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Avelumab and cetuximab as a therapeutic combination: An overview of scientific rationale and current clinical trials in cancer

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ABSTRACT

Treatment outcomes have improved with the advent of immune checkpoint inhibitors and small molecule inhibitors. However, many patients do not respond with single agents. Consequently, ongoing research is focused on the use of combination therapies to increase clinical efficacy by potential synergistic effects. Here, we outline ongoing trials and review the rationale and evidence for the combination of avelumab, an anti-programmed death ligand 1 (PD-L1) immunoglobulin G1 (IgG1) monoclonal antibody (mAb), with cetuximab, an anti-epidermal growth factor receptor (EGFR) IgG1 mAb. Avelumab is approved as a monotherapy for the treatment of Merkel cell carcinoma and urothelial carcinoma, and in combination with axitinib for renal cell carcinoma; cetuximab is approved in combination with chemotherapy for the treatment of squamous cell carcinoma of the head and neck (SCCHN) and *RAS* wild-type metastatic colorectal cancer, and in combination with radiation therapy for SCCHN. Avelumab binds to PD-L1 expressed on tumor cells and immune regulatory cells, thus blocking its interaction with programmed death 1 and reventing T-cell suppression; cetuximab inhibits the EGFR signaling pathway, inhibiting proliferation and inducing apoptosis. Both therapies have complementary mechanisms of action and may also activate the immune system to induce innate effector function through the binding of their Fc regions to natural killer (NK) cells. Furthermore, cetuximab combined with chemotherapy has been shown to induce immunogenic cell death and leads to an increase in tumor-infiltrating CD8+ T and NK cells, which should synergize with the immunostimulatory effects of avelumab. Prospective studies will investigate this combination and inform future treatment strategies.

Introduction

The use of immune checkpoint inhibitors (ICIs) has become prevalent in the treatment of cancer, with approvals in a wide range of solid and hematological malignancies [1–3]. These drugs are monoclonal antibodies (mAbs) that disrupt T-cell inhibition and mobilize the

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antitumor immune response [4]. The antitumor response generated by the immune system is mediated in part by T cells, which are primed and activated through interactions with their T-cell receptors; this process is regulated by immune checkpoint signaling, which includes inhibitory signals from receptors found on T cells such as programmed death 1 (PD-1), and its ligand, programmed death ligand 1 (PD-L1) [5,6]. ICIs, such as mAbs that block PD-L1 signaling, are approved for a wide variety of cancers and have shown promising outcomes [3,7,8]. However, the antitumor activity of ICIs, while durable, often remains limited to subsets of patients, with response rates of ≤20% in many common cancer types [1]. For instance, in 2 phase 3 studies of patients with squamous cell carcinoma of the head and neck (SCCHN) treated with the anti–PD-1 antibodies pembrolizumab and nivolumab, the objective response rate (ORR) was 16.9% and 13.3%, respectively [9,10]. The efficacy of ICIs can be increased by combining them with other therapeutics that may have complementary or nonredundant mechanisms of action, thus promoting synergistic activity and improving response rates [3,11].

Avelumab is a fully human anti–PD-L1 IgG1 mAb that binds to PD-L1, preventing its interaction with PD-1, which otherwise inactivates T cells [12]. Avelumab has been approved in various countries as monotherapy for metastatic Merkel cell carcinoma and locally advanced (LA) or metastatic urothelial carcinoma (first-line maintenance and second-line treatment), and in combination with axitinib for advanced renal cell carcinoma [13]. Avelumab also contains a wild-type (wt) IgG1 Fc region and has been shown in preclinical studies to promote antitumor activity mediated via both adaptive and innate immune effector cells [14]. Cetuximab is a chimeric IgG1 mAb that inhibits the epidermal growth factor receptor (EGFR) intracellular signaling pathway by binding to the extracellular domain of EGFR [15,16]. As of February 2020, cetuximab was approved in over 100 countries worldwide including in Europe, Asia, and North America, for the treatment of *RAS* wt metastatic colorectal cancer (mCRC) and/or SCCHN [17].

Preclinical studies suggest that cetuximab, like avelumab, exhibits innate immune effector function via natural killer (NK) cell activation and subsequent tumor cell death [18–20]. When used in combination with chemotherapy, cetuximab can induce immunogenic cell death, leading to the phagocytosis of dying tumor cells by dendritic cells (DCs) and subsequent initiation of a protective immune response from CD8+ T cells [21]. Cetuximab has been shown to significantly increase the number of peripheral blood CD3+ and CD8+ T cells and NK cells, while decreasing the number of T regulatory cells [22]. This innate immune effector function is unique to cetuximab, but not to panitumumab, an IgG2 isotype anti-EGFR mAb also approved for the treatment of *RAS* wt mCRC [23].

