Molecularly guided therapy versus chemotherapy after disease control in unfavourable cancer of unknown primary (CUPISCO): an open-label, randomised, phase 2 study

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Summary

Background Patients with unfavourable subset cancer of unknown primary (CUP) have a poor prognosis when treated with standard platinum-based chemotherapy. Whether first-line treatment guided by comprehensive genomic profiling (CGP) can improve outcomes is unknown. The CUPISCO trial was designed to inform a molecularly guided treatment strategy to improve outcomes over standard platinum-based chemotherapy in patients with newly diagnosed, unfavourable, non-squamous CUP. The aim of the trial was to compare the efficacy and safety of molecularly guided therapy (MGT) versus standard platinum-based chemotherapy in these patients. This was to determine whether the inclusion of CGP in the initial diagnostic work-up leads to improved outcomes over the current standard of care. We herein report the primary analysis.

Methods CUPISCO was a phase 2, prospective, randomised, open-label, active-controlled, multicentre trial done at 159 sites in 34 countries outside the USA. Patients with central eligibility review-confirmed disease (acceptable histologies included adenocarcinoma and poorly differentiated carcinoma) and an Eastern Cooperative Oncology Group performance status of 0 or 1, evaluated by CGP, who reached disease control after three cycles of standard first-line platinum-based chemotherapy were randomly assigned 3:1 via a block-stratified randomisation procedure to MGT versus chemotherapy continuation for at least three further cycles. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. The study is registered with ClinicalTrials.gov, NCT03498521, and follow-up is ongoing.

Findings From July 10, 2018, to Dec 9, 2022, 636 (42%) of 1505 screened patients were enrolled. Median follow-up in the treatment period was 24·1 months (IQR 11·6–35·6). Of 438 patients who reached disease control after induction chemotherapy, 436 were randomly assigned: 326 (75%) to the MGT group and 110 (25%) to the chemotherapy group. Median progression-free survival in the intention-to-treat population was 6·1 months (95% CI 4·7–6·5) in the MGT group versus 4·4 months (4·1–5·6) in the chemotherapy group (hazard ratio 0·72 [95% CI 0·56–0·92]; p=0·0079). Related adverse event rates per 100-patient-years at risk were generally similar or lower with MGT versus chemotherapy.

Interpretation In patients with previously untreated, unfavourable, non-squamous CUP who reached disease control after induction chemotherapy, CGP with subsequent MGTs resulted in longer progression-free survival than standard platinum-based chemotherapy. On the basis of these results, we recommend that CGP is performed at initial diagnosis in patients with unfavourable CUP.

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Introduction

Comprehensive genomic profiling (CGP) is a next-generation sequencing approach that enables detection of major genomic alterations (rearrangements; base substitutions; insertions and deletions; and copy number changes), as well as of genomic signatures, including tumour mutational burden, microsatellite instability, and genome-wide loss of heterozygosity. Molecular profiling leads to improved outcomes in lung cancer;[1] however, the clinical benefit of molecularly guided therapy (MGT) across tumour types remains under debate. Advances in exploration of the genomic cancer landscape have facilitated the US Food and Drug Administration approval of multiple MGTs in oncology between January, 2000, and October, 2022, during which time 223 (39%) of 573 oncology approvals were for biomarker-defined populations.[2]

Cancer of unknown primary (CUP) is a heterogeneous group of metastatic malignancies for which a primary origin site cannot be identified, despite standardised work-up at diagnosis.[3] CUP accounts for 2–5% of all malignancies, with 80–85% being of an unfavourable

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See Online for appendix

Research in context

Evidence before this study

Cancer of unknown primary (CUP) accounts for 2–5% of all malignancies, with 80–85% being of an unfavourable subset. We searched PubMed using "CUP", "cancer of unknown primary", "carcinoma of unknown primary", and "genomic profiling", for articles published in English, without restricting results. Platinum-based chemotherapy is the standard of care for first-line treatment of unfavourable CUP, resulting in a median overall survival of less than 1 year. The search confirmed that there has been little progress in improving outcomes for patients with CUP. Two randomised studies have recently shown that gene expression profiling-based tissue-of-origin identification with subsequent primary site-directed therapy does not improve prognosis in patients with newly diagnosed CUP compared with unspecific platinum-based chemotherapy. More than a third of patients with CUP harbour targetable genomic alterations. CUPISCO has tested the concept of using comprehensive genomic profiling (CGP) at diagnosis to inform a molecularly guided treatment strategy to improve patient outcomes compared with standard platinum-based chemotherapy.

