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Immune checkpoint blockade with anti-programmed cell death 1 (PD-1) monoclonal antibody (mAb) cemiplimab: ongoing and future perspectives in rare genital cancers treatment

Elisabetta Gambale,[1] Sara Fancelli,[1] Enrico Caliman,[1,2] Maria Cristina Petrella,[1] Laura Doni,[1] Serena Pillozzi,[1] Lorenzo Antonuzzo[1,2]

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[1]Clinical Oncology Unit, University Hospital Careggi, Firenze, Italy
[2]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

Correspondence to
Professor Lorenzo Antonuzzo; lorenzo.antonuzzo@unifi.it

ABSTRACT

Cemiplimab is a highly potent, hinge-stabilized human IgG4 monoclonal antibody (mAb) targeting programmed cell death 1 (PD-1) receptor approved for patients with locally advanced or metastatic cutaneous squamous cell carcinoma (SCC) who are not candidates for curative surgery or curative radiation. Recently, the phase 3 trial EMPOWER-Cervical 1 has investigated cemiplimab in patients with recurrent/metastatic cervical cancer. At interim analysis, overall survival (OS), progression free survival (PFS) and objective response rate (ORR) in overall and SCC populations favored cemiplimab over single agent chemotherapy. Cervical SCCs are the first for incidence among Human Papilloma Virus (HPV) related neoplasms and are highly correlated (about 95%) with the viral infection. Similarly, penile and vulvar SCC may develop on chronic HPV infections or on dermatological chronic conditions (ie, lichen). The molecular and viral similarities between external genital SCC and SCC originating from the cervical epithelium could be the rationale for using cemiplimab to treat locally advanced or metastatic penile and vulvar SCC as well. Some retrospective data have shown that cemiplimab may provide objective response and clinical benefit to some patients with penile or vulvar SCC and is overall safe to utilize in this population. Given the complexity of the immune activation and the considerable variability in tumor biology across patients and tumor types, the identification of biomarkers to warrant patient selection needs to be further explored. Ongoing clinical trials will hopefully shed light on the treatment paradigm of these rare tumors too, with special regard to the ideal combination and sequencing of immunotherapeutic strategies.

Cemiplimab is a highly potent, hinge-stabilized human IgG4 monoclonal antibody (mAb) targeting programmed cell death 1 (PD-1) receptor,[1] approved in September 2018 in the USA for patients with locally advanced or metastatic cutaneous squamous cell carcinoma (SCC) who were not candidates for curative surgery or curative radiation.[1] Cemiplimab also received US Food and Drug Administration (FDA) approval as first-line treatment for advanced non-small cell lung cancer (NSCLC) with high programmed death-ligand 1 (PD-L1) on the basis of the EMPOWER-Lung 1. Interestingly, this trial enrolled patients with chronic infections, such as HIV-1 or hepatitis, suggesting safe use and efficacy of cemiplimab also in these patients, usually excluded from clinical trials.[2] Cemiplimab was also FDA approved for basal cell carcinoma pretreated with hedgehog inhibitors on the basis of EMPOWER-BCC 1 (see online supplemental file 1). More recently, results from the phase III trial EMPOWER-Cervical 1 has investigated cemiplimab in patients with recurrent/metastatic cervical cancer, regardless of PD-L1 status or histology, who failed first-line platinum-based therapy. The EMPOWER-Cervical 1 randomly assigned a total of 608 patients to cemiplimab 350 mg every 3 weeks or investigator-choice (IC) single-agent chemotherapy, up to 96 weeks. Primary endpoint was overall survival (OS), while secondary endpoints were progression-free survival (PFS), objective response rate (ORR) and safety. At interim analysis OS, PFS and ORR in overall and SCC populations favored cemiplimab over single-agent chemotherapy. Median OS was 12 months with cemiplimab versus 8.8 months with IC chemotherapy (HR 0.69; 95% CI, 0.56 to 0.84; one sided p=0.001) in the overall population and 11.1 months with cemiplimab versus 8.8 months with IC chemotherapy (HR 0.73; 95% CI, 0.58 to 0.91; one-sided p=0.003) in SCC population, respectively. An acceptable safety profile was shown. These results led to the FDA acceptation for priority review

