Phase 2 study of the antitumour activity and safety of simlukafusp alfa (FAP-IL2v) combined with atezolizumab in patients with recurrent and/or metastatic cervical squamous cell carcinoma

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Summary

Background **Simlukafusp alfa (FAP-IL2v) is an immune cytokine engineered to selectively promote immune responses in the tumour microenvironment. We evaluated the antitumour activity and safety of FAP-IL2v plus atezolizumab in recurrent and/or metastatic cervical squamous cell carcinoma (SCC) in a phase 2 basket study (NCT03386721).**

Methods **Patients with confirmed metastatic, persistent or recurrent cervical SCC who had progressed on ≥1 anti-cancer therapy and had measurable disease were enrolled. FAP-IL2v 10 mg was administered once every 3 weeks**

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(Q3W) or once weekly (QW) for 4 weeks then once every 2 weeks (Q2W) with the corresponding Q3W or Q2W atezolizumab regimens. The primary endpoint was objective response rate by investigator assessment.

Findings Forty-eight patients were enrolled (Q3W: n = 47; QW/Q2W: n = 1). Among 45 response evaluable patients, objective responses occurred in 12 patients (27%; CI 16.0–41.0), including 3 complete and 9 partial responses. Responses occurred in 6/19 PD-L1 positive patients (32%; 95% CI 15.4–54.0) and 5/24 PD-L1 negative patients (21%; 95% CI 9.2–35.6). Median duration of response was 13.3 months (95% CI 7.6–NE). Median progression-free survival was 3.7 months (95% CI 3.3–9.0). Adverse events (AEs) were consistent with the known safety profile of each drug. AEs leading to withdrawal of either agent occurred in 6 patients (13%). Pronounced expansion and activation of natural killer and CD8 T cells in peripheral blood and increased tumour infiltration and inflammation were observed.

Interpretation FAP-IL2v plus atezolizumab is clinically active and has manageable safety in patients with recurrent and/or metastatic cervical SCC.

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Keywords: Cervical cancer; Squamous cell carcinoma; Immunotherapy; IL-2; PD-L1

Research in context

Evidence before this study

We searched PubMed for articles published in English language from database inception to April 30, 2023, using the search terms "recurrent" OR "metastatic" AND "cervical cancer" OR "cervical squamous cell carcinoma" AND "interleukin 2" OR "IL-2". The search yielded 236 results. Studies were reviewed if they reported results of clinical trials in patients with cervical cancer treated with a combination regimen that included an immune checkpoint inhibitor. Observational studies and studies that did not assess combination therapy were excluded from review. A total of 2 publications were identified as possibly reporting clinical trial results and upon further investigation, there were no clinical trials reporting results of an IL-2 immune cytokine plus an immune checkpoint inhibitor in patients with recurrent and/or metastatic cervical squamous cell carcinoma (SCC).

Added value of this study

This study reports outcomes for an IL-2 immune cytokine in combination with an immune checkpoint inhibitor in patients with recurrent and/or metastatic cervical SCC. The investigational regimen showed promising antitumour activity and manageable safety in this patient population of high unmet need. Responses were observed in patients with PD-L1-positive and PD-L1-negative tumours, many of which were durable.

Implications of all the available evidence

The results of the current study demonstrate the feasibility of combining an IL-2 immune cytokine and an anti-PD-L1 immune checkpoint inhibitor in patients with recurrent and/or metastatic cervical SCC and highlight the potential for clinically meaningful benefit.

Introduction

Cervical cancer (CC) is the fourth most frequently diagnosed cancer in women worldwide and has the fourth highest mortality rate.[1] Human papillomavirus (HPV) is a common aetiological factor in the development of CC and it is proposed that persistent HPV infection may lead to increased immunogenicity through direct or indirect counter-regulatory mechanisms, including upregulation of PD-L1, resulting in an immunosuppressive environment.[2] The majority of HPV-related cancers, including cervical cancer, are squamous cell carcinomas (SCC), with cervical SCC accounting for up to 90% of all cervical cancer cases.[3] Although CC is highly treatable and potentially curable, especially when detected early, outcomes for recurrent and/or metastatic disease are very poor.[3–5] The rationale for use of immunotherapies in CC is well described[6] and is further strengthened by data demonstrating that the majority of SCCs express programmed death-ligand 1 (PD-L1), a transmembrane protein that engages with programmed cell death-1 protein (PD-1), which is commonly expressed on the surface of immune cells.[7] Adaptive resistance to tumour immunity mediated by the PD-L1/PD-1 axis therefore represents a major therapeutic target in cervical SCC.[7]

Checkpoint inhibitors (CPIs), particularly PD-L1/PD-1 inhibitors, and antibody–drug-conjugates (ADCs) have emerged as a new standard of care for patients with

recurrent and/or metastatic CC after initial systemic treatment with chemotherapy with or without bevacizumab.[8] In this setting, currently approved treatments include pembrolizumab (a PD-1 inhibitor), with or without bevacizumab, in patients with PD-L1-positive tumours (United States only),[9] cemiplimab (a PD-1 inhibitor) in all patients (Europe only)[10] and tisotumab-vedotin (an ADC) in all patients (United States only).[11] Despite these advances, there remains an unmet need for novel therapies, particularly for unselected patient populations and CPI-unresponsive patients who progress after first-line treatment.[12]

