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Original Research

A phase II study of monalizumab in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: The I1 cohort of the EORTC-HNCG-1559 UPSTREAM trial

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KEYWORDS
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Abstract ***Purpose:*** Monalizumab is a monoclonal antibody targeting the inhibitory natural killer group 2A (NKG2A) receptor localised on natural killer (NK) and T cells. Its ligand, the human leukocyte antigen E (HLA-E), is overexpressed in squamous cell carcinoma of the head and neck (SCCHN). By targeting the HLA-E-NKG2A pathway, monalizumab may enhance NK and T cell activity.
Experimental design: The UPSTREAM trial is a biomarker-driven umbrella trial studying targeted therapies and immunotherapies in patients with recurrent/metastatic (R/M) SCCHN progressing after platinum therapy. The immunotherapy 1 (I1) cohort was a phase II, single-arm substudy evaluating monalizumab (10 mg/kg intravenously on day 1 of a 14-day cycle). The primary end-point was the objective response (OR) rate (Response Evaluation Criteria in Solid Tumours 1.1) over the first 16 weeks. A two-stage Simon design was used (H1 15%, H0 3%, α 8%, power 90%) with pre-planned interruption of accrual if no OR was observed after the first 25 patients.
Results: Twenty-six eligible patients were enrolled. Seventeen (65%) patients had received $\geq$2 previous lines of systemic treatment, and 15 (58%) patients were PD(-L)1 inhibitor pretreated. No OR was observed. Stable disease was observed in 6 patients (23%) with a median duration of 3.8 months (95% confidence interval [CI]: 2.7–NE). The median progression-free survival and overall survival were 1.7 months (95% CI: 1.5–1.8) and 6.7 months (95% CI: 3.0–9.6), respectively. The most frequent treatment-related adverse event was grade I/II fatigue (19%).
Conclusions: Monalizumab monotherapy has limited activity in R/M SCCHN. The I1 cohort did not meet its primary objective. Monalizumab combined with durvalumab is under investigation within UPSTREAM.

1. Introduction

Squamous cell carcinoma of the head and neck (SCCHN) is the seventh most common malignancy [1]. Most patients present with locally advanced disease, but despite multimodal treatment, more than 50% will relapse [2]. Platinum-based therapy [3] and pembrolizumab [4] improve survival in first-line treatment for recurrent/metastatic (R/M) SCCHN.

The European Organisation for Research and Treatment of Cancer (EORTC) is currently conducting the UPSTREAM trial (EORTC-HNCG-1559, NCT03088059), an umbrella trial dedicated to R/M SCCHN [5]. The UPSTREAM trial enrols patients with R/M SCCHN who have progressed after platinum-based therapy. Based on potential biomarkers and molecular alterations identified in a tumour biopsy, patients are allocated to different patient cohorts, evaluating the efficacy of various targeted therapies or immunotherapies. Non-eligible patients for the biomarker-driven cohorts are included in the immunotherapy cohorts.

Immunotherapy cohort 1 (I1) was the first immunotherapy cohort of the UPSTREAM trial, evaluating the efficacy of monalizumab as monotherapy.

Monalizumab is a human immunoglobulin G4 antibody targeting the natural killer group 2A (NKG2A) receptor, an inhibitory receptor expressed on natural killer (NK) cells and CD8+ T-lymphocytes [6]. Its ligand, the human leukocyte antigen E (HLA-E), is a non-classical major histocompatibility complex molecule that creates a way for cancer cells to escape immune surveillance. HLA-E is upregulated by different cancer cells, including SCCHN [7,8]. The binding of HLA-E to NK2GA inhibits the cytotoxic functions of CD8+ T lymphocytes and NK cells. Monalizumab, by targeting NK2GA, can restore the function of both T-cells and NK cells. A phase I/II non-randomised trial showed promising data for the combination of monalizumab and cetuximab in patients with R/M SCCHN previously treated with platinum-based chemotherapy [9]. However, there are no data of single-agent monalizumab in SCCHN. In this study, we present the results of the I1 cohort, a phase II, single-arm, proof-of-concept study evaluating monalizumab monotherapy in R/M SCCHN.

2. Methods

2.1. Patient eligibility

The UPSTREAM study design has been previously described [5]. UPSTREAM includes patients with histologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx or larynx not amenable to curative treatment who progress after platinum-based therapy, given as palliative treatment or as a part of multimodal curative treatment with progression within one year from the end of treatment. Previous treatment with PD-(L)1 inhibitors is allowed. The disease must be amenable to a core biopsy as a fresh biopsy of the disease is mandatory for trial entry. The study is approved by ethics committee and by the health authorities of each participating country and conducted in accordance with the Declaration of Helsinki (October 2000). Written informed consent is obtained for each patient twice: first at the screening phase (fresh tumour biopsy) and then again at the time of treatment allocation.