Table 1 Selected cemiplimab combination trials in advanced solid tumors*

ICIs ‡‡	Other agents	NCT trial number	Phase	Predictive biomarkers	Status
Cemiplimab in combination with other immunotherapy agents					
Cemiplimab	SAR-439459 (anti-TGF¶-beta mAb)	NCT04729725	Ib	Somatic mutations Change in protein expression Change in RNA expression Circulating- free DNA Peripheral mononuclear blood cells Cytokine levels TGF-beta Microbiome analysis	Recruiting
Cemiplimab	Pan-TGF¶-beta neutralizing abSAR439459	NCT03192345	I	Not available	Recruiting
Cemiplimab	CMP-001 (CpGA DNA Toll-like receptor 9 agonist)	NCT04916002	II	Not available	Not yet recruiting
Cemiplimab	REGN7075 (bispecific antibody directed against both EGFR†§ and the costimulatory T-cell-specific surface glycoprotein CD28)	NCT04626635	I and II	Not available	Recruiting
Cemiplimab or pembrolizumab	Cavrotolimod (Toll-like receptor 9 agonist)	NCT03684785	I and II	Tumor-infiltrating lymphocytes, PD-L1, and other checkpoint expression	Recruiting
Cemiplimab	REGN3767 (anti-LAG3† mAb)†	NCT03005782	I	Not available	Recruiting
Cemiplimab	SAR441000 (mRNA mixture encoding IL-12** sc, interferon alpha 2b, GM-CSF††, and IL-15 sushi)	NCT03871348	I	Not available	Recruiting
Cemiplimab in combination with chemotherapy					
Cemiplimab	Immunotherapy Chemotherapy	NCT04988074	II	Rate of induction tumor/ HPV HPV ctDNA clearance Characterization of immune microenvironment	Not yet recruiting
Cemiplimab or other ICIs	CP-506 (HAPs)‡ Carboplatin	NCT04954599	I II	Not available	Not yet recruiting Not yet recruiting

*As of November 8, 2021. Source: clinicaltrials.gov.
†Lymphocyte-activation gene 3.
‡Hypoxia-activated prodrugs.
§Human epidermal growth factor receptor.
¶ transforming growth factor
** Interleukin
††granulocyte-macrophage colony-stimulating factor
‡‡ Immune checkpoint inhibitors
HPV, human papilloma virus; mAb, monoclonal antibody; PD-L1, programmed death-ligand 1.

of the supplemental Biologics License Application, with target action date for final decision hopefully expected to be January 30, 2022.

Cervical SCCs are the first for incidence among human papilloma virus (HPV)-related neoplasms and are highly correlated (about 95%) with the viral infection. Similarly, rare genital squamous cell tumors may develop on chronic HPV infections or on dermatological chronic conditions (ie, lichen). HPV-specific viral genotypes, mostly 16 and 18, are involved in the occurrence of up to 30% of vulvar SCCs and up to 50% of penile SCCs. In vulvar and penile SCCs, HPV infection has a prognostic and predictive role. In particular, HPV-positive cancers have better survival (83% for vulvar SCC and 93% for penile SCC, respectively) and radiosensitivity than HPV-negative tumors. Of note, HPV-positive tumors can be susceptible to immunotherapy through modulation of effector T cells, which are the main cells involved in cellular immune response against antigens associated with cellular transformation in HPV-driven cancers. Indeed, increased inflammatory gene expression and CD8+ T-cell infiltration was observed in the tumor microenvironment of HPV-positive head and neck SCC. Moreover, enrichment of tumor-infiltrating lymphocytes (TILs) in HPV-positive tumors

were described in several reports: from an analysis of TILs in 12 cervical tumors resulted that 9 of the 12 patients had CD4+ T cells and 8 of the 12 patients had CD8+ T cells that were specific for HPV antigens.[3]

