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Emerging patient-specific treatment modalities in head and neck cancer – a systematic review

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Abstract

Introduction: Head and neck cancer (HNC) is an immunosuppressive disease that demonstrates heterogeneous molecular characteristics and features of tumor-host interaction. Beside radiotherapy and surgery, the current standard of care in systemic treatment involves the use of cytotoxic chemotherapy, monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs). There are also other modalities being developed under the category of immunotherapy, but they are overshadowed by the recent advancements of immune checkpoint inhibitors.

Areas Covered: This systematic review covers recent advancements in "patient-specific" treatment modalities, which can be only administered to a given patient.

Expert Opinion: Currently, patient-specific treatment modalities in HNC mainly consist of active immunotherapy using adoptive cell therapies and/or gene engineered vectors. Despite the slow pace of development, the interest continues in these treatment modalities. The future of HNC treatment is expected to be guided by biomarkers and personalized approaches with tailored combinations of local treatments (radiotherapy, surgery), systemic agents and immune system modulation. Systematic research is required to generate robust data and obtain a high-level of evidence for the effectiveness of such treatment modalities.

Article Highlights

- HNC is caused by exposure to carcinogenic substances (tobacco, alcohol, industrial chemicals) or oncogenic viruses (HPV, EBV) with distinct pathophysiology, biologic and immune profiles.
- The head and neck squamous-cell carcinoma tumor microenvironment is strongly immunosuppressive
- Currently, all patient-specific treatment modalities in HNC are under development and mainly consist of active immunotherapy using adoptive cell therapies and/or gene engineered vectors.
- Despite of the emergence of advanced techniques, the current data suggest, that it is unlikely to find the ultimate cure for HNC using off-the-shelf or patient-specific immunotherapy in the coming years.
- The future of HNC treatment is expected to be guided by biomarkers and personalized with tailored combinations of local treatments (radiotherapy, surgery), systemic agents, and modulation of patients' immune system.
- An ideal personalized and patient-specific treatment with 100% on-target action, efficacy and reproducibility, but 0% off-target action and toxicity is not expected in the near future.

1. Introduction

With an annual incidence of 600.000 cases, head and neck cancer (HNC) is the 6th most common malignancy and responsible for 1-2% of all cancer deaths worldwide [1]. It is a male-predominant (75%) disease and involves a group of tumors arising from anatomical subsites of upper aerodigestive tract, namely nasal and paranasal cavities, nasopharynx, oral cavity, oropharynx, larynx, and hypopharynx. Other non-mucosal subsites of the head and neck are out of the scope of this article. The survival is primarily predicted by stage (lower better), anatomical subsite (larynx best, hypopharynx worst), and human papillomavirus (HPV) association (better if present). There are etiologically two distinct biological categories of HNC. The classical majority is related to nicotine and alcohol consumption. The second group of HNC is caused by viral infections such as oncogenic Human Papillomavirus (HPV) and Epstein-Barr Virus (EBV). HPV-associated HNC is often diagnosed in oropharynx, whereas EBV is the main cause of type II and III nasopharyngeal carcinoma. As expected, the molecular and immunologic characteristics of these biological entities are profoundly different from each other [2–6]. A wider range of mutations (e.g. TP53, CDKN2A, FAT1) characterizes the carcinogen exposure-associated tumors, whereas the HPV and EBV-associated tumors mainly demonstrate oncoproteins expressed by the viral DNA integrated into the nuclei of the infected host cells.

HNC is staged with clinical examination, multimodal imaging, pan-endoscopy and biopsies according to Union for International Cancer Control (UICC) system. Current standard treatment modalities in curative setting involve radiotherapy and/or surgery alone or in combination with cytotoxic chemotherapy agents or cetuximab, the latter being a mAb targeting the extracellular domain of epidermal growth factor receptor (EGFR) [7–12]. The recommended options for the first line systemic treatment in the recurrent and/or metastatic (R/M) setting are various combinations of cytotoxic chemotherapy agents and cetuximab [13,14]. The recommended second-line options in R/M HNC are mono-therapies with immune checkpoint inhibitors (currently, nivolumab and pembrolizumab are approved) [15–17], EGFR tyrosine-kinase inhibitor (TKI) afatinib [18] or combinations of agents used for the first-line treatment.

Anti-Programmed Cell Death Protein 1 (PD-1)/PD-ligand (PD-L) checkpoint inhibitors, anti-EGFR mAbs and TKIs were not the only systemic treatment modalities under investigation in the last years. In the downstream cascade of EGFR pathway, mutations in PI3KCA is detected up to 35% in HNC [6]. Recently, the combination of

paclitaxel and the PI3K inhibitor buparlisib yielded modest but promising response rates [19]. mTOR inhibitor everolimus failed in two consecutive phase II trials [20,21], whereas temsirolimus, another agent from the same category demonstrated meaningful efficacy in another phase II trial [22]. The other downstream cascade of EGFR is the signal transducer and activator of transcription pathway, which is a potential target for novel small molecules (C188-9) and antisense oligonucleotides (AZD9150). Apart from the EGFR pathway, drugs designed to overcome hypoxia, induce apoptotic cancer cell death (e.g. second mitochondria-derived activator of caspase mimetics), inhibit other checkpoint receptors such as CTLA-4, activate co-stimulatory receptors of immune response (e.g. CD40, glucocorticoid-induced tumor necrosis factor receptor, toll-like receptors) and inactivate enzymes which deplete nutrients essential for T-cell proliferation (e.g. Indoleamine 2,3-dioxygenase, Arg1) or which produce toxins inhibiting T-cell proliferation (nitric oxide synthase 2, phosphodiesterase type 5), viral therapies and many others are under investigation [23,24].

The role of immunotherapy by means of the above-mentioned checkpoint inhibitors was clinically established within the last 2 years [15–17]. On the other hand, the term “immunotherapy” is not clearly defined, and its use is heavily influenced by marketing trends. At least concerning HNC, all systemic agents were labeled as “chemotherapy” until early 2000’s. After the publication of the IMCL-9815 [25] and EXTREME [13] trials, cetuximab and later other mAbs and TKIs were started to be referred as “immunotherapy” [26] or “biotherapy” [27], and the cytotoxic agents such as cisplatin and 5-fluoruracil remained as chemotherapeutics. With the establishment of anti-PD-1/PD-L immune checkpoint inhibitors and their accelerating trend, these agents took the role of “immunotherapy”. Ironically, the former mAbs and TKIs are now called “targeted” or “systemic” agents along the “chemotherapeutics”.

The last years in oncology were marked by the success of immune checkpoint inhibitors. In line with the latest trend, there is a bonanza of review articles about emerging mAbs and small molecules design to modulate immune response to solid tumors including HNC. Of note, although being impressive compared to conventional therapies, around 75-80% of HNC patients do not respond to immune checkpoint inhibitors. On the other hand, there are also other modalities under the category of immunotherapy, which are often overlooked, despite continued to be developed. Therefore, we decided to check the latest literature with a different perspective, without the restriction of above-mentioned shifting terms. Before starting to perform this systematic review, we allowed ourselves to define two categories to clarify our domain of interest. Throughout this manuscript, a

“personalized treatment” defines a treatment, which is indicated based on a biomarker identified in an individual, whereas a “patient-specific” treatment designates a treatment, which can be only administered to a given patient and not to another person (e.g. autologous cell transplantation). Nevertheless, these terms are not mutually exclusive. The main focus of this systematic review is the patient-specific treatments, which emerged or continued to be investigated within the last five years.