Patients enrolled in UPSTREAM were allocated to the I1 cohort if they met all the general inclusion criteria but were not eligible for one of the biomarker-driven cohorts defined as (i) the absence of predefined biomarkers for one of the biomarker-driven cohorts open during I1 recruitment as shown in the Supplementary Fig. 1, (ii) failure of the biopsy to pass molecular testing quality control in the central laboratory and (iii) allocation to one biomarker-driven cohort but with an exclusion criterion for the same cohort, or the specified cohort was closed for accrual at the time of inclusion. The main cohort-specific exclusion criteria for the I1 cohort included systemic treatment with steroids or other immunosuppressive agents and active autoimmune disease/inflammatory disorder.

The list of biomarkers performed for UPSTREAM has been previously published [5] and is detailed in the Supplementary Tables 1–3 with the information available for each patient. The tumour mutation burden was not part of our panel.

2.2. Study objectives and end-points

The primary objective of the I1 cohort was to assess the efficacy of monalizumab monotherapy in R/M SCCHN and previously pretreated with platinum-based therapy. The primary end-point was objective response rate (ORR) over the first 16 weeks of study treatment, defined as the proportion of patients who met the criteria for complete response or partial response as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 [10]. The secondary end-points were response duration, progression-free survival (PFS), overall survival (OS), ORR as per the use of modified RECIST in cancer immunotherapy trials (iRECIST) [11] and toxicity evaluated with the Common Terminology Criteria for Adverse events v4.03.

2.3. Study design

The I1 cohort was a single-arm substudy. Monalizumab was administered as an intravenous infusion at a dose of 10 mg per kilogramme over 60 min on day 1 of each 14-day cycle. No dose reductions were allowed. Disease evaluation was performed every 8 weeks. In the event of disease progression as per RECIST 1.1 and following iRECIST guidelines [11], continuation of treatment with monalizumab was permitted for patients who were clinically stable until the next imaging assessment, performed at least four weeks but not more than eight weeks after the date of the initial documented progression.

2.4. Statistical methods

A two-stage Simon minimax design was used with 90% power to reject the null hypothesis of ORR = 3% under the alternative hypothesis of ORR = 15%, with a one-sided type 1 error of 8%. The total sample size required was calculated at 34 patients evaluable for the primary end-point with a planned interruption of accrual at the interim analysis if no response was seen after the first 25 patients. The study would have been declared successful if at least three patients of the 34 evaluable patients responded to treatment as per RECIST 1.1 during the first 16 weeks of treatment.

3. Results

3.1. Patient characteristics

Between November 2017 and August 2018, 72 patients were enrolled in the UPSTREAM trial, of which 24 were allocated in a biomarker-driven cohort and 27 in the I1 cohort. The 27 patients of the I1 cohort were enrolled at 14 centres in three European countries (Belgium, France and Italy). The consort diagram of the trial is depicted in Fig. 1. The median follow-up was 23.5 months (quartiles Q1–Q3: 23.1–23.9). Twenty-six patients (25 men and 1 woman) were eligible, and their baseline characteristics are described in Table 1. One patient was not eligible as he was not previously pretreated with platinum-based therapy. Nineteen patients (73%) had an Eastern Cooperative Oncology Group performance status of 1. In total, 15 patients (58%) had been previously exposed to PD-(L)1 inhibitors. The reasons for allocation to the I1 cohort were the absence of any of the predefined biomarkers in 14 (52%) patients, failure of the biopsy to pass quality control in 11 (44%) patients and the presence of exclusion criteria for the assigned biomarker-driven cohort in 1 (4%) patient.

Of the 72 patients enrolled in UPSTREAM up to August 2018, the rate of biopsy that did not pass the quality control was 29%. For the patients enrolled in a cohort, the median number of days between tissue sampling and biomarker results and between biomarker results and treatment start was 14 and 8 days, respectively, leading to a median number of 21 days (range: 14–36) between tissue sampling and treatment start.

3.2. Efficacy

Among the 26 eligible patients, no objective response was observed (0%, exact 95% confidence interval [CI]: 0–13.2%) (Table 2). The study did not meet the criteria for success as defined in the study protocol, and accrual was closed after the first stage. The best responses were stable disease (SD) and progressive disease (PD) in six (23%, exact 95% CI: 9.0–43.7%) and 20 (77%, exact 95% CI: 56.4–91.0%) patients, respectively. The median duration of SD was 3.8 months (95% CI: 2.7–NE). One patient with SD died of tumour bleeding 9.6 months after the start of monalizumab without disease progression.

