1 the two arms, adjuvant RT or CRT depends on pathological findings. The primary endpoint is
2 major pathological response to neoadjuvant pembrolizumab and event free survival.
3
4 Neoadjuvant nivolumab before CRT in patients with high-risk HPV positive tumors is also
5 assessed in IMMUNEBOOST trial (NCT03838263). Primary endpoint is the feasibility of this
6 combination.
7
8
9

10
11 For patients with recurrent/metastatic HNSCC, only those with a CPS > 1 benefit from
12 immune checkpoint inhibitors. It could be the same for the combination with radiation
13 therapy as suggested by the subgroup analysis of JAVELIN HN 100 trial (25). How to select
14 the potential responders? In the CheckRad-CD8 multicenter phase II trial, patients with
15 locally advanced HNSCC received a cycle of docetaxel-cisplatin combined with durvalumab
16 and tremelimumab, an anti-CTLA4. They had a tumor biopsy three weeks later. Patients with a
17 pathological complete response (pCR) or with an increase in CD8 tissue infiltration of at least
18 20% compared to the initial biopsy received radiation therapy at a dose of 70 Gy with
19 concurrent durvalumab and tremelimumab followed a maintenance treatment with
20 durvalumab in maintenance for 8 months. The main objective was the feasibility with an
21 expected rate of patients receiving radiotherapy + immunotherapy of at least 80%. Among
22 the 80 patients included, 41 had pCR and 31 an increase in CD8 infiltrate. 82% received the
23 combination. The 2-year progression-free and overall survival rates were 73% and 86%,
24 respectively. However, 75% of patients experienced grade 3 or 4 toxicity, mainly dysphagia
25 (53%), leukopenia (48%), or hepatitis (10%). This approach is interesting. However, if the
26 survival data are encouraging, the significant toxicity of this combination raises questions,
27 especially on the benefit of tremelimumab. A validation on a larger number of patients and
28 in a randomized trial is mandatory.
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