ICIs and anti-EGFRs in treating tumor types of interest

ICIs and anti-EGFR antibodies are approved for the treatment of a wide variety of tumor types. Both ICIs and cetuximab are used in the treatment of SCCHN. Cetuximab is the only anti-EGFR mAb approved for the treatment of LA SCCHN in combination with radiotherapy, recurrent/metastatic (R/M) SCCHN in combination with platinum-based therapy, and in the USA and Asia as a single-agent therapy for R/M SCCHN in patients whose disease has progressed after platinum-based therapy [17,24,25]. The PD-1 inhibitors nivolumab and pembrolizumab are both approved as monotherapy for R/M SCCHN after disease progression on or after platinum-containing therapy in the USA and Europe (pembrolizumab is approved only for patients who express PD-L1 with a ≥50% tumor proportion score in Europe), while pembrolizumab is also approved as monotherapy for the first-line treatment of R/M SCCHN for patients who express PD-L1 with a combined positive score ≥1, and in combination with platinum and fluorouracil for all patients (USA) and those whose tumors express PD-L1 with a combined positive score ≥1 (Europe) [26,27]. Several clinical trials investigating the role of other ICIs in SCCHN, given alone as well as in combination with other agents, including chemoradiotherapy, are underway [28,29].

ICIs and anti-EGFR antibodies are also used for the treatment of mCRC. In the USA and Europe, cetuximab and panitumumab (anti-EGFR antibodies) are approved for the treatment of *RAS* wt mCRC in combination with chemotherapy, or as monotherapy in patients who have progressed after treatment with oxaliplatin- and irinotecan-containing chemotherapy (and fluoropyrimidine-containing treatment for panitumumab) [17,30–32]. In the USA, ICIs are also approved for the treatment of CRC: nivolumab, nivolumab in combination with ipilimumab, and pembrolizumab are approved for pretreated patients with mismatch-repair deficient (dMMR) and microsatellite instability (MSI)-high mCRC [26,27,31]. Because the use of ICIs is still limited to this small population of patients with dMMR and MSI-high pretreated mCRC, and given the recent failures of trials involving ICIs in mCRC as well as the immunoresistant nature of the disease, novel combinations are necessary to further expand treatment options for patients with mCRC [33–35].

ICIs have been approved for the treatment of non-small cell lung cancer (NSCLC) in the USA and Europe, including pembrolizumab and atezolizumab, which are approved in combination with chemotherapy, or bevacizumab + chemotherapy (atezolizumab), for the first-line treatment of metastatic non-squamous NSCLC (with no *EGFR* or *ALK* genomic tumor aberrations); pembrolizumab is also approved in combination with chemotherapy for the first-line treatment of metastatic squamous NSCLC. These ICIs are also approved as monotherapies for the first-line (pembrolizumab) and second-line (atezolizumab) treatment of NSCLC; however in the USA, pembrolizumab's approval is restricted to patients with NSCLC who express PD-L1 on ≥1% tumor cells [26,36]. Other ICIs approved for NSCLC include nivolumab, which is approved in the USA and Europe as a monotherapy for patients with LA or metastatic NSCLC with disease progression after chemotherapy, and durvalumab, which is approved as a treatment for unresectable, stage III NSCLC in the USA, and for LA unresectable NSCLC in patients who express PD-L1 on ≥1% of tumor cells in Europe [27,37].

Cemiplimab (anti–PD-1) is approved in the USA for the treatment of metastatic or LA cutaneous squamous cell carcinoma (cSCC) [38]. According to The National Comprehensive Cancer Network guidelines, cetuximab and other anti-EGFR antibodies may also be used to treat R/M cSCC for patients ineligible for ICIs or clinical trials, as well as inoperable or incompletely resected regional disease, although data remain limited [39,40]. In squamous cell carcinoma of the anal canal (SCCAC), carboplatin with paclitaxel is the standard recommended treatment for metastatic SCCAC [41], with both ICIs and cetuximab also showing promising activity in clinical trials [42,43].

Mechanisms of action for cetuximab, avelumab, and their combination

Preclinical data suggest that cetuximab functions by inhibiting the EGFR and exhibits an innate immune effector function via the activation of NK cells, leading to tumor death [18,20,44,45]. The Fc constant region of cetuximab binds to the activating receptor CD16/FcγRIII on NK cells, leading to NK cell activation and subsequent lytic activity on tumor cells by a process called antibody-dependent cell-mediated toxicity (ADCC) [20,46]. The lysis of tumor cells by active NK cells results in the release of tumor antigens, which are then presented to CD8+ T cells by DCs, thus priming the CD8+ T cells for further antitumor activity [20]. The tumor-cell death associated with cetuximab is immunogenic, with the innate immune effector function of cetuximab leading to an increased infiltration of the tumor with cytotoxic CD8+ T cells [18,20,45]. Furthermore, based on an analysis of immune cell infiltration in the liver metastatic sites of 53 patients with CRC, markers of immune filtration (including CD3+, CD8+, and CD56+ cells) were more abundant in the tumor specimens of patients who were treated with cetuximab and chemotherapy than in patients who received chemotherapy alone or no treatment [47]. In an analysis of the immune microenvironment of resected primary tumors and colorectal