No radiological assessment could be performed in five patients because of early death or clinical progression. All these patients were considered to have PD. Fig. 2 shows the waterfall and spider plots of the best change from the baseline in the sum of the diameters of the target lesions during the first 16 weeks of treatment according to investigators for 21 of the 26 evaluable patients. Tumour shrinkage of the target lesions was observed in one patient. No response was seen using iRECIST criteria. The best response over the first 16 weeks of treatment was stable disease (iSD) in 6 patients, unconfirmed progression (iUPD) in 14 patients and confirmed progression (iCPD) in 1 patient. For the vast majority, these iUPD were not confirmed because treatment was discontinued afterwards and no subsequent measurements were carried out.

All but one patient had disease progression during the follow-up. The median PFS was 1.7 months (95% CI: 1.5–1.8 months) (Fig. 3a). Twenty-four deaths (92%) were reported. The median OS was 6.7 months (95% CI: 3.0–9.6 months) (Fig. 3b), with an OS rate at six and 12 months of 53.8% (95% CI: 33.3–70.6%) and 19.2% (95% CI: 7.0–36.0%), respectively. Fifteen patients were exposed to PD-(L)1 inhibitors before monalizumab. An unplanned exploratory analysis of OS in accordance with prior PD-(L)1 inhibitor exposure showed a median OS of 8.0 months (95% CI: 2.3–10.5 months) in patients who had received PD-(L)1 inhibitors ($n = 15$). In patients who were PD-(L)1 inhibitor naïve ($n = 11$), the median OS was 4.7 months (95% CI: 2.1–11.3 months) (Fig. 3c).

3.3. Safety

In total, 11 patients of the 27 patients who were administered with monalizumab (41%) experienced a treatment-related AE. The most frequent grade I/II treatment-related AEs (TRAEs) were fatigue in five patients (19%) and diarrhoea, anaemia and myalgia in two patients each (7%) (Supplementary Table 4). Only one patient presented with a grade III TRAE, heart failure that was judged possibly related to monalizumab according to the investigator and led to treatment discontinuation.

3.4. Pharmacokinetics and immunogenicity (Supplementary data)

Pharmacokinetics were in line with previous monalizumab clinical trials [12,13]. The monalizumab anti-drug antibody detection performed in this cohort suggests that monalizumab has low immunogenicity.

4. Discussion

The I1 cohort is the first immunotherapy cohort of the UPSTREAM trial and the first cohort of this umbrella trial to report results on. This substudy failed to meet its primary objective because no response was seen. Disease stabilisation was observed in six patients (23%) with a median duration of 3.8 months (95% CI: 2.7–NE). The median PFS was 1.7 months and the median OS was 6.7 months in the overall population. These survival data appear similar to the median PFS (around 2 months) and OS (around 7 months) observed with single-agent