Added value of this study

CUPISCO is the largest interventional, randomised trial in CUP done to date, and the first study to show a survival benefit of molecularly guided therapy (MGT) over platinum-based chemotherapy, which has been the standard of care in CUP for the last three decades. The results of CUPISCO highlight that including early CGP by tissue-based or liquid-based testing, or both, and incorporation of MGT into the treatment armamentarium significantly improve progression-free survival in patients with CUP, and provide a new reference on which to base further treatment advances in this poor-prognosis malignancy.

Implications of all the available evidence

The results of CUPISCO support the use of CGP in the diagnostic work-up of patients with newly diagnosed, unfavourable CUP. Use of tissue and liquid biopsies for CGP could be a practice-changing strategy in these patients by enabling more relevant treatment options, and will likely evolve in future. Longer follow-up for overall survival is needed to assess the benefit–risk profile further.

subset.[3–8] There has been little progress in improving outcomes for patients with CUP. The unfavourable subset has a poor prognosis, with a median overall survival of less than 1 year[3–9] when treated with the current standard of care (non-specific platinum-based chemotherapy).[7,10] Studies have shown that gene expression-profiling-based tissue-of-origin identification with subsequent primary site-directed therapy did not improve progression-free survival or overall survival compared with platinum-based chemotherapy in patients with newly diagnosed CUP.[11,12] Unfavourable CUP might therefore be viewed as a model disease for the development of tumour-agnostic treatment strategies.

Up to one-third of patients with CUP harbour targetable genomic alterations, with a broad range of prevalence.[13–18] The CUPISCO trial was designed to test the concept of using CGP at diagnosis to inform a molecularly guided treatment strategy in order to improve outcomes over standard platinum-based chemotherapy in patients with newly diagnosed, unfavourable CUP. We herein report the primary analysis. The aim of the trial was to compare the efficacy and safety of MGT versus standard platinum-based chemotherapy in these patients. This was to establish whether the inclusion of CGP in the initial diagnostic work-up leads to improved outcomes over the current standard of care.

Methods

Study design and participants

CUPISCO was a phase 2, prospective, randomised, open-label, active-controlled, multicentre trial done at 159 sites of various types (see list in appendix pp 3–6) in 34 countries outside the USA. Full eligibility criteria are provided in the protocol (appendix). Briefly, patients were aged 18 years or older; had non-squamous CUP confirmed by a central eligibility review panel (as per 2015 European Society of Medical Oncology [ESMO] Clinical Practice Guidelines[7] and the diagnostic algorithms later adapted for the 2023 ESMO guidelines[3]); had had no previous systemic therapy for an unfavourable subset, non-squamous CUP; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (two patients with an ECOG performance status of 2 were included, which were protocol deviations at two study sites); a life expectancy of at least 12 weeks; and were eligible for platinum-based chemotherapy. Acceptable histologies included adenocarcinoma and poorly differentiated carcinoma. Eligibility also required at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and an available formalin-fixed, paraffin-embedded tumour block that was up to 4 months old at the start of screening for CGP with the FoundationOne CDx test (F1CDx; Foundation Medicine, Cambridge, MA, USA). Implementation of liquid biopsy testing with FoundationOne Liquid CDx test (F1LCDx) allowed patients with scarce tumour tissue to be considered for CUPISCO and served as an additional source of molecular information for cases where the tissue CGP test was not informative or a result could not be obtained. All CGP was done at a central reference pathology laboratory. Additionally, available local slides or tissue for central confirmation of CUP diagnosis was required. Key exclusion criteria included squamous cell carcinoma

