Immune-modulating antibodies in head and neck cancer: past, present, and future

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SUMMARY

Squamous cell carcinoma of the head and neck (SCCHN) has recently expanded the growing range of oncologic diseases successfully treated with immune-modulating agents. With the origins dating back to the nineteenth century, the concept of immunotherapy was repeatedly revisited and refined but also rejected and criticized. Currently, its armamentarium comprises tumour-specific antibodies, cancer vaccines, cytokines, adoptive T-cell transfer, and immune-modulating antibodies. Among these approaches it has been the latter one drawing major attention from healthcare professionals. Nivolumab and pembrolizumab are monoclonal immunoglobulins directed against programmed cell death protein-1 (PD-1), an immune-checkpoint negatively regulating T-cells. In second-line recurrent and/or metastatic SCCHN, two phase III studies demonstrated meaningful clinical benefit achieved by these drugs, dubbed checkpoint inhibitors, compared with standard monotherapy (methotrexate, docetaxel, or cetuximab). In the CheckMate-141 trial, nivolumab significantly improved median overall survival (OS) from 5.1 to 7.5 months. A similar benefit achieved by pembrolizumab in KEYNOTE-040 fell short of statistical significance (8.4 *vs*. 6.9 months), probably due to post-study immune-checkpoint therapy leading to a better-than-expected survival in the control arm. However, the classical outcome measures do not fully capture the exceptional activity of these agents. Apart from low frequency of severe adverse events (13% *vs*. 35% with standard therapy), these antibodies can induce durable tumour responses and retain activity even after several previous chemotherapy lines. With their advent in first-line palliative regimens and protocols for locally advanced disease, further progress is expected.Reliable predictive biomarkers are urgently needed, and several candidates are being evaluated. Among them, tumour mutational burden and gut microbiota offer an innovative approach to biomarker-enrichment strategy.

LOOKING BACK AT THE PAST DECADES

Big things have small beginnings. In the case of immunotherapy, the beginnings were scattered across centuries. It took some luck and a lot of effort to accomplish the individual steps and to fit them together as pieces of a jigsaw puzzle. In fact, the revolutionary discovery of vaccination against smallpox (*variola major*) by *Edward Jenner* in 1796 was preceded by a report of *John Fewster* on the protective efficacy of cowpox infection already 30 years earlier. Of note, the long-lasting history of purposeful inoculation with *variola minor* virus should be credited to the Ottoman Empire and probably also to ancient China, which were thus the first to manipulate the human immune system.[1] The implication of immune reactions in cancer biology was pointed out in the second half of the nineteenth century. At

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that time, *Rudolf Virchow* observed immune infiltrates in neoplastic tissues, linking the origin of cancer to sites of chronic inflammation.[2] Moving from preventive measures and laboratory observations, *William B. Coley* merits to be referred to as the forefather of modern immunotherapy. More than one hundred years ago, his experimental attempts with injections of non-infectious bacterial admixtures of *Streptococcus pyogenes* and *Serratia marcescens* yielded a 10% remission rate in patients with inoperable sarcomas, but were not adopted by others.[3] During that period, a pioneering insight into the pathophysiology was provided by *Paul Ehrlich*. He suggested the existence of specific receptors binding various antigens, which later evolved into his theory of tumours being recognised by the immune system.[4] The era of the two world wars did not favour research in this domain, and it was not until the late 1950s that further progress was made.

In 1957, *Isaacs and Lindenmann* announced the discovery of interferon.[5] Simultaneously, inspired by Ehrlich's work and murine tumour transplantation models, *Thomas and Burnet* proposed the hypothesis of immunosurveillance, where lymphocytes act as sentinels in protecting against transformed cells.[6] In 1959, the first cancer vaccine study was published. In a cohort of 114 advanced gynaecological cancer cases, the disease control rate (response or stabilization) reached a provocative 22%, which unfortunately went rather unnoticed.[7] The encouraging momentum in immunotherapy slowed down, when the theory of immunosurveillance was questioned by preclinical findings in athymic nude mice. In the 1974 work of *Osias Stutman*, athymic mouse models exhibited no increased susceptibility to chemically induced or spontaneous carcinogenesis compared with immunocompetent mice.[8] Nevertheless, this setback was compensated by a growth in the field of cell biology providing a number of important discoveries such as clarification of the cellular response in adaptive immunity in 1967, description of dendritic cells in 1973, and characterisation of natural killer cells in 1975, which all later helped to conceptualize some of the key principles of immunotherapy.[1]

Since the late 1970s, hematopoietic stemcell transplantation has become an accepted treatment option for selected haematological malignancies.[9] Subsequently, several multifunctional cytokines (e.g., interleukin-2, interferon-α) entered clinical testing, new data on tumour-associated antigens appeared, and adoptive T-cell transfer was used for the first time.[6,10] In 1997, rituximab expanded the therapeutic portfolio available to treat lymphoma, followed by the arrival of other tumour-specific monoclonal antibodies finding success in different malignant diseases.[11,12] It was not until the turn of the century that more light was cast on the experiments with athymic nude mice contradicting the hypothesis of immunosurveillance almost 30 years earlier. The seminal paper of *Shankaran et al*. showed that deeply immunocompromised mice, this time lacking the recombination activating gene-2 (*RAG2*), indeed, experienced a higher incidence of sarcomas.[13] Moreover, it became clear that the complex interplay between cancer and immunity cannot be sufficiently explained by a mere failure of immunosurveillance leading to immune evasion and tumour formation. In fact, the immune system is capable not only of preventing but also promoting the growth of neoplastic tissue. In this regard, immune pressure exerted on cancer cells selects those, which have reduced immunogenicity and are therefore prone to escape immune-mediated eradiation. Such tumours can thrive even in immunocompetent hosts. This dynamic interaction between the immune system and cancer cells has been referred to as cancer immune editing, comprising the following three phases: tumour elimination, equilibrium, and tumour escape to clinically overt disease.[1,6,13]