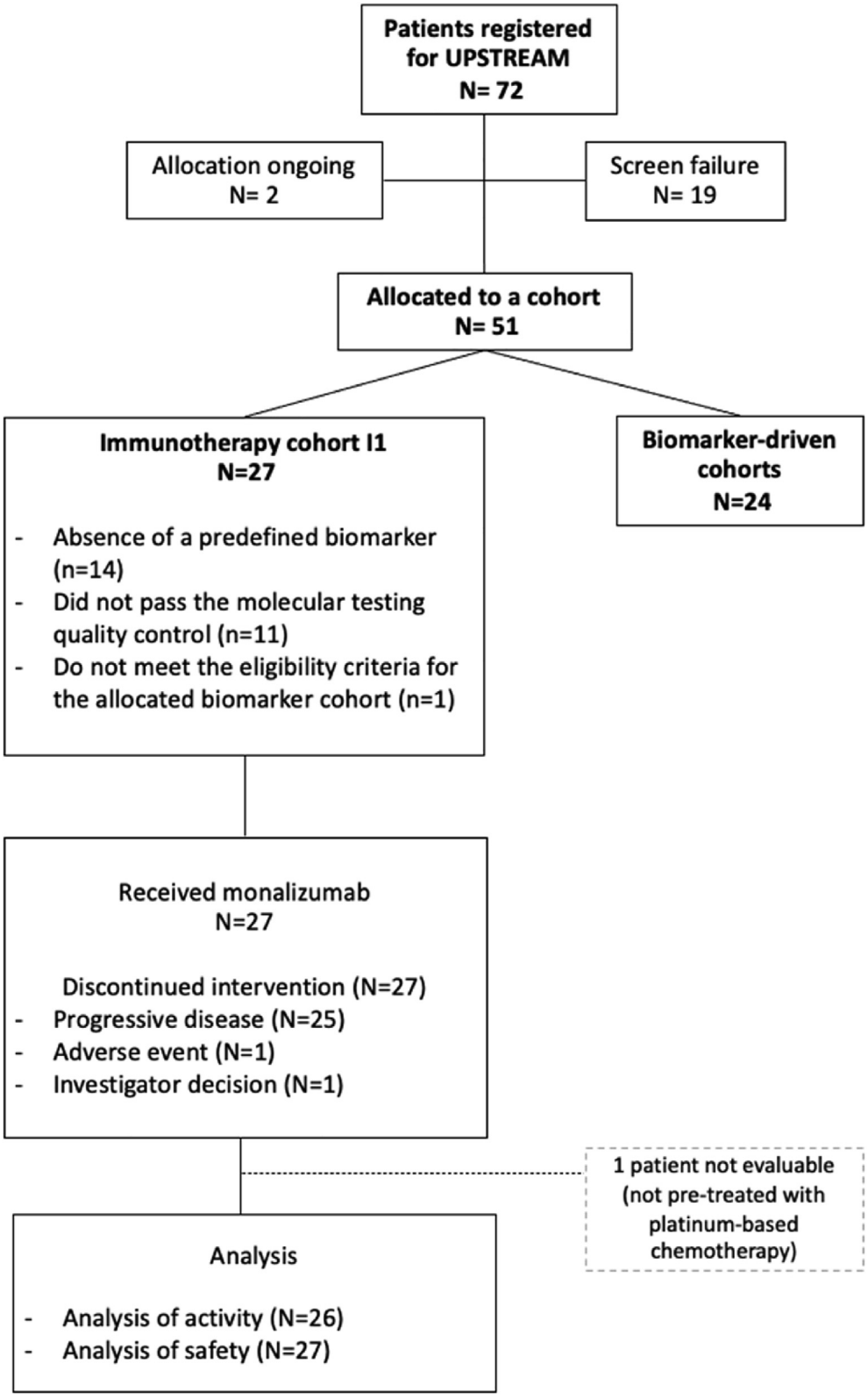

Fig. 1. Consort diagram of the trial.

PD-(L1) inhibitors in second-line treatment after platinum-based therapy [14,15]. Data of monalizumab monotherapy are available for gynaecological cancers, also showing no response but short-interval disease stabilisation [13]. Monalizumab monotherapy was safe as mainly grade I/II treatment-related adverse events were recorded. Of note, one heart failure possibly related to monalizumab was reported in one patient

Table 1
Patient characteristics of the eligible patients.

Baseline characteristics (n = 26)		
Median age—years (range)	62 (44–76)	
Male, n (%)	25 (96%)	
ECOG PS, n (%)		
0	7	(27%)
1	19	(73%)
Primary site, n (%)		
Oral cavity	7	(27%)
Oropharynx	10	(38%)
p16 negative	6	
p16 positive	3	
Unknown	1	
Hypopharynx	7	(27%)
Larynx	2	(8%)
Type of recurrence		
Locoregional recurrence only	8	(31%)
Distant recurrence with or without locoregional recurrence	18	(69%)
Prior lines of systemic treatment in the R/M setting		
Number of previous lines, median (range)	2	(0–4)
≤ 1 line	9	
2 lines	6	
≥ 3 lines	11	
Prior platinum-based therapy, n (%)	26	(100%)
Prior cetuximab, n (%)	23	(89%)
PD-(L)1 inhibitor exposure	16	(62%)
Pre-study PD-(L)1 inhibitors, n (%)	15	(58%)
Post-study PD-(L)1 inhibitors, n (%)	1	(4%)
Reasons for exclusion in biomarker-driven cohorts		
Absence of one of the pre-defined biomarkers	14	(52%)
Biopsy that did not pass molecular testing quality control	11	(44%)
Other (do not meet the eligibility criteria for the allocated biomarker cohort)	1	(4%)

ECOG PS, Eastern Cooperative Oncology Group performance status; R/M, recurrent/metastatic.

with smoking and ethylism habits and history of intermittent left bundle branch block and AV-nodal reentrant tachycardia. No other heart failure has been seen in other clinical trials with monalizumab [9,13].

Table 2
Best response as per RECIST 1.1 over the first 16 weeks of treatment.

Response (RECIST v1.1) (n = 26)	
Best response during the first 16 weeks of treatment, n (%)	
Complete/partial response	0 (0%) (exact 95% CI: 0–13.2%)
Stable disease	6 (23%) (exact 95% CI: 9.0–43.7%)
Progressive disease	20 (77%) (exact 95% CI: 56.4–91.0%)
Duration of disease stabilisation (months), median[a]	3.8 (95% CI: 2.7–NE)

RECIST, Response Evaluation Criteria in Solid Tumours; CI, confidence interval.
[a] Estimated using the Kaplan-Meier technique.

