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ORIGINAL ARTICLE

A phase II study of monalizumab and durvalumab in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: results of the I2 cohort of the EORTC-HNCG-1559 trial (UPSTREAM)

R. Galot[1]*, C. Le Tourneau[2,3,4], L. Licitra[5,6], J. Guigay[7], A. Kong[8], I. Tinhofer[9], C. Even[10], A. Daste[11], S. Henry[12], C. Borel[13], C. Abdeddaim[14], E. Seront[1], J. B. Prevost[15], A. Rutten[16], E. Saada-Bouzid[7], F. Rolland[17], P. Bonomo[18], M. Rasschaert[19], L. Dirix[20], C. Olungu[20], K. Tsechilidou[20], A. S. Govaerts[20], C. Fortpied[20], A. Joaquim[20] & J. P. Machiels[1]

[1]Service d'Oncologie Médicale and Institut de Recherche Clinique et Expérimentale, Université catholique de Louvain (UCLouvain), Brussels, Belgium; [2]Department of Drug Development and Innovation, Institut Curie, Paris & Saint-Cloud; [3]INSERM U900 Research Unit, Saint-Cloud; [4]Université de Paris-Saclay, Paris, France; [5]Head and Neck Cancer Medical Oncology Department, Fondazione IRCCS "Istituto Nazionale dei Tumori, Milan; [6]Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy; [7]Department of Medical Oncology, Centre Antoine Lacassagne, Nice cedex 2, France; [8]Head and Neck Oncology, Comprehensive Cancer Centre, King's College London, Guy's Campus, New Hunt's House, London, UK; [9]Department of Radiooncology and Radiotherapy, Charite — Universitaetsmedizin Berlin — Campus Mitte, Berlin, Germany; [10]Head and Neck Department, Gustave Roussy, Villejuif; [11]Département d'Oncologie Médicale, Hôpital Saint André, CHU de Bordeaux, Bordeaux Cedex, France; [12]Département d'Oncologie Médicale, Université catholique de Louvain, CHU UCL Namur, Site Ste Elisabeth, Namur, Belgium; [13]Institut de cancérologie Strasbourg Europe, Strasbourg; [14]Cancérologie, Centre Oscar Lambret, Lille; [15]Department of Oncology, Centre Pierre Curie, Beuvry, France; [16]Medische Oncologie, GZA Hospitals, Antwerp, Belgium; [17]Cancérologie, Institut de Cancérologie de l'Ouest, Saint-Herbain, France; [18]Radiation Oncology Unit, Azienda Ospedaliero Universitaria Careggi, University of Florence, Florence, Italy; [19]Medische Oncologie, Universitair ziekenhuis Antwerpen, Edegem; [20]European Organisation of Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium

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Background: Monalizumab (M), targeting the natural killer group 2A (NKG2A) receptor, has limited activity as monotherapy in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). Preliminary data of M and durvalumab (D) have shown encouraging activity in other tumor types.

Patients and methods: The UPSTREAM trial was an umbrella trial of targeted therapies and immunotherapy for R/M SCCHN. The immunotherapy 2 (I2) cohort was a phase II, randomized, open-label substudy evaluating the efficacy of D + M versus physician's choice (control). Patients non-eligible for the biomarker-driven cohorts and pretreated with PD(L)1, were included in the I2 cohort. The primary endpoint was the objective response rate (RECIST version 1.1) during the first 16 weeks.

Results: Sixty-six patients with R/M SCCHN were included in the I2 cohort, of whom 60 were assessable (D + M: $n = 42$, control: $n = 18$): median age 62 years; 87% with two or three previous lines of treatment. In the D + M arm, one partial response (PR) was recorded, and stable disease (SD) was observed in 11 (26%). One PR was reported in the control arm and SD in 8 (44%). The median progression-free survival (PFS) was 2.0 and 3.1 months in the D + M arm and control arm, respectively. The median overall survival (OS) was 4.3 months (95% confidence interval 3.3-8.9 months) and 8.0 months (95% confidence interval 3.1-14.9 months) in the D + M and control arms, respectively. In the D + M arm, 4 (9%) patients reported grade $\geq$3 treatment-related adverse events.

Conclusion: The I2 substudy failed to demonstrate an activity of D + M in heavily pretreated patients with SCCHN previously exposed to anti-PD(L)1. No benefit was seen in PFS and OS.

Key words: squamous cell carcinoma of the head and neck, immunotherapy, UPSTREAM, monalizumab, I2

INTRODUCTION

Squamous cell carcinoma of the head and neck (SCCHN) is the seventh most common malignancy, affecting ~700 000 patients per year worldwide.[1] Most patients present with locally advanced disease, but despite multimodal treatment with surgery and/or (chemo)radiation, >50% will relapse.[2] Most relapses are unfortunately not curable with a

*Correspondence to: Prof. Rachel Galot, Service d'Oncologie Médicale, Institut Roi Albert II, Cliniques universitaires Saint-Luc and Institut de Recherche Clinique et Expérimentale, Université catholique de Louvain (UCLouvain), Avenue Hippocrate 10, 1200 Brussels, Belgium. Tel: +32-27645106
E-mail: rachel.galot@uclouvain.be (R. Galot).