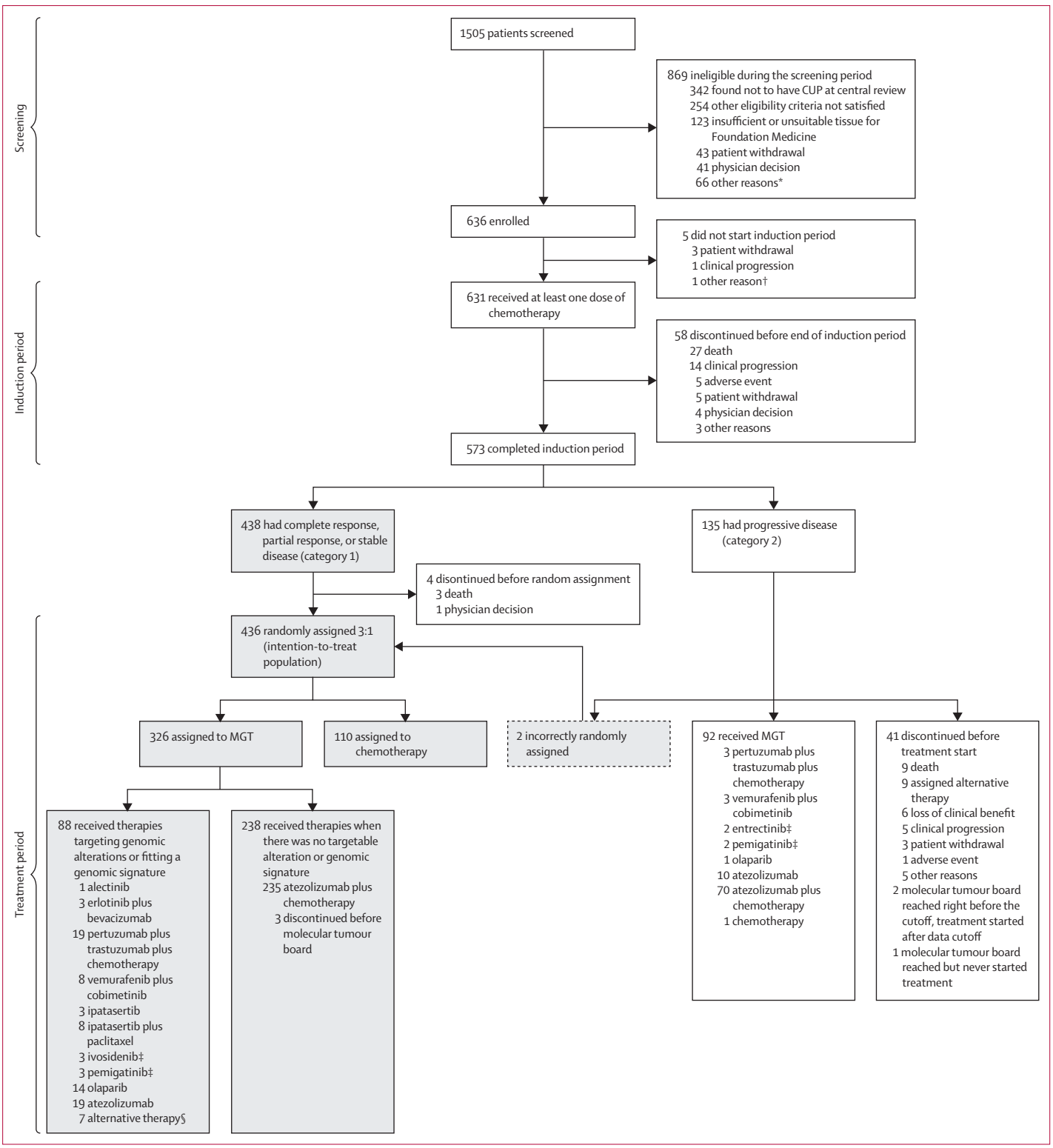

Figure 1: **Trial profile**

CUP=cancer of unknown primary. MGT=molecularly guided therapy. *20 rescreened; 19 died; and 27 other. †Not specified. ‡Entrectinib, pemigatinib, and ivosidenib were added after the study began. Other cohorts were available at the start of the study; however, there were no changes to the standard of care during the study period. No patients received entrectinib in category 1; only in category 2. No patients received vismodegib. §3 paclitaxel–carboplatin; larotrectinib; bicalutamide, triptorelin, trametinib, and carboplatin plus taxol and capecitabine; unknown; gemcitabine, cisplatin, capecitabine, paclitaxel, and FOLFIRI.

histology, favourable prognosis CUP subsets,[3,7] central nervous system metastases, or leptomeningeal disease (see appendix for full list).

CUPISCO was designed and overseen by a steering committee and an independent data monitoring committee and supported by F Hoffmann-La Roche. Eight independent data monitoring committee meetings were held, which also covered safety. The protocol and all amendments were approved by the relevant ethics committee or institutional review board at each site. CUPISCO was done in accordance with the principles of the Declaration of Helsinki. Patients provided written informed consent. The authors bear full responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial and this report to the protocol (appendix). This trial is registered with ClinicalTrials.gov, NCT03498521; recruitment is closed but follow-up is ongoing.

Randomisation and masking

CUPISCO comprised an induction period, a treatment period, and a safety follow-up visit. The trial design has been described previously.[17] Patients eligible after the screening period were required to have a confirmed diagnosis of previously untreated, unfavourable CUP,[7] and diagnosis by local pathologists and treating oncologists had to be confirmed by central pathology and clinical review by an eligibility review team, including a referent oncologist and radiologist. Upon confirmed eligibility, all patients had hybrid capture-based CGP of cancer tissue (with the F1CDx test) or blood (with the F1LCDx test), or both. CGP was used to select treatment, not to identify a primary tumour.

During the induction period, patients received three initial cycles of platinum-based chemotherapy per investigator's choice (carboplatin–paclitaxel, cisplatin–gemcitabine, or carboplatin–gemcitabine; appendix p 7). Following restaging after three cycles, patients were separated into two categories: category 1, which comprised patients who reached disease control (ie, a complete response, partial response, or stable disease) after three cycles; and category 2, which comprised patients with progressive disease during or after three cycles.