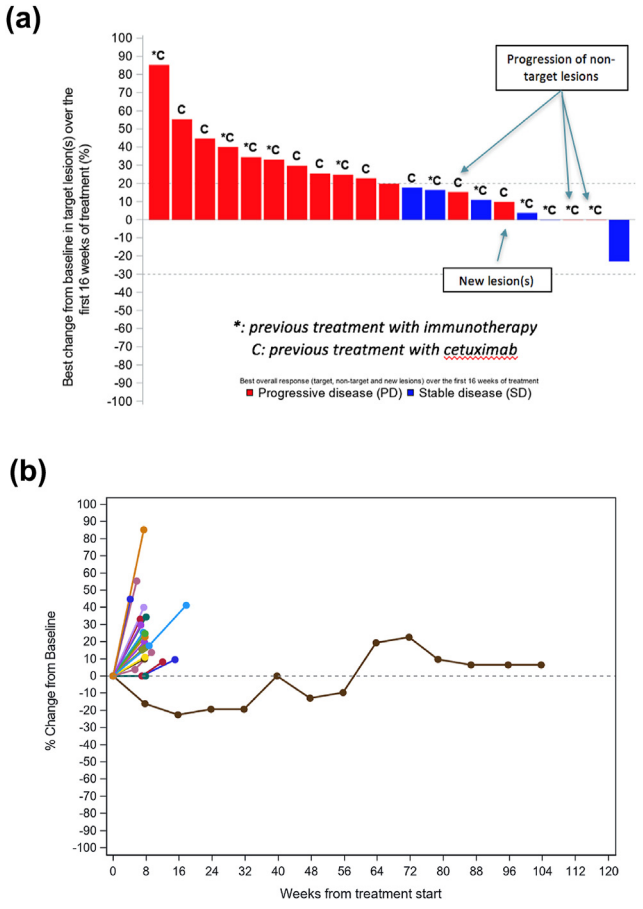

Fig. 2. **The waterfall plot (a) and spider plot (b) of tumour shrinkage in accordance with investigator assessments**. (a) The best change from the baseline in the sum of the diameters of the target lesions as per RECIST 1.1 during the first 16 weeks of treatment is shown (%) for the 21 patients evaluable for this analysis. Patients with progressive disease are indicated in red, and patients with stable disease (SD), in blue. * = patients pretreated with PD-(L)1 inhibitors; C = patients pretreated with cetuximab. RECIST, Response Evaluation Criteria in Solid Tumours. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