metastases, patients with metastases who had been treated with anti-EGFR therapy (mainly cetuximab) and a chemotherapy-based preoperative regimen had greater infiltration of CD8+ T cells, memory T cells, and regulatory T cells in the tumor microenvironment compared with patients who received anti-vascular endothelial growth factor treatment and chemotherapy or chemotherapy alone [48]. Another genomic and transcriptomic analysis of 35 *RAS* wt mCRC tumors found that response to cetuximab led to increased CD8+ T-cell infiltration and upregulation of PD-L1 expression, as well as a prolonged benefit from cetuximab in certain CRC tumor subtypes (such as consensus molecular subtype 2/transit amplifying [CMS2/TA]), suggesting that cetuximab and immunotherapy may be a potential treatment strategy for patients with these tumors [49].

Another important point to consider is that the innate effector function of cetuximab is specific to the IgG1 isotype of the antibody; panitumumab is another anti-EGFR mAb used for the treatment of mCRC, but because the antibody is an IgG2 isotype, it binds poorly to the Fc-gamma receptor (FcγR) [50]. As a result, even though panitumumab binds to the EGFR with higher activity than cetuximab, it has a much more diminished ability to interact with receptors on effector immune cells [51]. Activated NK cells that have bound cetuximab secrete IFNγ and stimulate the maturation of DCs, which not only prime CD8+ T cells, but can also activate NK cells to promote increased secretion of interferon-gamma (IFNγ) through NK-DC cross-talk [52,53].

While cetuximab has demonstrated clinical activity and can induce immune effector function, the immunostimulation associated with cetuximab can lead to the inhibition of T and NK cells through the negative feedback of immunosuppression by T regulatory cells and myeloid-derived suppressor cells (MDSCs) [20,21]. The blood and tumor microenvironment of patients with cancer is often enriched with T regulatory cells, and with an increase in transforming growth factor beta (TGF-β) signaling [54–57]. These T regulatory cells can inhibit the cytolytic capabilities of T cells and NK cells [20]. Furthermore, NK cell–associated markers of the innate effector function, such as CD16 (FcγRIII), granzyme B, and perforin, are decreased when populations of T regulatory cells are increased in the intratumoral space [58,59]. MDSC levels are also increased in patients with cancer, and with that comes increased TGF-β expression and suppression of the antitumor function of CD8+ T cells [20]. Although T cells can often be disinhibited by anti–PD-1 therapy, this treatment in turn stimulates myeloid cells to upregulate PD-L1, leading to the reinhibition of CD8+ T cells—a process that may be slowed down by continued treatment with ICIs [20,60]. These immunosuppressive mechanisms are thus triggered to counteract tumor cell lysis. Activation of T and NK cells triggers their secretion of IFNγ, which leads to upregulation of PD-L1 expression on tumor cells and T regulatory cells, and subsequent inhibition of the CD8+ T and NK cells [61,62]. When combined with other standard-of-care therapies such as chemotherapy and radiotherapy, cetuximab leads to high overall response rates, as demonstrated by the EXTREME, CRYSTAL, OPUS, and the Bonner et al. trials [20,63–66].

Avelumab inhibits the interaction between PD-L1 expressed on tumor cells and PD-1 expressed on T cells, an interaction that normally leads to T-cell suppression and inactivation. Additionally, as a fully human mAb with a native Fc region, avelumab may also confer innate effector function by inducing NK cell-mediated tumor cell destruction [14,67]. This occurs when avelumab, once bound to a tumor cell, interacts with the CD16 receptor/FcγRIII on NK cells via the antibody's Fc region. In vitro studies have shown that avelumab can induce the lysis of a wide variety of tumor cell types when NK cells and peripheral blood mononuclear cells are present, including a residential cancer stem cell population of chordoma cells, via the innate effector function [14,67]. Furthermore, given that blocking PD-L1 prevents suppression of T and NK cells via PD-L1–PD-1 binding, this mechanism may also facilitate the cytotoxic activity of cetuximab by allowing T and NK cells to remain active [19,20].

