Immunotherapy-Based Approaches for Treatment of Oral and Oropharyngeal Cancers

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Core Message

Immunotherapy is emerging as an effective therapeutic option in a variety of cancers. The introduction of immune checkpoint inhibitors (ICI) in the management of head and neck cancer (HNSCC) documents the shift of a paradigm – treating the immune system rather than the tumor.

Current research focuses on strategies to expand the subset of patients exhibiting durable responses to therapy suggesting that a broader understanding of cancer immunity is required. Immunity is largely influenced by a complex set of factors that include the biology of the tumor, the host, and environmental factors that underpin the strength and timing of the anticancer response. Clinical studies help us to characterize a range of factors to define the immune profiles of individual patients that can predict responses to immunotherapy.

28.1 Introduction: "Standard" of Treatment in Head and Neck Cancers

Reviewing the NICE guidelines [1] for the standard treatment of oral or oropharyngeal cancer several treatment options seem to exist.

A summary of the standard treatment options discussed in the earlier chapters is shown in the following scheme (Fig. 28.1):

Neoadjuvant chemotherapy has been used for a long time and is still discussed controversially. Current understanding has now come to the point where it should no longer be used, because of the initial toxicities that will keep patients from finishing the subsequent radiochemotherapy [2].

In many countries around the world the first-line treatment consists of surgery followed by radiation with or without adjuvant chemotherapy according to prognostic factors, e.g., surgically close margins or extracapsular spread of lymph node metastases. In other countries radiation seems to be first for advanced cancer stages followed by "salvage surgery" in case tumor eradication should not be sufficient.

First-line failure to the initial treatment was treated by either repetition of the above-mentioned techniques, surgery, and radiation or by treating the patients with EXTREME, a combination of Erbitux, cisplatinum, and 5-FU [3]. In second-line failure patients the therapeutic regimen was limited to schemes like EXTREME or other chemotherapeutic regimens with best supportive care.

In the past 10 years tremendous reconsideration and a paradigm shift has taken place. The tumor therapy targeting the tumor cells is currently supported by new approaches aiming at the restoration of the tumor-suppressed or tumor-educated immune cells, predominantly T cells being believed to be the most potent immune cell.

The "one size fits all "treatment approaches with choices of surgery or radiation or chemotherapy or combinations of each are being developed into a highly personalized system according to patient's individual cancer evolution and genomic patterns.

The treatment strategies have entered the era of immunotherapy with a variety of alternatives that currently are under clinical evaluation. Today's cancer patients, at some stage of their disease, will encounter an immunotherapeutic intervention.

Well-defined immunomonitoring procedures will help us to develop guidelines on new (immuno)therapies. The data accrued from these studies will facilitate the identification of novel prognostic or predictive biomarkers. Re-biopsies, the use of liquid biopsies, and definition of the individual genome, its transcriptome, and epigenetic heterogeneity of the cancer cells will become more relevant to identify and monitor the appropriate therapy.

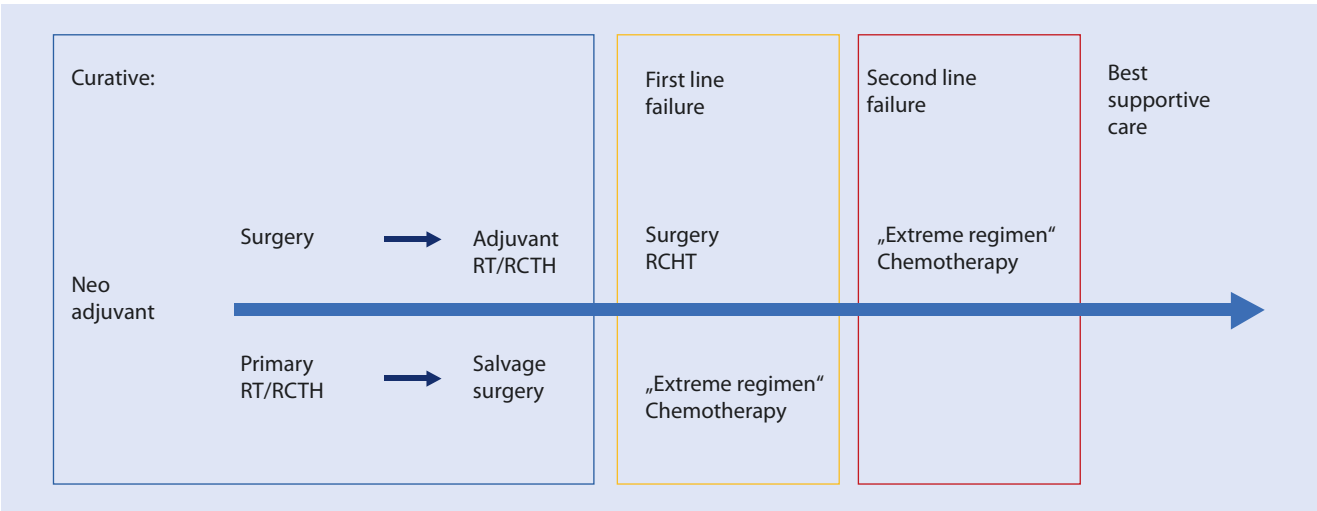

Fig. 28.1 Standard treatment options for oral or oropharyngeal HNSCC according to NICE guidelines [1]. With surgery, radiotherapy (RT), or combined radiochemotherapy (RCHT)

28.2 Immunotherapy

Immunotherapy dates back to the beginning of the twentieth century when Dr. Coley propagated that the defense of malignant tumors is associated with the immune system. It has been shown that the defense of infection simultaneously led to shrinkage of sarcomas. Today there is a broad understanding of the innate and acquired immune system, bearing specific cells that interact to provide a highly complex immune response to external or internal disturbances [4].