Simlukafusp alfa (also known as fibroblast activation protein [FAP]–interleukin-2 variant [IL-2v; FAP-IL2v]; RO6874281) is a monomeric, immune cytokine engineered to promote immune responses in the tumour microenvironment.[13,14] It was developed to overcome the safety concerns associated with wild-type interleukin-2 (IL-2) therapy, including the potential for severe capillary leak syndrome, neurologic toxicity, serious infections and renal toxicity.[15] FAP-IL2v comprises a single IL-2v moiety fused to a human immunoglobulin G1 (IgG1) antibody directed against FAP, a protein highly expressed on the cell surface of cancer-associated stroma cells in more than 90% of human epithelial malignancies.[14] FAP-IL2v has abolished binding affinity for IL-2 receptor α (CD25), but retains affinity for IL-2 receptor βγ, resulting in the activation of natural killer (NK) cells and CD4+/CD8+ T cells without the preferential activation of T regulatory cells (Tregs) that help mediate tumour immune evasion.[14] A first-in-human phase 1 clinical trial (NCT02627274) demonstrated the safety and preliminary activity of FAP-IL2v in patients with metastatic solid tumours, making it the first IL-2v to demonstrate single–agent activity in humans while maintaining an acceptable safety profile.[16] Atezolizumab is an engineered, humanised IgG1 monoclonal antibody that binds selectively to PD-L1 and blocks its binding with PD-1, which can reinvigorate inhibited tumour-specific cytotoxic T cells.[17,18]

We hypothesised that combining FAP-IL2v with atezolizumab might have an additive effect on the antitumour immune response and result in improved outcomes for patients with recurrent and/or metastatic cervical cancer. In particular, based on the mechanism of action, this signal seeking study explored squamous histologies to focus on tumours with pre-existing tumour infiltration and inflammation that would potentially be responsive to FAP-IL2v plus atezolizumab; moreover, previous data indicate that permissive microenvironments are more prevalent in squamous histologies than in other histologies.[19–21] Here, we report results from the cervical SCC cohort of a phase 2 basket study evaluating the safety and antitumour activity of FAP-IL2v plus atezolizumab in patients with recurrent and/or metastatic solid tumours across multiple cancer types.

Methods

Study design and patients

We report part of an open-label, multicentre, non-comparative phase 2 basket study of FAP-IL2v plus atezolizumab in patients with recurrent and/or metastatic solid tumours (BP40234; NCT03386721). Eligible patients in the cervical SCC cohorts were aged 18 years or older with a confirmed diagnosis of metastatic, persistent or recurrent cervical SCC regardless of PD-L1 status, progression on ≥1 anti-cancer therapy, measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (previously irradiated lesions were not considered measurable) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0/1. Patients were excluded if they had received radiotherapy within the 4 weeks before the start of study treatment, any previous CPI therapy or immunotherapy before study enrolment, had symptomatic or untreated central nervous system metastases, or a history of autoimmune disease. Full eligibility criteria are included in the supplement.

Ethics

The study protocol was approved by the institutional review board or ethics committee at each participating centre (full details can be found in the supplement) and complied with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and local laws. All patients provided written informed consent.

Study treatment

The study design included two investigational regimens. FAP-IL2v 10 mg was administered intravenously (IV) either once every 3 weeks (Q3W) in combination with the approved Q3W atezolizumab 1200 mg IV regimen (Q3W cohort) or once weekly (QW) for the first 4 weeks then once every 2 weeks (Q2W) in combination with the approved Q2W atezolizumab 840 mg IV regimen (QW/Q2W cohort). After data analyses from other cohorts in the study, the more intensive QW/Q2W regimen was abandoned due to considerations related to tolerability, convenience and potential treatment benefit. Accordingly, most patients were recruited into the Q3W cohort. Patients continued treatment until disease progression according to RECIST v1.1, unacceptable toxicity or withdrawal of consent. If treatment with FAP-IL2v was discontinued, treatment with atezolizumab could continue and vice versa.

Outcomes

The primary endpoint was ORR, defined as the proportion of patients achieving a complete response (CR) or partial response (PR) by investigator assessment using RECIST v1.1. Secondary endpoints included disease control rate (DCR), defined as the proportion of patients achieving a CR, PR or stable disease (SD), duration of response (DoR) and progression-free survival (PFS),

defined as the time from randomisation to the first occurrence of disease progression or death from any cause. Additional secondary endpoints included the incidence and severity of adverse events (AEs), changes in vital signs, physical findings, electrocardiogram parameters, and clinical laboratory results, pharmacokinetics, pharmacodynamics and pre-defined exploratory biomarker analyses.

Assessments

Response was assessed by the investigator using physical examinations and computed tomography scans (or magnetic resonance imaging) of the chest, abdomen and pelvis at screening, every 8 weeks after the initiation of study treatment for the first year, and then every 12 weeks. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Pharmacodynamic analyses were performed in patients from the Q3W cohort only, as only one patient was enrolled into the QW/Q2W cohort. Pharmacodynamic changes were assessed in paired baseline and on-treatment tumour biopsies and in whole blood or plasma, with samples analysed centrally (see Supplementary Table S1 for the schedule of key assessments). Changes in key immune cell subsets were assessed in whole blood using flow cytometry, while changes in soluble CD25 and C-reactive protein (CRP) were assessed in plasma using immunoassay. Tumour biopsies were assessed for FAP expression and markers of tumour inflammation and infiltration (e.g., PD-L1, CD8 tumour infiltrating lymphocytes [TILs]) using immunohistochemistry. PD-L1 expression on pretreatment samples was assessed using the Ventana PD-L1 (SP263) assay (Ventana Medical Systems; Tucson, AZ, USA) and was quantified by tumour area positivity (TAP) score (defined as the percentage of total tumour and immune cells expressing PD-L1 as a proportion of the tumour area), with a cut-off of ≥5% used to define PD-L1 positivity. Analysis was complemented by gene expression profiling using bulk RNA sequencing. Full methodology can be found in the supplement. Pharmacokinetic analyses were carried out on serum samples using an enzyme-linked immunosorbent assay.

