DOI: 10.1111/jdv.17404 JEADV

REVIEW ARTICLE

Management of partial and non-responding cutaneous squamous cell carcinoma

P. Jansen[1,2,*], G.C. Lodde[1,2], K.G. Griewank[1,2,3], E. Hadaschik[1,2], A. Roesch[1,2], S. Ugurel[1,2], L. Zimmer[1,2], E. Livingstone[1,2], D. Schadendorf[1,2]

[1]Department of Dermatology, University Hospital Essen, University Duisburg-Essen, Essen, Germany
[2]German Cancer Consortium, Partner Site Essen, Essen, Germany
[3]Dermatopathologie bei Mainz, Nieder-Olm, Germany
*Correspondence: P. Jansen. E-mail: philipp.jansen@uk-essen.de

Abstract Cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma are the most common types of skin cancer. For patients with locally advanced and metastatic cSCC, the programmed cell death 1 (PD-1) inhibitor cemiplimab is approved for systemic treatment. Despite this revolutionary immunomodulatory therapeutic approach, tumours may fail to respond either completely or partially. In addition to the previously established local treatment with radiotherapy or systemic treatment with chemotherapy and epidermal growth factor receptor inhibitors, ongoing trials are currently focussed on re-stimulating the antitumour immune response in patients with advanced cSCC refractory to PD-1 inhibitors. In this review, ongoing and recently finished trials with different therapeutic approaches will be discussed.
Received: 20 February 2021; Accepted: 18 May 2021

Conflict of interest

E. Livingstone served as consultant and/or has received honoraria from Amgen, Actelion, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Janssen, Medac, Sanofi, Sunpharma and travel support from Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, Amgen, Pierre Fabre, Sunpharma and Novartis, outside the submitted work. L. Zimmer served as consultant and/or has received honoraria from Roche, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Novartis, Pierre Fabre, Sanofi, and Sunpharma and travel support from MSD, BMS, Amgen, Pierre Fabre, Sunpharma, Sanofi and Novartis, outside the submitted work. G. C. Lodde has received travel support from Sun Pharma, outside the submitted work. A. Roesch declares research support from Novartis, BMS and Adtec, non-financial support from Amgen, Roche, Merck/MSD, Novartis, BMS, TEVA, Adtec, and personal fees from Merck/MSD. D. Schadendorf reports personal fees and non-financial support from Sanofi, during the conduct of the study; personal fees and non-financial support from Roche/ Genentech, grants, personal fees, non-financial support and others from BMS, personal fees and non-financial support from Merck Sharp & Dohme, personal fees and non-financial support from Merck Serono, grants, personal fees and non-financial support from Amgen, personal fees from Immunocore, personal fees from Incyte, personal fees from 4SC, personal fees from Pierre Fabre, personal fees from Array BioPharma, personal fees from Pfizer, personal fees from Philogen, personal fees from Regeneron, personal fees from Nektar, personal fees from Sandoz, grants, personal fees, non-financial support and other from Novartis, outside the submitted work. S. Ugurel declares research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Novartis and Roche, and travel support from Bristol Myers Squibb, and Merck Sharp & Dohme. The other authors declare that there is no conflict of interests.

Funding source

None.