2.1. Methods

An initial joint discussion between all co-authors was held, and consensus about the definitions and search terms was reached. The electronic search consisted of two parts: published literature and clinicaltrials.gov database.

2.1.1. Data Extraction from Literature

Two independent authors (OE and NC) conducted a systematic literature search in PubMed database for published articles between 4th of September 2013 and 4th of September 2018. The search terms implementing Boolean algorithms were: (“Head and Neck Neoplasms”[Mesh] NOT (“Esophageal Neoplasms”[Mesh] OR “Thyroid Neoplasms”[Mesh])) OR ((cancer OR carcinoma) AND ("head and neck" OR nasopharyn* OR "oral cavity" OR oropharyn* OR laryngeal OR larynx OR hypopharyn* OR "nasal cavity" OR sinonasal)) AND (“adoptive cell” OR “gene insertion” OR (“zinc finger nuclease” OR “ZFN”) OR “transcription activator-like effector nucleases” OR “TALENs” OR “adoptive immunotherapy” OR “cancer stem cell” OR “cancer stem cells” OR “tumor infiltrating lymphocytes” OR “active immunotherapy” OR “chimeric antigen receptor” OR “CAR-T” OR (autologous AND lymphocytes) OR (vaccine OR vaccination) OR immunotherapy OR “virus therapy” OR “viral therapy” OR “vector” OR “vectors” OR “clustered regularly interspaced short palindromic repeat” OR “CRISPR” OR “RNA interference” OR “RNAi” OR “gene edit” OR “gene editing” OR “gene therapy” OR “dendritic cell therapy” OR personalized OR personalised OR individualized OR individualised). PubMed categories of case reports and clinical study were enabled. No language restriction was applied. Additionally, meeting abstracts were manually searched in congress books of the American Society of Clinical Oncology, European Society of Medical Oncology, and European Cancer Congress between 2013 and September 2018. Reference crosscheck was performed in the analyzed full-text articles. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [28] were followed to document details on the search strategy and selection processes.

2.1.2. Data Extraction from clinicaltrials.gov

The XML records of all clinical trials registered at clinicaltrials.gov were downloaded on the 1st of June 2018 and a plain database was created to enable further analysis. The following fields were searched for head and neck cancer-related keywords: short title, scientific title and conditions. Systematic review of database entries was conducted independently by three authors (EVB, OE and NC).

2.1.3. Eligibility Criteria

We included publications concerning patients with HNC arising from the mucosal epithelium of nasal cavity, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx and larynx. At least one of the following endpoints had/planned to be reported: loco-regional control, disease-free survival, progression-free survival, overall survival, response rate, adverse events. All studies had to be clinical and interventional involving humans. Extracted data were recorded into standardized spreadsheets according to the following parameters: brief name of the treatment under investigation (text), number of treatment cycles, biomarker selection (yes/no) patient-specific (yes/no), mechanism of action (text) author, HNC only (yes/no), number of HNC cases in the study, anatomical head and neck subsites (category), disease category and treatment setting (local, locally-advanced, R/M), non-head and neck sites (yes/no – if yes, which), development phase (I, II, III), randomized allocation (yes/no), median follow-up for published data (months), response (text), grade ≥3 toxicity due to investigational therapy (percentage), status (published/ongoing), clinical trial ID, reference(s), remarks. Only "patient-specific" treatments were included in the final analysis. This term entitles a treatment which can be only administered to a given patient and not to another individual (e.g. autologous cell transplantation).

2.2. Results

2.2.1. Search Results

The literature search yielded a total of 164 published articles and 8 meeting abstracts. Only 7 of those, and 1 additional manuscript found via reference crosscheck met the eligibility criteria and were considered for detailed review. A flowchart detailing the number of screened, included and excluded articles, as well as the reasons for exclusion is provided in **Figure 1**. All included studies were published in the last 5 years. No articles had to be excluded because of language or endpoint parameters.

The first step of the search strategy in clinicaltrials.gov identified a total of 3950 out of 276971 trials meeting the keywords. Trials registered during the last five years (from 1st of June 2013 to 1st of June 2018) were selected for further manual review. After exclusion of prematurely terminated or those with unknown status and non-interventional studies, 1199 trials remained for further analysis. Three hundred and fifty-eight trials did not involve HNC (irrelevant keyword match) and were excluded after manual review. Furthermore, trials evaluating therapeutic or diagnostic methods other than personalized and/or patient-specific approach were filtered out. The remaining entries were reviewed for the entire content. Twenty-one studies were categorized as personalized but not as patient-specific, and 18 as patient-specific. **Figure 2** depicts the whole process with details and numbers.

2.2.2. Names of the Therapies and Number of Cycles

Most of the studies harness autologous cell transfer technology with various modifications. Interestingly, there is no naming convention even among studies using similar techniques (see the Tables 1, 2 and the section 2.2.4 below). This may be explained by the fact that the treatments are usually not off-the shelf agents, and therefore not manufactured by pharmaceutical industry. The number of administered treatment cycles vary between 1 and 6.

2.2.3. Selection Based on Biomarker

Two among 8 published and 5 among 17 ongoing (one completed but unpublished) trials include(d) patients based on the presence of biomarkers. The most common criterion was specified as the presence of human leukocyte antigen (HLA) phenotypes in candidates for autologous T-cell transfer. Other specified biomarkers were rather defined as thresholds of target antigen expression levels to be used as study inclusion criteria, such as EGFR, EBV copy number and Epithelial cell adhesion molecule (EpCAM).

2.2.4. Mechanisms of Action

In two [29,30] of the published studies, autologous monocyte-derived dendritic cells (DCs) were obtained through processes of apheresis, isolation, expansion and maturation with colony-stimulating factors and proinflammatory cytokines, and antigen-loading with specific proteins such as p53 [29] or patients' own tumor tissue lysate [30]. The route of administration was either as direct injection into uninvolved (non-head and neck, such as inguinal) lymph nodes [29] or via intravenous [30] route. The aim/rationale was to stimulate the natural killer (NK) and T-cells and achieve anti-tumor immune response. Both of these studies included a relatively broad spectrum of anatomical subsites for HNC [29] and other disease entities [30]. A similar approach seems to be adopted by

NCT02115958 and NCT03282617. However, these two studies explicitly focus on patients diagnosed with nasopharyngeal carcinoma. Another study (NCT03047525) suggests to combine autologous DCs and cytokine-induced NK cells. However, no further detailed description in the trial registry was provided, and contact with the sponsor could not be established.