For many years, all these individual discoveries were eagerly waiting to get translated into a powerful yet gentle anti-cancer modality. Until 2010, the medical community either viewed therapeutic attempts at the immune system with suspicion, or their toxicity was an issue, or the therapy intent was purely palliative, or the limited single-agent activity necessitated various combination protocols. This held true despite several innovative approaches including the topical immune-response modulator imiquimod and vaccination against human papillomavirus (HPV)-16 oncoproteins, both used in vulvar intraepithelial neoplasia, and sipuleucel-T, a vaccine based on autologous dendritic cells, which reduced the risk of death in metastatic castration-resistant prostate cancer and became the first therapeutic cancer vaccine to be approved by the United States Food and Drug Administration (FDA).[10,14]

However, the real challenge of translational medicine was how to effectively counteract tumour evasion strategies. The human organism disposes of a two-step protection system to prevent cancer outgrowth. Cancer is a genetic disease, therefore the deoxyribonucleic acid (DNA) repair mechanisms represent the first-line barri-

TABLE 1. Mechanisms of immune escape in cancer.[15-17]

Strategy	Mechanism	Specification
A. Reduced recognition by the immune system	1. Reduced antigen processing and presentation	Downregulation or mutation of HLA class molecules
B. Increased resistance or survival of cancer cells	1. Increased proliferation	Increased expression of STAT3
	2. Decreased apoptosis	Increased expression of STAT3 or BCL-2
C. Immunosuppressive microenvironment	1. Tumour-permissive cytokine profile	Increase of immunosuppressive cytokines: TGF-β, IL-6 Decrease of stimulatory cytokines: IL-2, IFN-γ
	2. Expression of immunoregulatory molecules	Production of IDO
	3. Cellular immune escape	Tregs, M2 macrophages, MDSCs
	4. Anergic T-cells 4a. by increase of co-inhibitory receptors 4b. by decrease of co-stimulatory receptors	 CTLA-4, PD-1, TIM-3, LAG-3 CD137, OX40

HLA, human leukocyte antigen; STAT3; signal transducer and activator of transcription 3; BCL-2, B-cell lymphoma 2; TGF-β, transforming growth factor-beta; IL, interleukin; IFN-γ, interferon-gamma; IDO, indoleamine 2,3-dioxygenase; Tregs, regulatory T-cells; MDSC, myeloid-derived suppressor cells; CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death protein-1; TIM-3, T-cell immunoglobulin mucin protein-3; LAG-3, lymphocyte-activation gene-3

er blocking malignant transformation. At the next stage of defence, the immune system acts as a safety net eliminating already transformed cells. From this perspective, a specifically targeted remedy could actually be considered a causal therapy, bringing the terms "treating" and "curing" even closer together (*Figure 1*). At present, we know that an oncologic disease employs several strategies to avoid immune-recognition and destruction as summarized in *Table 1*.[15-17] A new chapter of medicine began to unfold when we realized how to harness one of them.

THE AGE OF NEW HOPES

The inception of recent practice-changing medical breakthroughs can be traced back to the mid-1990s when *Jim Allison and colleagues* revealed the critical role of cytotoxic T-lymphocyte antigen-4 (CTLA-4) in negative regulation of T-cells and showed that its blockade results in a compelling anti-cancer activity.[18,19] Afterwards, it took less than a decade for the first phase III trial to start enrolling patients. When in 2010 the results were published, it was beyond any doubt that a serious attempt at causative anticancer treatment was finally made. Among 676 patients with unresectable or metastatic melanoma, *Hodi et al*. demonstrated a 3.5 month improvement in median OS with the CTLA-4 inhibitor ipilimumab, compared with a glycoprotein 100 peptide vaccine.[20] This discovery led to a dramatic expansion of a whole new array of targeted therapies that have been rewriting paradigms across different cancer diagnoses. Two recent novelties will probably have an even deeper impact on the medical oncology practice. On May 23, 2017, the inhibitor of the programmed cell death protein-1 (PD-1) pembrolizumab became the first-ever anti-cancer drug approved for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours, irrespective of primary tumour location.[21] The second revolutionary update is the approval of tisagenlecleucel, a novel chimeric antigen receptor T-cell therapy, for relapsed or refractory B-cell precursor acute lymphoblastic leukaemia and large B-cell lymphoma. This agent has drawn attention