Introduction

The majority of cutaneous squamous cell carcinoma (cSCC) can be cured by complete surgical excision of the primary tumour. According to different guidelines, local radiotherapy is recommended for patients whose cSCC cannot be excised completely (‘locally advanced’, lacSCC). For patients with metastatic cSCC (mcSCC), platinum-based chemotherapy has long been the recommended systemic therapy.[1] There are few heterogeneous and often small case series with partly unknown response criteria demonstrating overall response rates (ORR) varying from 14%–86% with a duration of responses (DOR) between 5–11.8 months. Patients often suffer from severe toxicity.[2] The discovery of molecular pathways inducing the development of cSCC and the elucidation of 'cancer cell—immune cell—interactions' revealed additional therapeutic approaches for lacSCC and mcSCC (advanced cSCC). Due to the elevated mutational burden in cSCC and the positive correlation between mutational burden and response rate to inhibitors of programmed cell death 1 (PD-1), immune checkpoint inhibitors (ICI) directed against PD-1 were considered promising candidates.[3] Inhibition of PD-1 prevents tumour-induced immunosuppressive modulation of T cells, leading to the restoration of the antitumour immune cell response.[4] In 2014, the first approval of PD-1 inhibitor therapy was given for malignant melanoma. Despite the revolutionary therapeutic approach, clinical studies revealed lack of response in 40%–45% of patients treated with PD-1 inhibitors.[5] Furthermore, long-lasting tumour control (over 5 years) was only achieved in roughly 1/3 of patients treated in first-line. For patients with advanced cSCCs, the PD-1 inhibitor cemiplimab was approved by the US Food and Drug Administration (FDA) in 2018 and by the European Medicines Agency in 2019.[1] In 2020, the PD-1 inhibitor pembrolizumab was approved by the FDA as well.[6] In a phase I study for patients with advanced cSCC, response rate to cemiplimab was 50% under therapy with 3 mg/kg every second week (Q2W).[7] In the phase II study with the same dose scheme, ORR was 49.2% with a durable disease control rate (DDCR, the proportion of patients without progressive disease for at least 105 days as defined in the clinical protocol) of 61%. In the phase II study for application of cemiplimab 350 mg Q3W, ORR was 41.1% with a DDCR of 57.1%.[8] In another phase II study, objective response was observed in 34 of 78 patients suffering from lacSCC and receiving cemiplimab 3 mg/kg Q2W.[9] For those patients with partial and missing response, there are currently no approved therapeutic alternatives. Clinical trials focus on re-stimulating the immune system and enhancing tumour immunogenicity for an antitumour immune response. In this review, ongoing and recently finished trials with potential therapeutic approaches for patients with advanced cSCC will be discussed regarding experience from other PD-1 inhibitor refractory cutaneous malignancies (Table 1).

EGFR inhibitors

An elevated expression of the epidermal growth factor receptor (EGFR) was found in both mcSCC and primary cSCCs with poor clinical outcome.[10] The stimulation of EGFR as part of the receptor tyrosine kinase family activates multiple pathways affecting cellular proliferation and resistance to apoptosis. Molecular therapies targeting EGFR have been shown to decrease signal transduction of the EGFR pathway. EGFR inhibitors as well as their combined use with radiotherapy and chemotherapy for the treatment of cSCC have been described in multiple reviews.[2,11] However, targeting EGFR led to ORR between 10%–31% with DOR between 4.7–8 months in different clinical studies while frequently inducing pruritus, acne-like rash and/or desquamation.[2] The application of EGFR therapy is expected to remodel the tumour environment favouring response to PD-1 inhibitor therapy.[12] The recently initiated phase II trial AliCe includes patients with advanced cSCC refractory to PD-1 inhibitor therapy. Patients receive the EGFR inhibitor cetuximab and the PD-L1 inhibitor avelumab (EudraCT 2018-001708-12, results pending). Additionally, patients with advanced cSCC and prior anticancer treatment can be included in an ongoing phase I trial for treatment with cetuximab and the tyrosine kinase inhibitor lenvatinib (NCT03524326). An interim analysis which also included therapy-naïve patients with head and neck SCC showed an ORR of 67% (n = 6/9 evaluable patients).[13] Further results on the treatment of advanced cSCC refractory to PD-1 inhibitor therapy with lenvatinib are pending, but an interim analysis on the combined use of lenvatinib and pembrolizumab in melanoma patients who had previously failed to respond to PD-1 inhibitor or other systemic therapy (n = 103) showed an ORR of 21.4% [two complete responses (CR), 20 partial responses (PR); NCT03776136].[14]