In a case report, Lakota et al. [31] harvested adipose tissue-derived mesenchymal stem cells of a patient diagnosed with a UICC stage II squamous-cell carcinoma of the tongue, and treated them with retroviral vectors to transduce cytosine deaminase-uracil phosphoribosyltransferase gene to the stem cells. At the end of the process [32], the adipose tissue-derived mesenchymal stem cells were capable to produce the enzyme with the aim to reach concentrated levels of 5-fluoruracil converted from the prodrug 5-fluorocytosine in the tumor tissue. These stem cells are also considered to be resistant to cytotoxic chemotherapy.

In another study by Jiang et al. [33], instead of harvesting DCs as described above, autologous T-cells were expanded ex vivo and stimulated with cytokines. However, the published article does not contain detailed information about any sensitization procedure against tumor cells. All remaining 4 published studies were focusing on EBV(+) nasopharyngeal carcinoma. Cytotoxic T-cells (CTLs) were selected after apheresis. Following stimulation and expansion, they were administered via intravenous route. In two studies [34,35], only EBV latent membrane protein (LMP) 2-specific CTLs targeting tumor cells were prepared. In other two studies [36–38], CTLs targeting a broader spectrum of antigens were utilized. Similar techniques are being used in the ongoing NCT02421640 and NCT02578641 studies also targeting EBV(+) nasopharyngeal carcinoma. An advanced version of this technique is applied in two ongoing studies. In NCT02065362, LMP/BARF1/EBNA1-specific CTLs are produced. But additionally, these CTLs also contain retrovirus-transduced dominant gene receptor DNA to overcome TGF-β resistance. The same approach is being used in NCT02379520 with E6/7-specific CTLs against HPV(+) oropharyngeal cancer.

A different technique used in NCT03083873 involves an excisional biopsy from the R/M tumor and generation of its ex vivo culture. The population of tumor infiltrating lymphocytes are selectively expanded and infused back to the patient, followed by IL-2 administration. Instead of using DCs or CTLs, NCT02507154 harvests and re-infuses autologous NK cells in combination of cetuximab, preceded and followed by IL-2 administration one day before and after in repeated cycles. This study is only recruiting patients diagnosed with R/M HNC, which exhibit EFGR expression above 80%.

Contemporary methods involve gene editing techniques such as sequence-specific RNA interference, chimeric antigen-expressing T-cells (CAR T-cell) therapy and clustered, regularly interspaced, short palindromic repeats – associated with cellular apoptotic susceptibility protein (CRISPR/Cas) [39–41]. For example, in NCT02980315 and NCT02915445, CAR T-cells are produced to specifically bind to LMP-1 on EBV(+) nasopharyngeal carcinoma cells and EpCAM on head and neck and breast cancer cells, respectively. In NCT03044743, autologous CRISPR-Cas9 mediated PD-1 knockout EBV-antigen-specific CTLs are generated to achieve high on-target specificity and overcome immune blockade. Another study (NCT02989064) implementing gene editing is including patients diagnosed with HNC, melanoma or bladder cancer. Autologous T-cells are isolated, expanded and affinity-enhanced via transfusion with a lentiviral vector containing melanoma-associated gene (MAGE)-A10^{c796} T-cell receptor directed towards a MAGE-A10 peptide expressed on tumors, and re-infused into the subject [42].

Two studies aim to generate a wide spectrum of patient-specific tumor-associated antigens and stimulate host's immune system via antigen presentation. NCT03265080 involves attenuated Listeria monocytogenes, which is specifically bioengineered to express patient-specific tumor antigens within the antigen presenting cells phagocytosing the bacteria. The investigators suggest that the presented antigens activate CTLs, and the bacterial infection itself decreases the immune-suppressing effect of Tregs and myeloid-derived suppressor cells in the tumor microenvironment [43]. NCT03289962 is testing the dose-limiting toxicity of RO7198457, an individualized mRNA compound against unique and multiple mutations identified in patients' tumors. It is administered intravenously in lipoplexes by alone or with anti-PD-L1 mAb atezolizumab.

Last but not least, innovative techniques involving the subcutaneous injection of inactivated tumor cells beside immune-stimulatory cells are being tested. One company is sponsoring two ongoing trials (NCT01998542, NCT02624999) exclusively including patients suffering from R/M HNC. A chaperone-rich tumor lysate is simultaneously injected with allogeneic effector T helper cells subcutaneously. Another company conducts NCT02999646, in which two capsules are implanted subcutaneously. One capsule contains irradiated autologous tumor cells. The other capsule, which is placed beside the first one, harbors genetically engineered allogenic cells to release Granulocyte-macrophage colony-stimulating factor as a continuous supply [44,45].

For further reading and detailed insight about the above-mentioned techniques, we cited some additional review articles [39–41,46,47] published recently.

2.2.5. Inclusion of Tumor Types and Anatomical Subsites

Two published and 7 ongoing studies involve other tumor entities in addition to HNC; including urothelial carcinoma, colon cancer, non-small cell lung cancer, HPV-associated tumors of the anogenital region, renal-cell carcinoma, breast cancer, ovarian cancer, prostate cancer, sarcoma, melanoma and EBV-induced lymphoma. In terms of HNC, thirteen studies were designed to include nasopharyngeal carcinoma only. Ten out of these 13 studies clearly defined the tumor of interest as EBV(+) nasopharyngeal carcinoma. Eight studies did not set any restriction in terms of anatomical subsite or specific histological subtype as eligibility criteria. Three studies allowed the non-nasopharyngeal mucosal HNC subsites, whereas 2 other studies focused on oropharyngeal cancer (one phase I study exclusively including HPV(+) oropharynx cancer).

2.2.6. Treatment setting

Three studies (Schuler et al. [29], Jiang et al. [33] and NCT02421640) were designed to include patients with local and locally-advanced tumors with a curative intent only. One study (NCT02115958) included HNC both in locally-advanced and R/M tumors with the eligibility criteria of showing clinical complete remission. Another study (NCT03282617) allows patients with locally-advanced and R/M disease, but allocates them into separate arms. However, the entry for the study NCT02980315 is missing the description of tumor stage and treatment setting in the clinicaltrials.gov registry. The remaining 20 studies were planned to include R/M disease only.

2.2.7. Study Phase and Patient Allocation

Among eight published articles, two were case reports, another two were phase I, three were phase II studies, and one was a phase I/II study. Unpublished studies consisted of seven phase I, three phase II, seven continuous phase I/II studies and one phase III study. One among published and six among ongoing studies were designed to allocate the patients in study arms randomly.

2.2.8. Severe Adverse Events

Adverse events were reported in all published studies. No grade 3 or higher toxicity was observed.

2.2.9. Oncologic and/or Survival Outcome

After evaluating the published studies, we decided not to describe or compare the oncologic and/or survival outcome in detail, mainly due to the heterogeneity in disease entities, treatment settings and reporting methodology of outcomes. Nevertheless, brief summaries of reported outcomes are provided in Table 1.