The molecular and viral similarities between external genital SCC and SCC originating from the cervical epithelium could be the rationale for using immunotherapy to treat locally advanced or metastatic penile and vulvar SCCs as well. A case series from a phase II basket study for rare tumors (NCT02721732) described three patients with locally advanced or metastatic penile SCC who progressed on a platinum-based chemotherapy triplet and were treated with the anti-PD-1 mAb pembrolizumab, achieving an objective and durable response only in the patient with a microsatellite instability high tumor. At ESMO congress 2021, Lee *et al* presented the interim results of the phase I dose escalation study of YBL-006, a novel anti-PD-1 mAb, in advanced solid tumors. Among 10 patients available for radiological tumor assessment, best overall responses included 1 complete response (CR) occurred in a patient with penile SCC. No data about the HPV status were reported. Intriguingly, tumor samples of the responders harbored high levels of tumor mutational burden (TMB). Furthermore, Pouessel and colleagues reported results of the penile cohort from the phase II, single arm, AcSè nivolumab trial, which is the largest prospective study evaluating an anti-PD-1 agent in patients with advanced penile SCC, to date. Despite a low ORR of 14%, the median OS was 8.5 months, higher than that reported in most studies. However, the predictive role of HPV status was not evaluated in the study. Regarding the use of cemiplimab for the treatment of penile SCC, no relevant studies or large case series are available. A recent published Italian retrospective study about real-world data of cemiplimab in locally advanced and metastatic cutaneous SCC showed a significant association between progression disease and primary tumor when originating from genital sites (p=0.057).[4] However, our literature research found three cases of patients with metastatic penile SCC successfully treated with cemiplimab. In the first, a patient with chemotherapy-refractory HPV-positive metastatic penile SCC originated from the glans was treated with cemiplimab, achieving a CR with prolonged duration of response.[5] In the second, an HIV-positive patient with advanced HPV-negative penile SCC received cemiplimab obtaining an outstanding response.[6] In the last one, a radiological CR from cemiplimab was achieved in a patient with metastatic penile SCC; the HPV status was unknown in this case.[7]

Limited results on locally advanced or metastatic vulvar SCC treated with cemiplimab were reported in the mentioned Italian retrospective study.[4] Conversely, few data on the use of other anti-PD-1 mAb, such as pembrolizumab or nivolumab, are available. Pembrolizumab was studied in the non-randomized, multicohort, open-label, KEYNOTE-158 phase II study in patients with pretreated locally advanced or metastatic vulvar SCC. Results showed a 10.9% (95% CI, 5.6% to 18.7%) ORR, with 1 CR and 10 partial responses (PR). Interestingly, response was irrespective of PD-L1 expression. In addition, among two patients, one with vaginal SCC and one with vulvar SCC, treated with single-agent pembrolizumab within a phase II basket study for rare tumors (NCT02721732), a PR to treatment was reported in the patient with HPV-positive vulvar SCC. In another case report, a patient with a PD-L1-positive vulvar SCC and treated with pembrolizumab achieved a CR.[8] In the phase I/II trial CheckMate 358, efficacy of nivolumab monotherapy in recurrent/metastatic vaginal or vulvar SCCs was evaluated in a small cohort of patients. Although the small sample size (two vaginal and three vulvar cancers), the investigators observed a 20% ORR (one PR in a patient with vulvar cancer) with 40% of patients who experienced 6 months of disease control.

A recent published meta-analysis on advanced cutaneous SCC reported that cemiplimab showed better OS as compared with pembrolizumab (HRs ranging from 0.21 to 0.52) and better PFS when data from the largest study (n=105) of pembrolizumab for cutaneous SCC were analyzed (HRs ranging from 0.49 to 0.55). Although this evidence has to be considered with caution as it results from an indirect treatment comparison and no randomized controlled trial are available, cemiplimab is the systemic therapy with the strongest evidence of clinical benefit supporting its use in patients with cutaneous SCC.[9] Because of their similarities, cemiplimab might represent a valid therapeutic option for patients with either locally advanced and metastatic penile or vulvar SCCs. However, there are no prospective data distinguish tumors originating in the skin of penis or vulva from tumors originating in the mucosal tissues of the vulva and in the superficial squamous epithelium of the glans.