Toll-like receptor agonists

Toll-like receptors (TLR) are a class of pattern recognition receptors with TLR9 being predominantly located intracellularly in immune cells, including dendritic cells, macrophages, natural killer cells and other antigen-presenting cells. Thus, TLR 9 agonists, like tilsotolimod, both stimulate those immune cells and induce interferon-α expression resulting in an enhanced antigen cross-presentation of tumour antigens and subsequent antitumoural immune response.[15] Intratumourally injected tilsotolimod in combination with systemic pembrolizumab or the CTLA-4 inhibitor ipilimumab was investigated in the ILLUMINATE-204 trial for melanoma patients who did not respond to prior PD-(L)1 inhibitor therapy (NCT02644967). The ORR in 49 patients was 22.4% with two CR.[16] In another phase Ib trial, the combination of the TLR9 agonist CMP-001 and pembrolizumab demonstrated an ORR of 23.5% in the dose-finding part I and 17.5% for CMP-001 monotherapy in part II (NCT02680184).[17] In an ongoing phase Ib/II trial with the intratumourally applicated TLR9 agonist cavrotolomid, an ORR of 21% could be determined for patients with advanced solid tumours treated with additional systemic pembrolizumab. In phase II of the trial, patients with advanced cSCC refractory to PD-1 inhibitor are treated with intratumoural cavrotolomid and intravenous cemiplimab (NCT03684785).[18] Via TLR 7/8 and the intracellular receptor retinoic acid-inducible gene I (RIG I) the non-coding RNA CV8102 activates the immune system

Table 1 Ongoing or recently finished clinical trials including patients with cutaneous squamous cell carcinoma refractory to PD-1 inhibitor therapy

ID	Start	End	Design	Intervention/application	Primary/Secondary outcomes
EGFR inhibitors					
EudraCT 2018-001708-12 ('AliCe')	Sep 2018	Ongoing	Multicentre, open-label, single-arm, phase II	Cetuximab 500 mg/m^2 i.v. Q2W + Avelumab 10 mg/kg i.v. Q2W	PO: ORR SO: PFS, OS, DoR, QoL
NCT 03524326	May 2018	April 2023	Multicentre, open-label, single-arm, phase I/Ib	Cetuximab (400 mg/m^2 once, 250 mg/m^2 weekly) i.v. + 3 + 3 dose de-escalation design of the tyrosine kinase inhibitor lenvatinib (24 mg/20 mg/14 mg/10 mg/4 mg daily) p.o.	PO: MTD
Toll-like receptor agonists					
NCT 03684785	Dec 2018	June 2023	Multicentre, open-label, two-part, randomized phase I/ phase II	Phase I: Cavrotolimod (TLR 9 agonist, dose determination via 3 + 3 dose escalation for 2, 4, 8, 16, and 32 mg) i.t. and adding pembrolizumab 2 mg/kg Q3W at the second cycle Phase II (for cSCC): Cavrotolimod i.t. + cemiplimab 350 mg Q3W i.v. (dose expansion following a modified Simon 2-stage optimal design)	PO: AE SO: RP2D, ORR, biomarkers (lymphocytes, PD-L1 expression, gene expression)
NCT 03291002	Sep 2017	Feb 2023	Multicentre, open-label, non-randomized, phase I/Ib	non-coding RNA CV8102 (TLR 7/8) (dose escalation for dose levels of 25–600 μg) i.t	PO: MTD, AE SO: TR, DS, survival
Interleukins					
NCT 03901573	Dec 2019	May 2024	Multicentre, open-label phase Ib/ Multicentre, open-label two-armed, non-randomized phase II	Treatment: NT-I7 (rhIL-7-hyFc) (IL-7 agonist) (3 + 3 dose escalation (in phase I)/expansion (phase II) (i.m.) + Atezolizumab (dose escalation/expansion) i.v. Two cohorts: 1 PD-1/PD-L1 inhibitor-naïve 2 PD-1/PD-L1 inhibitor- refractory	PO: MTD/DLT, RP2D, AE SO: ORR, DCR, DOR, PFS, OS, immunogenicity
NCT 04234113	June 2019	Mar 2022	Multicentre, open-label, non-randomized phase I/ Ib	SO-C101 (IL-15 agonist) +/− pembrolizumab	PO: DLT, AE, LTA, ECOG PSS SO: plasma concentration SO-C101, ORR, BOR, DOR, CBR, PFS, antibodies to SO-C101
Pathway regulators					
NCT 03590054	Aug 2018	Feb 2022	Single enter, open-label phase I	Abexinostat (HDAC inhibitor) (dose escalation: 20 mg/m^2, 30 mg/m^2, 45 mg/m^2) days 1–4 & 8–11 in 21 day cycle p.o. BID + pembrolizumab 200 mg i.v Q3W	PO: MTD, RP2D, ORR SO: ORR, DoR, PFS, AE
EudraCT Number: 2020-000864-42	?	?	Multicentre, open-label phase II	IFX-1 (anti-C5a monoclonal AB) in different dose regimen (400–1600 mg) +/− pembrolizumab 400 mg Q6W	PO: antitumour activity of IFX-1 (+/− pembrolizumab), MTD, SO: efficacy, safety profile, pharmacokinetics, immunogenicity, QoL
Oncolytic viruses					
NCT 03767348 ('IGNYTE')	Sep 2017	Nov 2024	Multicentre, open-label, non-randomized phase I/ II	RP1 (oncolytic HSV-1) i.t. +/− nivolumab i.v. (dose escalation and expansion)	PO: RP2D, AE, DLT, ORR, MTD SO: biologic activity, RP1 levels (urine, blood), CR, DOR, PFS, OS