median survival ranging between 10 and 17 months.[3,4] Incurable SCCHN is treated with palliative systemic treatment. Platinum-based therapy[5] and pembrolizumab[3] improve survival in first line for patients with recurrent/metastatic (R/M) SCCHN. Pembrolizumab monotherapy, as a first-line treatment, improves overall survival (OS) in patients whose tumors express programmed death-ligand 1 (PD-L1) with a combined positive score (CPS) $\geq$1. Similarly, pembrolizumab in combination with platinum-based therapy increases OS in the R/M first line, regardless of PD-L1 status. The median OS with programmed cell death protein 1 (PD-1) or PD-L1 inhibitors administered after platinum therapy ranges between 7.1 and 8.4 months.[6-8] There is no standard of care for patients who progress after platinum and PD-1 inhibitors, and patients have a dismal prognosis.

Although pembrolizumab and nivolumab are approved in SCCHN, a significant number of patients do not respond to PD-(L)1 inhibitors, and most patients will progress. As the molecular landscape of SCCHN harbors potentially actionable targets that could open the door to new treatment opportunities,[9] there is clearly a rationale to investigate new treatment strategies, including targeted therapies and immunotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) has conducted the UPSTREAM trial (EORTC-HNCG-1559, NCT03088059), an umbrella trial dedicated to R/M SCCHN.[10] The UPSTREAM trial has finished recruitment and has enrolled >400 patients with R/M SCCHN who have progressed after platinum-based therapy. Based on potential biomarkers and molecular alterations identified in a new tumor biopsy taken for the purpose of the trial, patients were allocated to different patient cohorts, which evaluated the efficacy of various targeted therapies or immunotherapies. Five biomarker-driven cohorts (B) were conducted: cohort B1 investigated afatinib in p16-negative SCCHN with epidermal growth factor receptor (EGFR) amplification or mutation and/or human epidermal growth factor receptor 2 (HER2) amplification or mutation and/or high expression of PTEN; cohort B2 investigated afatinib in cetuximab-naïve p16-negative SCCHN; cohort B3 investigated palbociclib in p16-negative SCCHN with CCND1 amplification; cohort B4 investigated niraparib in platinum-sensitive p16-negative SCCHN; and cohort B5 investigated niraparib in p16-positive oropharyngeal carcinoma. Non-eligible patients for the biomarker-driven cohorts were included in the immunotherapy cohorts.

Monalizumab (M) is a human immunoglobulin G4 (IgG4) antibody targeting the natural killer group 2A (NKG2A) receptor, an inhibitory receptor expressed on natural killer (NK) cells and CD8 +T-lymphocytes.[11] Its ligand, the human leukocyte antigen E (HLA-E), is a nonclassical major histocompatibility complex molecule that creates a way for cancer cells to escape immune surveillance. HLA-E is upregulated by different cancer cells, including colorectal cancer,[12] gynecological cancers,[13] and SCCHN.[14,15] In SCCHN, HLA-E is overexpressed in almost all tumors,[16] with overexpression of HLA-E with a score of 3 ($\geq$66% of positive cells) reported in up to 80% of the tumors.[11] The binding of HLA-E to NK2GA inhibits the cytotoxic functions of CD8+ T lymphocytes and NK cells.[11] M, by targeting NK2GA, can restore the function of both T and NK cells. We have previously reported the outcome of the I1 cohort of the UPSTREAM trial showing only limited activity of M as a monotherapy in SCCHN.[17] Preclinical data show that NKG2A is often coexpressed with PD-1 on CD8+ T cells.[11] 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.[11] NKG2A blockade in combination with PD-1/PD-L1 blockade also improved tumor control in mice.[11] Preliminary efficacy data have shown encouraging activity in patients with heavily pretreated microsatellite stable (MSS) colorectal cancer when M was combined with durvalumab (D), a PD-L1 inhibitor.[18] In lung cancer, the addition of M to D has shown improved progression-free survival (PFS) for unresectable stage III non-small-cell lung cancer (NSCLC)[19] and improved major pathological response rates in the neoadjuvant setting.[20] These data supported the investigation of M in combination with PD-1/PD-L1 inhibitors and were the rationale for the I2 cohort, the second immunotherapy cohort in the UPSTREAM trial that randomized patients between M combined with D and the best choice of the investigators. In this paper, we present the results of the I2 cohort, a phase II, randomized, proof-of-concept study evaluating the combination of D and M in R/M SCCHN previously exposed to anti-PD(L)1 therapy.