Statistics

No formal statistical analyses were performed. Descriptive analyses were based on the response-evaluable population (defined as all patients who received ≥1 dose of study treatment and had ≥1 baseline and ≥1 on-study tumour assessment, including those who discontinued treatment because of disease progression before the first on-study tumour assessment), and the safety population (defined as all patients who received ≥1 dose of study treatment). Demographic and baseline characteristics were summarised descriptively. ORR and DCR were computed along with their 95% CI, with Kaplan–Meier methodology used to estimate median DoR and PFS with associated 95% CI. AEs were documented using the electronic case report by the investigator and summarised by mapped term and appropriate thesaurus level. Pharmacokinetic and pharmacodynamic data were summarised using descriptive statistics.

For the cervical SCC cohort, a sample size of 20 response-evaluable participants was deemed sufficient to declare futility with 78% chance under the assumption that the true ORR was 5%, based on the posterior probability for ORR to be below 10% with a 70% confidence level. After clearing the futility boundary, the protocol allowed for up to 80 patients per cohort to be enrolled to allow robust evaluation of the investigational regimens.

Role of funders

The study was designed and funded by F. Hoffmann-La Roche Ltd. The funder was involved in the study design, data collection, data analysis, data interpretation and writing of the manuscript for publication. Authors who were employees of F. Hoffmann-La Roche Ltd (CH, DM, CB, DD, NS, SE, MR, CA, JC, AK, VT, NK) contributed to the writing and approval of the manuscript and had access to the raw data. Clinical data were collected by the academic authors and their research teams and were interpreted by the authors and the funder. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients

Between December 11, 2018, and December 18, 2021, 48 patients were enrolled into the cervical SCC cohort at 20 sites across nine countries (Fig. 1). Forty-seven patients were enrolled into the Q3W cohort and one patient into the QW/Q2W cohort.

Among all patients, median age was 53 years (range 25–69) and 33 patients (69%) had an ECOG performance status of 1 at baseline (Table 1). A total of 43 patients (90%) had metastatic disease and 5 (10%) had recurrent disease. Overall, 41 patients (85%) had received ≥1 previous line of anti-cancer therapy in the recurrent or metastatic setting. All patients were CPI-naïve and 17 (35%) had received prior treatment with bevacizumab. All patients had received prior platinum-based chemotherapy and 34 patients (71%) had received prior paclitaxel (metastatic setting, n = 28, including 2 patients who received paclitaxel as maintenance therapy; neoadjuvant, n = 5; adjuvant, n = 1).

At data cut-off (January 31, 2022), all patients had discontinued study treatment, primarily due to progressive disease (PD; Fig. 1). The median duration of combination therapy was 3.5 months (range 0.0–30.5) and the median duration of follow-up, defined as the

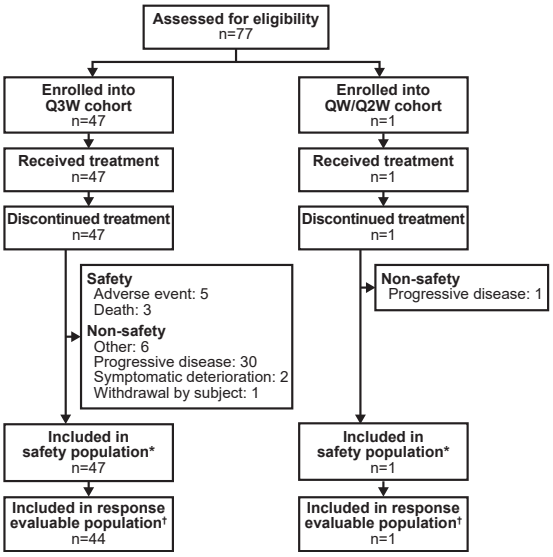

***Fig. 1:* CONSORT study diagram**. *All patients who received at least one dose of study treatment. †All patients who received at least one dose of study treatment and had at least one baseline and one on-study tumour assessment, including those who discontinued treatment because of disease progression before the first on-study tumour assessment. Two patients discontinued treatment due to AEs before the first tumour assessment and one patient was ineligible due to missing on-study tumour assessment.

	(N = 48)
Median age, years (range)	53 (25–69)
Race	
White	34 (71)
Native Hawaiian or Pacific Islander	1 (2)
Unknown	13 (27)
ECOG performance status score	
0	15 (31)
1	33 (69)
Tumour cell PD-L1 expression[a]	
TAP <5%	24 (50)
TAP ≥5%	19 (40)
Unavailable/unknown	5 (10)
Disease status	
Metastatic	43 (90)
Recurrent	5 (10)
Previous treatment settings	
Adjuvant	14 (29)
Neoadjuvant	9 (19)
Chemoradiotherapy	10 (21)
Maintenance	2 (4)
Recurrent/metastatic	41 (85)
Prior systemic therapy	
Platinum-based chemotherapy	48 (100)
Paclitaxel	34 (71)
Bevacizumab	17 (35)
Gemcitabine	7 (15)
Previous lines of systemic therapy in the recurrent/metastatic setting	
0	7 (15)
1	23 (48)
≥2	18 (38)

Data are n, (%), unless otherwise indicated. TAP, tumour area positive. [a]PD-L1 expression assessed using Ventana SP263 assay. Three patients (one PD-L1-positive, one PD-L1-negative, and one PD-L1 status unknown) were not evaluable per RECIST.