Avelumab and cetuximab have complementary mechanisms of action and may work synergistically to counteract immunosuppressive negative feedback. Cetuximab facilitates increased immune activity within the tumor microenvironment in the preclinical setting as well as in ex vivo patient tumor biopsies, thus priming the immune system to be more responsive to anti–PD-L1 therapy [20,45,53]. In the preclinical setting, cetuximab has been found to lead to the recruitment of immune effector cells to the tumor site and to induce immunogenic tumor cell death, while also resulting in the upregulation of PD-1+ T cells and PD-L1 expression on the tumor cells [20,45,68]. Avelumab, by binding to PD-L1, counteracts the upregulation of PD-1 and PD-L1 expression triggered by cetuximab, thus disinhibiting the PD-1+ immune effector cells in the tumor microenvironment [12]. Avelumab and cetuximab may both mediate immune effector function via the FcγR, with the combination uniquely being the only pairing of anti-EGFR and anti–PD-L1 antibodies in clinical trials where both drugs have been shown to have innate effector function in preclinical trials [20]. This combination has the potential for inducing additive innate effector function activity, and in turn generating a synergistic immune effect by priming and activating NK cells cooperatively. Both avelumab and cetuximab, when combined with activated NK cells in the preclinical setting, have been shown to enhance the cytotoxic activity of NK cells [14,69]. Additionally, the known safety profiles of avelumab and cetuximab do not seem to overlap, except for infusion-related reactions, although existing data from clinical trials are limited [20]. To date, no preclinical studies of the combination of avelumab and cetuximab administered together have been conducted.

Several clinical trials investigating the combination of cetuximab and other anti–PD-(L)1 therapies are already in progress. In a phase 2 trial of the combination of pembrolizumab and cetuximab in patients with R/M SCCHN (n = 33), 12 of 29 (41%) evaluable patients had a partial response (PR) by 6 months (1 PR became a complete response [CR] after 6 months), 6 (21%) had stable disease (SD), and 11 (38%) had progressive disease (PD); there were 10 grade 3 treatment-related adverse events (TRAEs)[70]. In a phase 1b/2 study of second-line or later treatment with pembrolizumab in combination with cetuximab in patients with *RAS* wt mCRC, irrespective of MSI status, 6 of 9 patients had SD lasting ≥16 weeks; grade 3 adverse events (AEs) were uncommon, and the combination was well tolerated [71]. Finally, the multiarm RTOG 3504 trial showed that nivolumab combined with cetuximab and standard radiotherapy is safe to be administered in patients with newly diagnosed intermediate- and high-risk LA SCCHN. In 39 of 40 evaluable patients, there were 29 grade ≥3 AEs related to nivolumab and 3 dose-limiting toxicities (DLTs; mucositis [n = 1], lipase/mucositis [n = 1], and fatigue [n = 1]); 2 of the 3 DLTs were observed in the nivolumab + radiotherapy alone arm, and 1 was observed in the nivolumab + cetuximab + chemoradiation arm (mucositis). Seventeen serious AEs were observed; no information regarding AEs related to cetuximab was reported [72].

Ongoing trials exploring the combination of avelumab and cetuximab

Squamous cell carcinoma of the head and neck

Many trials examining the combination of avelumab and cetuximab are in progress (Table 1). While cetuximab is already approved for the treatment of both LA and R/M SCCHN, combining it with avelumab may increase clinical efficacy, which may be further enhanced with the inclusion of radiotherapy. The use of radiotherapy in patients with LA SCCHN represents a unique opportunity to combine the radiosensitizing action with the immunostimulatory effects of cetuximab, while the addition of avelumab to this combination may potentially lead to an antitumor response in cancer cells that is distant from the primary target of localized radiation; this response is termed an abscopal effect [73–75]. Irradiation of tumors can prime and stimulate the immune response after inducing immunogenic tumor cell death, which then may

Table 1
Overview of current trials investigating the combination of avelumab and cetuximab.