PATIENTS AND METHODS

Patient eligibility

The design of the UPSTREAM trial has been previously published.[10,17] The trial included patients with R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx not amenable to curative treatment who progressed after platinum-based therapy, given as palliative treatment, or as part of multimodal curative treatment with progression within 1 year from the end of treatment. A fresh biopsy of the disease was mandatory for study entry. The study was approved by ethics committees, by the health authorities of each participating country, and conducted in accordance with the Declaration of Helsinki (October 2000). Written informed consent was obtained for each patient twice: first at the screening phase (fresh tumor biopsy) and then again at the time of cohort allocation. Patients enrolled in UPSTREAM were allocated to the I2 cohort if they met all the general inclusion criteria but were not eligible for one of the biomarker-driven cohorts defined as (i) absence of predefined biomarkers for one of the biomarker-driven cohorts open during I2 recruitment, (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 criteria for the same cohort, or the specified cohort was closed for accrual at the time of inclusion. The main cohort-specific inclusion criteria for the I2 cohort was

that patients needed to be previously exposed to PD-(L)1 inhibitor therapy. The main specific exclusion criteria for the I2 cohort included systemic treatment with steroids or other immunosuppressive agents, and active auto-immune disease/inflammatory disorder. To be eligible for the I2 cohort, patients could not have been treated with more than three lines of systemic treatment in the R/M setting before entering the study.

Study objectives and endpoints

The primary objective of the I2 cohort was to assess the efficacy of the combination of D + M in R/M SCCHN, previously pretreated with platinum-based therapy and PD-(L)1 inhibitors. The primary endpoint was the 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 (PR) according to RECIST 1.1. The secondary endpoints were response duration, PFS, OS, ORR according to the use of modified RECIST in cancer immunotherapy trials (immune RECIST [iRECIST]), and toxicity evaluated with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Study design

The I2 cohort was a phase II, randomized noncomparative, open-label, multicenter study. It was initially designed as a three-arm study, including a third arm for M monotherapy, but this arm was withdrawn before the first patient was enrolled because of the lack of efficacy of M monotherapy at a preplanned interim analysis of cohort I1. The study was amended and patients were randomized in a 2 : 1 ratio to the combination of D + M versus physician's choice. M was administered intravenously at the dose of 750 mg every 4 weeks (Q4W) for patients enrolled under protocol version 4.0 and at the dose of 750 mg every 2 weeks (Q2W) for patients enrolled under protocol version 5.0 and beyond due to new pharmacokinetic evidence showing that the Q4W regimen yields similar areas under the curves as the Q2W regimen at 750 mg dose. D was administered intravenously, 1500 mg every 4 weeks. In the control arm, patients were treated according to the physician's choice (methotrexate, paclitaxel, docetaxel, 5-fluorouracil, carboplatin, bleomycin, gemcitabine, mitomycin, or best supportive care). Treatment was administered until disease progression or unacceptable toxicity. No dose reductions were allowed in the experimental arm. Disease evaluation was carried out every 8 weeks. In the event of disease progression according to RECIST version 1.1 and, following iRECIST guidelines, continuation of treatment with D + M was permitted for patients who were clinically stable until the next imaging assessment, carried out at least 4 weeks but no more than 8 weeks after the date of the initial documented progression.

Statistical methods

The primary endpoint was ORR according to RECIST version 1.1 over the first 16 weeks of treatment. A two-stage Simon optimal design was applied to the D + M arm with 92% power to reject the null hypothesis of ORR of 3% under the alternative hypothesis of ORR of 15%, with a one-sided type 1 error of 10%. The required total sample size was determined to be 38 assessable patients (i.e. those with no deviation from eligibility criteria affecting the evaluation of the study and who have started their assigned treatment). It was planned to interrupt accrual at the interim futility analysis if no response was seen after the first 21 patients. The study would have been declared successful if at least 3 patients out of the 38 assessable patients responded to treatment according to RECIST version 1.1 during the first 16 weeks of treatment. It was expected that 19 assessable patients would be accrued in the physician's choice arm, leading to a total of 57 assessable patients in cohort I2. This arm was used as an internal reference, and no formal comparison between arms was intended. Patients were centrally randomized using a minimization technique for random treatment allocation with 2 : 1 ratio (combination D + M: physician's choice) and stratified by Eastern Cooperative Oncology Group (ECOG) 0 versus 1 and country.

RESULTS

Patient characteristics

From the start of the study up to the closure of the I2 cohort on 30 March 2022, a total of 235 patients were enrolled in the UPSTREAM trial, of which 142 were allocated to a biomarker-driven cohort, 27 in the I1 cohort and 66 to the I2 cohort (45 to the D + M arm and 21 to the control arm). Patients of the I2 cohort were enrolled at 19 centers in 4 European countries (France, Belgium, Italy, and the United Kingdom) between February 2019 and December 2021. The Consolidated Standards of Reporting Trials (CONSORT) diagram of the trial is depicted in Figure 1. The reasons for allocation to the I2 cohort were the failure of the biopsy to pass quality control in 26 (39%) patients, the absence of predefined biomarkers or other biomarker-driven cohort-specific inclusion criteria in 32 (49%), and the closure of the biomarker-driven cohort in 8 (12%). The median follow-up was 25.4 months (quartiles Q1-Q3: 20.9-33.3 months); 60 out of 66 patients were assessable for the primary endpoint (D + M: $n = 42$, control: $n = 18$). Six patients were not assessable: four patients did not start allocated treatment (two in each arm), one patient started treatment before randomization in the D + M arm, and one patient in the control arm had progressive brain lesions at inclusion. The baseline characteristics of the assessable patients are described in Table 1. Of the total patients, 45 (75%) were male and 46 (77%) had an ECOG performance status of 1; 87% of patients had already been treated with two or three previous lines of systemic treatment. In the control arm, patients were treated with the following chemotherapy regimens: docetaxel ($n = 3$), paclitaxel ($n = 4$), methotrexate ($n = 7$), carboplatin ($n = 1$), gemcitabine ($n = 1$), carboplatin—5-fluorouracil—cetuximab ($n = 1$), or cisplatin—5-fluorouracil—cetuximab ($n = 1$).