Table 1 *Continued*

ID	Start	End	Design	Intervention/application	Primary/Secondary outcomes
NCT 02978625	Sep 2017	June 2021	Multicentre, open-label, two-part, single-arm phase II	TVEC (oncolytic HSV-1) (i.t.) (+ nivolumab i.v. if no response after 12 weeks on day 1) Cycles repeat every 21 days for cycle 1 then every 14 days	PO: RR, best ORR SO: RR, PFS, OS, AE, contribution to curative surgery
Vaccination					
NCT 03773744 ('Pelican')	Jan 2020	Dec 2021	Multicentre, open-label, two-armed, non-randomized phase Ib	Single application of Ad-MAGE3 i.m. (, single application of the cyclophosphamide 300 mg/m^2 i.v., arm 1), + pembrolizumab 200 mg i.v. and of MG1-MAGE3 i.v. (and i.t.subsequently, arm 2) (dose escalation)	PO: safety, MTD SO: OR, DC, PFS, DOR
NCT 04160065	Mar 2020	Sep 2021	Multicentre, open-label, non-randomized phase I	IFx-Hu2.0 (plasmid DNA) (0.1 mg) i.t. (different frequencies of application)	PO: AE SO: number major protocol deviation, ORR

AE, adverse effects; DLT, dose-limiting toxicities; BID, bis in die/twice daily; CR, complete response; DOR, duration of response; DS, disease status; ECOG PSS, Eastern Cooperative Oncology Group Performance Status Score; i.m., intramuscular; i.t., intratumoural; i.v., intravenous; LTA, laboratory test abnormalities; MTD, Maximum tolerated doses; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; p.o., per os/oral administration; PO, primary outcome; Q2W/Q3W, once every 2/3 weeks; QoL, Quality of Life; RP2D, recommended phase II dose; RR, Response Rate; SO, secondary outcome; TR, tumour response.

after intratumoural injection. Patients with advanced cSCC refractory to anti-PD-1-inhibitor therapy can be included in an ongoing phase I trial in which they receive CV8102 as monotherapy (NCT03291002, results for cSCC pending).

Interleukins

Endogenous interleukins (IL) number among cytokines and physiologically modulate the immune system by stimulating the release of additional cytokines (e.g. interferon-γ), by activating the ontogeny, maturation (e.g. NK- and T cells by IL-15) and proliferation (e.g. NK- and T cells by IL-2) or maintaining survival (e.g. T cells by IL-7) of immune cells.[19] A recently published phase II trial with 22 melanoma patients showed that the repetitive intratumoural application of the plasmid IL 12 (tavokinogene telseplasmid; tavo) restored the responsiveness to pembrolizumab despite previous anticancer treatment failure. Anti-PD-1 antibody experienced and naïve patients showed an ORR of 41% (36% CR).[20] For SCC, the combined use of IL-7 and PD-1 inhibitors reduced immunosuppressive cell function in both murine and ex vivo human cells resulting in synergistic antitumour effects.[21] An ongoing phase Ib/IIa trial includes both patients with advanced cSCC naïve and refractory to PD-1 inhibitor therapy for combined treatment with intramuscular IL-7 [rhIL-7-hyFc (NT-I7)] and atezolizumab (PD-L1 inhibitor; NCT03901573, results pending). A recently initiated phase I trial includes patients with advanced cSCC refractory to PD-1 inhibitors who receive the IL-15 agonist SO-C101 as monotherapy or in combination with pembrolizumab (NCT04234113, results pending).