At the start of the treatment period, category 1 patients were randomly assigned 3:1 via a block-stratified randomisation procedure to either the MGT group or to continuation of the same chemotherapy regimen used in the induction period for at least three further cycles. Randomisation was done by an interactive response system. On the basis of previous genomic profiling studies, we estimated that only approximately a quarter to a third of patients with unfavourable subset CUP randomly assigned to receive MGT would be eligible for MGT. Therefore, in order to maximise the number of patients eligible for one of the targeted therapy cohorts of the MGT group, we implemented a randomisation ratio of 3:1. If no targetable alteration or a genomic signature (tumour mutational burden-high or microsatellite instability-high) was detected, patients randomly assigned to MGT were assigned to continuation of chemotherapy plus atezolizumab.

This was an open-label study. Randomisation was stratified by gender and chemotherapy response (complete response or partial response versus stable disease). Category 2 patients were treated with MGT. We report the primary analysis of category 1 patients (results from category 2 patients will be reported elsewhere).

Procedures

Treatment options for patients in the MGT group (figure 1; appendix p 8) were defined by the investigator with advice from a virtual molecular tumour board, which included the treating investigator, a referent pathologist, a referent oncologist, and, when required, a genomics expert from Foundation Medicine. The specific MGT was selected on the basis of the results of each patient's genomic profile from the F1CDx or F1LCDx test reports, or both, done on samples collected before chemotherapy initiation (dependent on availability of results from one or both assays). The molecular tumour board charter is shown in the appendix (p 10). Details of F1CDx and F1LCDx can be found online.[19,20] Further details on baseline mutational profiles of patients enrolled in the trial were reported by Westphalen and colleagues.[21]

Patients were treated until loss of clinical benefit, unacceptable toxicity, patient or investigator decision to discontinue, or death (whichever occurred first). Imaging assessments (eg, computed tomography scan, X-ray, or bone scan), were done every 9 weeks according to RECIST version 1.1 until disease progression. A monthly safety report was generated from the beginning of the study and is ongoing until 30 days after the final visit for all investigational medicinal products, and 90 days for atezolizumab cohorts, as per the protocol.

Outcomes

Endpoints for the primary analysis were assessed in category 1 patients. Outcomes for category 2 patients and endpoints specified in the statistical analysis plan (see appendix) but not included here will be reported elsewhere. The primary efficacy endpoint was investigator-assessed progression-free survival, defined as time from randomisation to first occurrence of disease progression per RECIST version 1.1 or death from any cause, whichever occurred first. The secondary endpoints were overall survival (time from randomisation to death from any cause); confirmed best overall response (the most favourable outcome, according to RECIST version 1.1, at any visit after the baseline tumour assessment date and up to the clinical cutoff date or the first documented disease progression, whichever occurred first); objective response rate (proportion of randomly assigned patients who exhibit a confirmed complete response or a confirmed partial response—ie, on two consecutive occasions at least

4 weeks apart, according to investigator assessment by use of RECIST version 1.1; see appendix); duration of response (time from first documentation of confirmed complete response or confirmed partial response to disease progression or death from any cause, whichever occurred first); and disease control rate (proportion of patients with best response assessed as having a confirmed complete response, partial response, stable disease, or a result that was not applicable [ie, patients who had a complete response at the end of induction; therefore, there was no measurable lesion at the start of treatment] per RECIST version 1.1; see appendix). Safety was also assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Health-related quality of life was an exploratory endpoint (see appendix).

Statistical analysis

CUPISCO was designed to detect a hazard ratio (HR) of 0·7 for a progression-free survival comparison of MGT versus chemotherapy (α=5%), assuming a median progression-free survival of 5 months under the standard of care for patients with CUP (ie, chemotherapy).[22] At least 330 events (400 patients) were needed to achieve 80% power for a two-sided hypothesis test. At data cutoff (Feb 14, 2023), the main analysis (intention-to-treat; all randomly assigned patients, whether or not the assigned study treatment was received) population (category 1 patients) comprised 436 patients (figure 1) with 341 progression-free survival events. Efficacy and patient-reported outcome analyses were done in the intention-to-treat population, with patients grouped according to their assigned treatment group. Safety analyses were done in all patients who received at least one dose of any study drug (safety-evaluable population).

The Kaplan–Meier method was used to estimate median progression-free survival for each group, and the Brookmeyer–Crowley method was used to estimate 95% CIs for median progression-free survival. Progression-free survival was compared between groups by the stratified log-rank test, with HRs and corresponding 95% CIs estimated by use of a stratified Cox proportional hazards model. Subgroup analyses of progression-free survival by group and actionability were post hoc.