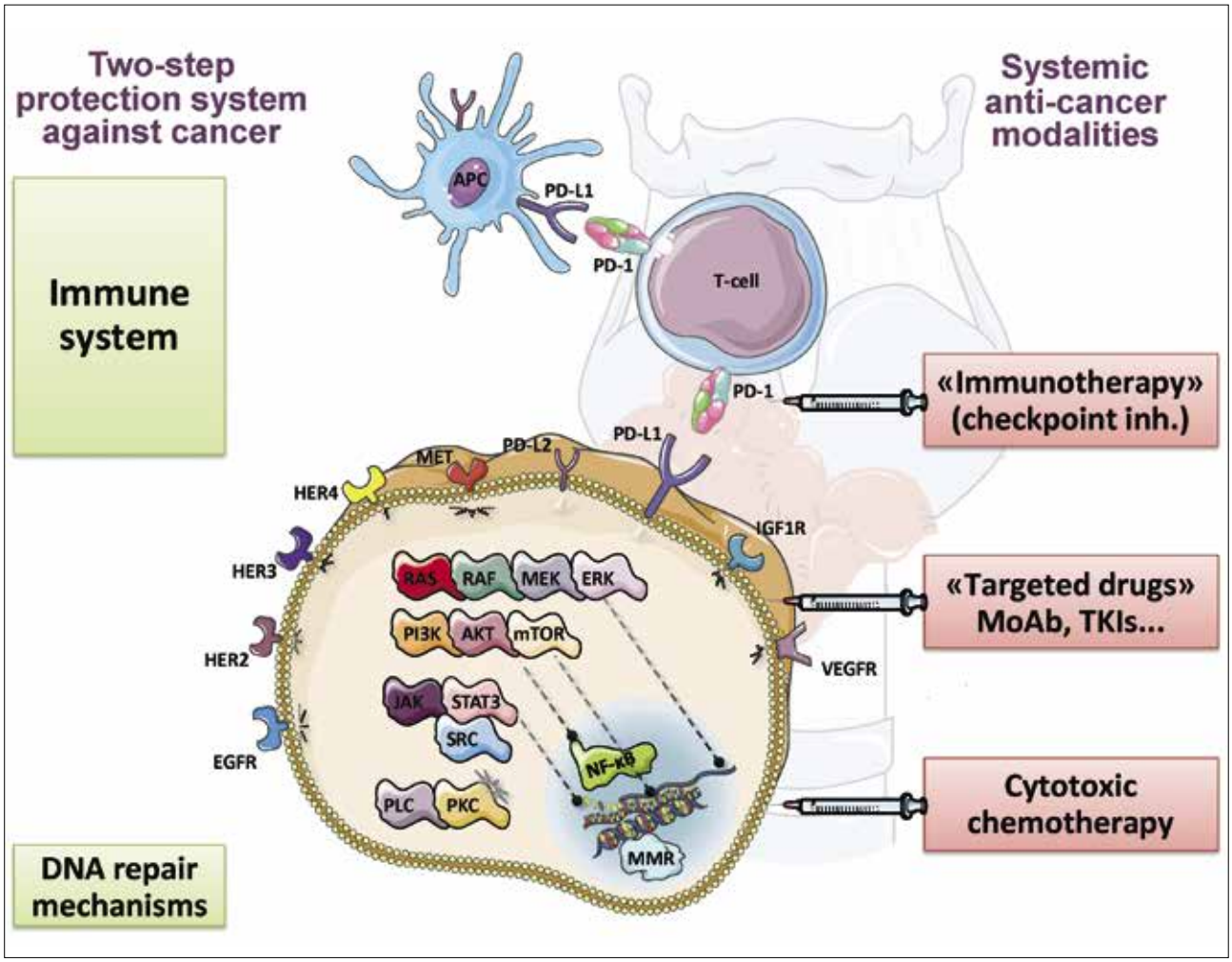

FIGURE 1. Simplified model illustrating the current portfolio of systemic anti-cancer drugs with respect to the two-step protection system against cancer consisting of the deoxyribonucleic acid (DNA) repair mechanisms and the immune system. While cytotoxic chemotherapy and targeted drugs against tumour antigens represent, in principle, palliative modalities, modern immunotherapy with immune-checkpoint inhibitors offers a possibility of causal interference with tumour outgrowth.

APC, antigen-presenting cell; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; MoAb, monoclonal antibody against tumour antigens; TKIs, tyrosine kinase inhibitors; MMR, DNA mismatch repair; EGFR, HER2, HER3, HER4, MET, IGF1R, and VEGFR, targetable cell surface receptors; RAS, RAF, MEK, ERK, PI3K, AKT, mTOR, JAK, STAT3, SRC, PLC, PKC, NF-κB, components of downstream signalling pathways.

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not only because of its spectacular efficacy, but also due to its not less astonishing price tag of $475,000 for a single, one-time infusion.[22,23]

The current perception of immunotherapy relies on a classification into several subgroups including tumour-specific antibodies (e.g., cetuximab), cancer vaccines (sipuleucel-T), cytokines (e.g., interleukin-2), adoptive T-cell transfer (e.g., tisagenlecleucel), immune-modulating antibodies and other immunomodulators (e.g., imiquimod). In routine practice, the terms immunotherapy and immune-modulating antibodies have often been used interchangeably, although it is evident that the situation is much more complex. Immune-modulating antibodies demonstrated efficacy where conventional therapies failed, and its success brought about a renaissance of cancer immunotherapy eight years ago. These antibodies can be further divided into two classes, i.e., drugs blocking negative regulatory pathways in effector lymphocytes, which encompass CTLA-4 signalling and co-inhibitory pathways (see below), and drugs enhancing co-stimulatory signals. Referring to the latter category, agonistic monoclonal antibodies against OX-40 (MEDI0562) and

TABLE 2. Ongoing large phase III trials with monoclonal antibodies against PD-1 (pembrolizumab, nivolumab), PD-L1 (avelumab, durvalumab), and CTLA-4 (ipilimumab) in squamous cell carcinoma of the head and neck cancer as of July 2018 (according to ClinicalTrials.gov).

Trial	Clinical setting	Actual or estimated enrolment	Regimen (treatment arms A-D)	Primary completion date
REACH	LA, definitive	688	A: Cisplatin + RT B, C: Cetuximab + avelumab + RT D: Cetuximab + RT	10/2019
KEYNOTE-412	LA, definitive	780	A: Pembrolizumab + cisplatin + RT B: Placebo + cisplatin + RT	04/2021
JAVELIN Head and Neck 100	LA, definitive	640	A: Avelumab + cisplatin + RT B: Placebo + cisplatin + RT	04/2021
NIVOPOSTOP	LA, adjuvant	484	A: Cisplatin + RT B: Cisplatin + RT + nivolumab	12/2021
NCT03349710	LA, definitive	1046	A: Nivolumab + cetuximab + RT B: Placebo + cetuximab + RT C: Nivolumab + cisplatin + RT D: Placebo + cisplatin + RT	11/2022
KESTREL	R/M, 1st line	823	A: Durvalumab B: Durvalumab + tremelimumab C: PFE	12/2018
KEYNOTE-048	R/M, 1st line	825	A: Pembrolizumab B: Pembrolizumab + PF C: PFE	12/2018
CheckMate-651	R/M, 1st line	930	A: Nivolumab + ipilimumab B: PFE	04/2020
CheckMate-141	R/M, 2nd line	361	A: Nivolumab B: SoC	11/2015
KEYNOTE-040	R/M, 2nd line	495	A: Pembrolizumab B: SoC	05/2017
EAGLE	R/M, 2nd line	736	A: Durvalumab B: Durvalumab + tremelimumab C: SoC	11/2018

PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; CTLA-4, cytotoxic T-lymphocyte antigen-4; LA, locoregionally advanced; R/M, recurrent and/or metastatic; RT, radiotherapy; PFE, platinum/5-fluorouracil/cetuximab regimen according to the EXTREME trial; SoC, standard of care (e.g., methotrexate)
ainhibitor of indoleamine 2,3-dioxygenase-1 (IDO1)

CD137 (urelumab, utomilumab) or a small molecule toll-like receptor 8 agonist (motolimod) have already entered early clinical development, among others in head and neck cancer.[24]

Following the 2010 report on the CTLA-4 inhibitor ipilimumab, the co-inhibitory pathways, also dubbed immune checkpoints, quickly moved into the spotlight. The signal transduction pathway initiated by the PD-1 receptor binding its ligand, PD-L1, became extensively studied in different tumour types including squamous cell carcinoma of the head and neck (SCCHN). Expression of PD-1 was documented on the surface of activated T- and B-lymphocytes and myeloid elements. The ligands PD-L1 (CD274/B7-H1) and PD-L2 (CD273/B7-DC) are transmembrane proteins transmitting negative signals down regulating T-lymphocyte activation. Under physiological condition, normal cells expressing PD-1 help modulate the duration and activity of T-cells to prevent autoimmune reactions. Cancer cells may escape immune recognition by an increased expression of PD-L1 and PD-L2. Alternatively, a

TABLE 3. Comparison between CheckMate-141 and KEYNOTE-040 phase III trials in second-line recurrent and/or metastatic squamous cell carcinoma of the head and neck.29,34

Parameter	CheckMate-141	KEYNOTE-040
Inclusion period	06/2014 – 08/2015	12/2014 – 05/2016
Number of patients	361	495
Treatment arms	A: nivolumab	A: pembrolizumab
	B: methotrexate or docetaxel (weekly) or cetuximab	B: methotrexate or docetaxel (three-weekly) or cetuximab
Inclusion criteria regarding previous platinum treatment	progression within 6 months after platinum	progression within 3-6 months after platinum-based chemoradiation or progression after 1st or 2nd line palliative platinum
Results obtained with immunotherapy (arm A):		
Hazard ration for death	0.71; 95% CI, 0.55-0.90	0.82; 95% CI, 0.67-1.01
Overall survival [months][a]	7.5	8.4
12-month overall survival	36%	37%
Progression-free survival [months][a]	2.0	2.1
Time to response [months][a]	2.1	4.5
Duration of response [months][a]	9.7	18.4
Objective response rate	13%	15%
[a]*median*		

high-fraction of CTLA-4 or PD-1 positive T-cells in the microenvironment may have the same impact.[16]

In SCCHN, several immune checkpoint inhibitors have already progressed to advanced clinical testing in locoregionally advanced and recurrent and/or metastatic (R/M) settings (*Table 2*). Pembrolizumab (MK-3475) and nivolumab (ONO-4538) are monoclonal antibodies of the immunoglobulin G4 type with a high affinity for PD-1. Durvalumab (MEDI4736), atezolizumab (MPDL3280A), and avelumab (MSB0010718C) block PD-L1. Until present, final or preliminary results of the phase 1 KEYNOTE-012 trial with pembrolizumab, the phase 2 KEYNOTE-055 trial with pembrolizumab, the phase 2 HAWK trial with durvalumab, and a phase 1 trial with atezolizumab were published in peer-reviewed journals or presented at international conferences.[25-28] In addition, data from two large phase III studies were reported. Both evaluated PD-1 inhibitors, nivolumab and pembrolizumab, and had overlapping designs. In the section below we will concentrate on these two trials highlighting their similarities and differences (*Table 3*).[2]

CHECKMATE-141 VERSUS KEYNOTE-040

At the 2016 annual meeting of the American Association for Cancer Research (AACR), the investigators of the randomized global CheckMate-141 phase III trial declared nivolumab to become the first drug ever to improve survival in patients with platinum refractory R/M-SCCHN.[31] As published later in The New England Journal of Medicine, the study evaluated the efficacy and safety of nivolumab at a dose of 3 mg/kg intravenously every two weeks versus weekly intravenous single-agent chemotherapy (methotrexate 40-60 mg/m^2, docetaxel 30-40 mg/^{2}) or cetuximab (400 mg/m^2 once, then 250 mg/m^2).[29] A recent report updated the findings after a minimum follow-up of 11.4 months, and another conference abstract provided efficacy and safety data by age.[32,33] Presented at the 2017 European Society for Medical Oncology congress, the KEYNOTE-040 trial randomized R/M-SCCHN patients to receive either pembrolizumab 200 mg every 3 weeks or the same standard-of-care medication as in CheckMate-141 with the exception of docetaxel which was administered every 3 weeks at a dose of 75 mg/m^2.[34] An update on quality-of-life aspects was given at the 2018 congress of