Pathway regulators

Histone deacetylases (HDAC) regulate the expression levels of genes by controlling histone acetylation. In tumours, elevated activity of HDAC may misregulate the expression of tumour suppressor genes and/or proto-oncogenes favouring tumour growth. The inhibition of HDAC may influence tumour immunogenicity and 're-sensitize' tumour cells to PD-1 inhibitor therapy.[22] For Merkel cell carcinoma (MCC), the ongoing phase II trial MERKLIN 2 includes patients refractory to PD-(L) 1 inhibitor therapy. Patients receive avelumab in combination with domatinostat (HDAC inhibitor; NCT04393753). Similarly, melanoma patients primary refractory to PD-1 inhibitors receive combined treatment with pembrolizumab and domatinostat in the phase Ib/II trial SENSITIZE (NCT03278665). Patients with advanced cSCC (of the head/neck) refractory to PD-(L)1 inhibitor therapy can be included in an ongoing phase I trial for treatment with pembrolizumab i.v. and different dose scheme of the HDAC inhibitor abexinostat p.o. (NCT03590054, results pending).

An impaired pathway of the tumour suppressor p 53 is a major contributor to the development of cSCC. Murine double minute chromosome 2 (MDM2) is activated in several tumour types and inhibits the function of p53. As antitumour drug, KRT-232 binds to MDM2 and inhibits the MDM2/p53 interaction. Both *in vitro* and *in vivo*, KRT-232 has been shown to inhibit the growth of tumour cells.[23] First results of the clinical use of KRT-232 could be generated in a phase II trial with 11 patients suffering from MCC refractory to PD-L1 inhibitor therapy (NCT 03787602). In interim analysis, ORR was 33%.[24]

The inflammation mediator C5a is part of the complement system. C5a and its receptor C5aR1 contribute to the regulation of squamous carcinogenesis by promoting cancer-associated inflammation. Elevated expression of C5aR1 was determined in SCCs of patients with impaired survival.[25] In mice, inhibition of C5a promoted antitumour efficacy of PD-(L)1 blockade.[26] In the IFX-1-P2.8 trial, the anti-C5a monoclonal antibody IFX-1 will be given in different dose regimens as monotherapy or together with pembrolizumab. IFX-1-P2.8 will include patients with advanced cSCC who have progressed on PD-1 inhibitor therapy.

Oncolytic viruses

Oncolytic viruses are genetically modified viruses that preferentially replicate in tumours and promote immunogenic cell death. The subsequent release of tumour antigens is thought to trigger a generalized host immune effect inducing a systemic antitumour immune response. In 2015, the oncolytic virus talimogene laherparepvec (TVEC), a genetically modified herpes simplex virus type 1 (HSV-1), was approved for the treatment of advanced melanoma. In combination with PD-1 inhibitors, the application of oncolytic viruses induced enhanced T-cell levels and PD-L1 expression both in the injected tumour and in non-injected tumours.[27] In two different ongoing trials (NCT02978625 and NCT03767348) patients with advanced cSCC refractory to prior anticancer therapy receive one of the genetically modified HSV-1 TVEC or RP1 as monotherapy or in combination with PD-1 inhibitors, respectively (results for cSCCs refractory to PD-1 inhibitors pending). In an interim analysis, three of four melanoma patients refractory to PD-1 inhibitors showed immune activation in tumour biopsies, including recruitment of $CD8^+$ T cells and increased PD-L1 expression after exposition to RP1 and nivolumab.[28]