Overall survival analyses were done as for progression-free survival. We report interim overall survival results; a final analysis is planned at study closure.

Duration of response was analysed in patients who reached an objective response rather than in patients who were randomly assigned. As such, analyses were done similarly as for progression-free survival, but did not include stratification or hypothesis testing.

Objective response rate and disease control rate were compared between groups by use of the stratified Cochran–Mantel–Haenszel test. Differences in objective response rate and disease control rate between groups were estimated, along with 95% CIs calculated by use of the Clopper–Pearson method.

One single null hypothesis comprising two study groups was prespecified in terms of a predefined main primary endpoint with no interim analysis; therefore, no type I error adjustment was done, as per European Medicines Agency guidelines.[23] All secondary and exploratory endpoints were of a supportive nature.

All stratified analyses used gender and response to platinum-based induction chemotherapy (complete response or partial response versus stable disease) as stratification factors. Adverse events were graded per NCI-CTCAE, version 5.0. Patient-reported outcome

	Molecularly guided therapy (n=326)	Chemotherapy (n=110)
Age, years	61·0 (53·0–70·0)	62·5 (55·0–69·0)
Age group		
<65 years	188 (58%)	61 (55%)
≥65 years	138 (42%)	49 (45%)
Gender		
Male	165 (51%)	57 (52%)
Female	161 (49%)	53 (48%)
Race		
American Indian or Alaskan Native	4/325 (1%)	3/110 (3%)
Asian	31/325 (10%)	12/110 (11%)
Black or African American	5/325 (2%)	0
White	242/325 (74%)	81/110 (74%)
Unknown	43/325 (13%)	14/110 (13%)
Weight, kg	n=312; 70·8 (60·5–81·6)	n=101; 71·0 (61·45–80·0)
BMI	n=312; 25·0 (22·1–28·1)	n=101; 25·7 (22·6–28·4)
Tobacco use		
Current	65 (20%)	15 (14%)
Previous	128 (39%)	45 (41%)
Never	133 (41%)	50 (45%)
Eastern Cooperative Oncology Group performance status		
0	123/312 (39%)	41/101 (41%)
1	188/312 (60%)	59/101 (58%)
2*	1/312 (<1%)	1/101 (1%)
Time since initial diagnosis, months	n=307; 0·79 (0·26–1·41)	n=105; 0·99 (0·49–1·77)
Intended chemotherapy regimen during induction period		
Carboplatin–paclitaxel	172 (53%)	66 (60%)
Cisplatin–gemcitabine	99 (30%)	27 (25%)
Carboplatin–gemcitabine	55 (17%)	17 (15%)
Response to chemotherapy in the induction period		
Partial or complete response	113 (35%)	39 (35%)
Stable disease	213 (65%)	71 (65%)

Data are median (IQR) or n (%). *Protocol deviation from the study sites.

Table 1: **Patient demographics and baseline characteristics of category 1 patients included in the treatment period (intention-to-treat population)**

assessments are described in the appendix (p 2). Time to deterioration analyses were post hoc. SAS (version 9.4) was used for all statistical analyses.

Role of the funding source

The funder of the study had a role in study design, provision of study drugs, protocol development, regulatory and ethics approvals, safety monitoring, data collection, data analysis, data interpretation, and writing of the report, in collaboration with the study authors.

Results

The trial profile is shown in figure 1. Between July 10, 2018, and Dec 9, 2022, 1505 patients were screened and 636 were enrolled, of whom 94 (15%) had a tissue biopsy only, 55 (9%) had a liquid biopsy only, 483 (76%) had both, and four (1%) had none. 573 (90%) of 636 patients completed the induction period and overall response to chemotherapy during the induction period is shown in the appendix (p 11). 438 (76%) of 573 patients reached disease control and were included in category 1.

Patient demographics and baseline characteristics of category 1 patients are shown in table 1. MGT was assigned to 62 (19%) of 326 patients on the basis of tissue samples only, to 29 (9%) patients on the basis of liquid samples only, and to 233 (71%) patients on the basis of both liquid and tissue samples. Two patients did not provide samples owing to technical problems (appendix p 18). Assigned therapy cohorts are shown in the appendix (p 12). The distribution of actionable alterations in category 1 patients in the intention-to-treat populations of the MGT and control groups are shown in the appendix (p 14). Median follow-up in the treatment period was 24·1 months (IQR 11·6–35·6). The data cutoff for the main analysis was Feb 14, 2023.