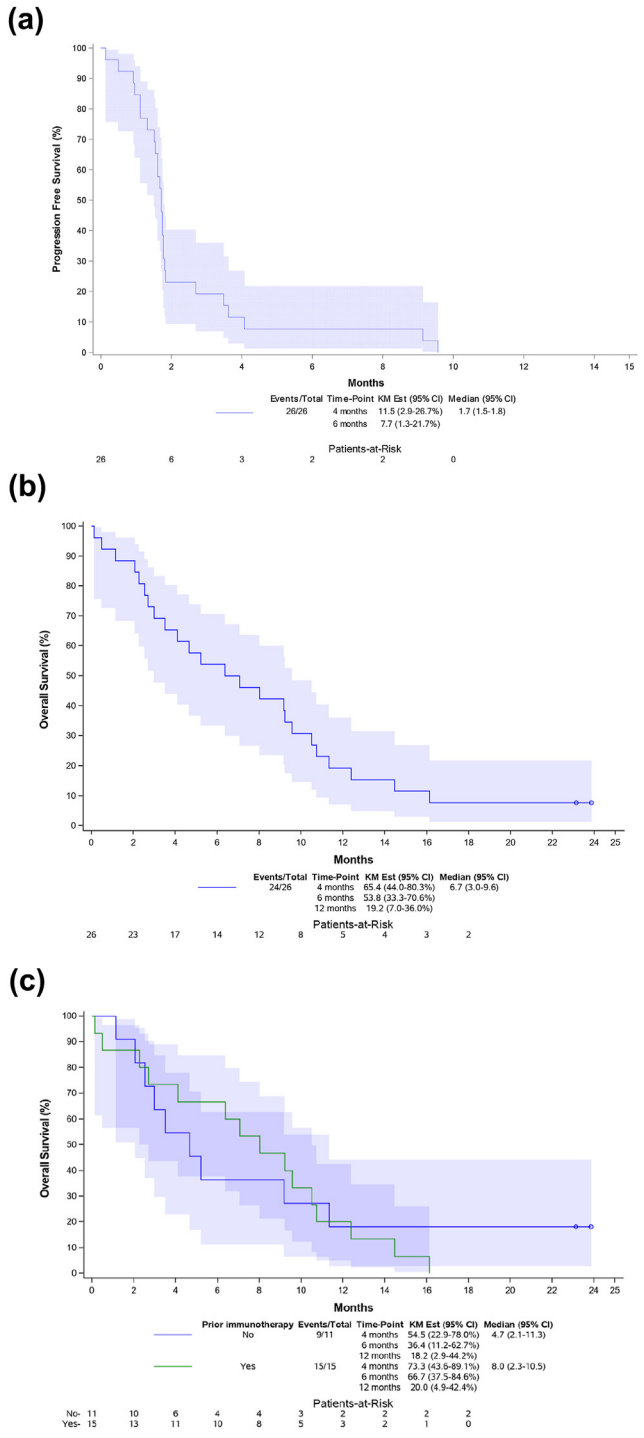

Fig. 3. **Kaplan-Meier estimates of progression-free survival (a) and survival (b) for all eligible patients (n = 26). Kaplan-Meier estimates of overall survival in accordance with previous PD-(L)1 inhibitor exposure (c)**. Green curve = patients previously exposed to PD-(L)1 inhibitors (n = 15). Blue curve = PD-(L)1 inhibitor naïve patients (n = 11). CI, confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The I1 cohort included a heavily pretreated population as 65% of the patients had received two or more previous lines of systemic treatment in the R/M setting. Importantly, the I1 cohort was initiated before PD(L)1 inhibitors were available in all participating countries. Therefore, only 16 patients were treated with PD(L)1 inhibitors, mostly after platinum therapy. Nowadays, practice has changed, and pembrolizumab is the new standard of care as first-line therapy for PD-L1 expressing R/M SCCHN. On the other hand, given the fresh biopsy mandatory for study entry, the time frame (median 14 days) needed for the biopsy results to come back could have select patients in good condition with less rapidly progressing disease. A potential confounding factor is the fact that only those patients who were not eligible for one of the biomarker-driven cohorts were included in the I1 cohort. However, 48% of the I1 cohort's patients were allocated to I1 because of inadequate biopsy quality. These patients could thus potentially also harbour some of the predefined biomarkers, making them similar to the rest of the UPSTREAM population. In UPSTREAM, the rate of the biopsies that did not pass the quality control was 29% and is similar to other biomarker-driven studies [16–20].

Monalizumab has been investigated in combination with cetuximab in patients with R/M SCCHN who progressed after platinum therapy (anti-PD(L)1 naïve or pretreated) and after two or fewer prior lines of therapy [9]. This single-arm trial showed an ORR of 27% and a median OS of 8.3 months. A second expansion cohort of that same study reported a response rate of 20% in patients previously treated with both prior platinum-based chemotherapy and PD-(L)1 inhibitors, including immunotherapy-resistant patients [21]. These results compare favourably with cetuximab monotherapy after platinum therapy [22] (ORR: 13% and median OS: 5.8 months), suggesting that monalizumab could have some level of activity in combination with cetuximab.

We performed an exploratory analysis of OS in accordance with PD-(L)1 inhibitor exposure. Patients previously exposed to PD-(L)1 inhibitors had a median OS of 8.0 months (95% CI: 2.3–10.5 months), whereas for PD-(L)1 inhibitor–naïve patients, the median OS was 4.7 months (95% CI: 2.1–11.3 months). Interestingly, this finding was also reported in the trial that investigated the combination of monalizumab and cetuximab in R/M SCCHN where the OS of IO-pretreated patients was 12.8 months versus 7.8 months in IO-naïve patients [9].

Although patient numbers are low, CIs are wide, indicating low precision of the estimates, and it is not a pre-planned analysis; the observed median survival of PD-(L)1 inhibitor–exposed patients in the two monalizumab SCCHN trials is worth to be discussed. Several hypotheses could explain these results: (i) the biased population entering the study which may have included a favourable group of patients because the patients treated with PD(L)1 inhibitors had received fewer previous lines of systemic treatment than the patients not

exposed to PD(L)1 inhibitors (data not shown), (ii) potential synergism between monalizumab and PD-(L)1 inhibitors, particularly if we consider that the biological activity of PD-(L)1 inhibitors could still be present at the time we initiated monalizumab (15 patients had received prior PD-(L)1 inhibitors, for which it was the last systemic treatment in 8 patients), (iii) or, in contrast, slower disease progression due to the activity of PD-(L)1 inhibitors alone (iv) or better activity of subsequent treatment. Preclinical data show that NKG2A is often co-expressed with PD-1 on CD8+ T cells [6]. As PD-1 is a marker of exhausted T cells [23], this might suggest that targeting NKG2A could reverse T-cell exhaustion. Moreover, it has been shown that HLA-E is more frequently expressed than PD-L1 in several cancer types and may potentially be responsible for the lack of response to PD-(L)1 inhibitors in some cancers [6]. Targeting the NKG2A-HLA-E pathway in combination with PD-1/PD-L1 blockade also improved tumour control in mice [6]. Finally, preliminary efficacy data have shown encouraging activity in patients with heavily pretreated microsatellite stable colorectal cancer when monalizumab was combined with durvalumab, a PD-L1 inhibitor [24]. These data support the investigation of monalizumab in combination with PD-1/PD-L1 inhibitors in randomised trials. Therefore, we have opened a second immunotherapy cohort (I2) in UPSTREAM that is currently randomising patients between monalizumab combined with durvalumab or the best choice of the investigators.