***Table 1:* Baseline demographic and clinical characteristics.**

time from first treatment to censoring for progression, was 14.3 months (95% CI 13.8–NA).

Antitumour activity

At data cut-off, 45 patients were response evaluable (Fig. 1). Three patients were not evaluable: two who discontinued treatment due to AEs before the first tumour assessment and one who was ineligible due to a missing on-study tumour assessment. Best confirmed ORR was 27% (95% CI 16.0–41.0), with CR in 3 patients and PR in 9 patients. DCR was 67% (CR 7%; PR 20%; SD 40%) and median DoR (n = 12) was 13.3 months (95% CI 7.6–not estimable [NE]) (Fig. 2a and b; Table 2). PD-L1 status was available for 43 patients and was unavailable for 2 patients due to the absence of baseline/archival biopsy or analysis failure. Objective responses were observed in 6/19 patients (32%) with PD-L1 positive tumours and 5/24 patients (21%) with PD-L1-negative tumours. Median DoR was 13.3 months for responders with PD-L1 positive tumours and 10.2 months for responders with PD-L1-negative tumours (Table 2).

Median PFS was 3.7 months (95% CI 3.3–9.0) in the response-evaluable population (Fig. 2c), 9.9 months (95% CI 3.6–13.2) in patients with PD-L1-positive tumours and 3.0 months (95% CI 1.9–5.9) in patients with PD-L1-negative tumours (Fig. 2d; Table 2). The three patients who achieved a CR had received 0, 2 and 4 prior lines of therapy, respectively, all in the metastatic setting. All three patients initially had low tumour burden compared with the median of the cohort in terms of the sum of diameter of target lesions. Additional information on these patients is provided in the supplement.

Safety

At data cut-off, all patients were safety evaluable (Fig. 1). All patients experienced at least one AE, most commonly pyrexia (n = 37, 77%), anaemia (n = 23, 48%), asthenia (n = 23, 48%), increased aspartate aminotransferase (AST; n = 22, 46%), increased alanine aminotransferase (ALT; n = 21, 44%) and nausea (n = 20, 42%) (Table 3). Expected IL-2 class-specific AEs included: pyrexia (n = 37, 77%); liver function test abnormalities (n = 33, 69%), including increased ALT,