To conclude, many questions are raised about the optimal dose, fractionation, timing, target volume, and field size of RT when combined with immunotherapy. Even if the first results are disappointing, there is still a lot of hope generated by these new therapeutic combinations.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394- 424.
2. Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Étude à partir des registres des cancers du réseau Francim. Résultats préliminaires. Rapport. 1990;161.
3. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet Lond Engl.* 18 mars 2000;355(9208):949- 55.
4. Pignon J-P, Maître A le, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. *Radiother Oncol.* 1 juill 2009;92(1):4- 14.
5. Lacas B, Carmel A, Landais C, Wong SJ, Licitra L, Tobias JS, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. *Radiother Oncol J Eur Soc Ther Radiol Oncol.* mars 2021;156:281- 93.
6. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al. Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med.* 9 févr 2006;354(6):567- 78.
7. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol.* janv 2010;11(1):21- 8.
8. Burtneß B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet Lond Engl.* 23 nov 2019;394(10212):1915- 28.
9. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science.* 25 mars 2011;331(6024):1565 - 70.
10. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity.* 25 juill 2013;39(1):1- 10.
11. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* 3 avr 2015;348(6230):124- 8.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
12. Klempner SJ, Fabrizio D, Bane S, Reinhart M, Peoples T, Ali SM, et al. Tumor Mutational Burden as a Predictive Biomarker for Response to Immune Checkpoint Inhibitors: A Review of Current Evidence. *The Oncologist*. janv 2020;25(1):e147- 59.
13. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. *Nature*. 22 août 2013;500(7463):415- 21.
14. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 10 nov 2016;375(19):1856- 67.
15. Demaria S, Ng B, Devitt ML, Babb JS, Kawashima N, Liebes L, et al. Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys*. 1 mars 2004;58(3):862- 70.
16. Weichselbaum RR, Liang H, Deng L, Fu Y-X. Radiotherapy and immunotherapy: a beneficial liaison? *Nat Rev Clin Oncol*. juin 2017;14(6):365- 79.
17. Oweida A, Lennon S, Calame D, Korpela S, Bhatia S, Sharma J, et al. Ionizing radiation sensitizes tumors to PD-L1 immune checkpoint blockade in orthotopic murine head and neck squamous cell carcinoma. *Oncoimmunology*. 2017;6(10):e1356153.
18. Kim SS, Shen S, Miyauchi S, Sanders PD, Franiak-Pietryga I, Mell L, et al. B Cells Improve Overall Survival in HPV-Associated Squamous Cell Carcinomas and Are Activated by Radiation and PD-1 Blockade. *Clin Cancer Res Off J Am Assoc Cancer Res*. 1 juill 2020;26(13):3345- 59.
19. Weiss J, Sheth S, Deal AM, Grilley Olson JE, Patel S, Hackman TG, et al. Concurrent Definitive Immunoradiotherapy for Patients with Stage III-IV Head and Neck Cancer and Cisplatin Contraindication. *Clin Cancer Res Off J Am Assoc Cancer Res*. 15 août 2020;26(16):4260- 7.
20. Tao Y, Aupérin A, Sun X, Sire C, Martin L, Coutte A, et al. Avelumab–cetuximab–radiotherapy versus standards of care in locally advanced squamous-cell carcinoma of the head and neck: The safety phase of a randomised phase III trial GORTEC 2017-01 (REACH). *Eur J Cancer*. 1 déc 2020;141:21- 9.
21. Powell SF, Gitau MM, Sumey CJ, Reynolds JT, Lohr M, McGraw S, et al. Safety of pembrolizumab with chemoradiation (CRT) in locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). *J Clin Oncol*. 20 mai 2017;35(15_suppl):6011- 6011.
22. Powell SF, Gold KA, Gitau MM, Sumey CJ, Lohr MM, McGraw SC, et al. Safety and Efficacy of Pembrolizumab With Chemoradiotherapy in Locally Advanced Head and Neck Squamous Cell Carcinoma: A Phase IB Study. *J Clin Oncol Off J Am Soc Clin Oncol*. 20 juill 2020;38(21):2427- 37.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
23. Bauman JE, Harris J, Uppaluri R, Yao M, Ferris RL, Chen J, et al. NRG-HN003: Phase I and Expansion Cohort Study of Adjuvant Pembrolizumab, Cisplatin and Radiation Therapy in Pathologically High-Risk Head and Neck Cancer. *Cancers*. 9 juin 2021;13(12):2882.
24. Gillison ML, Ferris RL, Harris J, Colevas AD, Mell LK, Kong C, et al. Safety and disease control achieved with the addition of nivolumab (Nivo) to chemoradiotherapy (CRT) for intermediate (IR) and high-risk (HR) local-regionally advanced head and neck squamous cell carcinoma (HNSCC): RTOG Foundation 3504. *J Clin Oncol*. 20 mai 2019;37(15_suppl):6073- 6073.
25. Lee NY, Ferris RL, Psyrri A, Haddad RI, Tahara M, Bourhis J, et al. Avelumab plus standard-of-care chemoradiotherapy versus chemoradiotherapy alone in patients with locally advanced squamous cell carcinoma of the head and neck: a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial. *Lancet Oncol*. 1 avr 2021;22(4):450- 62.
26. Machiels J-PH, Licitra L, Rischin D, Waldron J, Burtness B, Gregoire V, et al. KEYNOTE-412: Pembrolizumab (pembro) in combination with chemoradiation versus chemoradiation alone in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). *J Clin Oncol*. 20 mai 2017;35(15_suppl):TPS6090- TPS6090.
27. Siva S, MacManus MP, Martin RF, Martin OA. Abscopal effects of radiation therapy: A clinical review for the radiobiologist. *Cancer Lett*. 1 janv 2015;356(1):82 - 90.
28. Forner D, Horwich P, Trites JR, Hollenhorst H, Bullock M, Lamond NWD. The abscopal effect in head-and-neck squamous cell carcinoma treated with radiotherapy and nivolumab: a case report and literature review. *Curr Oncol*. déc 2020;27(6):330- 5.
29. Yazici G, Gullu I, Cengiz M, Elmali A, Yilmaz MT, Aksoy S, et al. The Synergistic Effect of Immune Checkpoint Blockade and Radiotherapy in Recurrent/Metastatic Sinonasal Cancer. *Cureus*. 10(10):e3519.
30. McBride S, Sherman E, Tsai CJ, Baxi S, Aghalar J, Eng J, et al. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. *J Clin Oncol*. 1 janv 2021;39(1):30- 7.
31. Bahig H, Aubin F, Nguyen-Tan PF, Souliere D, Palma DA, Charpentier D, et al. Initial analyses of a phase I/II trial of durvalumab (D) plus tremelimumab (T) and stereotactic body radiotherapy (SBRT) for oligometastatic head and neck carcinoma. *J Clin Oncol*. 20 mai 2020;38(15_suppl):6531- 6531.
32. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med*. 16 nov 2017;377(20):1919- 29.
33. Dammeijer F, van Gulijk M, Mulder EE, Lukkes M, Klaase L, van den Bosch T, et al. The PD-1/PD-L1-Checkpoint Restrains T cell Immunity in Tumor-Draining Lymph Nodes. *Cancer Cell*. 9 nov 2020;38(5):685-700.e8.

34. Uppaluri R, Campbell KM, Egloff AM, Zolkind P, Skidmore ZL, Nussenbaum B, et al. Neoadjuvant and Adjuvant Pembrolizumab in Resectable Locally Advanced, Human Papillomavirus-Unrelated Head and Neck Cancer: A Multicenter, Phase II Trial. Clin Cancer Res Off J Am Assoc Cancer Res. 1 oct 2020;26(19):5140-52.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Table 1 - Selection of ongoing randomized trials assessing the combination of radiation therapy and immunotherapy for locally advanced head and neck squamous cell carcinoma.

NCT number	Phase	N pts	Treatment arm	Primary endpoint
NCT03452137 (IMVOKE010)	III	400	Adjuvant atezolizumab 1 year Placebo	EFS, OS
NCT03040999 (KEYNOTE-412)	III	780	CRT 70 Gy + cisplatin + pembro CRT 70 Gy + cisplatin + placebo	EFS
NCT03765918 (KEYNOTE-689)	III	704	Pembro x 2 - surgery - adjuvant pembro x 15 +/- (CRT) Surgery +/- (CRT)	mPR, EFS
NCT03576417 (NIVOPOSTOP)	III	680	CRT 70 Gy + cisplatin + nivo CRT 70 Gy + cisplatin	DFS
NCT03838263 (IMMUNEBOOST)	IIR	61	Nivolumab x 2 then CRT 70 Gy + cisplatin CRT 70 Gy + cisplatin	Feasibility

Abbreviations: N pts, number of patients; CRT, chemoradiotherapy; pembro, pembrolizumab; EFS, event free survival; OS, overall survival; DFS, disease free survival; mPR, major pathological response.