Median progression-free survival was 6·1 months (95% CI 4·7–6·5) for the MGT group versus 4·4 months (4·1–5·6) for the chemotherapy group (HR 0·72 [95% CI 0·56–0·92]; p=0·0079; figure 2; appendix p 15). Median progression-free survival in the subgroup of patients with an actionable molecular profile treated with MGT (a targeted therapy or atezolizumab monotherapy) was 8·1 months (95% CI 4·6–8·7) versus 4·7 months (4·0–6·6) in patients with an actionable molecular profile treated with chemotherapy (HR 0·65 [95% CI 0·42–0·99]; figure 3). In the subgroups of patients without an actionable molecular profile, median progression-free survival was 5·5 months (95% CI 4·5–6·4) for those treated with atezolizumab plus chemotherapy and 4·4 months (4·2–5·6) for those treated with chemotherapy (HR 0·76 [95% CI 0·54–1·06]; figure 3). The HRs in most subgroups were consistent with that for the primary analysis (figure 4). Interim overall survival data are shown in the appendix (pp 15, 19). Median overall survival was 14·7 months (95% CI 13·3–17·3) for the MGT group versus 11·0 months (9·7–15·4) for the chemotherapy group.

Progression-free survival and overall survival by individual therapy cohorts are shown in the appendix (p 20). The largest numerical differences were seen in patients with tumour mutational burden-high or

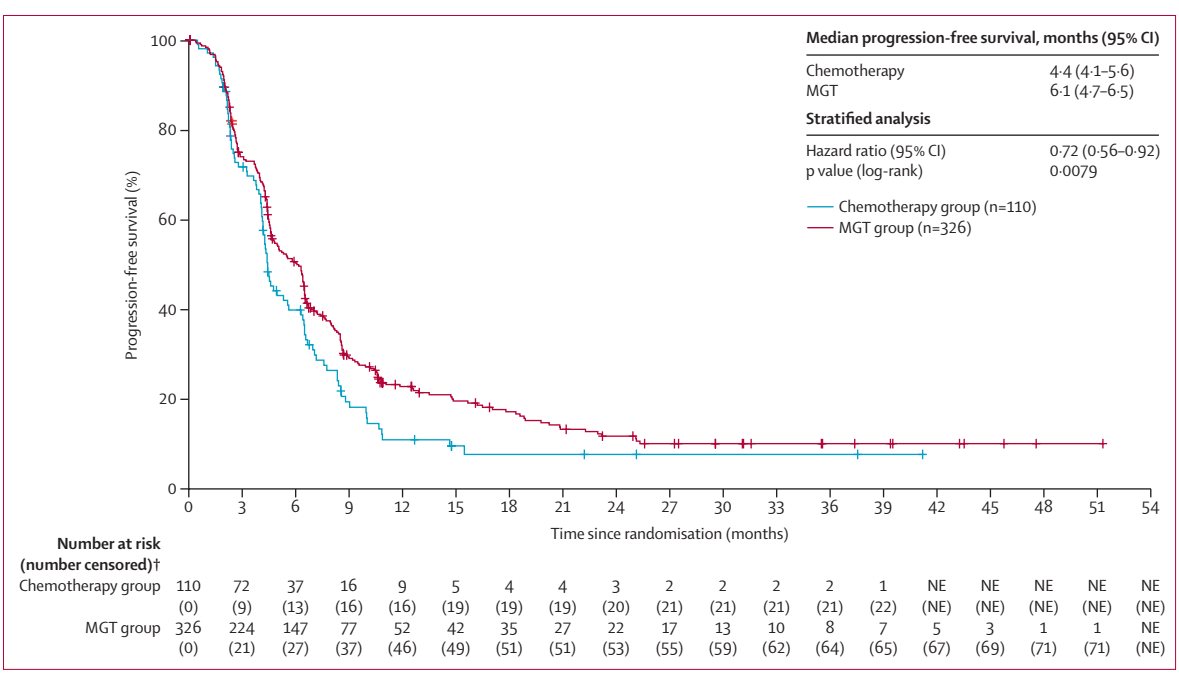

Figure 2: **Progression-free survival in the intention-to-treat population,* category 1 patients**
MGT=molecularly guided therapy. NE=not evaluable. *All patients who were randomly assigned, whether or not the assigned study treatment was received. †Cumulative number censored.