Two studies included only patients with non-metastatic local or locally-advanced HNC. However, it is not possible to comprehend in this setting, whether a reported oncological outcome is a result of the standard therapy or the following experimental treatment. Among the remaining six studies including R/M disease, none indicate a modality, which necessarily seems to be worth pursuing. In two of them experimenting on EBV+ nasopharyngeal carcinoma with autologous EBV-antigen-specific CTLs [36–38], a total of 4 out of 56 patients showed complete remission. But, these patients also received chemotherapy while waiting for the experimental therapy, where durable complete remission in selected cases with chemotherapy is not a very rare observation [48]. In earlier published series, durable complete responses were also reported in few patients diagnosed with R/M nasopharyngeal cancer [49] and other HNC subsites [50]. Similarly, most of these patients also underwent other conventional treatment modalities, which makes the interpretation of the results quite difficult.

3. Conclusion

Most of the identified studies involve some form of adoptive cell transfer. To our knowledge, the first studies involving HNC were published in 2000 and 2001 by To et al. [50], and Chua et al. [51], respectively. Both groups demonstrated the feasibility and a favorable safety profile in a total of 21 HNC patients, majority suffering from R/M disease with mixed responses. Our systematic search results indicate a continued interest in these treatment modalities in HNC and other solid tumors. On the other hand, the pace of research in this field is slower than expected. After almost two decades, most of the published and prospective studies within the last five years are still in the early phases of development. Due to that and heterogeneity in endpoints, investigated disease entities and treatment settings; it was not plausible to report and compare the outcomes between the published studies. Future prospective trials involving various patient-specific treatment modalities in later phases of development are required to generate solid data and obtain high-level of evidence for effectiveness.

4. Expert Opinion

Although being used rather vaguely, terms like personalized and precision medicine keep intriguing the public as well as healthcare professionals. However, concerning the treatment of cancer, the goal of a successful immunotherapy depicts an ideal, which has not been established so far. Modulating the immune system to defeat cancer is an ambitious rationale going back to the end of 19th century [52]. With the understanding of cytokines'

role in immune system, researchers tried to treat malignancies with immunotherapy in a second wave in 1970s without achieving the expected success. The aim of immunotherapy is to re-modulate and kick-start individuals' immune system to fight against their tumor and eradicate it without introducing various morbidities associated with surgery, radiotherapy, and systemic agents. The partial success recently demonstrated by immunotherapy in solid tumors including HNC is owed to the development of novel off-the-shell agents, especially those targeting the PD-1 receptor and PD-L1/2. According to latest data, around 75-80% of HNC patients do not profit from immune checkpoint inhibitors. An individualized "vaccine" approach promising major success rates in the treatment of solid tumors including HNC is still missing. New combinations with chemotherapy, radiotherapy, surgery, and agents targeting other components of immune system are being tested in loco-regional and R/M settings.

Our aim before performing the systematic search was not necessarily focused on immunotherapy. However, our definition of patient-specific treatments yielded results, which inevitably fell into the category of immunotherapy. On the other hand, many off-the-shelf immunotherapy modalities were excluded. The published studies described in this article pursue the ideal of personalized and precision medicine for being completely individualized. The limited number of published studies, which involved HNC, demonstrated a favorable safety profile, but a modest response rate if any. The preparation phase of the treatment before administration is cumbersome and long, which may be shorter in the future. To bridge these delays and avoid tumor progress, patients in some studies are treated with cytotoxic chemotherapy, which is obviously against the notion of personalized and patient-specific treatments. Also, the practicality we are accustomed with the off-the-shelf systemic agents is lacking, which might be one of the factors holding back the investigators and the industry from investigation in this field. On the other hand, there seems to be a relatively week but increasing interest by the industry as well. Compared to the already published studies, the current proportion of ongoing industry-initiated projects is significantly higher.

Outside of the field of HNC, the most remarkable example of patient-specific treatments is CAR T-cells for hematologic tumors, which took three decades to be developed and approved [53–55] for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia [56] and refractory or relapsed adult diffuse large-B cell lymphoma [57]. In terms of solid tumors, other promising results with CAR T-cells and other forms of autologous CTLs were observed in neuroblastoma [58], melanoma and sarcoma[59]. Another success was

reported with an autologous DC vaccine in the treatment of prostate cancer[60]. On the other hand, reflecting the success of patient-specific treatments in hematologic cancers on solid tumors poses several challenges. Unlike the solid tumors, B-cells express CD19, which is an ideal, almost tumor-exclusive antigen to target, which allows specificity, therefore a wide therapeutic window. Additionally, in contrast to hematologic malignant cells, solid tumors usually reside in not readily-accessible sites via lympho-vascular circulation, isolated by dense stroma and tumor microenvironment which harbor immunosuppressive leukocytes and cytokines. Barriers against CTL migration also include preference to non-target organs such as lungs, liver and spleen, limited lymphocyte extravasation due to oncotic pressure caused by the abnormal vascular formation, downregulated expression of adhesion molecules on tumor vasculature and reduced release of lymphocyte-attracting chemokines. Last but not least, tumor heterogeneity in solid tumors poses a challenge against antigen selection. As a consequence of those discoveries, the following challenges need to be tackled in the future studies: off-target actions causing toxicity, limited lymphocyte trafficking to the tumor site(s), short persistence of the lymphocytes that arrive into the tumor tissue, tumor-induced immunosuppression, and the heterogeneity and ongoing evolution of multiple tumor-associated antigens [61].

A considerable number of studies addressing HNC are coming from Asia, most probably due to the endemic EBV+ nasopharynx cancer, which demonstrates a relatively well-defined protein expression profile. One ongoing trial involves a similar approach with E6 and E7-specific CTLs combined with gene editing technology to overcome immune-resistance. Newer studies are also more innovative by combining the patient-specific treatment with off-the-shelf checkpoint inhibitors with a reasonable rationale. The contemporary techniques integrating the gene editing techniques on immune cells or attenuated bacterial/viral vectors may offer more precise on-target specificity.

In addition to develop more streamlined and faster preparation techniques, further in-depth understanding of tumor biology concerning driver pathways for proliferation, survival and therapy resistance, interactions with immune system and development in bioinformatics to tackle the mounting data output is required to achieve success. Solid tumors, especially HNC, harbor heterogeneous clones within the tumor, lymph nodes, and metastases. Current standard is to probe a part of the tumor, therefore only a part of the whole molecular spectrum and mutanome [62] is revealed via modern techniques. Moreover, the genetic evaluation of the tumor in the natural course of the disease and via selection pressures by various treatment modalities poses a

challenge in R/M disease. Although it is currently not easy and realistic to chase these genetic alterations over the course of the disease, repeated assays of circulating tumor cells and cell-free tumor DNA/RNA may offer a potential solution for this problem. It becomes less likely to still have one-size-fits-all treatments in the future. The vast possible combinations of various existing and emerging modalities, inter- as well as intra-patient heterogeneity in the genetic, epigenetic and immunologic landscape require smart, practical and dynamic trial designs. Basket [63], umbrella [64] and multi-arm, multi-stage (MAMS) [65] platform trial designs incorporating high-throughput diagnostic technologies may significantly increase the pace of advancement in this field. Similar trials testing multiple mAbs in R/M HNC recently started (e.g. NCT03088059), which prove the feasibility of such contemporary designs.

