Personalized biomarker-based treatment strategy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: Results of the biomarker-driven cohorts of the EORTC-HNCG-1559 trial (UPSTREAM).

Rachel Galot, Christophe Le Tourneau, Lisa F. Licitra, Joel Guigay, Anthony Kong, Inge Tinhofer, Caroline Even, Amaury Daste, Esma Saada-Bouzid, Frederic Rolland, Stephanie Henry, Sylvie Rottey, Emmanuel Seront, Annemie Rutten, Philip R. Debruyne, Konstantina Tsechilidou, Catherine Fortpied, Ana Joaquim, Anne-sophie Govaerts, Jean-Pascal H. Machiels; Service d'oncologie médicale, Laboratoire d'Oncologie médicale (IREC/MIRO/ONCO), Brussels, Belgium; Department of Drug Development and Innovation (D3i), Institut Curie, Paris-Saclay University, Paris, France; Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; CentreAntoineLacassagne, Nice, France; Comprehensive Cancer Centre, King's College London, London, United Kingdom; Charité - Universitätsmedizin Berlin, Berlin, Germany; Institut Gustave Roussy, Villejuif, France; Department of Medical Oncology, Hôpital Saint-André, University of Bordeaux-CHU, Bordeaux, France; Centre de Lutte Contre le Cancer Antoine Lacassagne, Nice, France; Institut de Cancérologie de l'Ouest, Site René Gauducheau, Saint-Herblain, France; Université Catholique de Louvain, Namur, Belgium; Gent University Hospital, Gent, Belgium; Institut Roi Albert II, Cliniques universitaires Saint Luc, Université Catholique de Louvain, Brussel, Belgium; AZ Sint-Augustinus, Antwerpen, Belgium; AZ Groeninge, Jabbeke, Belgium; EORTC, Brussels, Belgium; EORTC HQ, Woluwe-Saint-Lambert, Belgium; EORTC Headquarters, Brussels, Belgium; Department of Medical Oncology, Institut Roi Albert II, Cliniques Universitaires Saint-Luc and Institut de Recherche Clinique et Expérimentale, Université Catholique de Louvain (UCLouvain), Brussels, Belgium

Background: Platinum-refractory recurrent/metastatic squamous cell carcinoma (R/M SCCHN) has a poor prognosis. Several molecular pathways are dysregulated in SCCHN, providing potential targets for treatment. The UPSTREAM trial aimed to develop a personalized treatment strategy for R/M SCCHN. **Methods:** UPSTREAM was a biomarker-driven umbrella trial for post-platinum R/M SCCHN, investigating the activity of targeted agents in patients (pts) with tumors harboring pre-defined biomarker(s) identified on a fresh biopsy. Five biomarker-driven (B) cohorts were conducted as distinct phase 2 trials. The first 4 cohorts focused on p16-negative disease: cohort B1 investigated afatinib in pts with *EGFR* amp/mut and/or *HER2* amp/mut and/or PTEN high; cohort B2 investigated afatinib in cetuximab-naïve pts; cohort B3 investigated palbociclib in pts with *CCND1* amp and cohort B4 investigated niraparib in platinum-sensitive disease. Cohort B5 investigated niraparib in p16 positive oropharyngeal carcinoma. Cohorts B1, B2 and B3 were randomized (versus physician's choice of treatment) with progression-free survival rate at 16 weeks (PFSR 16W) as primary endpoint. Cohorts B4 and B5 were single-arm trials with objective response rate (ORR) over the first 16 weeks as primary endpoint. **Results:** A total of 250 pts were enrolled in UPSTREAM across 5 European countries, of whom 152 were allocated to a biomarker-driven cohort. Only B1 met its primary endpoint. In B1 (n=38 under afatinib), the PFSR 16W was 34.2%. B2 cohort experienced slow recruitment, with only 8 patients treated with afatinib, the PFSR 16W was 12.5%. In B3 (n=12 under palbociclib), PFSW 16W was 16.7%. In B4 (n=28) and B5 (n= 33), the ORR with niraparib was 3.6% (1/28) and 6.1% (2/33), respectively. More detailed results are shown in the table. **Conclusions:** UPSTREAM demonstrated the feasibility of conducting a biomarker-driven clinical trial in R/M SCCHN. The clinical activity observed across the biomarker-driven cohorts is limited. Potential explanations for these results include the absence of clearly identified high-level drivers in SCCHN, the limited evidence supporting some biomarkers (mainly derived from genomic data), and the use of single-agent treatment approaches. These findings highlight the need for further research to identify and refine biomarkers to explore new treatment strategies. Clinical trial information: NCT03088059. Research Sponsor: Boehringer Ingelheim; Pfizer; GSK.

Cohort	Biomarker	Drug	N evaluable patients	ORR	Median PFS (months)	Median OS (months)
B1	p16- and *EGFR* amp/mut or *HER2* amp/mut or PTEN high	afatinib	38	10.5%	2.2	7.2
		physician's choice	17	5.9%	2.4	5.0
B2	p16- and cetuximab-naïve	afatinib	8	0%	2.6	10.7
		physician's choice	4	0%	4.0	4.0
B3	p16- and *CCND1* amp	palbociclib	12	8.3%	1.9	4.3
		Physician's choice	6	0%	1.9	5.1
B4	p16- and platinum-sensitive	niraparib	28	3.6%	2.0	6.8
B5	P16 pos OPC	niraparib	33	6.1%	1.8	6.9