Study	Phase	N*	Tumor type	NCT or EudraCT identifier	Other treatments	Regimen	Primary endpoints	Selected secondary endpoints	Primary data expected
Squamous cell carcinoma of the head and neck (SCCHN)									
Avelumab + cetuximab + palbociclib	1	24	R/M SCCHN	NCT03498378	Palbociclib	Avelumab IV Q2W + cetuximab 400 mg/m^2 IV QW + palbociclib 75, 100, or 125 mg PO QD on days 1–21 of 28-day cycle	MTD	ORR, PFS, OS, safety	February 2020[†]
REACH [79]	3	707[‡]	LA SCCHN	NCT02999087	RT, cisplatin	Stratification by fit/unfit for cisplatin 100 mg/m^2 IV, followed by randomization to RT by IMRT + cisplatin (arm A), or avelumab 10 mg/kg Q2W + cetuximab 400 mg/m^2 on day 8, then 250 mg/m^2 QW + RT by IMRT, followed by avelumab maintenance 10 mg/kg IV Q2W for 12 months (patients fit for cisplatin [arm B] or unfit for cisplatin [arm C]), or cetuximab 400 mg/m^2 on day 8, then 250 mg/m^2 QW + RT by IMRT (arm D)	PFS	OS, safety	December 2027
EACH [80]	2	16[‡]	R/M SCCHN	NCT03494322	N/A	Avelumab 10 mg/kg IV Q2W + cetuximab 500 mg/m^2 (day 1 and 15; dose dependent on safety run-in phase) (arm A) or avelumab 10 mg/kg IV Q2W	DLT	ORR, DCR, DOR, OS, PFS, safety	October 2021
Bioimmunoradiotherapy [84]	1	10[‡]	LA SCCHN	NCT02938273	RT	Avelumab 10 mg/kg IV (days –7, 7, 21, and 35, then as maintenance Q2W for 6 months) + cetuximab 400 mg/m^2 IV (day –7) then 250 mg/m^2 IV QW (wk 1–7) + RT 5×/wk for 7 weeks	Grade ≥ 3 toxicities	ORR	September 2019[§]
Colorectal cancer (CRC)									
AVETUX [85]	2	43[‡]	*RAS* wt, *BRAF* wt, MSI or MSS mCRC	NCT03174405	mFOLFOX6	Avelumab 10 mg/kg IV (day 1, from cycle 2 onwards) + cetuximab 250 mg/m^2 IV (days 1 and 8, first dose 400 mg/m^2) + mFOLFOX6 (oxaliplatin 85 mg/m^2 IV [day 1], 5-FU 400 mg/m^2 IV bolus [day 1], 5-FU 2400 mg/m^2 IV [days 1–3])	12-month PFS rate	ORR, PFS, OS, safety	July 2021
AVETUXIRI [86]	2	23[‡]	*BRAF* wt, MSS mCRC	NCT03608046	Irinotecan	Avelumab 10 mg/kg Q2W (wk 3 onwards) + cetuximab 400 mg/m^2 IV (wk 1), 250 mg/m^2 IV (wk 2), 500 mg/m^2 IV (wk 3 onwards) + irinotecan 180–150[‖] mg/m^2 IV Q2W (wk 1 onwards)	ORR per iRECIST and safety	DCR, PFS, OS	December 2023
CAVE mCRC [88]	2	77[‡]	*RAS* wt mCRC	2017-004392-32	N/A	Avelumab 10 mg/kg IV Q2W + cetuximab 400 mg/m^2 IV first dose, then 250 mg/m^2 IV QW until PD or unacceptable toxicity (3L rechallenge)	OS	ORR, PFS, safety	February 2020
FIRE-6 [89]	2	55	*RAS* wt, *BRAF* wt mCRC	2018-002010-12	FOLFIRI	Cetuximab + FOLFIRI for 4 cycles, then avelumab + cetuximab + FOLFIRI for 4 cycles, then avelumab	PFS per RECIST 1.1	ORR, irPFS per irRECIST, OS, DOR, safety	N/A

(*continued on next page*)

Table 1 (*continued*)

Study	Phase	N*	Tumor type	NCT or EudraCT identifier	Other treatments	Regimen	Primary endpoints	Selected secondary endpoints	Primary data expected
						maintenance until disease progression or unacceptable toxicity			
AVETRIC [90]	2	N/A	*RAS* wt, *BRAF* wt, mCRC	2019-0041501-24	FOLFOXIRI	Cetuximab + avelumab + FOLFOXIRI, then maintenance avelumab + cetuximab until PD	N/A	N/A	N/A
Non-small cell lung cancer (NSCLC)									
Avelumab + cetuximab + gemcitabine + cisplatin	2a	40†	Stage IV R/M squamous NSCLC	NCT03717155	Gemcitabine + cisplatin	Avelumab 800 mg IV (days 1 and 8 of each 3-wk cycle for the first 4 cycles) + cetuximab 250 mg/m^2 IV (day 1), 500 mg/m^2 IV (day 8) for the first 4 cycles + gemcitabine 1250 mg/m^2 IV (days 1 and 8 of each 3-wk cycle up to 4 cycles) + cisplatin 75 mg/m^2 IV (day 1 of each 3-wk cycle up to 4 cycles), followed by maintenance with avelumab 800 mg IV Q2W + cetuximab 250 mg/m^2 IV Q2W until PD or unacceptable toxicity	BOR	PFS, DOR, OS, safety, PK/PD	January 2021
Cutaneous squamous cell carcinoma (cSCC)									
AliCE	2	52	Stage III/IV cSCC	2018-001708-12	N/A	Avelumab + cetuximab IV	ORR	PFS, DOR, OS, QoL, safety	N/A
Avelumab + cetuximab	2	59	Advanced cSCC	NCT03944941	N/A	Avelumab IV Q2W (up to 24 28-day cycles) + cetuximab IV QW (up to 12 28-day cycles) until PD or unacceptable toxicity	PFS	ORR, CBR, OS, safety	December 2022
Squamous cell carcinoma of the anal canal (SCCAC)									
CARACAS [96]	2	60‡	Unresectable, LA, or metastatic SCCAC	NCT03944252	N/A	Avelumab 10 mg/kg IV Q2W + cetuximab 500 mg/m^2 IV Q2W until PD or unacceptable toxicity	ORR	PFS, OS, safety	February 2021