Vaccination

Based on the principles of vaccination, injection of tumour antigens is expected to induce an immune system response. The phase I trial Pelican includes patients with advanced cSCC who have failed standard of care treatment. Patients are treated with different dose scheme of (cyclophosphamide, arm 1) Ad-MAGE-A3, pembrolizumab and MG1-MAGEA3 (NCT03773744). Melanoma-associated antigen 3 (MAGEA3) is one of several cancer-testis antigens that are found on different cancer types and is considered a possible stimulator of the immune system. Ad-MAGE3 is an adenovirus vaccine and MG1-MAGEA3 is an MG1 Maraba oncolytic virus considered to restore the sensitivity to ICI.[29] In another trial patients refractory to standard therapy receive the plasmid DNA IFx-Hu2.0 encoding the streptococcal membrane protein Emm55 (NCT04160065). Preliminary correlative laboratory data of advanced melanoma patients showed an immune response after intralesional injection.[30]

Conclusion

Despite the recent advances in immunomodulatory antitumour therapy, there are currently no approved systemic treatment alternatives for patients with advanced cSCC who have shown partial response or lack of response to PD-1 inhibitor therapy. Ongoing trials on toll-like receptors, ILs, pathway regulators, oncolytic viruses and vaccination constitute complementary approaches to multidimensionally stimulate the immune system in patients with advanced cSCC refractory to PD-1 inhibitors and potentially enhance responsiveness to anticancer therapy.

Acknowledgements

Open Access funding enabled and organized by Projekt DEAL.

References

1 Stratigos AJ, Garbe C, Dessinioti C *et al*. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: part 2. Treatment. *Eur J Cancer* 2020; **128**: 83–102.
2 Gellrich FF, Huning S, Beissert S *et al*. Medical treatment of advanced cutaneous squamous-cell carcinoma. *J Eur Acad Dermatol Venereol* 2019; **33**(Suppl 8): 38–43.
3 Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med* 2017; **377**: 2500–2501.
4 Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat Rev Immunol* 2020; **20**: 651–668.
5 Mooradian M, Sullivan R. What to do when anti–PD-1 therapy fails in patients with melanoma. *Oncology* 2019; **33**: 141–148.
6 Administration USFaD. FDA Approves Pembrolizumab for Cutaneous Squamous Cell Carcinoma, 2020. URL https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-cutaneous-squamous-cell-carcinoma (last accessed: 3 February 2021).
7 Migden MR, Rischin D, Schmults CD *et al*. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med* 2018; **379**: 341–351.
8 Rischin D, Migden MR, Lim AM *et al*. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. *J Immunother Cancer* 2020; **8**: e000775.
9 Migden MR, Khushalani NI, Chang ALS *et al*. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. *Lancet Oncol* 2020; **21**: 294–305.
10 Canueto J, Cardenoso E, Garcia JL *et al*. Epidermal growth factor receptor expression is associated with poor outcome in cutaneous squamous cell carcinoma. *Br J Dermatol* 2017; **176**: 1279–1287.
11 Maubec E. Update of the management of cutaneous squamous-cell carcinoma. *Acta Derm Venereol* 2020; **100**: adv00143.
12 Sugiyama E, Togashi Y, Takeuchi Y *et al*. Blockade of EGFR improves responsiveness to PD-1 blockade in EGFR-mutated non-small cell lung cancer. *Sci Immunol* 2020; **5**: eaav3937.
13 Dunn L, Ho AL, Eng J *et al*. A phase I/Ib study of lenvatinib and cetuximab in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). *J Clin Oncol* 2020; **38**(15_suppl): 6541
14 Fernandez AMA, O'Day SJ, LdlC M *et al*. LBA44 Lenvatinib (len) plus pembrolizumab (pembro) for advanced melanoma (MEL) that progressed on a PD-1 or PD-L1 inhibitor: Initial results of LEAP-004. *Ann Oncol* 2020; **31**: S1173.
15 Karapetyan L, Luke JJ, Davar D. Toll-like receptor 9 agonists in cancer. *Onco Targets Ther* 2020; **13**: 10039–10060.
16 Haymaker C, Andtbacka RHI, Johnson DB *et al*. 1083MO Final results from ILLUMINATE-204, a phase I/II trial of intratumoral tilsotolimod in

