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Baseline mutational profiles of patients with CUP enrolled onto CUPISCO

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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.

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Introduction

- CUP describes a heterogeneous group of metastatic cancers without an identifiable primary tumour, despite thorough clinical work-up.[1] Although the incidence of CUP has decreased over the last few decades,[2–4] this has not correlated with improved survival, highlighting the unmet medical need for better therapeutic options.[3–6]
- 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.[7] 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.[8] We present a preliminary, descriptive molecular analysis of ~50% of patients designated for enrolment in CUPISCO.

Methods

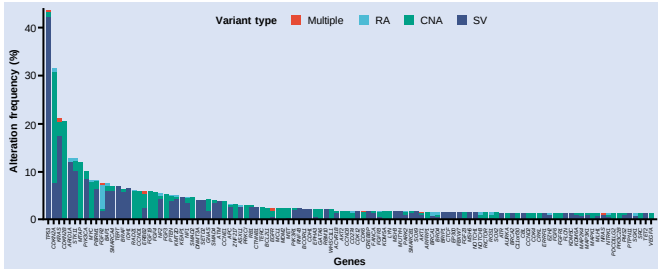
- Upon enrolment in CUPISCO, CGP, including determination of MSI and TMB, was performed on formalin-fixed, paraffin-embedded tissue using the FoundationOne®CDx assay (Foundation Medicine, Inc., Cambridge, MA, USA).
- GAs in ≥3% of patients were analysed using multiple correspondence analyses and hierarchical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

Results

- Median age was 62 years (range: 22–84; N = 346 [cut-off: April 2021]) and median TMB was 2.5 mutations/Mb (0–63.0; 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 GAs were *TP53* (44%), *CDKN2A* (32%), *KRAS* (21%; *G12C*: 2%), *CDKN2B* (21%), *ARID1A* (13%), *STK11* (13%), *MTAP* (12%), *PIK3CA* (10%), *MYC* (8%), *PBRM1* (8%), *FGFR2* (8%) and *BAP1* (8%; Figure 1).
- In our analysis, at least 30% of patients carried a potentially targetable GA (Supplementary Figure 1).
  - Beyond *PIK3CA* and *FGFR2*, some of the other targetable GAs included *BRAF* (6%; *V600E*: 3%), *ERBB2* (6%), *EGFR* (2%), *MET* (2%), *ROS1* (1%), *NTRK1* (1%) and *ALK* (0.3%).

- 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).[9]

Figure 1. GA frequencies across the cohort



*N = 346; only genes with an alteration frequency ≥1% are reported.

Figure 2. Patient clusters based on mutational profiles

*TP53 SVs were prevalent in the majority of clusters.
†Homozygous deletions only.

Cluster	Distinctive GA co-occurrences / prevalent GAs*
1	Co-occurrences: CN amplifications in *FGF3*, *FGF4*, *FGF19*, *CCND1*
2	Co-occurrences: CN deletions† in *CDKN2A*, *CDKN2B*, *MTAP*
3	Prevalent GAs: RA in *FGFR2*, SVs in *BAP1*
4	Prevalent GAs: SVs in *TP53*, *ARID1*, *PIK3CA*, *IDH1*; a sub-cluster of patients with almost no GAs
5	Co-occurrences: CN amplifications in *RAD21*, *MYC*
6	Co-occurrences: SVs in *STK11*, *KRAS*, *KEAP1*

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.[9]
- 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 samples identifies therapeutically relevant GAs in a significant proportion of patients and could thus guide personalised treatment of these tumours.

Abbreviations
Ampl, amplification; CGP, comprehensive genomic profiling; CN(A), copy number alteration; CUP, carcinoma-of-unknown-primary-origin; Del, deletion; GA, gene alteration; Mb, megabase; MSI, microsatellite instability; RA, rearrangement; SV, short variant; TMB, tumour mutational burden.

References
1. Stella GM, et al. J Transl Med 2012;10:12; 2. Rassy E, et al. Cancer Epidemiol 2019;61:139-141; 3. Binder C, et al. Cancer Med 2018;7:4814-4824; 4. Urban D, et al. Br J Cancer 2013;109:1318-1324; 5. Fizazi K, et al. Ann Oncol 2015;26:133-138; 6. Hemminki K, et al. Ann Oncol 2011;23:1854-1863; 7. Singh AP, et al. Cancers 2020;12:1156; 8. Krämer A, et al. Ann Oncol 2018;29:Abstract 445TiP; 9. Ross JS, et al. Oncologist 2021;26:e394-e402.

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Conflicts of interest
CBW reports honoraria from Bayer, Celgene, Ipsen, Servier, Taiho and F. Hoffmann-La Roche Ltd, has participated in an advisory board for Celgene, Shire/Baxalta, Rafael Pharmaceuticals, RedHill BioPharma and F. Hoffmann-La Roche Ltd, has received travel/accommodation 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 author conflicts of interest. This analysis was sponsored by F. Hoffmann-La Roche Ltd. CUPISCO (NCT03498521) is sponsored by F. Hoffmann-La Roche Ltd.