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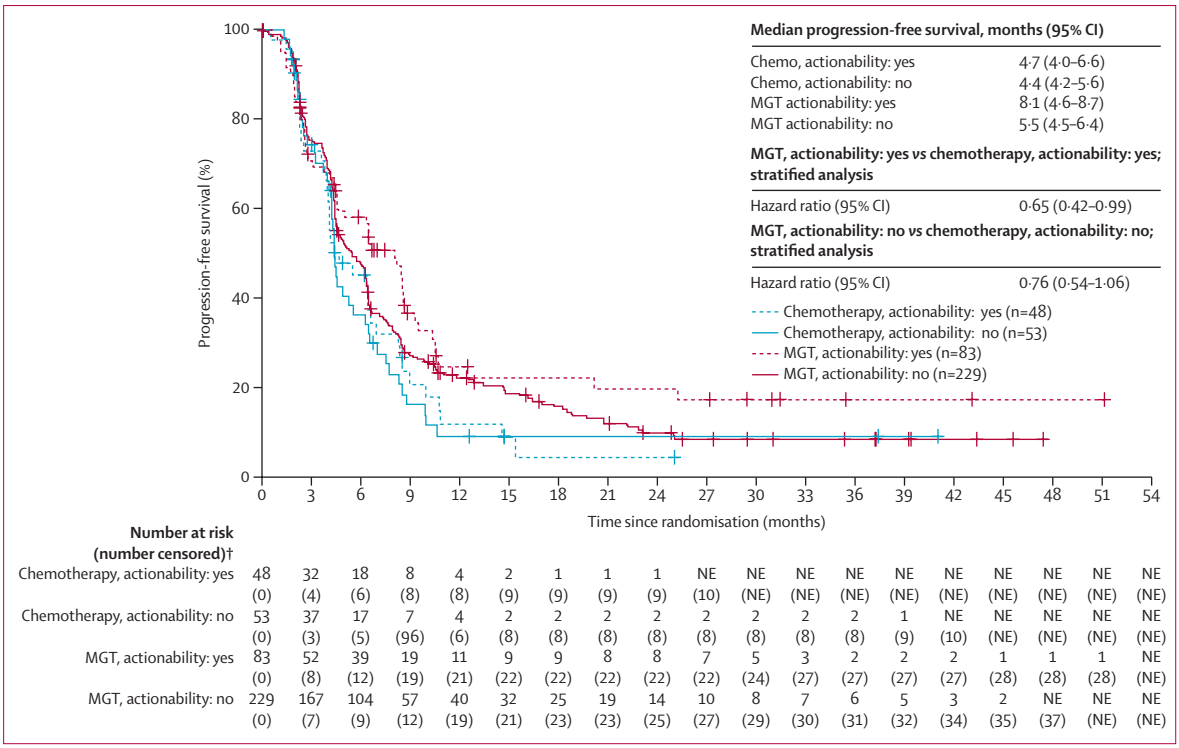

Figure 3: **Progression-free survival for category 1 patients by study group and availability of an actionable molecular profile in the safety population***
MGT=molecularly guided therapy. NE=not evaluable. *The safety population included all patients who received at least one dose of any study drug. †Cumulative number censored.

microsatellite instability-high treated with atezolizumab, *BRAF V600* alterations or *K601E* treated with vemurafenib plus cobimetinib, and in patients with *FGFR1*, *FGFR2*, or *FGFR3* alterations treated with pemigatinib.

Best confirmed overall response rate during the treatment period and following initial response to chemotherapy is shown in the appendix (p 16). Rates were 18% (95% CI 13·8–22·4) in the MGT group and 8% (95% CI 3·81–15·0) in the chemotherapy group, with a difference of 9·6% (95% CI 2·4–16·8). No difference in duration of response was observed (appendix p 24), nor was there a difference in disease control rate (appendix p 17).

Due to differing exposure times between cohorts, adverse events were adjusted for patient-years at risk (shown in table 2). Patients receiving MGT had lower than or similar adverse event rates to those receiving chemotherapy in all adverse event categories, except for serious adverse events leading to withdrawal of treatment and adverse events with fatal outcomes.

No evidence was seen of a different time to deterioration of quality of life in patients in the MGT group compared with those in the chemotherapy group, as measured by the patient-reported outcomes scores (appendix p 25). Time to deterioration of quality of life by cohorts is shown in the appendix (p 26); results were consistent with the respective progression-free survival and overall survival cohort profiles (ie, the relative difference between cohorts appeared similar across endpoints). Patients receiving atezolizumab monotherapy (tumour mutational burden-high or microsatellite instability-high), vemurafenib plus cobimetinib (for *BRAF V600* alterations or *K601E*), or pemigatinib (for *FGFR1*, *FGFR2*, or *FGFR3* alterations) showed longer time to deterioration in self-rated health and general wellbeing quality of life.

