Introduction

• CUP describes a heterogeneous group of metastatic cancers without an identifiable primary tumour, despite thorough clinical work-up. Although CUP has increased over the last few decades, this has not correlated with improved survival, highlighting the urgent medical need for better therapeutic options.

• CGP is a next-generation sequencing approach that detects novel and known variants of all the main classes of genomic alterations in cancer-related genes, as well as the genomic signatures MSI, TMB and genome-wide loss of heterozygosity. CGP may reveal more personalised and effective therapeutic options for patients with poor-prognosis CUP.

• CUPISCO (NCT03498521) is an ongoing, phase II randomised study of targeted therapy/cancer immunotherapy vs platinum-based chemotherapy in patients with unfavourable CUP, defined per the European Society for Medical Oncology guidelines. We present a preliminary, descriptive molecular analysis of ~50% of patients designated for enrolment in CUPISCO.

Baseline mutational profiles of patients with CUP enrolled onto CUPISCO

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Results

• Median age was 62 years (range: 22–84; N = 346 [cut-off: April 2021]) and median TMB was 2.5 mutations/Mb (0–60.0; Supplementary Table 1). The frequency of MSI- and TMB-high (≥16 mutations/Mb) samples was 3% and 9%, respectively (Supplementary Table 1).

• The most frequent prevalent GAs were CCND1 (44%), CDKN2A (32%), KRAS (21%); CDK2, CDKN2B (21%), ARID1A (13%), STK11 (13%), MTAP (12%), PIK3CA (10%), MYC (8%), PBRM1 (8%), FGFR2 (8%) and BAP1 (7%) (Figure 1).

• In our analysis, at least 30% of patients carried a potentially targetable GA (Supplementary Figure 1). • Based on hierarchical clustering of co-mutational profiles, multiple clusters were identified and characterised by specific GA co-occurrences (clusters 1, 2, 5 and 6) or GA frequencies (clusters 3 and 4; Figure 2 and Supplementary Figure 2).

• Most GA co-occurrences were also found after analysing a similar population with the same methodology (FoundationCore dataset). 3

Abbreviations

Ampl: amplification; CGP: comprehensive genomic profiling; CNA: copy number alteration; CUP: carcinoma of unknown primary origin; Del: deletion; GA: gene alteration; Mb: megabase; MSI: microsatellite instability; TNM: tumour, node, metastasis; SV: short variant; TMB: tumour mutational burden.

References


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Conlicts of interest

CBW reports honoraria from Bayer, Celgene, Ipsen, Servier, Taiho and F. Hoffmann-La Roche Ltd; has participated in advisory boards for Celgene, Shire/Baxalta, Pfizer/PharmaScience, RedHill BioPharma and F. Hoffmann-La Roche Ltd; has received travel/xcommodation expenses from Bayer, Celgene, RedHill BioPharma, F. Hoffmann-La Roche Ltd, Servier and Taiho; and has received research support (medical writing support) from F. Hoffmann-La Roche Ltd. Please refer to the Supplementary for all other conflicts of interest. This analysis was sponsored by F. Hoffmann-La Roche Ltd. CUPISCO (NCT03498521) is sponsored by F. Hoffmann-La Roche Ltd.

Methods

• Upon enrolment in CUPISCO, CGP, including determination of MSI and TMB, was performed on formalin-fixed, paraffin-embedded tissue using the FoundationOne®CDx assay (Foundation Medicine, Inc., Cambridge, MA, USA). MA, GAs in ≤3% of patients were analysed using multiple correspondence analyses and hierarchical clustering to identify co-occurrences.

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Summary

Results from this analysis demonstrate the ability to cluster CUP cases based on molecular profiling. Results also suggest that CGP can identify actionable GAs in a significant proportion of patients with poor-prognosis CUP, potentially offering more personalised treatments that may improve outcomes for these patients.

Conclusions

• The overall distribution and co-occurrence of GAs from patients enrolled in CUPISCO, including in targetable genes, was comparable with data from a similar, independent CUP population.

• This descriptive analysis sheds further light on the molecular landscape in patients with poor-prognosis CUP.

• Our analyses demonstrate that CUP cases can be clustered based on molecular profiling; further analyses and studies are needed to determine if these clusters carry clinical relevance.

• Our early results suggest that CGP of CUP cases identifies therapeutically relevant GAs in a significant proportion of patients and could thus guide personalised treatment of these tumours.