Data from ClinicalTrials.gov and the European Union Drug Regulating Authorities Clinical Trials Database (accessed 26 November 2020).
5-FU, 5-fluorouracil; BOR, best overall response; CBR, clinical benefit rate; cSCC, cutaneous squamous cell carcinoma; DCR, disease control rate, DOR, duration of response; DLT, dose-limiting toxicity; iRECIST, immune RECIST; irPFS, immune-related PFS; irRECIST, immune-related RECIST; IMRT, intensity-modulated radiation therapy; IV, intravenous; LA, locally advanced; mCRC, metastatic colorectal cancer; MSI, microsatellite instable; MSS, microsatellite stable; MTD, maximum-tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QD, once per day; QoL, quality of life; QW, every week; Q2W, every 2 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; R/M, recurrent/metastatic; RT, radiotherapy; SCCAC, squamous cell carcinoma of the anal canal; wk, week.

* Estimated enrollment.
† Actual primary completion date.
‡ Actual enrollment.
§ Actual study completion date.
‖ Irinotecan starting dose amended to 150 mg/m^2 for the last 8 patients.

lead to the regression of non-irradiated distant tumors [75–77]. Furthermore, radiotherapy induces the expression of molecules such as Major histocompatibility complex (MHC) class I, which mediate antigen presentation and activation of immune effector cells [75,78]. The REACH trial (NCT02999087) compares avelumab + cetuximab + radiotherapy in patients with LA SCCHN who are either fit or unfit for high-dose cisplatin (experimental arms B and C, respectively) vs radiotherapy + cisplatin (arm A; patients with LA SCCHN who are fit for high-dose cisplatin) and vs radiotherapy + cetuximab (arm D; patients with LA SCCHN who are unfit for high-dose cisplatin). As of August 2018, 82 patients had been randomized, including 41 patients to the experimental arms (arm B, n = 21; arm C, n = 20), with all patients but one receiving the entire course of radiotherapy. In experimental arms B and C, 19 (90%) and 16 (80%) respective patients received ≥7 cycles of cetuximab, and 20 (95%) and 16 (80%) respective patients received the planned number of avelumab doses. Grade 3 AEs occurred in 35 (85%) of the 41 patients in the experimental arms. The most common grade ≥3 AEs were radiation dermatitis, mucositis, and dysphagia; grade ≥4 AEs occurred in 5 (12.2%) patients (1 grade 5 AE occurred in arm A). Given the tolerability of this combination in patients with LA SCCHN, the trial was approved to be continued beyond the safety phase [79].

The EACH trial (NCT03494322) compares avelumab + cetuximab vs avelumab alone in patients with R/M SCCHN who have progressed on prior treatment with a platinum-containing agent. As of October 2019, a total of 16 patients had been enrolled. In the safety run-in phase, avelumab + cetuximab was well tolerated and promising responses were observed with this combination. Grade 3 AEs occurred in 4 patients, and 1 grade 5 AE occurred in 1 patient; none were treatment-related and there were no treatment related deaths. Of the 10 patients evaluable for response, the ORR was 50% with CR in 2 (20%) and PR in 3 (30%) [80].

Palbociclib, an inhibitor of cyclin-dependent kinases (CDK4 and CDK6), is being investigated in combination with avelumab and cetuximab in patients with R/M SCCHN (NCT03498378; primary completion date, 4 February 2020). CDK4/6 inhibitors, which induce cell cycle arrest, can also generate an immune response by enhancing antigen presentation by tumor cells, stimulating effector T-cell activation, and reducing the proliferation of T regulatory cells [81,82]. Preclinical data show that combining CDK4/6 inhibition and PD-1 blockade results in a synergistic inhibition of tumor growth in mouse models of human triple-negative breast cancer [83]. Therefore, adding cetuximab to this combination of drugs may result in increased synergy among the 3 drugs.