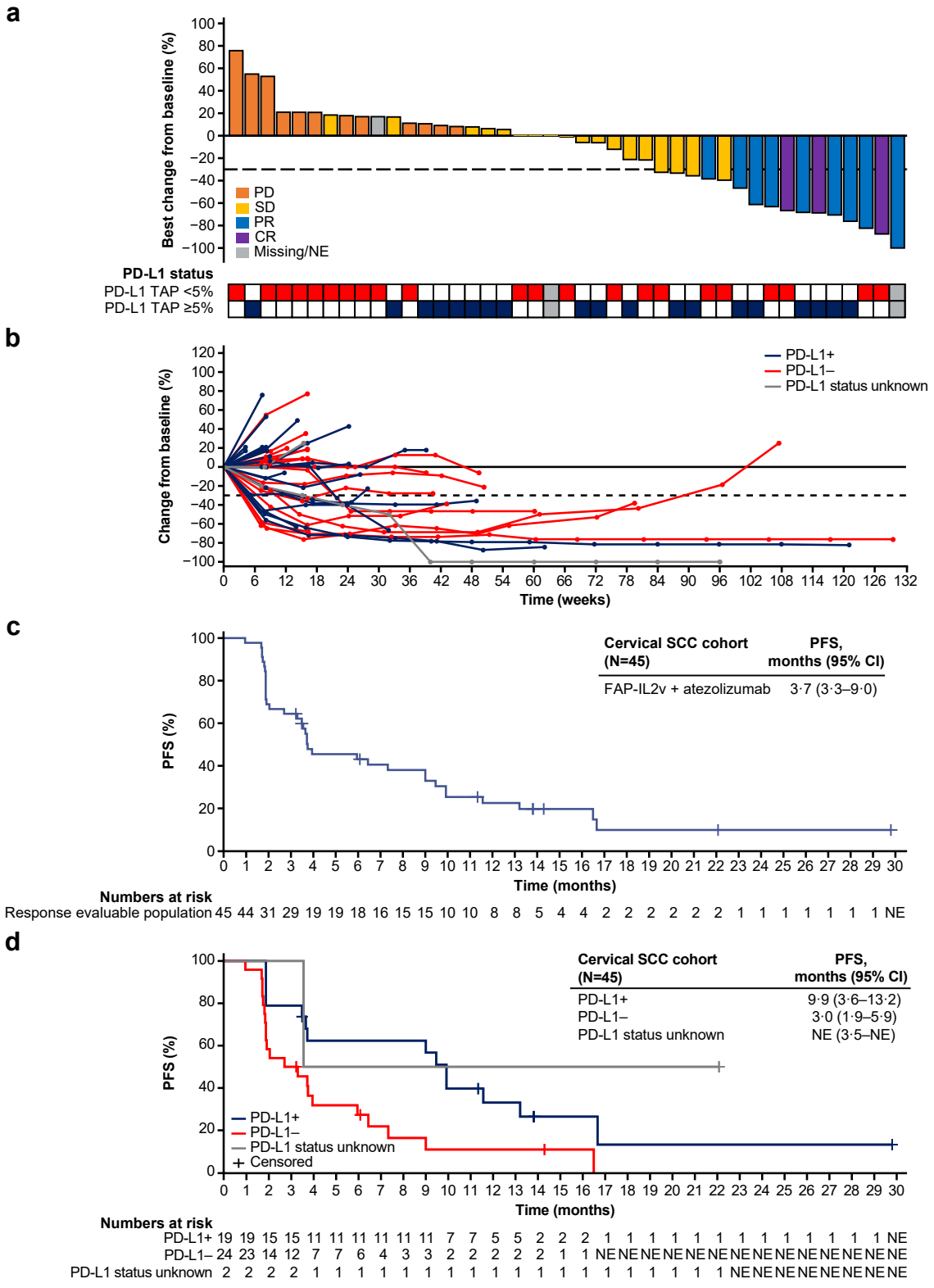

Fig. 2: **Antitumour activity following treatment with FAP-IL2v plus atezolizumab**. (a) Best percent change in sum of diameters of target lesion from baseline (column colour indicates confirmed best overall response), and (b) change in sum of target lesion over time in the

	Overall (n = 45)	Tumour cell PD-L1 expression[a]	
		PD-L1-positive (TAP ≥5%) (n = 19)	PD-L1-negative (TAP <5%) (n = 24)
DCR	30 (67)	15 (79)	13 (54)
95% CI	52.1–78.6	56.7–91.5	35.1–72.1
ORR	12 (27)	6 (32)	5 (21)
95% CI	16.0–41.0	15.4–54.0	9.2–40.5
CR	3 (7)	1 (5)	2 (8)
95% CI	2.3–17.9	0.9–24.6	2.3–25.9
PR	9 (20)	5 (26)	3 (13)
95% CI	10.9–33.8	11.8–48.8	4.3–31.0
SD	18 (40)	9 (47)	8 (33)
95% CI	27.0–54.6	27.3–68.3	18.0–53.3
PD	13 (29)	4 (21)	9 (38)
95% CI	17.7–43.4	8.5–43.3	21.2–57.3
Missing/not evaluable	2 (4)	0	2 (8)
Median DoR, months	13.3	13.3	10.2
95% CI	7.6–NE	7.9–NE	2.5–NE
Median PFS, months	3.7	9.9	3.0
95% CI	3.3–9.0	3.6–13.2	1.9–5.9

Data are n, (%), unless otherwise indicated. [a]PD-L1 expression assessed using Ventana SP263 assay. The PD-L1 status of 2 of the response evaluable patients could not be defined due to the absence of baseline/archival biopsy or analysis failure. TAP = tumour area positive.

Table 2: **Efficacy of FAP-IL2v plus atezolizumab in the response-evaluable population.**

AST, gamma-glutamyl transferase (GGT), blood bilirubin, and alkaline phosphatase; infusion-related reaction (IRR; n = 12, 25%); and oedema (n = 10, 21%). One patient experienced two AEs of capillary leak syndrome; both events resolved but were considered serious and related to FAP-IL2v treatment by the investigator.

Grade 3 AEs occurred in 41 patients (85%) and were considered treatment-related in 33 patients (69%), while Grade 4 AEs occurred in 19 patients (40%) and were considered treatment-related in 15 patients (31%) (Table 3). The most frequently reported grade 3–4 AEs were anaemia (n = 11, 23%), GGT increased (n = 9, 19%), lymphopenia (n = 8, 17%) and ALT increased (n = 7, 15%) (Supplementary Table S2). Overall, 100 serious AEs (SAEs) occurred in 33 of 48 patients, of which IRR (15%) and pyrexia (8%) were the most common (Supplementary Table S3). IRR (n = 7, 13%) and pyrexia (n = 5, 6%) were also the most frequently reported SAEs considered to be related to FAP-IL2v by the investigator.

There were 69 AEs that led to dose interruption or modification of FAP-IL2v, reported in 27 of 48 patients. AEs leading to withdrawal of FAP-IL2v and/or atezolizumab occurred in 6 patients: Grade 5 pelvic infection (considered unrelated to either agent by the investigator; both agents withdrawn); Grade 4 Stevens-Johnson syndrome (considered related to both agents; both agents withdrawn); Grade 3 infusion-related reaction (considered related to atezolizumab; atezolizumab withdrawn); Grade 2 infusion-related reaction (considered related to both agents; FAP-IL2v withdrawn) and Grade 3 hepatotoxicity (considered related to atezolizumab; atezolizumab withdrawn); Grade 4 vaginal haemorrhage (considered unrelated to either agent; both agents withdrawn); and Grade 2 weight increased (considered related to FAP-IL2v; FAP-IL2v withdrawn).

A total of 22 patients died. Nineteen deaths were due to PD. Grade 5 (fatal) AEs of COVID-19 and pelvic infection accounted for 2 additional deaths; both events were considered unrelated to study treatment (Table 3). The other death (due to unknown reasons) occurred during follow-up after discontinuation of the study.