Apart from the medical aspects, these modalities also have to become affordable and financially attractive for the public health sector and private enterprises. Last but not least, the future of the patient-specific treatments depends on the results the ongoing research is going to yield, as well as on the achievements in the competing fields of cancer research.

Currently, it is difficult to predict any breakthrough in the near future with any given technique presented and discussed in this article. New generation techniques involving gene engineering and/or combination of immune checkpoint modulators may hold promise and should be investigated further. As demonstrated by decades of research and experience, it seems unlikely to find a “magic bullet” for biologically heterogeneous malignancies such as HNC. The future of cancer treatment is expected to be more personalized, biology-driven and involve tailored combinations of different treatment modalities based on patient factors, initial tumor biology, its interaction with the host’s immune system and their evolution through the course of the treatment.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA. Cancer J. Clin. [Internet]. 2015;65:87–108. Available from: http://onlinelibrary.wiley.com/doi/10.3322/caac.21262/abstract.

[2] Hammerman PS, Neil Hayes D, Grandis JR. Therapeutic insights from genomic studies of head and neck squamous cell carcinomas. Cancer Discov. 2015;5:239–244.

[3] Hayes DN, Van Waes C, Seiwert TY. Genetic Landscape of Human Papillomavirus-Associated Head and Neck Cancer and Comparison to Tobacco-Related Tumors. J. Clin. Oncol. [Internet]. 2015;33:3227–3234. Available from: http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.62.1086.

[4] Ferris RL. Immunology and Immunotherapy of Head and Neck Cancer. J. Clin. Oncol. [Internet]. 2015;33:3293–3304. Available from: http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.61.1509.

[5] Bruce JP, Yip K, Bratman S V., et al. Nasopharyngeal Cancer: Molecular Landscape. J. Clin. Oncol. [Internet]. 2015;33:3346–3355. Available from: http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.60.7846.

[6] Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature [Internet]. 2015;517:576–582. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25631445. **** A comprehensive landmark article demonstrating the genetic profile of head and neck squamous cell carcinoma**

[7] Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck [Internet]. 2005 [cited 2013 Nov 25];27:843–850. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16161069.

[8] Pignon J-P, le Maître A, Bourhis J. Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC): an update. Int. J. Radiat. Oncol. Biol. Phys. [Internet]. 2007 [cited 2013 Nov 28];69:S112-4.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/17848275.

[9] Bonner JA, Harari PM, Giralt J, 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. [Internet]. 2010 [cited 2013 Sep 18];11:21–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19897418.

[10] Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother. Oncol. [Internet]. 2011 [cited 2014 Jun 6];100:33–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21684027.

[11] Blanchard P, Lee A, Marguet S, et al. Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis. Lancet. Oncol. [Internet]. 2015;16:645–655. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1470204515701269.

[12] Sun Y, Li W-F, Chen N-Y, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol. [Internet]. 2016;17:1509–1520. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1470204516304107.

[13] Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N. Engl. J. Med. [Internet]. 2008 [cited 2015 Jan 6];359:1116–1127. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18784101.

[14] Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet [Internet]. 2016;388:1883–1892. Available from: http://dx.doi.org/10.1016/S0140-6736(16)31388-5.

[15] Ferris RL, Blumenschein G, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N. Engl. J. Med. [Internet]. 2016;375:1856–1867. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1602252. *** First clinical study establishing the role of immune checkpoint inhibitors in the treatment of R/M head and neck cancer**

[16] Cohen EE, Harrington KJ, Le Tourneau C, et al. LBA45_PRPembrolizumab (pembro) vs standard of care (SOC) for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): Phase 3 KEYNOTE-040 trial. Ann. Oncol. [Internet]. 2017;28. Available from:

http://academic.oup.com/annonc/article/doi/10.1093/annonc/mdx440.040/4109952/LBA45PRPembrolizumab-pembro-vs-standard-of-care.

[17] Hsu C, Lee S-H, Ejadi S, et al. Safety and Antitumor Activity of Pembrolizumab in Patients With Programmed Death-Ligand 1–Positive Nasopharyngeal Carcinoma: Results of the KEYNOTE-028 Study. J. Clin. Oncol. [Internet]. 2017;35:JCO.2017.73.367. Available from: http://ascopubs.org/doi/10.1200/JCO.2017.73.3675.

[18] Machiels J-PH, 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, randomised phase 3 trial. Lancet. Oncol. [Internet]. 2015;16:583–594. Available from: http://www.sciencedirect.com/science/article/pii/S1470204515701245.

[19] Soulières D, Faivre S, Mesía 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 randomised, double-blind, placebo-controlled phase 2 trial. Lancet. Oncol. [Internet]. 2017;18:323–335. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28131786.

[20] Massarelli E, Lin H, Ginsberg LE, et al. Phase II trial of everolimus and erlotinib in patients with platinum-resistant recurrent and/or metastatic head and neck squamous cell carcinoma. Ann. Oncol. 2015;26:1476–1480.

[21] Geiger JL, Bauman JE, Gibson MK, et al. Phase II trial of everolimus in patients with previously treated recurrent or metastatic head and neck squamous cell carcinoma. Head Neck [Internet]. 2016;38:1759–1764. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27232378.

[22] Dunn LA, Fury MG, Xiao H, et al. A phase II study of temsirolimus added to low-dose weekly carboplatin and paclitaxel for patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Ann. Oncol. 2017;28:2533–2538.

[23] Santuray RT, Johnson DE, Grandis JR. New Therapies in Head and Neck Cancer. Trends in cancer [Internet]. 2018;4:385–396. Available from: https://doi.org/10.1016/j.trecan.2018.03.006.

[24] Elicin O, Ozsahin M. The latest prospects of investigational drugs for head and neck cancer. Expert Opin. Investig. Drugs [Internet]. 2017;26:265–268. Available from:

https://www.tandfonline.com/doi/full/10.1080/13543784.2017.1279145.

[25] Bonner J a, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N. Engl. J. Med. [Internet]. 2006;354:567–578. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3638633&tool=pmcentrez&rendertype=abstract. *** First and still the last positive phase III clinical trial demonstrating the role of a targeted mAb in combination to radiotherapy in the curative treatment setting of head and neck cancer**

[26] Lee SC, López-Albaitero A, Ferris RL. Immunotherapy of head and neck cancer using tumor antigen-specific monoclonal antibodies. Curr. Oncol. Rep. [Internet]. 2009;11:156–162. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19216848.

[27] Ou D, Levy A, Blanchard P, et al. Concurrent chemoradiotherapy with cisplatin or cetuximab for locally advanced head and neck squamous cell carcinomas: Does human papilloma virus play a role? Oral Oncol. [Internet]. 2016;59:50–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27424182.

[28] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J. Clin. Epidemiol. [Internet]. 2009 [cited 2014 Jul 23];62:e1-34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19631507.