Results of EMPOWER-Cervical 1 are encouraging and provide evidence that immunotherapy with cemiplimab leads to substantial benefit for patients with metastatic genital cancer. These findings, together with data from literature, even if only case reports, afford interesting signals of efficacy of immunotherapy for penile and vulvar SCC. An important aspect of the EMPOWER-Cervical 1 trial relates to PD-L1 status, as patients were enrolled regardless of PD-L1 expression. On the other hand, the EMPOWER-Lung-1 provided confirmatory evidence for the role of PD-L1 expression as a predictive biomarker in NSCLC.[2] Conversely, high PD-L1 expression seems to correlate with an unfavorable outcome in vulvar and penile SCCs, but there is still a lack of data on its role as predictive biomarkers for anti-PD-1 mAbs in genital cancers. Moreover, exploratory correlative science objectives results of EMPOWER-CSCC-1 indicated that PD-L1 and TMB are not predictive biomarkers in cutaneous SCCs.[1] Thus, a biomarker-agnostic approach might be used to treat vulvar and penile SCCs with anti-PD-1 mAbs. Ongoing trials will hopefully examine the role of cemiplimab as monotherapy or in combination regimens in the treatment of advanced solid tumors, including penile and vulvar SCCs, as summarized in table 1. Predictive

biomarkers (possibly established in other SCC cohorts such as cervical, anal, or head and neck cancers), beyond PD-L1 and TMB, should be investigated to identify patients who would derive the greatest clinical benefit from treatment with cemiplimab and other immunotherapies. For example, inhibition of the polycomb proteins EZH2, which are often overexpressed in SCCs and are known to repress innate immune response through downregulation of MHC class I, could result in enhanced antigen presentation and may be able to circumvent anti-PD-1 resistance, as demonstrated in head and neck SCC.[10] In future studies, it could be worth exploring both in tumor microenvironment or in peripheral blood of patients the presence of biomarkers that could led to tailored immunotherapy and a more appropriate selection of patients for anti-PD-1/anti-PD-L1 treatment. Moreover, recent data from the phase III trial KEYNOTE-826 evidenced significant longer PFS and OS with upfront pembrolizumab plus platinum-based chemotherapy in patients with recurrent/metastatic cervical cancer. In light of these evidences, FDA approved this regimen for patients whose tumors express PD-L1 (combined postitive score (CPS)≥1). Despite these encouraging results, efforts are required to shed light on the treatment paradigm with regard to the ideal combination and sequencing of therapeutic strategies.

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REFERENCES

1 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.
2 Sezer A, Kilickap S, Gümüş M, *et al*. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet* 2021;397:592–604.
3 Shamseddine AA, Burman B, Lee NY, *et al*. Tumor immunity and immunotherapy for HPV-related cancers. *Cancer Discov* 2021;11:1896–912.
4 Baggi A, Quaglino P, Rubatto M, *et al*. Real world data of cemiplimab in locally advanced and metastatic cutaneous squamous cell carcinoma. *Eur J Cancer* 2021;157:250–8.
5 Steck S, Went P, Cathomas R, *et al*. Profound and durable responses with PD-1 immune checkpoint inhibitors in patients with metastatic penile squamous cell carcinoma. *Curr Probl Cancer* 2021;3:100045.
6 Proietti I, Skroza N, Filippi L, *et al*. Metastatic penile squamous cell carcinoma successfully treated with cemiplimab in an HIV patient. *Dermatol Ther* 2021;34:e14744.
7 Denis C, Sakalihasan S, Frères P, *et al*. Cemiplimab for cisplatin resistant metastatic penile cancer. *Case Rep Oncol* 2021;14:972–6.
8 Shields LBE, Gordinier ME. Pembrolizumab in recurrent squamous cell carcinoma of the vulva: case report and review of the literature. *Gynecol Obstet Invest* 2019;84:94–8.
9 Keeping S, Xu Y, Chen C-I, *et al*. Comparative efficacy of cemiplimab versus other systemic treatments for advanced cutaneous squamous cell carcinoma. *Future Oncol* 2021;17:611–27.
10 Zhou L, Mudianto T, Ma X, *et al*. Targeting EZH2 enhances antigen presentation, antitumor immunity, and circumvents anti-PD-1 resistance in head and neck cancer. *Clin Cancer Res* 2020;26:290–300.