Cancer cells use cells of the immune system during their immune escape to support their growth and shift the immune equilibrium from defense to tolerance. Therefore many of the immune cells are in the direct focus of immunotherapeutic strategies in order to revert the influence of cancer and restore the high potency of the human immune system eliminating cancer cells. Immunotherapy stands for the attempt to stimulate or activate the body's own immune system to recognize tumor as "foreign" mounting an adequate immune response. The aim is to restore the immune equilibrium, with direct control or elimination of cancer [4].

Cancer immunotherapy can be distinguished in passive and active strategies, based on their ability to activate immune cells against malignant cells [5].

Definition

Active immunotherapeutic agents are engineered to interact with cells of the immune system to alter immunity and thus target the cancer through enhancement of the host immune system.

28.2.1 Current Approaches to Stimulate the Immune System Passive Forms

Passive forms of anticancer immunity are therapeutics that can display antineoplastic activities on tumor cells directly. Predominantly this group covers the antibodies that target specific proteins on a tumor cell, the tumor-associated antigens (TAA). Passive immunotherapy is also delivered by ex vivo prefabricated cells, e.g., T cells or NK cells (among those CAR cells; see below) or oncolytic viruses.

- Tumor targeting antibodies aim at the inhibition of special signal transduction pathways targeting tumor progression (e.g., anti-epidermal growth factor receptor (EGF-R) signaling) or any mechanism that supports tumor progression indirectly. They bind directly to tumor-associated antigens (TAA) expressed on the malignant cell or supporting cells like the neighboring tumor stroma or other components of the tumor microenvironment. It is known that tumor cells have a high metabolism producing immunosuppressive products that could hamper immune cells or are competing for metabolites. Many newly developed antibodies therefore target and inhibit the immunosuppressive metabolism of cancer cells. Applied intravenously the antibodies will patrol through the body binding to a specific target and evoking an immune response at the binding site as many of the antibodies used are not only displaying direct tumor-inhibitory activity but also the activation of an anticancer immune response. For example, cetuximab, in addition to inhibiting EGFR signaling, also promotes antibody-dependent cytotoxicity (ADCC) [6] that mediates immunostimulatory effects. Some of those tumor targeting antibodies can also increase lymphocytic infiltrates in tumors [7].
- Adoptive T Cell Transfer
  In immunotherapy T cells are assumed to be the most potent cells to detect and fight intruders. They are also among the most adaptive cells of the body. The assumption is that T cells recognize tumor cells and learn to mount an immune response. Yet as tumor cells grow exponentially and have a huge variety of escape mechanism they can outweigh T cell responses. Still there are tumor-specific T cells present and one approach is to collect exactly those tumor-specific circulating or tumor-infiltrating lymphocytes. In a series of steps those cells were selected, modified, expanded, activated in vitro, and readministered to the patient [8–10]. In this way a selected host cell population enriched in potentially tumor-reactive immune effectors can be achieved that are expanded to recognize one specific antigen on the tumor cell and adoptively transferred back into the patient.
- CAR T Cells ("Chimeric Antigen Receptor")
  Genetic engineering has been used in peripheral blood lymphocytes (PBLs) in order to improve their functions, like: specificity, an improved secretory profile, a unique antigen specificity [11], an elevated tumor-infiltrating capacity [12], superior cytotoxicity [13], or increased proliferative potential and persistence in vivo [14]. This genetic alteration essentially modifies a so-called chimeric antigen receptor (CAR), which is a transmembrane protein of the binding domain of an immunoglobulin linked to one or more immunostimulatory domains. This enables T cells to recognize and kill TAA-expressing cells in an MHC-independent way.
- CAR NK Cells ("Chimeric Antigen Receptor")
  The adoptive transfer of purified natural killer (NK) cells or CAR NK cells to cancer patients alone or in combination with supportive cytokines is currently under investigation for optimization in vivo. Due to a frequent loss of MHC class I and II components in HNSCC, the non-MHC-based treatment with NK cells could be promising [15, 16].
- Oncolytic Viruses
  Oncolytic viruses derived from nonpathogenic viral strains that are found to specifically infect cancer cells, triggering the cellular destruction, and generate immune responses that target the tumor by promoting the release of tumor-associated proteins in an immunostimulatory context. The viral infection acts by several mechanisms

directly interacting with the host cell causing cytopathic effects [17].
Oncolytic viruses can be genetically modified to be even more cytopathic by including genes coding for enzymes that are capable of converting a prodrug into a cytotoxic agent [18] or proteins that trigger off lethal signaling cascades in tumor cells only [19]. Another mechanism is through short-hairpin RNAs as they target factors that are strictly essential for the survival of transformed cells, but not required by normal cells [20]. The drawback of oncolytic virus therapy bases on the way of i.v. application as they can be neutralized by mononuclear phagocytic system found in the liver and spleen, the complement system, and neutralizing antibodies already present in patients.

28.2.2 Current Approaches to Stimulate the Immune System Active Forms

Active immunotherapeutic agents are engineered to interact with cells of the immune system to alter immunity and thus target the cancer through interaction with the host immune system [21–22].