Possible biomarkers predictive of response to monalizumab could include HLA-E expression. However, in a previous trial studying the combination of monalizumab and cetuximab, HLA-E was observed in all analysed tumour samples and was not predictive of response in that cohort [12]. The limited number of patients with a biopsy of good quality in our cohort precluded further biomarker analysis. The PD-L1 status of our patients was also unknown because it was not part of the standard management at the time of this study.

In conclusion, this report demonstrates the feasibility of UPSTREAM, an umbrella trial dedicated to SCCHN. Single-agent monalizumab has limited activity in R/M SCCHN. Monalizumab continues to be investigated in combination with durvalumab within the EORTC UPSTREAM trial and with the cetuximab ± PD(L)1 inhibitor in another phase II trial (NCT02643550). A randomised phase III trial study will compare cetuximab with or without monalizumab in patients with R/M SCC (NCT04590963).

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Author contributions

Rachel Galot: Conceptualisation, Methodology, Investigation, Writing – original Draft, Writing – Review & Editing; **Christophe Le Tourneau:** Methodology, Investigation, Writing – Review & Editing; **Esma Saada-Bouzid:** Investigation, Writing – Review & Editing; **Amaury Daste:** Investigation, Writing – Review & Editing; **Caroline Even:** Investigation, Writing – Review & Editing; **Philip Debruyne:** Investigation, Writing – Review & Editing; **Stéphanie Henry:** Investigation, Writing – Review & Editing; **Sylvie Zanetta:** Investigation, Writing – Review & Editing; **Anemie Rutten:** Investigation, Writing – Review & Editing; **Lisa Licitra:** Methodology, Investigation, Writing – Review & Editing; **Jean-Luc Canon:** Investigation, Writing – Review & Editing; **Marie-Christine Kaminsky:** Investigation, Writing – Review & Editing; **Pol Specenier:** Investigation, Writing – Review & Editing; **Sylvie Rottey:** Investigation, Writing – Review & Editing; **Joël Guigay:** Methodology, Investigation, Writing – Review & Editing; **Anthony Kong:** Methodology, Investigation, Writing – Review & Editing; **Inge Tinhofer:** Methodology, Writing – Review & Editing; **Edith Borcoman:** Investigation, Writing – Review & Editing; **Lieve Dirix:** Project administration, Writing – Review & Editing; **Tiana Raveloarivahy:** Software, Data Curation, Writing – Review & Editing; **Catherine Fortpied:** Methodology, Formal analysis, Writing – Review & Editing; **Maureen Vanlancker:** Data Curation, Writing – Review & Editing; **Marie Morfouace:** Methodology, Data Curation, Writing – Review & Editing; **Anne-Sophie Govaerts:** Methodology, Data Curation, Writing – Review & Editing; **Jean-Pascal Machiels:** Conceptualisation, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: R.G. declares a role in an advisory board without compensation for Innate Pharma and travelling compensation from Amgen and Astellas. E.S-B. has received consulting fees for advisory boards and travelling from BMS and MSD. A.D. has received consulting fees or honorarium from MSD, BMS and Merck and accommodation and travelling expenses for meetings from BMS, Merck and AstraZeneca. C.E. has received consulting fees for advisory boards for BMS, MSD, Innate Pharma and Merck Serono. S.H. declares a consulting or advisory role for AstraZeneca, Merck, Novartis, MSD Oncology, BMS and Sanofi and travelling expenses for meetings from Roche and MSD Oncology. A.K. received fees for consulting, advisory, speaker's

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.09.003.