combination with ipilimumab in PD-1 inhibitor refractory advanced melanoma. *Ann Oncol* 2020; **31**: S736.
17 Milhem M, Zakharia Y, Davar D *et al*. 304 Intratumoral injection of CMP-001, a toll-like receptor 9 (TLR9) agonist, in combination with pembrolizumab reversed programmed death receptor 1 (PD-1) blockade resistance in advanced melanoma. *J Immunother Cancer* 2020; **8**(Suppl 3): A186–A187.
18 O'Day S, Perez C, Wise-Draper T *et al*. 423 Safety and preliminary efficacy of intratumoral cavrotolimod (AST-008), a spherical nucleic acid TLR9 agonist, in combination with pembrolizumab in patients with advanced solid tumors. *J Immunother Cancer* 2020; **8**(Suppl 3): A257–A258.
19 Berraondo P, Sanmamed MF, Ochoa MC *et al*. Cytokines in clinical cancer immunotherapy. *Br J Cancer* 2019; **120**: 6–15.
20 Algazi AP, Twitty CG, Tsai KK *et al*. Phase II trial of IL-12 plasmid transfection and PD-1 blockade in immunologically quiescent melanoma. *Clin Cancer Res* 2020; **26**: 2827–2837.
21 Pfannenstiel LW, Diaz-Montero CM, Tian YF, Scharpf J, Ko JS, Gastman BR. Immune-checkpoint blockade opposes CD8(+) T-cell suppression in human and murine cancer. *Cancer Immunol Res* 2019; **7**: 510–525.
22 Yeon M, Kim Y, Jung HS, Jeoung D. Histone deacetylase inhibitors to overcome resistance to targeted and immuno therapy in metastatic melanoma. *Front Cell Dev Biol* 2020; **8**: 486.
23 Sun D, Li Z, Rew Y *et al*. Discovery of AMG 232, a potent, selective, and orally bioavailable MDM2-p53 inhibitor in clinical development. *J Med Chem* 2014; **57**: 1454–1472.
24 Wong MKK, Kelly CM, Burgess MA *et al*. KRT-232, a first-in-class, murine double minute 2 inhibitor (MDM2i), for TP53 wild-type (p53WT) Merkel cell carcinoma (MCC) after anti–PD-1/L1 immunotherapy. *J Clin Oncol* 2020; **38**(15_suppl): 10072.
25 Medler TR, Murugan D, Horton W *et al*. Complement C5a fosters squamous carcinogenesis and limits T cell response to chemotherapy. *Cancer Cell* 2018; **34**: 561–578.e6.
26 Zha H, Han X, Zhu Y *et al*. Blocking C5aR signaling promotes the anti-tumor efficacy of PD-1/PD-L1 blockade. *Oncoimmunology* 2017; **6**: e1349587.
27 Thomas S, Kuncheria L, Roulstone V *et al*. Development of a new fusion-enhanced oncolytic immunotherapy platform based on herpes simplex virus type 1. *J Immunother Cancer* 2019; **7**: 214.
28 Middleton MR, Aroldi F, Sacco J *et al*. An open-label, single-arm, phase II clinical trial of RP1, an enhanced potency oncolytic herpes virus, combined with nivolumab in four solid tumor types: initial results from the skin cancer cohorts. *J Clin Oncol* 2020; **38**(15_suppl): e22050.
29 Martin AD, Wang X, Sandberg ML *et al*. Re-examination of MAGE-A3 as a T-cell therapeutic target. *J Immunother* 2020; **44**: 95–105.
30 Markowitz J, Brohl A, Sarnaik AA *et al*. Trial in progress: IFx-Hu2.0 (plasmid DNA coding for Emm55 streptococcal antigen in a cationic polymer) phase I first in human study for unresectable stage III or stage IV cutaneous melanoma, American Association for Cancer Research Annual Meeting, Washington, DC, 2020.