Pharmacodynamics

Paired biopsies were available for 7 patients in the Q3W group only. Treatment was associated with a pronounced expansion and accumulation of TILs. Augmented PD-L1 expression was also observed,

response-evaluable population. Kaplan–Meier estimate of progression-free survival in (c) the overall antitumour-evaluable population, and (d) by PD-L1 status. Sum of diameter of target lesions post-baseline and PD-L1 status was unavailable for two patients (PD-L1 status could not be determined due to the absence of baseline/archival biopsy or analysis failure). PD-L1 status was determined using the Ventana SP263 assay with a cut-off of TAP ≥5% and was unavailable for two additional patients. Tick marks on the Kaplan–Meier plots show censoring of the data at the last time the patient was known to be alive. TAP, tumour area positive.

Patients with ≥1 of the following	(N = 48)
Total AEs, n	1252
Patients with any AE	48 (100)
AEs related to any study treatment, n	817
Patients with an AE considered related to any study treatment	45 (94)
Grade 3–4 AEs, n	196
Patients with Grade 3 AEs	41 (85)
Patients with a Grade 3 AE considered related to any study treatment	33 (69)
Patients with Grade 4 AEs	19 (40)
Patients with a Grade 4 AE considered related to any study treatment	15 (31)
SAEs, n	100
Patients with an SAE	33 (69)
Patients with SAE considered related to any study treatment	19 (40)
AEs leading to FAP-IL2v dose interruption/modification, n	69
Patients with an AE leading to FAP-IL2v dose interruption/modification	27 (56)
Patients with an AE leading to withdrawal of any study treatment	6 (13)
Patients with an AE leading to withdrawal of FAP-IL2v	5 (10)
Patients with an AE leading to withdrawal of atezolizumab	5 (10)
Patients with an AE resulting in a fatal outcome[a]	2 (4)
Most common AEs reported in >20% of patients	
Pyrexia	37 (77)
Anaemia	23 (48)
Asthenia	23 (48)
AST increased	22 (46)
ALT increased	21 (44)
Nausea	20 (42)
Vomiting	19 (40)
Diarrhoea	17 (35)
GGT increased	16 (33)
Urinary tract infection	15 (31)
Chills	13 (27)
Blood bilirubin increased	12 (25)
IRR	12 (25)
Decreased appetite	12 (25)
Blood ALP increased	11 (23)
Fatigue	10 (21)
Back pain	10 (21)
Abdominal pain	10 (21)

Data are n, (%), unless otherwise indicated. ALP, alkaline phosphatase. [a]One death was due to a grade 5 AE of COVID-19, and one death was due to pelvic infection.

Table 3: **Summary of adverse events in the safety population.**

especially on infiltrating immune cells (Fig. 3a). Transcriptomic analyses revealed increased expression of gene signatures on treatment, indicative of increased T and NK cell infiltration and effector function, as well as formation of tertiary lymphoid structures (Fig. 3b). The pharmacodynamic profile was consistent with the proposed mechanism of action of FAP-IL2v. Analysis of peripheral blood showed a pronounced and sustained expansion of total lymphocytes and specifically NK cells with treatment (Supplementary Figure S1; Fig. 3c), while the proportion of Tregs remained unchanged (Fig. 3c). T-cell expansion in early and later cycles was driven by proliferation (Ki67) and was associated with sustained and systemic immune activation evident in the increased levels of soluble CD25 (Fig. 3d) and CRP in plasma on-treatment compared with baseline (Supplementary Figure S1).

At baseline, tumour biopsies in responders (CR/PR) had a higher degree of tumour infiltration compared with non-responders (SD/PD), particularly for total CD3+ T cells, proliferating CD8+ T cells (Ki67+), and cytotoxic T and NK cells (Fig. 3e). Baseline levels of Tregs were higher in responders than in non-responders, while baseline PD-L1 expression (tumour and immune cells) was similar in both responders and non-responders (Fig. 3f). Transcriptomic analyses of tumour tissue showed that higher baseline T effector (Treg and NK) signature scores were associated with prolonged PFS, while expression of FAP as a single gene, or gene signatures indicative of angiogenesis or myeloid inflammation, did not have any association with improved PFS (Supplementary Figure S2). Baseline counts of peripheral B cells were associated with prolonged PFS, but baseline counts of T and NK cells were not (Supplementary Figure S2).

Pharmacokinetics

Pharmacokinetic analyses were performed in patients who received the Q3W schedule only, as only one patient received the QW/Q2W schedule. Pharmacokinetics and immunogenicity were assessed to characterise FAP-IL2v behaviour in combination with atezolizumab (Supplementary Figure S3). Approximately 40% of patients were anti-drug antibody-positive, with no apparent impact on exposure, and no association between ADA positivity and efficacy was found.

Discussion

There is an unmet need for novel therapies to treat recurrent and/or metastatic CC, particularly for unselected patient populations and patients who progress after first-line treatment.[8,12] This phase 2 study explored clinical outcomes with FAP-IL2v plus atezolizumab in CPI-naïve patients with recurrent and/or metastatic cervical SCC, regardless of PD-L1 status, and progression on ≥1 previous anti-cancer therapy. The combination was clinically active, with an ORR of 27% in all patients; responses were durable, with a median DoR of 13.3 months in all responders.