The Bioimmunoradiotherapy trial (NCT02938273) in patients with LA SCCHN who were unfit for cisplatin examined the combination of avelumab + cetuximab + radiotherapy followed by avelumab maintenance; this was the first study to examine the combination of anti-PD-L1 therapy with standard-of-care treatment for patients with LA SCCHN. Ten patients were enrolled; median follow-up time was 12 months at the time of analysis. Of the 9 evaluable patients, 4 had recurrence of the disease after a median of 10 months following radiotherapy, 3 patients had no recurrence, and 2 patients dropped out. No grade 4/5 toxicities were observed; grade 3 immune-related toxicities were observed in 4 patients (2 cases of pneumonitis, 1 case each of maculopapular rash and elevated alanine aminotransferase) and were all considered related to avelumab; all immune-related toxicities were manageable and transient. No grade 3/4 AEs were considered related to cetuximab; grade 1/2 rash was observed in 5 patients [84]. Because patients with SCCHN tend to be older individuals with extensive comorbidities, this therapeutic approach showed that this combination of avelumab, cetuximab, and radiotherapy is feasible in patients with LA SCCHN who are unfit for treatment with cisplatin.

Colorectal cancer

Cetuximab is also approved in patients with *RAS* wt mCRC, and the addition of avelumab may increase clinical efficacy in a wider variety of patient populations. The AVETUX trial (NCT03174405) investigated the combination of avelumab + cetuximab + mFOLFOX6 (folinic acid + fluorouracil + oxaliplatin) in patients with untreated *RAS/BRAF* wt, MSI, or microsatellite stable (MSS) mCRC. Forty-three patients were enrolled; 2 (4.7%) had MSI-high tumors, 1 (2.3%) had MSI-low tumors, and the remaining 40 (93.0%) had MSS mCRC. Four patients (9.3%) were excluded after enrollment due to *RAS* or *BRAF* mutations detected based on local testing. Patients received avelumab + cetuximab + mFOLFOX6 for a median duration of 5.4 months. The ORR was 79.5% (31/39 patients) with CR in 6 and PR in 25. The disease control rate was 92.3%, as 5 patients had stable disease. The early tumor shrinkage rate (≥20% after 8 weeks) was 79.5%. The primary endpoint—progression-free survival (PFS) rate at 12 months—was 40%; after a median follow-up of 16.2 months, the median PFS time was 11.1 months and the overall survival (OS) rate was 84.6%. Treatment was well tolerated; avelumab did not add any unexpected AEs to the safety profile of the standard cetuximab + FOLFOX regimen, and 52 serious AEs were observed in 23 (60.5%) of the 38 patients in the safety population (1 patient from the efficacy population did not receive avelumab) [85].

Several additional trials are currently ongoing or planned in patients with mCRC. The combination of avelumab + cetuximab + irinotecan is being examined in the AVETUXIRI (NCT03608046) trial in patients with *BRAF* wt MSS mCRC who are refractory to standard chemotherapy and anti-EGFR treatment; patients with *RAS* wt mCRC were enrolled into cohort A, and those whose tumors had *RAS* mutations were enrolled into cohort B. The 2 primary endpoints were overall response rate, defined as either a CR or PR according to immune RECIST (iRECIST), and safety. As of January 2020, 23 patients had been enrolled and received treatment. Three patients in cohort A achieved a PR, and none achieved a CR or PR in cohort B. No unexpected safety events occurred; grade 3 diarrhea related to irinotecan occurred in 5 (21.7%), and all cases were resolved after irinotecan dose reduction or interruption. Median PFS in cohorts A and B was 4.2 months and 3.8 months, respectively; median OS was 12.7 months and 14.0 months [86]. The CAVE mCRC trial (EudraCT 2017-004392-32) is investigating the combination of avelumab and cetuximab as third-line rechallenge therapy in patients with *RAS* wt mCRC who received cetuximab in combination with chemotherapy in the first line and progressed to second-line therapy [87,88]. As of February 2020, 77 patients had been enrolled and had received treatment. Among the 65 patients who were evaluable for response, 1 (1.5%) patient achieved a CR and 3 (4.6%) achieved a PR. The primary endpoint was median OS, which was 13.1 months; median pPFS was 3.6 months. This treatment strategy was well tolerated; grade 3 AEs occurred in 22% of patients. The most common grade 3 AEs were rash (n = 10; 13%) and diarrhea (n = 3; 4%) [88]. Finally, the combination of avelumab and cetuximab with the FOLFIRI (folinic acid + fluorouracil + irinotecan) regimen, followed by maintenance with avelumab, is being investigated in patients with previously untreated *RAS* and *BRAF* wt mCRC in the FIRE-6 trial (EudraCT 2018-002010-12) [89], and the combination of avelumab + cetuximab + FOLFOXIRI (folinic acid + fluorouracil + oxaliplatin + irinotecan) is being investigated in patients with *RAS* wt CRC in the AVETRIC trial in Italy (EudraCT 2019-0041501-24) [90].