the American Society of Clinical Oncology (ASCO).[35]
In both studies, OS was the primary objective. The key eligibility criteria were also similar: R/M-SCCHN of the oral cavity, pharynx, or larynx not amenable to local therapy with curative intent, good Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1), and no active brain metastases, autoimmune diseases, systemic immunosuppression, or previous administration of PD-1/PD-L1 or PD-L2 inhibitors. However, there were two important differences concerning the definition of prior platinum (carboplatin or cisplatin) failure and the number of prior chemotherapy lines, which both might have influenced the outcomes. In CheckMate-141, patients were enrolled only if they had disease progression within 6 months after platinum-based chemotherapy administered irrespective of clinical setting. In KEYNOTE-040, platinum failure was defined according to clinical setting. In R/M disease, disease progression had to occur during or somewhere after a platinum-containing regimen in the first or second line. In locally advanced disease (or in recurrent SCCHN amenable to chemoradiotherapy with curative intent), recurrence or progression had to be confirmed within 3 to 6 months of previous multimodality treatment containing platinum. That is to say that patients treated with the CheckMate protocol might have had a more aggressive disease with faster progression and heavier pre-treatment.

The enrolment periods partly overlapped, extending from June 2014 to August 2015 and from December 2014 to May 2016 in CheckMate-141 and KEYNOTE-040, respectively. In the former trial, patients were randomised in a 2:1 ratio to receive either nivolumab (236 of 240 assigned) or a single-agent investigator's choice (111 of 121 assigned), while the latter study equally allocated 495 patients to pembrolizumab (246 of 247 assigned) or the same standard-of-care arm (234 of 248 assigned). The majority of patients received nivolumab or pembrolizumab in the second line and about one third in the third line. As indicated above, the CheckMate-141 protocol allowed recruitment of patients pre-treated with further treatment lines, finally accounting for about 20% of the study population. Treatment-related adverse events occurred at markedly similar rates in both trials. All grade toxicities were reported in 59% and 78% of patients in the nivolumab and control arms, respectively, and in 63% and 84% of patients in the pembrolizumab and control arms, respectively. Analogously, severe acute side effects appeared in 13% and 35% in the nivolumab trial, respectively, and in 12% and 35% in the pembrolizumab study. In the anti-PD-1 cohorts, fatigue (13-14%), nausea (5-9%), rash (8%), and diarrhoea (7-8%) were the most common side effects of any grade. Apart from the skin reactions, adverse events with a potential immunologic aetiology comprised endocrine (8-15%, primarily hypothyroidism), gastrointestinal (colitis), hepatic, pulmonary, infusion-related, and renal toxicities. There were two treatment-related deaths in the nivolumab arm (versus one in the respective standard arm) and four in the pembrolizumab arm (versus two in the respective standard arm).
After a median follow-up of 5.1 and 7.5 months, subjects assigned to nivolumab and pembrolizumab had a 30% (HR[97.73%CI], 0.70; 0.51-0.96; p=0.01) and 18% (HR[95%CI]: 0.82[0.67-1.01]; one-sided p=0.0316) reduction in the risk of death compared to their control arms, respectively. Correspondingly, the median OS was 7.5 *vs*. 5.1 months and 8.4 *vs*. 6.9 months in CheckMate-141 and 37% in KEYNOTE-040. At 12 months, the estimated OS among patients on one of the checkpoint inhibitors was remarkably similar (36% in CheckMate-141 and KEYNOTE-040, respectively), while clearly more patients treated with a standard-of-care agent were alive in the latter trial (17% and 27%). When looking at the magnitude of the survival benefit according to the chosen standard-of-care agent, docetaxel seemed to offer superior outcomes to methotrexate and cetuximab. This came to the forefront especially in KEYNOTE-040 where the hazard ratio for death with three-weekly docetaxel was 0.97 (95%CI: 0.73-1.30) relative to 0.82 (0.53-1.28) attained with weekly docetaxel in CheckMate-141.
Compared with the respective standard arms, the objective response rates (ORR) were in favour of nivolumab (13% *vs*. 6%) and pembrolizumab (15% *vs*. 10%) which was in line with the number of complete responses being 6 *vs*. 1 and 4 *vs*. 1, respectively. Interestingly, the median progression-free survival (PFS) was around 2 months irrespective of the assigned treatment strategy. Pembrolizumab induced long-lasting but delayed responses with median time to response and duration of response of 4.5 and 18.4 months, respectively (*vs*. 2.2 and 5 months with a standard of care agent, respectively). In contrast, the median time to response in CheckMate-141 was comparable in both arms (about 2 months), while the duration of response was better with nivolumab but still numerically inferior to the results obtained with pembrolizumab (median: 9.7

months *vs.* 4.0 months with a standard of care agent). Pre-planned biomarker analyses suggested that the advantageous effect on survival of the anti-PD-1 drugs was greater in PD-L1 positive tumours. The benefit of the experimental treatment was also noted when evaluating patient-reported quality-of-life measures, which were stable or slightly improved in contrast to the standard-of-care arm, where patients generally showed a decline.

In summary, monoclonal antibodies with high affinity for PD-1 are well-tolerated drugs with beneficial effects against head and neck cancer. At the cost of infrequent, yet potentially fatal complications, they prolong OS and produce long-lasting but often delayed responses. The lack of a statistical significance in the KEYNOTE-040 survival analysis can be attributed to a better-than-expected outcome in the control arm due to subsequent immune checkpoint therapy. In this study, another noteworthy observation is the survival analysis according to chronological age, which indicated the greatest benefit in patients of 65 years or more. This is something rare in oncology trials where geriatric evaluation is not usually employed to select fit elderly patients, hence the results are commonly biased by different aspects of frailty. Paradoxically, it may also be the case of KEYNOTE-040, because we might hypothesize that elderly patients receiving standard-of-care therapy might not have been fit enough to receive further treatment lines (including immunotherapy). As such, the difference in survival between the experimental and a standard agent in this subgroup might merely reflect the real potential of pembrolizumab better and may not have anything to do with an exclusive efficacy in the aged population. In CheckMate-141, the efficacy of nivolumab, particularly in terms of response rate and milestone survival at 30 months, was maintained regardless of age, although the improvement in median OS was less than 1 month in senior individuals. Finally, it should be made clear that despite all these encouraging results, immune checkpoint inhibitors have limited efficacy in a substantial proportion of patients prompting a call for innovative, biomarker-enrichment strategies.