- Dendritic Cell (DC) or Antigen-Presenting Cell (APC)-Based Immunotherapies
  Dendritic cells form a unique pool of antigen-presenting cells at the interface between innate and adaptive immunity and some DC subsets can prime strong, therapeutically applicable anticancer immune responses [23]. This impact is used to upload certain tumor-associated antigens (TAA) or TAA-coding molecules (TAA-derived peptides, mRNAs coding for one or more specific TAA, expression vectors coding for one or more specific TAA, bulk cancer cell lysates) onto DC ex vivo, making them able to prime TAA-targeting immune responses upon reinfusion [24]. General problems are encountered by generating the right source of dendritic cells in an up-to-date very costly personalized manner.
  Besides dendritic cells there are more antigen-presenting cells, e.g., B cells that can be transfected or loaded with TAA-specific signals. This approach is based on the fact that resident DCs (or other APCs) acquire the ability to present the TAA-derived epitopes while maturing, hence priming a robust TAA-specific immune response [25, 26]. One of the most suitable TAA for oropharyngeal cancer is the human papillomavirus type 16 (HPV-16) protein-associated E6 or E7 antigen.
- Immunostimulatory Cytokines
  Cytokines are small proteins (5–20 kDa) that are important in cell signaling. Their release has an influence on the behavior of cells in the vicinity. Cytokines act as immunomodulating agents as they are involved in autocrine signaling, paracrine signaling, and endocrine signaling. They include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors. Cytokine production comes from many classes of immune cells, including macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells. Acting via receptors they modulate the balance between humoral and cell-based immune responses and regulate the maturation, growth, and responsiveness of particular cell populations. Some cytokines also have the ability to enhance or inhibit the action of other cytokines in complex ways. Especially in the era of gene therapy there have been many studies to introduce various cytokines either administered as recombinant protein or via genetically transduced cells permanently releasing the cytokine [27]. Due to several factors, e.g., the metabolism within the host, interfering circadian rhythms of natural cytokine secretion, the induction of unexpected cascades through administration of external cytokines, and many more factors, the administration of this type of immunotherapy requires further exploration.
- Pattern Recognition Receptor (PRR) Agonists
  Pattern recognition receptors (PRRs) play an important role in the functioning of the innate immune system. PRRs are germline-encoded host sensors, which are able to detect molecules typical for the pathogens. They are proteins expressed, mainly, by cells of the innate immune system, such as dendritic cells, macrophages, monocytes, neutrophils, and epithelial cells to identify two classes of molecules: pathogen-associated molecular patterns (PAMPs), which are associated with microbial pathogens, and damage-associated molecular patterns (DAMPs), which are associated with components of host's cells that are released during cell damage or death. PRRs also mediate the initiation of antigen-specific adaptive immune response and release of inflammatory cytokines [28]. Some malignant cells express PRRs implying that PRR agonists may not be completely devoid of intrinsic tumor-modulating functions [29]. The literature from experimental and clinical studies indicates that the antineoplastic effects of PRR agonists stem from their ability to engage the host immune system. Thus, PRR agonists constitute active immunotherapeutics. First clinical studies adding, e.g., motolimod, a TLR8 agonist, to the EXTREME regimen (clinical trials: NCT01836029) was well tolerated by the recipients but did not improve progression-free survival (PFS) or overall survival (OS). A subgroup analysis showed a significant benefit in HPV-positive patients and those with injection site reactions, suggesting that TLR8 stimulation may benefit subset- and biomarker-selected patients [30].

Important

In contrast to most currently approved antibodies for cancer therapy, antibodies that block immune checkpoints do not target the cancer cells directly; instead they target lymphocyte receptors or their ligands in order to enhance endogenous antitumor activity.

- Immune Checkpoint Inhibitors (ICI)
  The immune system comprises two systems: the inborn innate immune system and the adaptive, acquired immune system. Within the adaptive system T cells are thought to be the major tool in reacting toward "foreign" influences.

T cell-mediated immunity includes multiple sequential steps. Cancer cells release tumor-specific and tumor-associated proteins, so-called antigens that can be picked up by dendritic cells undergoing a clonal selection in the periphery. They migrate to the locoregional lymph node where those antigens are presented to T cells, which are activated and proliferate in secondary lymphoid tissues. These cells will escalate the immune response and traffic to the site of tumor antigen and inflammation. In the best case they enter the tumor, recognize, and kill cancer cells that share the same antigen that has been released by the cancer cells initially. Each step is regulated by counterbalancing stimulatory and inhibitory signals, prone to dysregulation [31].

A central mechanism in fine-tuning T cells response are the so-called checkpoints. T cell response in amplitude and quality is regulated by antigen recognition via the T cell receptor (TCR) and is regulated by a balance between co-stimulatory and inhibitory signals – the so-called immune checkpoints.

Both signals are needed to decide between antigen-specific activation or inactivation [4, 32]. Under physiological conditions, immune checkpoints are crucial for the maintenance of self-tolerance preventing autoimmunity. T cell checkpoints can be activating or inhibitory; their regulation prevents tissue damage when the immune system is responding to pathological conditions, e.g., infections. In cancer they are most meaningful as targeting cancer expressed checkpoint inhibitors can restore activation of preexisting tumor inactivated T cells, liberating the tumor break through checkpoint inhibitors. When examining the mechanisms of action of inhibitors of various immune checkpoints, one recognizes the diversity of immune functions that they regulate.