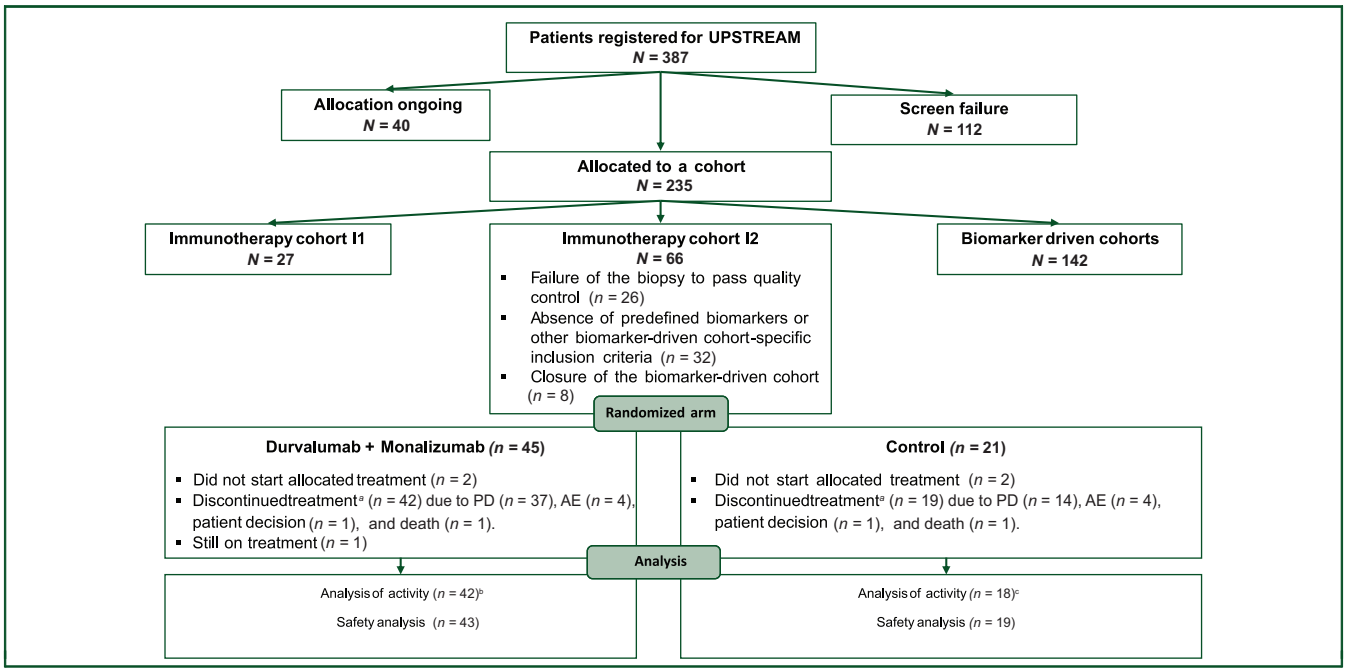

Figure 1. The Consolidated Standards of Reporting Trials (CONSORT) flowchart of the trial.
AE, adverse event; PD, progressive disease; SD, stable disease.
[a]More than one reason could be reported.
[b]One patient excluded (started treatment before randomization).
[c]One patient excluded due to ineligibility.

Table 1. Patient's characteristics in the I2 cohort

Characteristics	Monalizumab + durvalumab (*n* = 42)	Control (*n* = 18)	Total (*n* = 60)
Age (years), median (range)	62 (49-80)	63 (24-81)	62
Male, *n* (%)	31 (74)	14 (78)	45 (75)
Eastern Cooperative Oncology Group performance status, *n* (%)			
0	11 (26)	3 (17)	14 (23)
1	31 (74)	15 (83)	46 (77)
Primary disease, *n* (%)			
Oral cavity	8 (19)	3 (17)	11 (18)
Oropharynx	16 (38)	9 (50)	25 (42)
p16 positive[a]	4 (25)	3 (33)	7 (28)
Hypopharynx	7 (17)	5 (28)	12 (20)
Larynx	11 (26)	1 (5)	12 (20)
Type of recurrence, *n* (%)			
Locoregional only	9 (21)	6 (33)	15 (25)
Locoregional + distant metastases	26 (62)	4 (22)	30 (50)
Distant metastases only	7 (17)	8 (44)	15 (25)
Prior lines of treatment in the recurrent/metastatic setting			
Number of previous lines, *n* (%)			
1 line	4 (9)	4 (22)	8 (13)
2 lines	26 (62)	10 (56)	36 (60)
3 lines	12 (29)	4 (22)	16 (27)
Prior platinum-based therapy, *n* (%)	42 (100)	18 (100)	60 (100)
Prior cetuximab, *n* (%)	34 (81)	13 (72)	47 (78)
Prior PD-(L)1, *n* (%)	42 (100)	18 (100)	60 (100)

PD-L1, programmed death-ligand 1.
[a]% calculated with denominator = number of patients with oropharyngeal disease.