[29] Schuler PJ, Harasymczuk M, Visus C, et al. Phase I dendritic cell p53 peptide vaccine for head and neck cancer. Clin. Cancer Res. [Internet]. 2014;20:2433–2444. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24583792.

[30] Bapsy PP, Sharan B, Kumar C, et al. Open-label, multi-center, non-randomized, single-arm study to evaluate the safety and efficacy of dendritic cell immunotherapy in patients with refractory solid malignancies, on supportive care. Cytotherapy [Internet]. 2014;16:234–244. Available from: http://dx.doi.org/10.1016/j.jcyt.2013.11.013.

[31] Lakota J, Gocarova K, Spanik S. Treatment of metastatic head and neck cancer with mesenchymal stem cells combined with prodrug gene therapy. Exp. Oncol. [Internet]. 2015;37:298. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26710845.

[32] Kucerova L, Altanerova V, Matuskova M, et al. Adipose tissue-derived human mesenchymal stem cells mediated prodrug cancer gene therapy. Cancer Res. 2007;67:6304–6313.

[33] Jiang P, Zhang Y, J Archibald S, et al. Adoptive cell transfer after chemotherapy enhances survival in patients with resectable HNSCC. Int. Immunopharmacol. [Internet]. 2015;28:208–214. Available from: http://dx.doi.org/10.1016/j.intimp.2015.05.042.

[34] Lutzky VP, Crooks P, Morrison L, et al. Cytotoxic T cell adoptive immunotherapy as a treatment for nasopharyngeal carcinoma. Clin. Vaccine Immunol. [Internet]. 2014;21:256–259. Available from: http://cvi.asm.org/cgi/doi/10.1128/CVI.00121-13.

[35] Eom H, Choi BK, Lee Y, et al. Phase I Clinical Trial of 4-1BB-based Adoptive T-Cell Therapy for Epstein-Barr Virus (EBV)-positive Tumors. J. Immunother. [Internet]. 2016;39:140–148. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26938947.

[36] Chia W-K, Teo M, Wang W-W, et al. Adoptive T-cell Transfer and Chemotherapy in the First-line Treatment of Metastatic and/or Locally Recurrent Nasopharyngeal Carcinoma. Mol. Ther. [Internet]. 2014;22:132–139. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1525001616311273.

[37] Huang J, Fogg M, Wirth LJ, et al. Epstein-Barr virus-specific adoptive immunotherapy for recurrent, metastatic nasopharyngeal carcinoma. Cancer [Internet]. 2017;123:2642–2650. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28222215.

[38] Toh H., Hopkins R, Ching Q, et al. Cellular immune biomarkers to prognosticate for survival to adoptive T-cell therapy in advanced nasopharyngeal cancer. J. Clin. Oncol. 2017;35:abstr 6047.

[39] Miliotou AN, Papadopoulou LC. CAR T-cell Therapy: A New Era in Cancer Immunotherapy. Curr. Pharm. Biotechnol. [Internet]. 2018;19:5–18. Available from: http://www.eurekaselect.com/161365/article.

[40] Shaikh MH, Clarke DTW, Johnson NW, et al. Can gene editing and silencing technologies play a role in the treatment of head and neck cancer? Oral Oncol. [Internet]. 2017;68:9–19. Available from: http://dx.doi.org/10.1016/j.oraloncology.2017.02.016.

[41] Legut M, Dolton G, Mian AA, et al. CRISPR-mediated TCR replacement generates superior anticancer transgenic t cells. Blood. 2018;131:311–322.

[42] Hong DS, Butler MO, Sullivan RJ, et al. A phase I single arm, open label clinical trial evaluating safety of MAGE-A10 T in subjects with advanced or metastatic head and neck, melanoma, or urothelial tumors (NCT02989064). J. Clin. Oncol. 2017;35:abstr TPS3098.

[43] Lm Technology [Internet]. [cited 2018 Sep 13]. Available from: https://www.advaxis.com/lm-technology-

2/.

[44] Mach N, Vernet R, Belkouch M-C, et al. MVX-ONCO-1 phase 1 final results of the first personalized cell-based immunotherapy using cell encapsulation technology. Ann. Oncol. [Internet]. 2016;27:2016. Available from: http://academic.oup.com/annonc/article/doi/10.1093/annonc/mdw378.12/2799841/MVXONCO1-phase-1-final-results-of-the-first.

[45] Lathuilière A, Mach N, Schneider BL. Encapsulated cellular implants for recombinant protein delivery and therapeutic modulation of the immune system. Int. J. Mol. Sci. [Internet]. 2015;16:10578–10600. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26006227.

[46] Tan YS, Sansanaphongpricha K, Prince MEP, et al. Engineering Vaccines to Reprogram Immunity against Head and Neck Cancer. J. Dent. Res. [Internet]. 2018;97:627–634. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29533731.

[47] Klebanoff CA, Rosenberg SA, Restifo NP. Prospects for gene-engineered T cell immunotherapy for solid cancers. Nat. Med. 2016;22:26–36.

[48] Laccourreye O, Marret G, Rubin F, et al. Ten-year outcome of curative “exclusive” chemotherapy in N0M0 squamous cell carcinoma of the larynx and pharynx with complete clinical response. Head Neck [Internet]. 2019;1–7. Available from: http://doi.wiley.com/10.1002/hed.25674.

[49] Louis CU, Straathof K, Bollard CM, et al. Adoptive transfer of EBV-specific T cells results in sustained clinical responses in patients with locoregional nasopharyngeal carcinoma. J. Immunother. 2010;33:983–990.

[50] To WC, Wood BG, Krauss JC, et al. Systemic adoptive T-cell immunotherapy in recurrent and metastatic carcinoma of the head and neck: a phase 1 study. Arch Otolaryngol Head Neck Surg [Internet]. 2000;126:1225–1231. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11031409.

[51] Chua D, Huang J, Zheng B, et al. Adoptive transfer of autologous Epstein-Barr virus-specific cytotoxic T cells for nasopharyngeal carcinoma. Int. J. cancer [Internet]. 2001;94:73–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11668481.

[52] Decker WK, da Silva RF, Sanabria MH, et al. Cancer Immunotherapy: Historical Perspective of a Clinical Revolution and Emerging Preclinical Animal Models. Front. Immunol. [Internet]. 2017;8:829. Available

from: http://www.ncbi.nlm.nih.gov/pubmed/28824608. *** A recommended read for those who have interest in the historcal development of immunotherapy in the field of oncology.**

[53] Eshhar Z, Waks T, Gross G, et al. Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the gamma or zeta subunits of the immunoglobulin and T-cell receptors. Proc. Natl. Acad. Sci. [Internet]. 1993;90:720–724. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.90.2.720.

[54] Stancovski I, Schindler DG, Waks T, et al. Targeting of T lymphocytes to Neu/HER2-expressing cells using chimeric single chain Fv receptors. J. Immunol. [Internet]. 1993;151:6577–6582. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7902379.

[55] Novartis. Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah™ (tisagenlecleucel, CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice [Internet]. 2017. Available from: https://novartis.gcs-web.com/novartis-receives-fda-approval-for-KymriahTM.