The discovery of T cell checkpoints can be regarded as one of the currently most meaningful developments in modern medicine and has been awarded with the Nobel Prize in medicine 2018 to Dr. Tasuku Honjo (PD1-/PD-L1-axis) and James Allison (CTLA-4 in the initiation phase of T cells).

As this is clinically the most important approach in HNSCC it will be addressed in a special section.

28.3 Immunomodulatory mAbs Targeting T Cell Checkpoints in HNSCC

28.3.1 Relevant Immune Checkpoint Inhibitors (ICI) Currently Tested in HNSCC

Currently in HNSCC there are two immunomodulatory mechanisms in clinical phase III studies that have the capacity to alter the treatment guidelines. It is the inhibition of immunosuppressive receptors expressed by activated T lymphocytes, such as cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PD-1), and the inhibition of the principal ligands of these receptors, such as the PD-1 ligand CD274 (best known as PD-L1 or B7-H1).

For the sake of completeness it must be mentioned that a lot more checkpoint targeting antibodies (e.g., TIM3, LAG3, Ox40) are also already being tested in earlier clinical studies.

- CTLA-4
  The first checkpoint molecule with inhibitory function that could be influenced by therapeutic antibodies was the "cytotoxic T lymphocyte-associated protein 4," CTLA-4 (CD152). Blocking CTLA-4 through monoclonal antibodies could stop the inactivation of T cells making cancer cells become visible for the immune system again. In HNSCC the relevant antibodies ipilimumab and tremelimumab are currently under investigation in clinical studies. In melanoma these antibodies have already proven a long-lasting tumor control.
- PD-1 and PD-L1
  The second, currently clinically most relevant checkpoint molecule is the "programmed cell death protein 1," PD-1 (CD279). PD-1 is recognized by its ligands PD-L1 (B7homolog1) (CD274) and PD-L2 (CD273).
  PD1, expressed on activated T cells upon chronic stimulation, minimally expressed on resting cells also binds to the PD ligands on tumor cells and healthy tissue. To date it is known that exosomes [33] and many more cells express PD ligands, such as circulating tumor cells, NK cells, endothelial cells, MDSCs [21], and platelets [34], but the immunologic relevance is not fully understood yet.
  The expression of PD-L1 will be upregulated as response to inflammatory cytokines (IFN-y, TNF-a, GM-CSF, IL-4) potentially arising from the tumor micromilieu.
  The stronger the interaction between PD1 activated immune cells and PD-L1 expressing cancer cells is the weaker is the immune response. By inhibition of the receptor or the ligand through monoclonal antibodies immune response can be restored.
  Current immunologic research shows that cancer cells or non-transformed cells in the tumor microenvironment can also express such T cell inactivating checkpoint molecules as one major mechanism of immune escape. There is a difference in the way antibodies that block immune checkpoints work compared to the way most approved antibodies for cancer therapy work. They do not target cancer cells directly but their action relates to targeting lymphocyte receptors or their ligands.
  The blockade of immune checkpoints by which the cancer cell inhibits T cells unleashes a potent immune response (Fig. 28.2).

Meanwhile PD1, PD-L1, and CTLA4 have been developed and tested by many pharmaceutical companies with different epitopes tested. Thus it will be interesting for future research to find differences between the drugs available concerning plasmatic availability, binding avidity, and many more pharmacokinetic issues.