Efficacy

The efficacy endpoints are reported in Table 2. In the D + M arm, the best response observed during the first 16 weeks of treatment was PR in one patient [2.4%, 95% confidence interval (CI) 0.1% to 12.6%]. Hence, although the trial passed a preplanned interim analysis for futility, it did not meet its primary endpoint. The best response was stable disease (SD) in 11 patients (26%, 95% CI 12.9% to 39.5%) and progressive disease (PD) in 19 (45%, 95% CI 29.9% to 61.3%). In the control arm, one PR (5.6%, 95% CI 0.1% to 27.3%), 8 SD (44%, 95% CI 21.5% to 69.2%), and 6 PD (33%, 95% CI 11.6% to 55.1%) were reported. The median duration of disease stabilization was 1.6 months (95% CI 0.1-1.8 months) and 1.9 months (0.0-6.8 months) in the D + M arm and control arm, respectively. The spider plot (Figure 2) shows the change from baseline in tumor size for target lesions in the D + M arm. Interestingly, long-term follow-up data reported after the present analysis was conducted showed that one patient with SD at week 16 had a

Table 2. Response to treatment in the I2 cohort

Best response during the first 16 weeks of treatment	Monalizumab + durvalumab (*n* = 42), *n* (%)	Control (*n* = 18), *n* (%)	Total (*n* = 60), *n* (%)
Partial response	1 (2)	1 (6)	2 (3)
Stable disease	11 (26)	8 (44)	19 (32)
Progressive disease	19 (46)	6 (33)	25 (42)
Early death	8 (19)	1 (6)	9 (15)
Not assessable	3 (7)	2 (11)	5 (8)

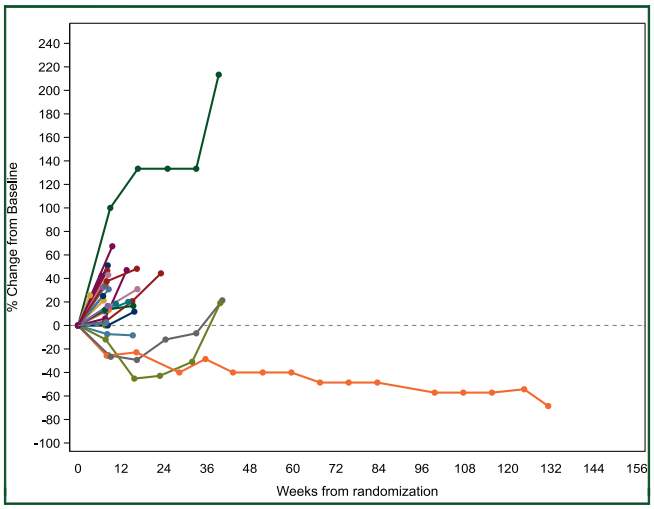

Figure 2. Spider plot showing the change from baseline in tumor size for target lesions in the durvalumab + monalizumab (D + M) arm.
CR, complete response; PR, partial response; SD, stable disease.

complete response after 3 years of treatment. Using iRECIST criteria in the D + M arm, the best response over the first 16 weeks of treatment was iPR in 1 patient, SD (immune stable disease) in 11 patients, unconfirmed progression (immune unconfirmed progressive disease) in 17, and confirmed progression (immune confirmed progressive disease) in 2.

In the D + M arm, 8 (19%) patients died before the first disease evaluation (early death), 7 of them due to progressive disease and 1 due to an adverse event. There was one early death in the control arm, due to an adverse event.

The median PFS was 2.0 months (95% CI 1.8-2.4 months) and 3.1 months (95% CI 1.9-3.9 months) in the D + M arm and in the control arm, respectively (Figure 3). The median OS was 4.3 months (95% CI 3.3-8.9 months) and 8.0 months (95% CI 3.1-14.9 months) in the D + M and control arms, respectively (Figure 4).

Safety

The most frequent treatment-related adverse events (TRAEs) in the D + M arm were fatigue (19%), diarrhea (12%), pruritus (9%), nausea (7%), and vomiting (7%) and were all grade 1-2. Grade ≥3 (G3) TRAEs were reported in 4 (9%) patients in the D + M arm (dyspnea, pneumonitis, immune-related nephritis, and hyperglycemia, each reported in 1 patient).

The most frequent TRAEs in the control arm were mucositis (32%), fatigue (26%), anemia (21%), neutrophil count decreased (11%) and anorexia (11%). The frequency of grade ≥3 TRAEs was 26% in the control arm (anemia, neutrophil count decreased, sepsis, and peripheral neuropathy, each in one patient, and mucositis in two patients). There was no toxic death in either arm.