Consistent with the anticipated mechanism of action from adding an immune cytokine to a CPI, and the results of previous studies evaluating CPI or CPI-containing therapies in patients with recurrent, persistent or metastatic CC,[22–26] the greatest clinical benefit was observed in patients with PD-L1-positive tumours (ORR: 32%; DoR: 13.3 months). However, enduring clinical responses were also observed in the subgroup of patients with PD-L1 negative tumours (ORR: 21%; DoR: 10.2 months). These findings suggest a potential role for CPI-based therapies augmented by IL-2 cytokines in

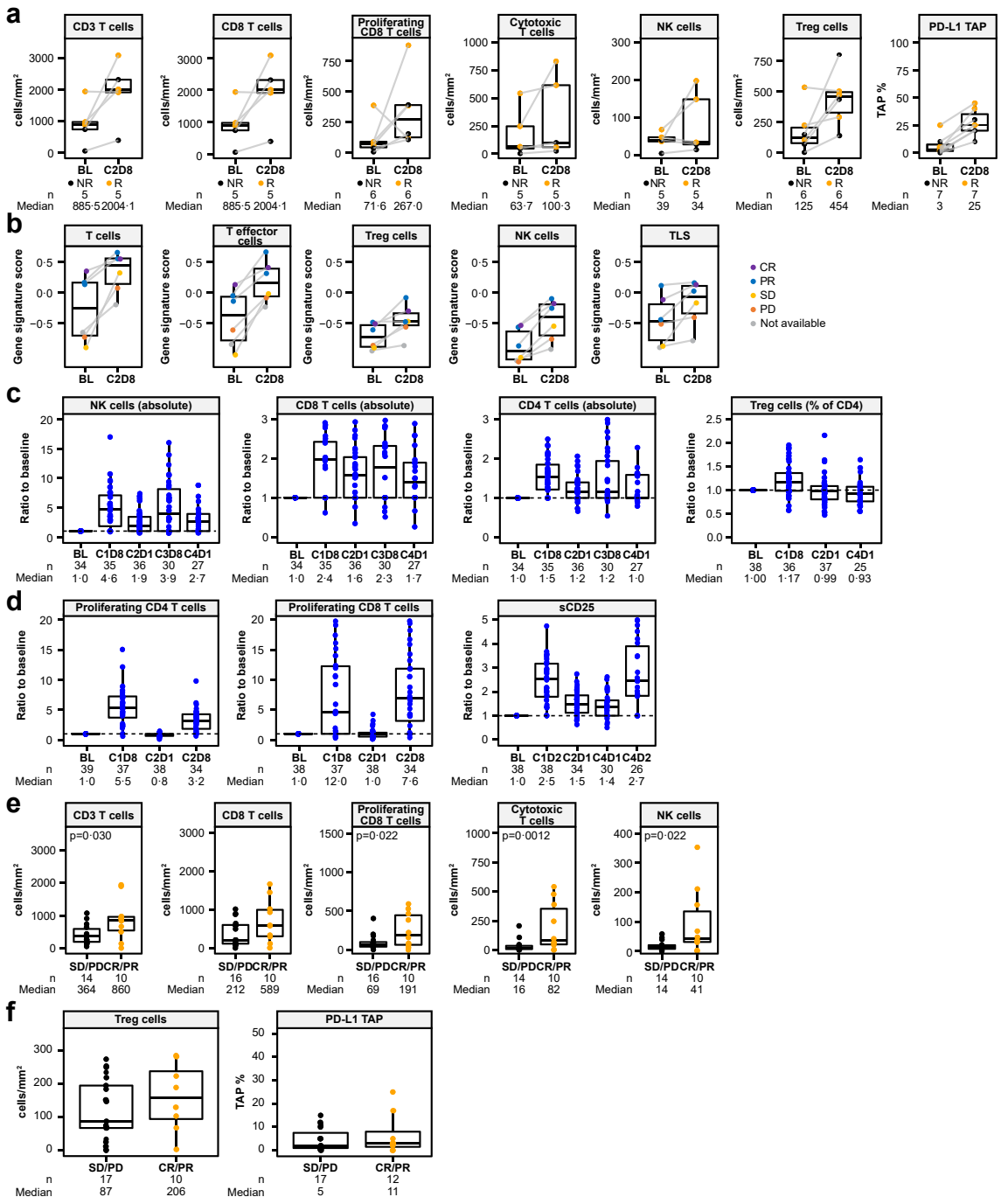

***Fig. 3*: Pharmacodynamics in tumour tissue and peripheral blood following treatment with FAP-IL2v plus atezolizumab (Q3W schedule).** (a) Immune cell infiltration of the tumour microenvironment (CD3+ and CD8+ T cells, proliferating CD8+ T cells, perforin-positive cytotoxic T and NK cells) and PD-L1 expression in immune cells, as measured by IHC in paired tumour biopsies from baseline and on-treatment (C2D8). (b) Transcriptomic changes in paired tumour biopsies from baseline and on-treatment (C2D8). Only patients with paired BL and on-treatment (C2D8) samples are shown for A and B. (c) Peripheral immune effector cell expansion (NK, CD8+, CD4+ T cells) from baseline measured by flow cytometry. (d) Immune cell activation (sCD25) and peripheral T cell proliferation (Ki67+) from baseline measured in plasma by immunoassay and flow cytometry, respectively. (e) Immune effector cell infiltration at baseline in responders (CR/PR) *vs* non-responders (SD/PD) as measured in tumour biopsies by IHC. (f) Treg tumour infiltration at baseline and PD-L1 expression (tumour and immune cells) in responders (CR/PR) *vs* non-responders (SD/PD) as measured in tumour biopsies by IHC. Drug administration: pre-dose = CxD1; 1 week/7 days post-administration = CxD8; duration of 1 cycle = 21 days. Samples from the same patient are joined by grey lines. Point colour indicates best overall response. Gene signature scores summarise the expression levels of all genes that are in a given signature. BL, baseline; C, cycle; D, day; IC, immune cell; IHC, immunohistochemistry; NR, non-responder; R, responder; TC, tumour cell.

patients with PD-L1 negative recurrent and/or metastatic CC, for whom there are a distinct lack of treatment options.