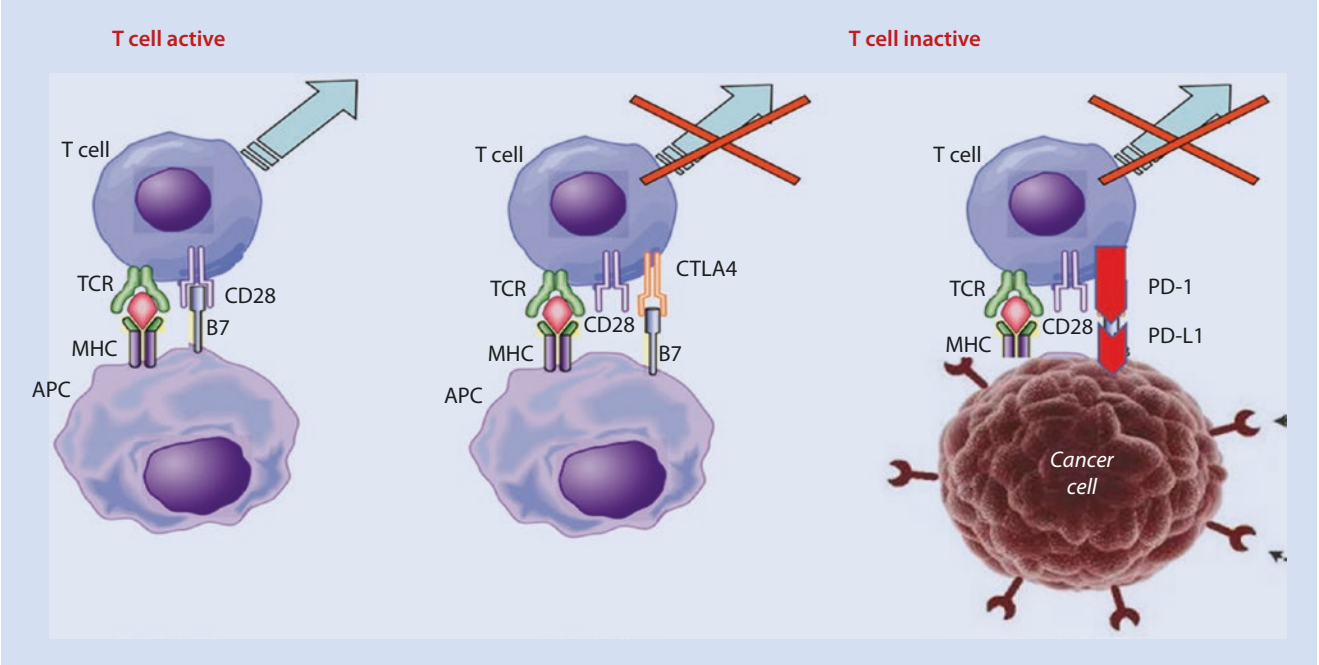

Fig. 28.2 Mechanism of immune checkpoint inhibition (graph adapted from Pardoll 2012). T cells need a specific antigen recognition and an activation signal to become fully active. In control of T cell responses so-called checkpoints can inactivate the T cell response at different time points of immunity. Currently CTLA4 and PD1/PD-L1 are in frequent clinical testing. PD-L1 can also be expressed on cancer cells and mimic the physiological inactivation of T cells

28.3.2 Current Studies, as Every Half Year New Study Results Appear: Phase III Studies Using Immunomodulatory mABs Targeting T Cell Checkpoints in HNSCC

Immunotherapy with Checkpoint Inhibitors in the Second-Line Failure

In order to test the use of PD1-directed antibodies, there are two relevant randomized, open-label, phase 3 trial studies that document the benefit of PD1-directed antibodies in HNSCC: the Checkmate 141 study (ClinicalTrials.gov NCT02105636) [35] testing nivolumab (Opdivo®) and the Keynote 40 study (ClinicalTrials.gov NCT02252042) [36] testing pembrolizumab (Keytruda®). Both studies randomized patients with recurrent or metastatic squamous cell carcinoma of the head and neck who had received platinum chemotherapy and considered to be having very poor prognosis. The treatment arms were either the PD1 antibody alone or chemotherapeutic agents of investigator's choice. Among patients with platinum-refractory, recurrent squamous cell carcinoma of the head and neck, treatment with PD1 antibodies resulted in prolonged overall survival compared with standard, single-agent therapy.

Both studies showed a clinically significant prolongation of overall survival, progression-free survival, and favorable safety profile of the PD1 antibodies in patients with recurrent or metastatic head and neck squamous cell carcinoma supporting further evaluation of PD1 antibodies as a monotherapy (Fig. 28.3).

Eyecatcher

Pembrolizumab provides a clinically meaningful prolongation of overall survival and a favorable safety profile when used for treating patients with recurrent or metastatic head and neck squamous cell carcinoma.

For nivolumab there are already 2-year follow-up data available and it could be shown that the overall survival remains superior in the PD1 antibody group (16.9%) compared to investigator's choice (IC) (6.0%). The overall survival remains particularly good in patients with a PD-L1 expression on cancer cells ≥1%, but is also relevant for patients with PD-L1 expression <1% [35].

Especially interesting is the safety profile and lower toxicity of the checkpoint inhibitors experienced by trial subjects compared to chemotherapeutic agents. Compared to the chemotherapy arm 36.9% (IC) the toxicity of nivolumab ranged with 15.3% relevantly lower. This lower toxicity is also reflected in the quality of life profile of, e.g., nivolumab. Especially the area of general functionality and pain control