[56] Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N. Engl. J. Med. [Internet]. 2018;378:439–448. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29385370. *** A landmark study establishing the clinical indication of CAR T-cells for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia**

[57] Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N. Engl. J. Med. [Internet]. 2017;377:2531–2544. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29226797. *** A landmark study establishing the clinical indication of CAR T-cells for refractory or relapsed adult diffuse large-B cell lymphoma**

[58] Louis CU, Savoldo B, Dotti G, et al. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma. Blood [Internet]. 2011;118:6050–6056. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21984804.

[59] Robbins PF, Morgan RA, Feldman SA, et al. Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. J. Clin. Oncol. [Internet]. 2011;29:917–924. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21282551.

[60] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N. Engl. J. Med. [Internet]. 2010;363:411–422. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20818862.

[61] Filley AC, Henriquez M, Dey M. CART Immunotherapy: Development, Success, and Translation to Malignant Gliomas and Other Solid Tumors. Front. Oncol. [Internet]. 2018;8:1–19. Available from: https://www.frontiersin.org/article/10.3389/fonc.2018.00453/full. *** A recommended review article focusing on the current landscape of clinical research in patient-specific treatments in solid tumors, and the potential barriers against achieving success**

[62] Overwijk WW, Wang E, Marincola FM, et al. Mining the mutanome: developing highly personalized Immunotherapies based on mutational analysis of tumors. J. Immunother. cancer [Internet]. 2013;1:11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24829748.

[63] Tao JJ, Schram AM, Hyman DM. Basket Studies: Redefining Clinical Trials in the Era of Genome-Driven Oncology. Annu. Rev. Med. [Internet]. 2018;69:319–331. Available from: http://www.annualreviews.org/doi/10.1146/annurev-med-062016-050343.

[64] Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. [Internet]. 2017;28:34–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28177494. *** A recommended review article describing and distinguishing basket, umbrella and other contemporary clinical trial designs.**

[65] Ghosh P, Liu L, Senchaudhuri P, et al. Design and monitoring of multi-arm multi-stage clinical trials. Biometrics [Internet]. 2017;73:1289–1299. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28346823.

Table 1: Published Studies in the Last Five Years

Clinical Trial ID and/or Reference	Name of the Treatment (n of cycles)	Biomarker Selection	Mechanism of Action	HNC only (n)	HNC Subsites	Treatment Setting of HNC	Non-HNC Sites	Phase	Randomization	Other Arms	Median Follow-up in Months	Response	Status
NCT00404339 Schuler et al. 2014[29]	DC p53 Vaccine after curative mono- or multimodal treatment (3)	HLA-A2.1+	p53 antigen presentation via patients' autologous DC to stimulate immune response against tumor cells	yes (16)	CUP, H, L, OC, OP, S	local and locally-advanced	no	Ib	yes	Arm 2: additional Th tetanus toxoid peptide Arm 3 (not randomized, only for HLA-DR4+ patients): additional Th wild-type p53-specific peptide	32	2-years DFS: 88%	published
NCT00690872 Chia et al. 2014[36] Toh et al. 2017[38]	Adoptive EBV-CTL transfer after 4 cycles of gemcytabine and carboplatin (6)	no	Autologous EBV-antigen-specific CTLs targeting tumor cells	yes (35)	EBV+ N	R/M	no	II	no	no	29.9	CR: 3; PR: 22 2- and 3-year OS: 62.9 and 37.1%, respectively	published
N/A Lutzky et al. 2014[34]	Adoptive EBV-CTL transfer (6)	no	EBV-LMP2-specific CTLs targeting tumor cells	yes (1)	EBV+ N	R/M	no	case report	no	no	9.8	PR 3 months after treatment	published
CTRI/2011/07/001917 Bapsy et al. 2014[30]	DC immunotherapy (6)	no	Stimulation of NK and T cells via autologous DC formulation loaded with whole tumor lysate	no (7)	N/A	R/M	multiple solid tumors (44)	II	no	no	NR	ORR: 28.9%, no CR Median OS: 13 months	published
Lakota et al. 2015[31]	Adipose tissue-derived mesenchymal stem cells (1)	no	Delivery of cytosine deaminase-uracil phosphoribosyltransferase gene–expressing cells by retrovirus transduction with the aim to reach concentrated levels of	yes (1)	OC	R/M	no	case report	no	no	1.3	PD	published

			5-fluoruracil converted from the prodrug 5-fluorocytosine in the tumor tissue										
Eom et al. 2016[35]	EBV-induced Natural T cell: "EBViNT" (1)	HLA-A02+ or A24+	Autologous EBV/LMP2A-specific CTLs targeting tumor cells	no (4)	EBV+ N	R/M	lympho ma (4)	I	no	no	NR	Only descriptive reporting. No CR	published
NCT00431210 NCT00834093 Huang et al. 2017[37]	EBV-specific CTL (4)	no	Autologous EBV-antigen-specific CTLs targeting tumor cells	yes (21)	EBV+ N	R/M	no	I/II	no	no	NR	Median PFS and OS: 2.2 and 16.7 months, respectively. 1 CR lasting until last visit (>100 months). ORR: 4.8%	published
Jiang et al. 2015[33]	Cytokine-induced killer cells (2) alone or after 1 cycle of docetaxel, cisplatin and 5-fluoruracil	no	Expanded and cytokine-stimulated autologous T cells	yes (21)	OC, S	local and locally-advance d	no	II	no	yes, but NR	48	median PFS: 56; OS: 58 months	results of the subgroup, which received chemother apy published

CR: complete response; CTL: cytotoxic T-cell; CUP: carcinoma of unknown primary; DC: dendritic cell; DFS: disease-free survival; EBV: Epstein-Barr virus; H: hypopharynx; HLA: human leukocyte antigen; HNC: head and neck cancer; L: larynx; LMP: latent membrane protein; N: nasopharynx; n: number; N/A: not available; NR: not reported; OC: oral cavity; OP: oropharynx; OS: overall survival; PD: progressive disease; R/M: recurrent and/or metastatic; S: sinonasal; PR: partial response; Th: T-helper cell