FUTURE CONSIDERATIONS

Although there is a flux of novel anti-cancer drugs, with some showing real benefit, there is also a downside to this. Cost-effectiveness analyses have questioned the real value of some of these new medicines, and this situation has even farther-reaching consequences with a potential harmful impact on patient lives. As mentioned by *Prasad et al.*, regulatory authorities in some countries have shown a willingness to approve drugs and indications providing only a marginal level of clinical benefit. Given the escalated costs of new agents hitting the market, certain concerns have been raised that pharmaceutical companies may ultimately pursue development of ineffective drugs to generate potentially profitable trials. The field of immunotherapy seems to be particularly vulnerable to this undesirable transformation of clinical research. The number of phase I to III trials with immune checkpoint inhibitors has already exceeded 1,500. However, a limited or even missing biological rationale and redundant study designs are rather suggestive of companies trying to maintain sufficient trial portfolio. This behaviour might increase the risk of missed opportunities for patients recruited to studies evaluating dubious or inert compounds.[36,37] The complex nature of this issue prevents any simple solution, and it has become clear that despite an enormous improvement in cancer care, many new challenges marked by economical, ethical, and biological dimensions remain unresolved. In this chapter, leaving such provocative assumptions aside, we will address several topics specific for modern immunotherapeutic approaches, which may have direct implications for future development in this area.

Statistical considerations

It has turned out that some of the classical outcome measures like median OS and PFS may not fully capture the exceptional activity of immune checkpoint inhibitors. Unlike cytotoxic drugs (e.g., cisplatin) and tumour-specific antibodies (e.g., cetuximab), these drugs typically elicit delayed clinical effects with a possibility of durable off-treatment survival for a small proportion of patients.[38,39] Intriguing results were obtained in a long-term prospective follow-up of almost 2,000 ipilimumab-treated patients with advanced melanoma. About 3 years after randomization, the OS curve started to plateau slightly above 20%, extending up to 10 years at a rate slightly below 20%.[40] In R/M-SCCHN, this seems to hold true also for nivolumab, although the available estimates do not reach beyond two years.[32] Another characteristic feature seen in Kaplan-Meier plots is a late separation of survival curves, starting several months after randomization. This probably mirrors the time necessary to unlock the natural anticancer powers of the immune system and to translate them into clinical benefit.[38,41]

KEY MESSAGES FOR CLINICAL PRACTICE

- **Since 2010, immune checkpoint inhibitors have revolutionized cancer care.**
- **Head and neck carcinoma is a good candidate for this new generation of immunotherapy.**
- **Nivolumab and pembrolizumab are inhibitors of programmed cell death protein-1 (PD-1).**
- **Both anti-PD-1 agents are well tolerated offering durable responses for about 20-30%, even heavily pre-treated patients.**
- **Tumour mutational burden and gut microbiota represent promising new biomarkers.**

Importantly, all the class-specific attributes have implications for study design, since they prolong study duration and necessitate introduction of intermediate clinical endpoints including milestone survival assessed cross-sectionally at pre-specified time points (e.g., 1- and 2-year overall survival rates). However, it should be kept in mind that milestone analyses do not consider the totality of survival data. Thus, a combination of both approaches might pave the way for upcoming clinical trials.[42] In addition, trialists will probably be confronted with profound conceptual changes in the near future heralded by doubts about the traditional stepwise approach to drug development from phase 1 to phase 2 and later 3. This came to the forefront with the pembrolizumab KEYNOTE-001 study resulting in unprecedented regulatory approvals. Using multiple expansion cohorts, the investigators were finally able to enrol more than 1,200 patients.[43,44]

Activity considerations

Soon after immunotherapy onset, about 10% of patients with advanced melanoma experience a specific phenomenon called pseudoprogression. While resembling true neoplastic growth, it merely reflects a transient immune cell infiltration of the tumour. The possibility of its occurrence, not exceeding 1% in SCCHN, should always be weighed against the risk of futile complications in the course of immunotherapy continued beyond progression as well as the risk of missed opportunities for a timely treatment switch.[25,29,45] In clinical practice, findings from both radiological and physical examinations must be considered. While a deterioration of general status accompanied by ambiguous radiological imaging portends a real progression, in case of sustained clinical benefit, tumour size increment should not automatically imply a change in patient management. In this respect, both CheckMate-141 and KEYNOTE-040 allowed treatment continuation after initial radiological progression conditioned upon stable clinical evaluation and a repeated imaging at at least 4 weeks. This approach was adopted by the immune-related Response Criteria (irRC) replacing the conventional Response Evaluation Criteria in Solid Tumours (RECIST) in this scenario. irRC should preferably be used in routine medical care as well.