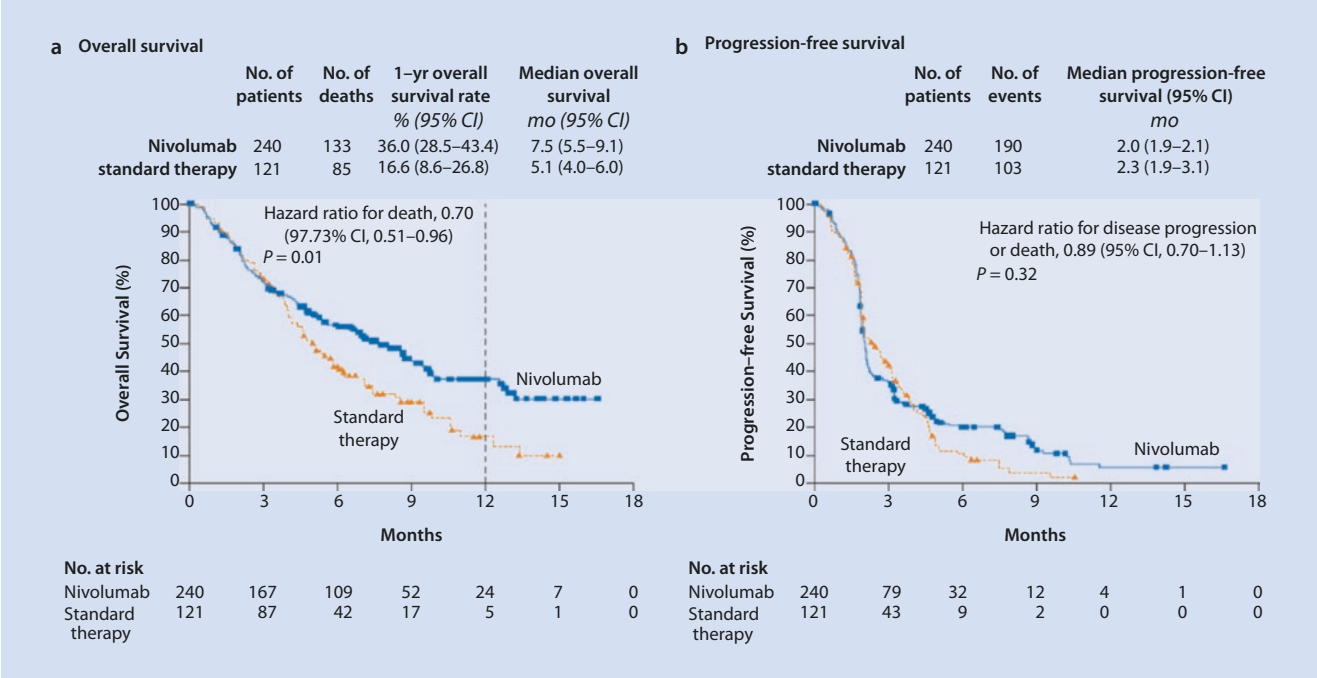

Fig. 28.3 Survival data from the Checkmate 141 [35] using nivolumab showing a remarkable survival benefit for ICI-treated patients

patients relevantly benefitted from the checkpoint treatment. It could be shown that patients treated with nivolumab although probably not responding to the substance showed a significantly reduced pain perception [37].

Detailed subgroup analyses are on the way for both studies. The response rates might vary among different subgroups, e.g., different ethnic groups, patients pretreated with cetuximab, gender, or other factors.

For the treatment of head and neck squamous cell carcinoma, there is another study, using another PD1 targeting antibody pembrolizumab by MSD comparing the efficacy and safety of pembrolizumab versus standard-of-care therapy (ClinicalTrials.gov, number NCT02252042), the so-called Keynote 40 study [36].

The results of these trials indicated a significant improvement in overall survival and favorable safety profile of pembrolizumab in patients with advanced disease. These findings support the further evaluation of pembrolizumab as a monotherapy and as part of combination therapy in earlier stages of disease [38].

A major question that still needs to be addressed, which patient would be best suitable to be treated with the highly costly PD1 antibody therapy. Many concerns on biomarkers are currently under consideration and will be further eluted in the ▶ Chapter 14 on "biomarkers."

The encouraging data from the second-line failure studies led to earlier application of the PD1 antibodies and a very relevant study is the Keynote 48.

Immunotherapy with Checkpoint Inhibitors in the First-Line Failure

Following the great success of the first studies of PD1 antibodies in the second-line failure HNSCC patients, it was important to test the PD1 antibodies versus the standard of therapy EXTREME (combination therapy of cisplatin, 5-fluorouracil (5-FU), and EGFR antibody Erbitux®) (clinical trial identification NCT02358031). The Keynote 48 study addressed this issue and the first data were presented during ESMO 2018.

For first-line recurrent and metastatic HNSCC, pembrolizumab (P) significantly improved overall survival over Extreme (E) in the PD-L1 CPS ≥ 20 and ≥1 populations and was noninferior in the total population with favorable safety. Pembrolizumab plus chemotherapy significantly improved OS in the total population with safety comparable to Extreme. Pembrolizumab mono and pembrolizumab plus chemotherapy responses were durable. These data support pembrolizumab and pembrolizumab + platinum +5-FU as new first-line standards of care for recurrent metastatic HNSCC. The study is ongoing to the final OS analysis. Further analyses concerning the data and pathomechanisms still remain open (Fig. 28.4).

Nonetheless the preliminary data of KN48 have the capacity to alter the scheme of treatment of oral and oropharyngeal cancers after drug approval in the first line. With the newest data future treatment algorithm will change into the following (Fig. 28.5):

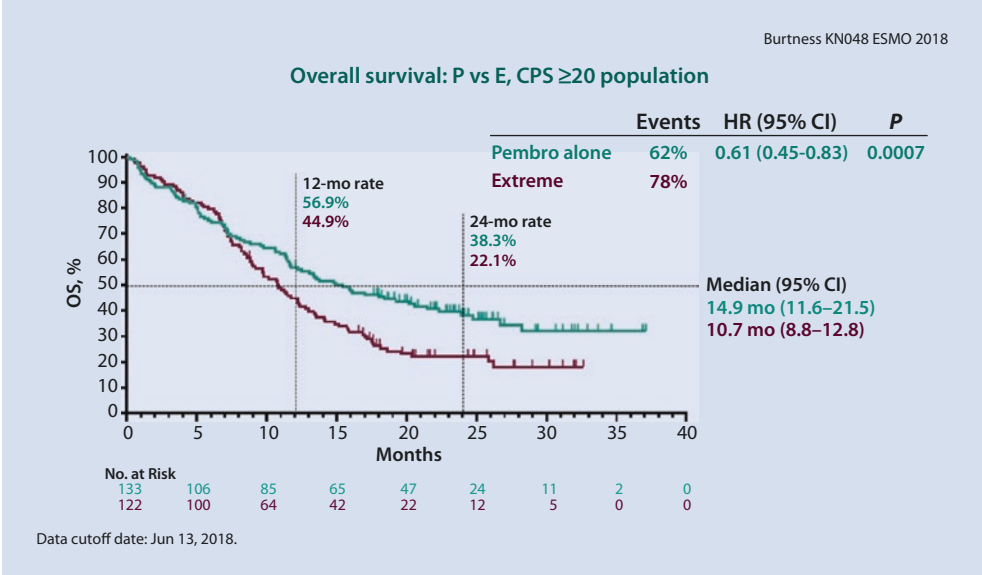

Fig. 28.4 Preliminary results from the Keynote 48 study presented by Burtness B, ESMO 2018, Abstract LBA8 [39]