Table 2: Ongoing and Unpublished Studies in the Last Five Years

Clinical Trial ID and Reference	Name of the Treatment (n of cycles)	Biomarker Selection	Mechanism of Action	HNC only (n)	HNC Subsites	Treatment Setting	Non-HNC Sites	Phase	Randomization	Other Arms	Status
NCT01998542 http://www.immunovative.com/products/allostim	AlloVax™ (4)	no	AlloVax™ is Chaperone Rich cell lysate combined with AlloStim™ cells which are allogeneic Th1 effector cells	yes	no restriction	R/M	no	I/II	yes	Placebo	ongoing
NCT02065362	TGF-β Resistant Cytotoxic T-lymphocyte (2)	no	LMP/BARF1/EBNA1-specific CTLs, which also contain retrovirus-transduced Dominant Gene Receptor DNA to induce TGF-β resistance	yes	EBV+ N	R/M	no	I	no	N/A	ongoing
NCT02115958	Cancer Stem Cell Vaccine (undetermined)	no	cancer cell antigen-loaded DC primed CTCs	yes	N	locally advanced and R/M with CR	no	I/II	yes	Placebo	completed, no results
NCT02379520	HPV-16/18 E6/E7-Specific T Lymphocytes (in 3 sequential dose escalation cycles)	no	E6/7-specific CTLs, which also contain retrovirus-transducted gene to induce TGF-β resistance	no	HPV+ OP	R/M	HPV+ genitoanal	I	no	N/A	ongoing
NCT02421640	Concomitant Radiochemotherapy +/- tumor infiltrating lymphocytes (1)	plasma EBV DNA ≥4000 copies/ml	autologous EBV-antigen-specific CTLs targeting tumor cells	yes	EBV+ N	locally advanced	no	II	yes	Concomitant radiochemotherapy with cisplatin only	ongoing
NCT02507154	autologous NK cells activated with Cetuximab and IL-2 (2)	EGFR expression >80%	Cetuximab and IL-2 (Day 1) and infusion of activated expanded autologous NK cells (Day 2) continued with additional Cetuximab and IL-2 infusions	yes	no restriction	R/M	no	I/II	no	N/A	ongoing
NCT02578641	Adoptive EBV-CTL transfer after 4 cycles of gemcytabine	no	autologous EBV-antigen-specific CTLs targeting tumor cells	yes	EBV+ N	R/M	no	III	yes	6 cycles of gemcitabine and carboplatin	ongoing

	and carboplatin (6)										
NCT02624999 http://www.immunovative.com/products/allostim	AlloVax™ (4)	no	AlloVax™ is Chaperone Rich cell lysate combined with AlloStim™ cells which are allogeneic Th1 effector cells	yes	no restriction	R/M	no	II	yes	6 cycles of cisplatin and 5-fluoruracil	ongoing
NCT02915445	EpCAM CAR T-cells (1)	EpCAM >25% on tumor surface	EpCAM CAR T-cells produced by lentiviral transduction	no	N	R/M	breast	I	no	N/A	ongoing
NCT02989064 Hong et al. 2017[42]	MAGE-A10^{c796}T (1)	HLA-A*02:01+ and/or A*02:06+	Autologous T cells are isolated, expanded and affinity enhanced via a lentiviral vector containing MAGE-A10^{c796} T-cell receptor directed towards a MAGE-A10 peptide expressed on tumors,and re-infused into the subject.	no	no restriction	R/M	bladder, melanoma	I	no	N/A	ongoing
NCT02980315	LMP-1 CAR T-cells (1)	no	LMP-1 CAR T-cells (vector undefined)	yes	EBV+ N	N/A	no	I/II	yes	placebo	ongoing
NCT02999646 Mach et al. 2016[44]	MVX-ONCO-1 (6)	no	Subcutaneous capsule 1: irradiated autologous tumor cells 4x10^6 Subcutaneuous capsule 2: containing allogeneic cells, genetically engineered to release the strong adjuvant GM-CSF	yes	H, L, OC, OP	R/M	no	I/II	no	N/A	ongoing
NCT03044743	PD-1 Knockout EBV-CTLs (4)	HLA-A02, HLA-A24 or HLA-A11	CRISPR/Cas9 mediated PD-1 knockout EBV-antigen-specific CTLs from autologous origin	no	EBV+ N	R/M	EBV+ lymphomas and gastric carcinoma	I/II	no	N/A	ongoing
NCT03047525	Dendritic and Cytokine-induced Killer Cells + standard of care	no	no detailed description available	no	N	R/M	colorectal, lung and renal cell cancers	I/II	no	N/A	ongoing

	chemotherapy (4)										
NCT03083873	LN-145 Autologous Tumor Infiltrating Lymphocytes (1)	no	infusion of autologous tumor infiltrating lymphocytes followed by IL-2	yes	no restriction	R/M	no	II	no	N/A	ongoing
NCT03265080 https://www.advaxis.com/lm-technology-2/	ADXS-NEO (Advaxix-NEO) (1)	no	Bioengineered attenuated Listeria monocytogenes expresses patient-specific tumor antigens and that activates CTLs via antigen presenting cells phagocytosing the bacteria	no	no restriction	R/M	colon and lung cancer	I	no	N/A	ongoing
NCT03282617	CD137L-DC-EBV-VAX (5-7)	no	cancer cell antigen-loaded DC primed CTCs	yes	EBV+ N	R/M (Cohort A) or locally-advanced completed radiochemotherapy	no	I	no	N/A	ongoing
NCT03289962 https://www.cancer.gov/publications/dictionaries/cancer-drug/def/personalized-cancer-vaccine-ro7198457 https://www.gene.com/medical-professionals/pipeline	RO7198457 (RG6180) +/- Atezolizumab (not provided)	no	An mRNA-based individualized, therapeutic cancer vaccine targeting an unspecified number of tumor-associated antigens that are specifically expressed in the patient's cancer. Upon administration, the personalized cancer vaccine RO7198457 is taken up and translated by APCs and the expressed protein is presented via major histocompatibility complex molecules on the surface of the APCs. This leads to an induction of both CTL- and memory T-cell-dependent immune responses	no	no restriction	R/M	multiple solid tumors	I	no	N/A	ongoing

APC: antigen-presenting cells; CAR: chimeric antigen receptor; CRISPR/CAS: clustered, regularly interspaced, short palindromic repeats – associated with cellular apoptotic susceptibility protein; CTL: cytotoxic T-cell; DC: dendritic cell; EBV: Epstein-Barr virus; EpCAM: epithelial cell adhesion molecule; H: hypopharynx; HLA: human leukocyte antigen; HNC: head and neck cancer; HPV: Human

Papillomavirus; IL: interleukin; L: larynx; LMP: latent membrane protein; MAGE: Melanoma-associated gene; N: nasopharynx; n: number; N/A: not available; NK: natural killer; OC: oral cavity; OP: oropharynx; R/M: recurrent and/or metastatic; Th: T-helper cell

Figure 1: Flowchart of Literature Search

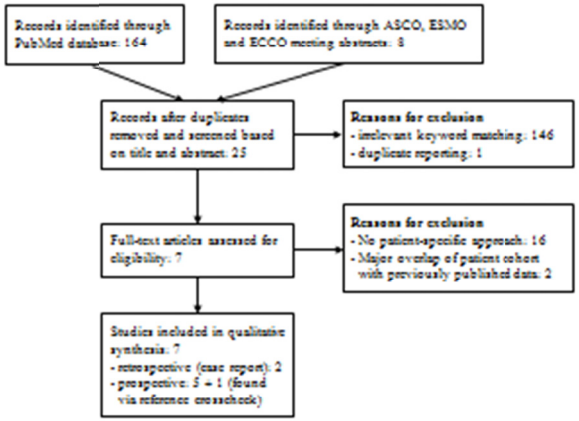

Figure 2: Flowchart of clinicaltrials.gov Search