This year's annual ASCO meeting brought valuable new insights into the field of immunotherapy. After a median follow-up of almost four years, an updated report of the KEYNOTE-006 trial confirmed the superiority of pembrolizumab over ipilimumab in terms of long-term survival of melanoma patients. Interestingly, the plateau phase seemed to decline more steeply with the anti-PD-1 agent with 2- and 4-year OS rates of 55% and 44% in the pembrolizumab arm, and 43% and 36% in the ipilimumab arm, respectively.[46,47] This observation suggests that not all effects of immunotherapy are easily transposable across the whole group of immune checkpoint inhibitors. Another consideration gaining more and more attention from practicing physicians is treatment choice beyond immunotherapy. Earlier data in non-small cell lung cancer (NSCLC) found higher response rates to single-agent chemotherapy after immunotherapy exposure compared with historical controls.[48] A recent retrospective French study In SCCHN found an overall response to salvage chemotherapy of 30% with 3 cases (4%) of complete remission.[49] Such outcomes are usually attained in the first-line setting and therefore warrant further exploration.[50] A logical question that now arises is whether re-challenge with immunotherapy also represents a viable option. *Watanabe and colleagues* retrospectively analysed re-administration of immune checkpoint inhibitors in patients with NSCLC previously treated with immune checkpoint inhibitors and chemotherapy. Unlike giving chemotherapy right after immunotherapy, a re-challenge with immunotherapy did not meet with

the same level of success. Among 14 patients, only one partial response was noted after receiving the same immune-modulating agent (1 out of 8 cases), but not a different one (0 out of 6 cases).[51]

Patient selection considerations

In the field of immunotherapy, the key challenge for future research will be to identify long-term survivors and to develop more effective treatment protocols by investigating new drugs and testing combinations of different immunotherapies and combinations of immunotherapies with other systemic agents and modalities such as radiotherapy and surgery.[5] At present, we know that in R/M-SCCHN, classic cytotoxic chemotherapy yields disease stabilisation in about 40%. This proportion halves in patients receiving checkpoint inhibitors where the greatest benefit can be expected in those achieving an objective response.[45] But who are these patients? A promising candidate for a stratification factor might be the PD-L1 expression on tumour cells and in the microenvironment. However, a lack of measurement standardization and still a vague definition of an optimal cut-off value have been hindering a successful translation of the PD-L1 marker into clinical practice as yet.[29,53]

It is compelling to say that the new era of immunotherapy needs a new concept of biomarker selection. Maybe the time has come to abandon the traditional understanding of biomarkers as cell surface proteins or other similarly quantifiable molecules. We already discussed the revolutionary approval of pembrolizumab for MSI-H or dMMR tumours. Unfortunately, only a minority of patients qualify for such treatment and even if they do so, half of them will not respond.[54] Recently, two novel approaches involving tumour mutational burden (TMB) and gut microbiota have been proposed. TMB reflects the total number of genomic alterations per coding area carried by cancer cells. In a phase III trial of stage IV or recurrent NSCLC patients treated with first-line nivolumab plus ipilimumab, the PFS was significantly longer than with chemotherapy in patients having a high tumour mutational burden (i.e, at least 10 mutations per megabase), regardless of PD-1 expression.[53] Besides that, the gut microbiome emerged as an intriguing biomarker modulating response to anti-PD-1 agents in malignant melanoma. A working group from the MD Anderson Cancer Center showed that patients with a gut microbiome characterised by a high diversity and abundance of *Ruminococcaceae/Faecalibacterium*, but not *Bacteroidales*, exhibit improved anti-tumour immune responses.[55] From this perspective, a recently reported negative role of antibiotics altering the microbiome composition in patients treated with immunotherapy merits further attention from clinicians and trialists.[56]

CONCLUSIONS

Recurrent and/or metastatic disease is the most difficult to treat scenario in head and neck cancer. Here, only two molecularly targeted strategies have provided significantly longer median OS than their respective control arms. The epidermal growth factor receptor (EGFR) inhibitor cetuximab underwent prospective testing as an adjunct to the platinum/5-fluorouracil doublet in the first-line EXTREME trial (Erbitux in first-line treatment of recurrent or metastatic head and neck cancer).[57] About ten years later, new immunotherapeutic approaches emerged as detailed in this review article. The remarkable outcomes yielded by the two monoclonal antibodies with a high affinity for PD-1, nivolumab and pembrolizumab, are a practice-changing step forward in the management of platinum-refractory disease. Data from trials performed in the locoregionally advanced and first-line palliative settings will follow and are eagerly awaited. The landscape of immunotherapy is continuously changing, and we are still learning how to master this powerful therapeutic tool. Preferably, the future development should not prioritize efficacy at any price, but should represent a responsible investment into global healthcare within the intentions of a cost-effective approach.

REFERENCES

1. Decker WK, et al. Cancer Immunotherapy: Historical Perspective of a Clinical Revolution and Emerging Preclinical Animal Models. Front Immunol 2017; 8: 829.
2. Virchow R. Cellular pathology as based upon physiological and pathological histology. Philadelphia: J. B. Lippincott; 1863.
3. Wiemann B, et al. Coley's toxins, tumor necrosis factor and cancer research: a historical perspective. Pharmacol Ther 1994;64:529-64.
4. Strebhardt K, et al. Paul Ehrlich's magic bullet concept: 100 years of progress. Nat Rev Cancer 2008;8:473-80.
5. Isaacs A, et al. The interferon. Proc R Soc Lond B Biol Sci 1957;147:258-67.
6. Dunn GP, , et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002;3:991-8.
7. Graham JB, et al. The effect of vaccine on cancer patients. Surg Gynecol Obstet 1959;109:131-8.
8. Stutman O. Tumor development after 3-methylcholanthrene in immunologically deficient athymic-nude mice. Science 1974;183:534-6.
9. Thomas ED. A history of haemopoietic cell transplantation. Br J Haematol 1999;105:330-9.

10. Lesterhuis WJ, et al. Cancer immunotherapy--revisited. Nat Rev Drug Discov 2011;10:591-600.

11. Grillo-López AJ. Rituximab: an insider's historical perspective. Semin Oncol. 2000;27(6 Suppl 12):9-16.

12. Scott AM, et al. Monoclonal antibodies in cancer therapy. Cancer Immun 2012;12:14.

13. Shankaran V, et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature 2001;410:1107-11.

14. Kantoff PW, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411-22.

15. Beatty GL, et al Immune escape mechanisms as a guide for cancer immunotherapy. Clin Cancer Res 2015;21:687-92.

16. Ferris RL. Immunology and Immunotherapy of Head and Neck Cancer. J Clin Oncol 2015;33:3293-304.

17. Muenst S, et al. The immune system and cancer evasion strategies: therapeutic concepts. J Intern Med 2016;279:541-62.