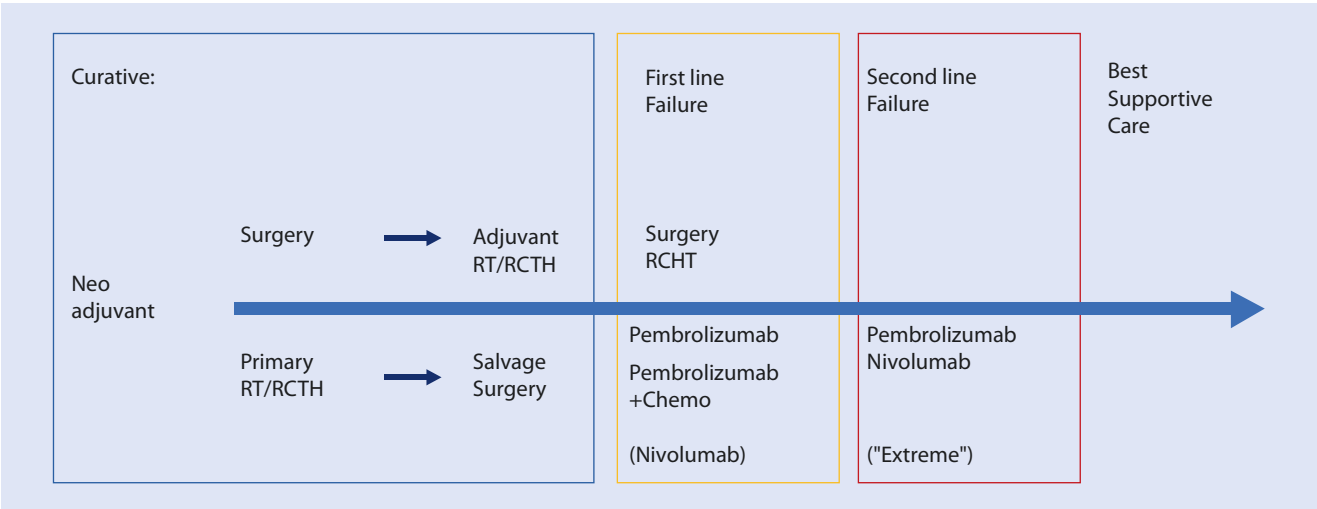

Fig. 28.5 A proposed paradigm change after approval for first line therapy

Nivolumab has been approved for patients with failure of treatment regimens containing cisplatinum. Thereby it can also be applied in the first-line failure setting, although it has never been directly tested comparatively to EXTREME.

This scheme can only roughly serve as an orientation, as currently many studies are ongoing.

28.4 Side Effects of Checkpoint Targeting Antibodies

The mechanism of checkpoint inhibitors bases among other mechanisms on the activation of T cells.

The current data also reveal promising data not only for the overall survival but also for the quality of life of the patients associated with a lower toxicity of the checkpoint inhibitors compared to chemotherapeutic agents. It appears that fewer patients will experience side effects in the checkpoint group but the severity of the side effects outranges those of the SOC group. It is necessary to reevaluate the composite side effects in more detail and on the longer term.

Classical side resulting from chemotherapy, such as bone marrow suppression, nausea, or vomiting, can hardly be observed with checkpoint inhibitors. Undesirable side effects of checkpoint therapy are directly related to autoimmune processes and form a special entity of morbidity. Clinicians and patients need to be informed and especially advised. Many companies hold the service of pocket cards that summarize the most frequent side effects and adequate treatment options. It is especially important to advice patients to mention that they are being treated with checkpoint inhibitors specially in an emergency room situation.

The most frequent toxicities are outlined by Hryniewicki [40]:

- Cardial toxicity
- Colitis and diarrhea
- Pneumonitis and dyspnoe
- Endocrinologic markers of thyroid and liver
- Neurotoxicity

Some of the side effects can be life-threatening, especially cases of grad two toxicities according to the common toxicity criteria (CTC) of the National Cancer Institute which make it necessary to discontinue treatment and to immediately start with immunosuppressive treatment. Side effects can be dose dependent, e.g., with CTLA-4, but can be completely dose or time of treatment independent like with PD-1/PD-L1 targeting antibodies. So thoughtful monitoring is mandatory throughout the treatment.

It might be helpful to know that patients with a preliminary cardiac insult (myocardial infarction, heart defect, myocarditis) present with a massively increased risk for cardiac side effects and need to be strictly monitored [41].

28.5 Patient Selection: Clinically Relevant Biomarkers

Many of the initially performed studies with checkpoint inhibitors in the HNSCC have been started the so-called "all-comer" studies – each patient could be included with the cisplatinum failing tumor diagnosis. Only retrospectively various subgroups of patients were identified that responded particularly well.

Comparing the survival curves there appear to be at least three different phases of resistance: initial resistance, initial response, and then development of resistance over varying timeframes clinically relating to partial response or stable disease, initial or acquired response leading to complete response, and remission of the cancer.