Non-small cell lung cancer

In NSCLC, the combination of avelumab + cetuximab + gemcitabine + cisplatin is being explored in patients with stage IV R/M squamous NSCLC (NCT03717155). The combination of cisplatin and gemcitabine has previously been shown to synergize with EGFR inhibition, via necitumumab in metastatic squamous NSCLC in the double-blind, randomized phase 3 SQUIRE trial [91], and via cetuximab in R/M NSCLC in a randomized phase 2 trial [92]. Additionally, in the randomized, open-label, phase 3 FLEX trial, the combination of cetuximab + cisplatin + vinorelbine was shown to be a safe and effective treatment option for patients with NSCLC [93]. Furthermore, platinum-based doublet chemotherapy has been shown to synergize with PD-1– or PD-L1–blocking antibodies in NSCLC, including squamous cell carcinomas [94,95]. A regimen comprising all 3 agents—platinum-based doublet therapy, an anti–PD-1 or PD-L1–targeting agent, and an EGFR antibody—may synergize to result in enhanced clinical antitumor activity.

Cutaneous squamous cell carcinoma and squamous cell carcinoma of the anal canal

The combination of avelumab and cetuximab is also under investigation in cSCC for the treatment of patients with unresectable stage III/IV disease in the single-arm ALiCE trial (EudraCT 2018-001708-12), and in comparison with avelumab alone in patients with advanced disease (NCT03944941). The open-label, randomized (1:1) phase 2 CARACAS trial (NCT03944252) examines avelumab alone (arm A) vs avelumab + cetuximab (arm B) as second-line or later therapy in patients with locally advanced or metastatic SCCAC. After a median follow-up of 11 months, 60 patients had been enrolled (n = 30 in each arm). In arm A vs arm B, the ORR (primary endpoint) was 10% vs 17% and the disease control rate was 50% vs 57%. Median PFS was 2.05 months in arm A vs 3.88 months in arm B; OS data are not yet mature. The most common TRAEs (grade not specified) in arm A and B, respectively, were fatigue (occurred in 17% of patients in arm A) and skin and subcutaneous disorders (occurred in 87% of patients in arm B) [96].

Conclusions

While ICIs and targeted therapies are now considered proven treatment options for patients with various cancers, response rates remain low for many indications, and treatment options remain limited for patients seeking later-line therapies [2,4,25,31]. In the search for new

avenues of treatment, the combination of avelumab and cetuximab has been shown to function via complementary mechanisms of action [14,20,45,53], and the combination may result in synergistic activity that counteracts immunosuppressive negative feedback and increases the efficacy of anti-EGFR and anti–PD-L1 activity. Cetuximab is capable of priming the immune system for treatment with avelumab by recruiting CD8+ T cells to the intratumoral space, and the associated negative feedback from PD-(L)1–mediated immunosuppression can be reduced through the administration of avelumab [20,45,53]. The combination also offers a unique opportunity to explore the additive effects of 2 drugs that both induce innate immune effector function. This property is unique to cetuximab but not to panitumumab, as the latter does not have innate immune effector function activity and does not result in PD-L1 upregulation [23]. The combination of avelumab and cetuximab may also provide further value when combined with chemotherapy or radiotherapy; ongoing clinical trials with these combinations are underway. These clinical trials have already shown that the combination is tolerable and does not result in any unexpected toxicities; further investigation will show whether this combination represents a promising new treatment regimen in patients with SCCHN, CRC, NSCLC, cSCC, and SCCAC.

Disclosures

JB reports providing a consulting or advisory role and receiving travel expenses from Merck KGaA, Darmstadt, Germany.

AStein reports providing a consulting or advisory role for Amgen, Bristol Myers Squibb, Merck KGaA, Merck & Co., and Roche; speakers services for Amgen, Bristol Myers Squibb, Celgene, Eli Lilly, Merck KGaA, Roche, Sanofi, and Servier; receiving research funding from Bristol Myers Squibb, Merck KGaA, Roche, Sanofi, and Servier; and travel expenses from Bristol Myers Squibb, Merck KGaA, and Roche.

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MM was an employee of Pfizer Pharma GmbH at the time this review was written.

ASchroeder is an employee, received travel expenses, and owns stock in Merck KGaA, Darmstadt, Germany.

GP is an employee of EMD Serono Research & Development Institute, Inc.; an affiliate of Merck KGaA, Darmstadt, Germany.

SSalmio is an employee of Merck KGaA, Darmstadt, Germany.

RE is an employee and owns stock in Merck KGaA, Darmstadt, Germany.

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All authors met the criteria for authorship set forth by the International Committee of Medical Journal Editors and were involved in conception, preparation, and approval of the manuscript for submission.

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