18. Krummel MF, et al. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995;182:459-65.

19. Leach DR, et al. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734-6.

20. Hodi FS, , et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.

21. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm. Accessed on June 22, 2018.

22. Bach PB, et al. FDA Approval of Tisagenlecleucel: Promise and Complexities of a $475 000 Cancer Drug. JAMA 2017;318:1861-2.

23. Chow VA, et al. Translating anti-CD19 CAR T-Cell therapy into clinical practice for relapsed/refractory diffuse large B-Cell lymphoma. Blood. 2018; Epub ahead of print.

24. Bauman JE, et al. Immunotherapy of head and neck cancer: eEmerging clinical trials from a National Cancer Institute Head and Neck Cancer Steering Committee Planning Meeting. Cancer 2017;123:1259-71.

25. Seiwert TY, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956-65.

26. Bauml J, , et al. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. J Clin Oncol 2017;35:1542-9.

27. Bahleda R, et al. Long-Term Safety and Clinical Outcomes of Atezolizumab in Head and Neck Cancer: Phase Ia Trial Results. Ann Oncol 2017; 28(suppl_5): v372-94.

28. Zandberg D, et al. Durvalumab for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): preliminary results from a single-arm, phase 2 study. Ann Oncol 2017; 28(suppl_5): v372-94.

29. Ferris RL, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375:1856-67.

31. Gillison ML, et al. Nivolumab versus investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (SCCHN): CheckMate-141. AACR 2016, New Orleans, April 16-20, 2016.

32. Gillison ML, et al. CheckMate 141: 1-Year Update and Subgroup Analysis of Nivolumab as First-Line Therapy in Patients with Recurrent/Metastatic Head and Neck Cancer. Oncologist. 2018; Epub ahead of print.

33. Saba NF, et al. Nivolumab (nivo) vs investigator's choice (IC) in patients (pts) with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): Analysis of CheckMate 141 by age. J Clin Oncol 2018; 36 (suppl; abstr 6028).

34. Cohen EE, et al. Pembrolizumab (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.2017;28(suppl_5): Abstract LBA45_PR.

35. Cohen EEW, et al. Health-related quality of life (HRQoL) of pembrolizumab (pembro) vs standard of care (SOC) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) in KEYNOTE-040. J Clin Oncol 2018; 36(suppl); Abstract 6013.

36. Prasad V, et al. Low-value approvals and high prices might incentivize ineffective drug development. Nat Rev Clin Oncol 2018;15:399-400.

37. Tang J, et al. Comprehensive analysis of the clinical immuno-oncology landscape. Ann Oncol 2018;29:84-91.

38. McDermott D, et al. Durable benefit and the potential for long-term survival with immunotherapy in advanced melanoma. Cancer Treat Rev 2014;40:1056-64.

39. McKay RR, et al. Outcomes of PD-1/PD-L1 responders who discontinue therapy for immune-related adverse events (irAEs): Results of a cohort of patients (pts) with metastatic renal cell carcinoma (mRCC). J Clin Oncol 2017; 35(suppl 6S); Abstract 467.

40. Schadendorf D, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol 2015;33:1889-94.

41. Steele SD, et al. Highlighting the challenge of delayed overall survival (OS) curve separation in immunotherapy clinical trials. J Clin Oncol 2013; 31(suppl); Abstract 3009.

42. Chen TT. Milestone Survival: A Potential Intermediate Endpoint for Immune Checkpoint Inhibitors. J Natl Cancer Inst 2015;107.

43. Chakiba C, et al. Encouraging Trends in Modern Phase 1 Oncology Trials. N Engl J Med 2018;378:2242-3.

44. Kang SP, et al. Pembrolizumab KEYNOTE-001: an adaptive study leading to accelerated approval for two indications and a companion diagnostic. Ann Oncol 2017;28:1388-98.

45. Baxi SS, et al. Amidst the excitement: aA cautionary tale of immunotherapy, pseudoprogression and head and neck squamous cell carcinoma. Oral Oncol 2016;62:147-8.

46. Schachter J, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390:1853-62.

47. Long GV, et al. 4-year survival and outcomes after cessation of pembrolizumab (pembro) after 2-years in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in KEYNOTE-006. J Clin Oncol 2018;36(suppl); Abstract 9503.

48. Schvartsman G, et al. Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. Lung Cancer 2017;112:90-5.

49. Saleh K, et al. Response to salvage chemotherapy after progression on

immune checkpoint inhibitors in patients with squamous cell carcinoma of the head and neck. J Clin Oncol 2018;36(suppl); Abstract 6015.

50. Szturz P, et al. Systemic Treatment of Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck. In Bernier J (ed): Head and Neck Cancer - Multimodality Management, 2nd edition. Cham: Springer International Publishing AG 2016: 711-29.

51. Watanabe H, , et al. The effect and safety of an immune checkpoint inhibitor rechallenge in non-small cell lung cancer. J Clin Oncol 2018; 36 (suppl); Abstract e21147.

52. Szturz P, et al. Immunotherapy in head and neck cancer: aiming at EXTREME precision. BMC Med 2017;15:110.

53. Hellmann MD, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med 2018;378:2093-104.

54. Le DT, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-13.

55. Gopalakrishnan V, et al. Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 2018;359:97-103.

56. Do TP, et al. Antibiotic use and overall survival in lung cancer patients receiving nivolumab. J Clin Oncol 2018; 36 (suppl); Abstract e15109.

57. Vermorken JB, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.

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