To date it remains a major problem to identify those patients which are most suitable to immunotherapy which will profit from checkpoint therapeutic approaches. Considering the high costs of checkpoint treatment, it is currently in the focus of research to identify biomarkers with high predictive value for a personalized medicine [42].

It turned out that tumors with dense immune cell infiltrate mirroring a preexisting immunity can be targeted the best. Those tumors are termed "hot" for the inflammation going on. Tumors which are immune-excluded (immune cells line up at the margin but cannot enter the tumor) or immune-ignorant tumors that do not have an immune infiltrate at all (cold tumors) cannot be targeted well.

Lymphocytic infiltration of the tumor is tightly associated with the expression of neoantigens, originating from a high mutational burden of the tumor cells [43]. One of those relevant neoantigens is the expression of PD-L1 on the tumor cells divided by all tumor cells termed the "tumor proportion score" (TPS) or additionally the "combined positive score" counting all PD-L1-positive cells – tumor cells but also cellular infiltrate, macrophages, endothelial cells divided by all tumor cells (CPS).

To date the analyses of the microbiota of the gut [44] seem to play a very important but undefined role. Patients treated with checkpoint targeting drugs should not be put on antibiotics that eliminate potentially important germs of the intestinal flora.

Other biomarkers such as single genomic patterns, instability of microsatellites (MSI-H), defect DNA repair mechanisms, or analyses of the T cell repertoire could not be implemented in clinic on a routine base. A good survey of potentially suitable biomarkers can be found in the "immunogram" [45]. Besides the quality and quantity of the cellular infiltrate, factors like tumor micromilieu or metabolic activities are important.

28.6 Future Combinatorial Strategies of Checkpoint Targeting mAB with Standard Therapeutic Procedures in HNSCC

As mentioned earlier, the best suitable patients for immunotherapy with immune checkpoint inhibition (ICI) are those with preexisting immunity that can be restored. More challenging are those tumors that are immune excluded or immune deserted. Combinatorial strategies therefore focus on turning the "cold" tumors into "hot tumors" establishing a new immune cell infiltration on the basis of inducing a beneficial inflammation.

The new study design therefore focuses on combinations of IO and radiation or chemotherapy. The local effect of both therapies will lead to necrotic cells whose clearance will induce some kind of immune response involving all the relevant immune cells that can be targeted by checkpoint antibodies.

Currently many studies address this question of combining radiation and checkpoint inhibitors. It will be interesting to perceive the data from, e.g., the Keynote 412: *Phase 3 Trial of Pembrolizumab Plus Chemoradiation (CRT)* vs *CRT Alone for Locally Advanced Head and Neck Squamous Cell Carcinoma.*

As several studies have already documented the benefit from checkpoint inhibitors (ICI), they are used as "backbone" of the new therapeutic strategy to add other drugs from different drug categories. During the last ESMO or ASCO meetings several very promising combinations have been presented already tested in phase I studies. Examples of such drugs would be:

- Poly ADP-ribose-polymerase (PARP) inhibitors
- Cyclin-dependent (CDK4/6) inhibitors
- Phosphoinositide (PI3K) inhibitors

- Histone deacetylase (HDAC) inhibitors
- Oncolytic viruses (e.g., T-VEC)
- Tyrosine kinase inhibitors (TKIs)
- KIR receptor targeting on natural killer cells
- Antibodies targeting the micromilieu like indoleamine 2,3-dioxygenase-1 (IDO)

The aim is to alter the micromilieu of the tumor the way that blocking a relevant signal transduction pathway will cause cell destruction leading to inflammation and to elicit an immune response with the influx of the relevant cells. Those could be then addressed and supported by ICI.

Even combinations with drug from targeted therapies, e.g., cetuximab, tyrosine kinase inhibitors, VEGF inhibitors, mTOR inhibitors, or inhibitors of tumor metabolites, are under investigation [46].

Other ideas attempt to combine immunostimulating approaches, e.g., cytokines, antibodies, immunomodulatory drugs, vaccine, cell-based immunotherapies, and others [47]. Basically on an annual basis new drugs arise and new combinations are being tested.

A completely new idea is to use ICI as an induction. Two phase I studies have already proven that ICI induction can lead to a higher response rate to ICI with relevant tumor shrinkage with no relevant delay or complication of surgery. It can be shown that the therapeutic effect occurs in the tumor as well as in the locoregional lymph nodes. The primary tumor and the lymph nodes can respond simultaneously or separately in the patients. For completeness sake it should not be unmentioned that some patients react with a "hyperprogression" – an exploding increase in tumor growth to ICI. So far there is no really conclusive explanation to why this happens.

Warning

Further research is needed to guide clinicians as to which patients would be best suitable to be treated with the high cost PD1 antibody therapy.

28.7 Conclusions

Since the first publication of the benefits accrued from the use of checkpoint inhibitors in melanoma patients, scientists have been keen to find out whether similar benefits could be obtained for HNSCC. To date, several immunotherapeutic strategies, among those several checkpoint inhibitors, are being evaluated in various clinical settings in trials designed with diverse drugs and treatment combinations applied at different time points of the disease. Primary data and expertise currently available primarily focus on targeting the PD1/PD-L1 axis. The results are so promising that PD1 antibodies have the potential to alter treatment guidelines in head and neck cancer and implement PD1 targeting antibodies in standard of care.

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