DISCUSSION

The I2 cohort was the second immunotherapy cohort of the UPSTREAM trial exploring the combination of a PD-L1 inhibitor, D, and M, an NKG2A inhibitor, in patients with R/M SCCHN progressing after anti-PD-(L)1 therapy. The I2 cohort failed to meet its primary endpoint. Only one PR was

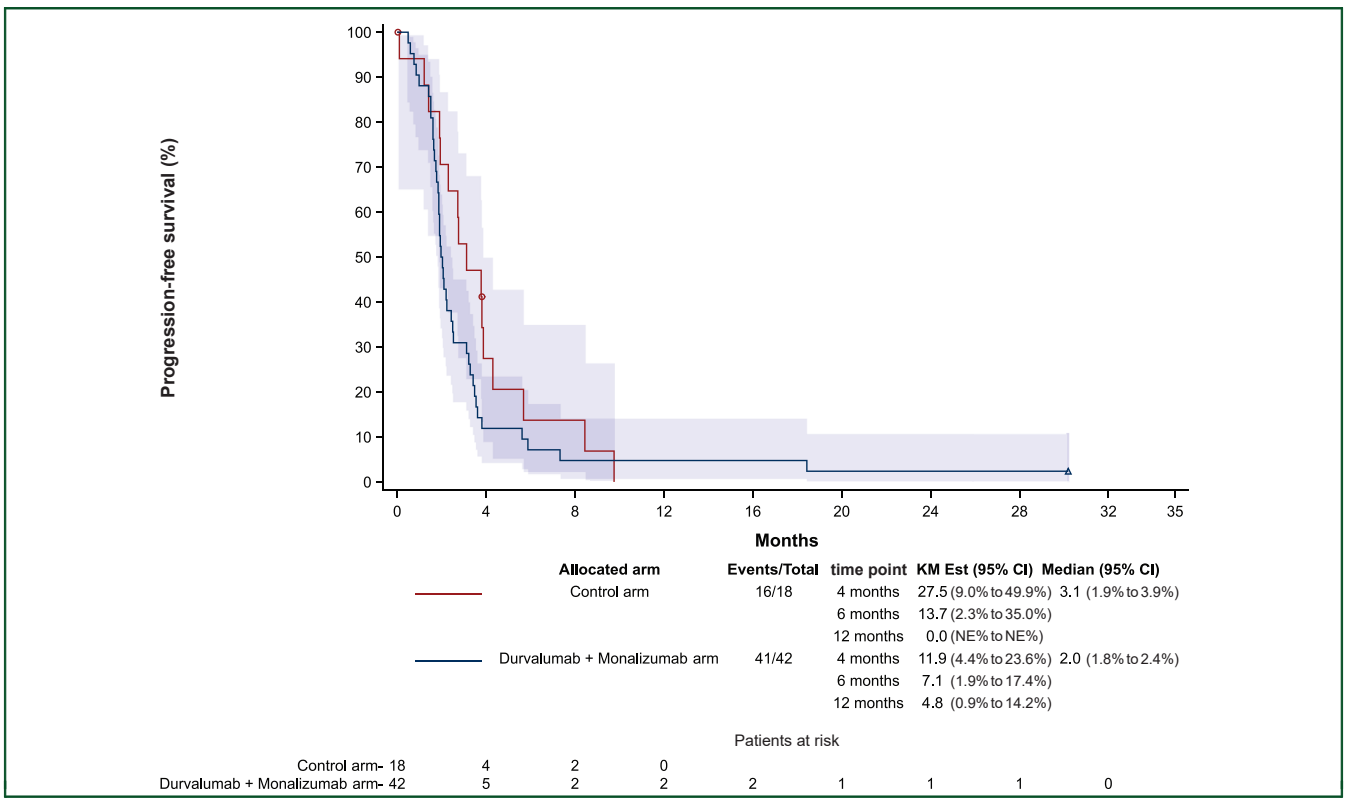

Figure 3. Progression-free survival in the I2 cohort.
CI, confidence interval; KM, Kaplan–Meier; NE, not estimable.