References

[1] http://globocan.iarc.fr.
[2] Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92(1):4–14. https://doi.org/10.1016/j.radonc.2009.04.014.
[3] Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359(11):1116–27. https://doi.org/10.1056/NEJMoa0802656.
[4] Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro Jr G, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019;394(10212):1915–28. https://doi.org/10.1016/S0140-6736(19)32591-7.
[5] Galot R, Le Tourneau C, Guigay J, Licitra L, Tinhofer I, Kong A, et al. Personalized biomarker-based treatment strategy for patients with squamous cell carcinoma of the head and neck: EORTC position and approach. Ann Oncol 2018;29(12):2313–27. https://doi.org/10.1093/annonc/mdy452.
[6] Andre P, Denis C, Soulas C, Bourbon-Caillet C, Lopez J, Arnoux T, et al. Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells. Cell 2018;175(7). https://doi.org/10.1016/j.cell.2018.10.014. 1731–1743.e13.
[7] Silva TG, Crispim JC, Miranda FA, Hassumi MK, de Mello JM, Simoes RT, et al. Expression of the nonclassical HLA-G and HLA-E molecules in laryngeal lesions as biomarkers of tumor invasiveness. Histol Histopathol 2011;26(12):1487–97. https://doi.org/10.14670/HH-26.1487.
[8] Nasman A, Andersson E, Nordfors C, Grun N, Johansson H, Munck-Wikland E, et al. MHC class I expression in HPV positive and negative tonsillar squamous cell carcinoma in correlation to clinical outcome. Int J Canc 2013;132(1):72–81. https://doi.org/10.1002/ijc.27635.
[9] Cohen RB, Lefebvre G, Posner MR, Bauman JR, Salas S, Even C, et al. Monalizumab in combination with cetuximab in patients (pts) with recurrent or metastatic (R/M) head and neck cancer (SCCHN) previously treated or not with PD-(L)1 inhibitors (IO): 1-year survival data. Ann Oncol 2019;30(suppl_5):v449–74. https://doi.org/10.1093/annonc/mdz252.026.
[10] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Canc 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.
[11] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18(3):e143–52. https://doi.org/10.1016/S1470-2045(17)30074-8.
[12] Cohen. Monalizumab in combination with cetuximab in R/M SCCHN: clinical results and preliminary biomarker analyses. SITC 2018; 2018.
[13] Tinker AV, Hirte HW, Provencher D, Butler M, Ritter H, Tu D, et al. Dose-ranging and cohort-expansion study of monalizumab (IPH2201) in patients with advanced gynecologic malignancies: a trial of the Canadian cancer trials group (CCTG): IND221. Clin Canc Res 2019;25(20):6052–60. https://doi.org/10.1158/1078-0432.CCR-19-0298.
[14] Ferris RL, Blumenschein Jr G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375(19):1856–67. https://doi.org/10.1056/NEJMoa1602252.
[15] Zandberg DP, Algazi AP, Jimeno A, Good JS, Fayette J, Bouganim N, et al. Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: results from a single-arm, phase II study in patients with >/=25% tumour cell PD-L1 expression who have progressed on platinum-based chemotherapy. Eur J Canc 2019;107:142–52. https://doi.org/10.1016/j.ejca.2018.11.015.
[16] Le Tourneau C, Delord JP, Goncalves A, Gavoille C, Dubot C, Isambert N, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 2015;16(13):1324–34. https://doi.org/10.1016/S1470-2045(15)00188-6.
[17] Rodon J, Soria JC, Berger R, Miller WH, Rubin E, Kugel A, et al. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. Nat Med 2019;25(5):751–8. https://doi.org/10.1038/s41591-019-0424-4.
[18] Middleton G, Popat S, Fletcher P, Summers Y, Greystoke A, Gilligan D, et al. National Lung Matrix Trial (NLMT) First results from an umbrella Phase II trial in advanced non-small cell lung cancer (NSCLC). JTO 2019;14(10):S7. Supplement.
[19] Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. JAMA 2014;311(19):1998–2006. https://doi.org/10.1001/jama.2014.3741.
[20] Meric-Bernstam F, Brusco L, Shaw K, Horombe C, Kopetz S, Davies MA, et al. Feasibility of large-scale genomic testing to facilitate enrollment onto genomically matched clinical trials. J Clin Oncol 2015;33(25):2753–62. https://doi.org/10.1200/JCO.2014.60.4165.
[21] Cohen RBBJ, Salas S, Colevas D, Even C, Cupissol D, Posner M, et al. Combination of monalizumab and cetuximab in recurrent or metastatic head and neck cancer patients previously treated with

platinum-based chemotherapy and PD-(L)1 inhibitors. J Clin Oncol 2020;38(15_suppl). https://doi.org/10.1200/JCO.2020.38.15_suppl.6516. 6516–6516.

[22] Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25(16):2171–7. https://doi.org/10.1200/JCO.2006.06.7447.

[23] Hashimoto M, Kamphorst AO, Im SJ, Kissick HT, Pillai RN, Ramalingam SS, et al. CD8 T cell exhaustion in chronic infection and cancer: opportunities for interventions. Annu Rev Med 2018;69:301–18. https://doi.org/10.1146/annurev-med-012017-043208.

[24] Segal NHNJ, Curigliano G, Patel S, Sahebjam S, Papadopoulos KP, Gordon MS, et al. First-in-human dose escalation of monalizumab plus durvalumab, with expansion in patients with metastatic microsatellite-stable colorectal cancer. J Clin Oncol 2018;36(15_suppl). https://doi.org/10.1200/JCO.2018.36.15_suppl.3540. 3540-3540.