Currently, approved treatment options for patients with recurrent and/or metastatic CC are limited, with treatment still relying heavily on backbone chemotherapy regimens.[6,8] Recent approvals for advanced and/or metastatic CC are encouraging, where pembrolizumab has emerged as an effective first-line treatment and alternative to chemotherapy, although the label is limited to PD-L1-positive tumours.[9,27] Many patients will progress beyond first-line treatment and, despite recent approvals for pembrolizumab monotherapy (United States only),[9] cemiplimab (Europe only)[10] and tisotumab-vedotin (United States only)[11] in the second-line setting, treatment strategies remain scarce. Recent phase II studies evaluating balstilimab plus zalifrelimab[28] and camrelizumab plus apatinib[29] in patients with advanced cervical cancer have reported promising activity and manageable toxicity, but pivotal data are lacking. While the clinical activity observed with FAP-IL2v plus atezolizumab in the current study appears promising in the context of the abovementioned regimens, additional studies are needed to establish the role of IL-2 immune cytokines within the treatment landscape for recurrent and/or metastatic CC.

Pharmacodynamic analyses of combined FAP-IL2v and atezolizumab treatment in paired tumour biopsies demonstrated a pronounced expansion and accumulation of TILs, augmenting the expression of PD-L1, especially on infiltrating immune cells. Despite some initial signals in the association between PD-L1 expression and response in some patients, there was no clear association in the cohort overall, although it should be noted that these observations were taken from a very small sample size. Despite a lack of clear evidence to define a biomarker-enriched subgroup, peripheral B cell count was associated with prolonged PFS, supporting the emerging role of B cells as a prognostic indicator of response to PD-1 blockade in cervical SCC and an area that warrants further exploration.[30] Pharmacokinetic results were similar to historical results with FAP-IL2v.[16] Despite clear signals, there were no pre-treatment blood or tumour biomarkers that were predictive of response to treatment.

In the current study, FAP-IL2v plus atezolizumab had a manageable safety profile that was consistent with the known safety profile of each drug. No unexpected or overlapping toxicities were identified and the expected IL-2 class-specific AEs were manageable, with AEs leading to withdrawal of FAP-IL2v and/or atezolizumab reported in 6 patients (13%) only. This profile contrasts with that typically associated with the IL-2 analogue aldesleukin, which is approved the treatment of metastatic renal cell carcinoma and metastatic melanoma in the United States.[15] At effective (high) doses, aldesleukin is associated with a challenging safety profile, including the potential for severe capillary leak syndrome, neurologic toxicity, serious infections, and renal toxicity; immune-mediated adverse reactions and severe hypersensitivity reactions have also been reported.[15,31] Given this profile, patients who receive high-dose aldesleukin often require hospitalisation for close monitoring, and as such, its use is limited. Although low-dose aldesleukin is less toxic than high-dose aldesleukin, it is not as clinically active or effective, possibly because when in low abundance IL-2 binds preferentially to its high-affinity receptor expressed on Tregs.[15,31]

Strengths of the current study include the clinical hypothesis of combining an IL-2 agonist with CPI in the study population, a well-represented patient population, and a meaningful sample size for signal seeking. A limitation of the study is the absence of an atezolizumab monotherapy cohort to inform the contribution of FAP-IL2v to the observed efficacy and safety profile. Interpretation of the available data is also complicated by differences in enrolment criteria and methods used to assess PD-L1 status in the current study and in the studies of the approved and investigational agents described above, preventing meaningful cross-study comparison. Additionally, no overall survival analysis was performed due to the early discontinuation of the study and the inconsistent collection of survival data between study sites.

In conclusion, FAP-IL2v plus atezolizumab is clinically active and has manageable safety in patients with recurrent and/or metastatic cervical SCC. Although the development of FAP-IL2v has been deprioritised in all indications by the study sponsor for strategic reasons, IL-2-based immune cytokines remain a promising approach for enhancing CPI treatment. Additional research may be warranted to establish the role of IL-2 immune cytokines in the current treatment paradigm for recurrent and/or metastatic CC and other cancer types, including patients with PD-L1-negative tumours.

Contributors

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Data sharing statement

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing. Anonymised records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient re-identification.

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L. Verlingue reports grants from Bristol-Myers Squibb; royalties or licenses from RESOLVED; payment or honoraria from Bristol-Myers Squibb; leadership or fiduciary role as CEO of RESOLVED; stock or stock options from RESOLVED; as part of the Drug Development Department (DITEP) of Gustave Roussy and Early Phase Unit of Centre Léon Bérard, L. Verlingue reports being Principal/Sub-Investigator of clinical trials for AbbVie, Adaptimmune, Aduro Biotech, Agios Pharmaceuticals, Amgen, argenx, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, AVEO pharmaceuticals, Basilea Pharmaceutica, Bayer, BBB Technologies, BeiGene, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol-Myers Squibb, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Cullinan-Apollo, Daiichi Sankyo, Debiopharm, Eisai, Eli Lilly, Exelixis, Faron Pharmaceuticals, F. 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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105374.

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