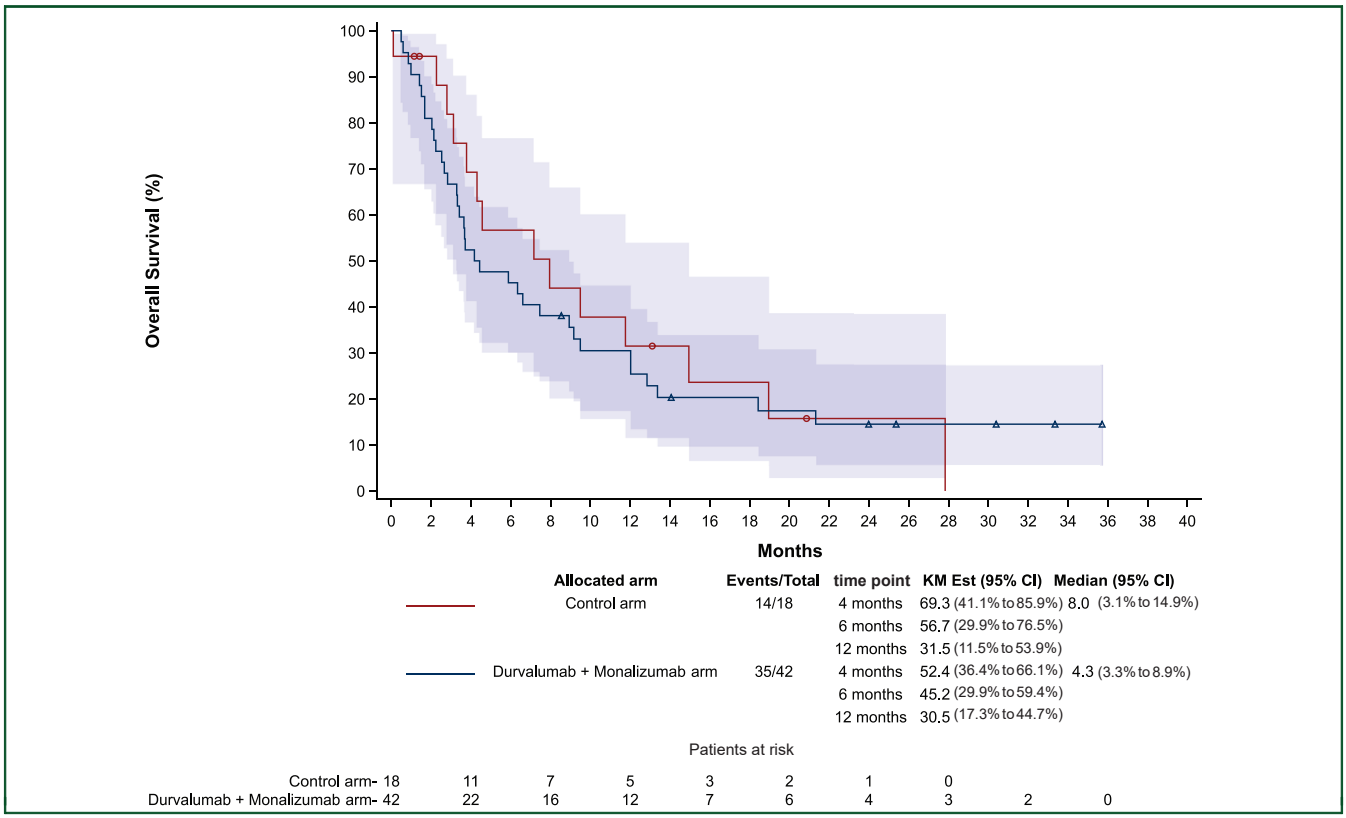

Figure 4. Overall survival in the I2 cohort.
CI, confidence interval; KM, Kaplan–Meier.

observed during the first 16 weeks of treatment. Disease stabilization was seen in 11 (26%) patients with a limited median duration of 1.6 months. Eight patients presented with early death, seven out of them due to progressive disease. The median PFS (2.0 months) and OS (4.8 months) were disappointing compared with initial expectations. The combination of D + M was safe.

The patients included in the UPSTREAM trial were a heavily pretreated population; in the I2 cohort, 87% of patients had already received two or three lines of systemic treatment including anti-PD(L)1 therapies. Seven patients died due to progressive disease. Although the trial was not designed for a formal comparison, the number of early deaths reported in the experimental arm was higher than that in the control arm and we observed a higher median OS rate in the control arm. Hyperprogression has been documented in the literature with anti-PD-(L)1 therapies in SCCHN.[21] The tumor growth kinetics from previous treatments were not available for the patients in the I2 cohort, which made it difficult to evaluate this hypothesis. However, the median OS reported aligns with the natural history of untreated head and neck cancer.[22] Therefore, it is more likely that the early disease progression observed in our study was due to the aggressive nature of the disease which was already resistant to all approved drugs. In addition, better outcomes with salvage chemotherapy after immunotherapy have been reported.[23] This could partially explain the better median OS observed in the control arm compared with historical data.

Although preclinical and clinical data were promising for the combination of M with anti-PD(L1) compounds,[11,19,20] this study did not demonstrate the activity of the combination in this specific population of PD(L)1-exposed patients who were not eligible for a biomarker-driven cohort of the USPTREAM trial. The very advanced setting is likely not the optimal one for investigating newer drugs. M has been investigated in a phase II trial as a first-line treatment for R/M SCCHN in combination with D and cetuximab.[24] The combination showed a promising ORR of 33% in this small sample size ($N = 40$) with a manageable safety profile. However, the combination of pembrolizumab and cetuximab has reported an ORR of 45%.[25] Therefore, the potential added value of M in this triplet, when studied in the first-line setting, remains to be determined. Moreover, the phase III INTERLINK-1 study (NCT04590963), investigating the combination of M and cetuximab versus cetuximab monotherapy in SCCHN progressing after platinum-based therapy and anti-PD-1, was interrupted for futility.[26,27]

Despite the poor results observed in SCCHN, M is being investigated in earlier settings in other cancer types, such as in the neoadjuvant setting for NSCLC, following encouraging results from the NEO-COAST trial.[20]

Although the overall results of this trial are negative, it is interesting to note that on top of the PR recorded for the primary endpoint, additional follow-up data showed that

another patient presented a complete response. This patient had a known regional recurrence of p16-negative oropharyngeal SCC. He had previously progressed on nivolumab (short exposure with rapid progression) and a combination of platinum-based chemotherapy and cetuximab. He presented with SD at week 16 under D + M treatment. Thereafter, tumor shrinkage was observed, leading to a complete response for ∼3 years. This patient discontinued the treatment due to the development of another malignancy (hepatocarcinoma).

One of the aims of biomarker-driven umbrella trials such as UPSTREAM is to include translational research to refine some biomarkers and to carry out biomarker discovery. The immunotherapy cohorts included in this trial were meant to (i) offer treatment possibilities to patients that had undergone a biopsy for entering the trial and that have none of the predefined biomarkers or a tumor that did not pass the quality check for further molecular analysis and (ii) explore new immunotherapy approaches. Unfortunately, the two patients that presented with a response did not have good-quality material, hampering more in-depth molecular analysis to make some hypotheses regarding their exceptional response. At the time the UPSTREAM trial was designed, PD-1 inhibitors were not yet widely implemented, so it was not planned to collect the initial PD-L1 status of the patient. As such, we do not have that information available for the patients. The limited number of patients with a biopsy of good quality in our cohort precluded further biomarker analysis.

Conclusion

The I2 cohort of the UPSTREAM trial failed to demonstrate the activity of the combination of D + M in a heavily pretreated population of patients with SCCHN previously exposed to anti-PD(L)1 therapy. The current clinical data do not support further investigation of D + M in advanced SCCHN. This report highlights the challenge of investigating new drug combinations in patients with very advanced disease. The report of two patients with responses in an otherwise negative study highlights the importance of translational research in identifying potential biomarkers of response in earlier settings, such as the neoadjuvant setting, as explored with M in NSCLC.

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DISCLOSURE

RG declares a role on an advisory board without compensation for Innate Pharma, as well as institutional fees for serving as an invited speaker for MSD and travel compensation from MSD and Daiichi Sankyo. AK received fees for consulting, advisory, and speaker roles, as well as research funding, from PUMA Biotechnology, AstraZeneca, Merck, MSD, Bristol-Myers Squibb, and Avvinity Therapeutics. CB received fees for serving on advisory boards for AstraZeneca, Merck Serono, and MSD, as well as fees for being an invited speaker for AstraZeneca, BMS, Merck Serono, and MSD. FR received fees for serving as an invited speaker for Merck Serono and MSD. LL received consulting fees from MSD IT, Merck Serono Spa Healthcare Professional, Merck Healthcare KGaA, GSK, F. Hoffmann-La Roche Ltd, EMD Serono Research & Development Institute, Inc., Boehringer Ingelheim International GmbH, Simon-Kucher & Partners Strategy & Marketing Consultants, Rgenta Therapeutics, Inc., Alentis Therapeutics AG, and MedImmune; received limited payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Merck Serono Spa, MSD IT, Merck Healthcare KGaA, Adlai Nortye, Bristol-Myers Squibb [K.K.], and ALTIS Omnia Pharma Service Srl; received support for attending meetings and/or travel from TAE Life Science; received fees for participation on a data safety monitoring board or advisory board from Merck Healthcare KGaA, Merck & Co., Inc., MSD IT, EMD Serono Research & Development Institute, Inc., F. Hoffmann-La Roche Ltd, Janssen Research & Development, LLC, Seagen International GmbH, Genmab US, Inc., AstraZeneca UK Limited, AbbVie Srl, Simon-Kucher & Partners Strategy & Marketing Consultants, and Purple Biotech, Ltd; received grants or contracts (research funds donated directly to the institution for clinical trials) from Adlai Nortye, AstraZeneca, BMS, Debiopharm International SA, Eisai, Eli Lilly and Company, Exelixis, Hoffmann-La Roche Ltd, Isa Therapeutics, Kura Oncology, Merck Serono, MSD, Merck Sharp & Dohme Corp., Nektar Therapeutics, Novartis, Regeneron, Roche, Sanofi, Syneos, Sun Pharmaceuticals, Incyte Biosciences International Sàrl, Gilead Sciences, Inc., Genmab, and Merck Healthcare KGaA. CA received fees as an invited speaker for AstraZeneca and MSD; fees for serving on advisory boards for AstraZeneca, GSK, Merck, and MSD; fees as a principal investigator from Debiopharm, Epizyme, GSK, MSD, and Zentalis. JPM declares roles as an advisory board member or speaker with honoraria managed by the institution for Pfizer, Roche, AstraZeneca, Bayer, Innate, Merck Serono, Boehringer, BMS, Novartis, Janssen, Incyte, Cue Biopharma, ALX Oncology, iTeos, and eTheRNA; travel expenses covered by Amgen, BMS, Pfizer, and MSD; participation on a data safety monitoring board with honoraria for PsiOxus; and uncompensated advisory role for MSD. The other authors have declared no potential conflicts of interest.

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