Discussion

Despite recent efforts, effective treatment for unfavourable subset CUP has proven elusive.[11,12] To our knowledge, CUPISCO is the first randomised study of MGT for newly diagnosed unfavourable subset CUP and reports positive results. The results from the CUPISCO study show that, compared with standard platinum-based chemotherapy, MGT conferred a significant and clinically meaningful improvement in progression-free survival to patients with previously untreated, unfavourable, non-squamous CUP who reached disease control during an induction period with three platinum-based chemotherapy cycles. Effects were generally consistent across subgroups, with a greater benefit observed in patients who had an actual actionable molecular target for MGT, and in patients treated with MGT who reached a complete response with chemotherapy during the induction period. Although overall survival data were immature at the time of writing, preliminary analyses

	Chemotherapy (n=110)		MGT (n=326)		Hazard ratio (95% Wald CI)
	Number of events/number of patients, n	Median progression-free survival, months (95% CI)	Number of events/number of patients, n	Median progression-free survival, months (95% CI)	
All patients	**87/110**	**4·4 (4·14–5·59)**	**254/326**	**6·0 (4·70–6·47)**	**0·75 (0·59–0·96)**
Gender					
Male	48/57	4·6 (4·07–6·44)	129/165	5·0 (4·47–6·47)	0·74 (0·53–1·03)
Female	39/53	4·4 (3·91–6·47)	125/161	6·4 (5·19–6·67)	0·77 (0·53–1·10)
Response to platinum induction chemotherapy*					
Complete response or partial response	30/39	6·4 (4·24–8·51)	75/113	8·2 (6·37–9·30)	0·73 (0·48–1·12)
Stable disease	57/71	4·2 (3·75–4·57)	179/213	4·9 (4·44–6·28)	0·71 (0·53–0·97)
Response to platinum induction chemotherapy†					
Complete response	2/3	6·5 (4·73–NE)	4/9	23·2 (6·51–NE)	0·38 (0·06–2·37)
Partial response	30/38	6·4 (4·14–8·38)	75/107	6·5 (5·45–8·57)	0·76 (0·50–1·17)
Stable disease	54/68	4·2 (3·75–4·57)	174/209	4·9 (4·44–6·28)	0·71 (0·52–0·97)
Progressive disease‡	1/1	3·2 (NE–NE)	1/1	5·3 (NE–NE)	<0·01 (0·00–NE)
Tobacco use					
Current	13/15	4·1 (3·78–4·50)	53/65	4·6 (4·14–6·44)	0·58 (0·31–1·09)
Previous	34/45	5·6 (4·07–7·13)	98/128	5·0 (4·40–6·47)	0·92 (0·62–1·36)
Never	40/50	4·3 (3·61–6·64)	103/133	6·5 (5·52–7·98)	0·66 (0·46–0·95)
Intended chemotherapy regimen during induction period					
Carboplatin plus gemcitabine	14/17	4·5 (2·37–7·13)	46/55	4·4 (3·94–6·31)	1·02 (0·56–1·86)
Paclitaxel plus gemcitabine	51/66	4·5 (4·14–6·37)	126/172	6·4 (4·93–6·67)	0·69 (0·50–0·96)
Cisplatin plus gemcitabine	22/27	4·2 (2·30– 8·31)	82/99	6·3 (4·57–7·62)	0·73 (0·46–1·48)

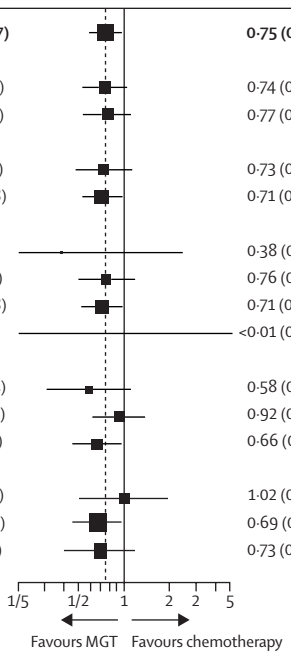

Figure 4: **Progression-free survival for category 1 patients by subgroups**
MGT=molecularly guided therapy.eCRF=electronic case report form. NE=not evaluable. *Interactive voice or web-based response system. †Electronic case report form. ‡Protocol deviations.

suggest that MGT might also result in an overall survival benefit. The best confirmed overall response rate was in favour of MGT versus chemotherapy. We did not find evidence of an effect of MGT on duration of response or disease control rate.

Despite the broad spectrum of MGTs provided, more than two-thirds of patients in the MGT group did not have an actionable target and were treated with continued chemotherapy plus atezolizumab in the absence of any molecular guidance, as suggested by empirical data from other cancer types at the time of study conception.[24,25] The CUPISCO trial was not powered to assess the benefit of adding atezolizumab to chemotherapy. Accordingly, the current results do not allow for firm conclusions to be drawn in this subgroup, but suggest that chemotherapy plus cancer immunotherapy combinations should be further explored for this patient cohort. A dedicated analysis of CUPISCO data would be needed to obtain an unbiased HR estimate and a corresponding test for the effect of atezolizumab plus chemotherapy, controlling for other potential sources of confounding. Similarly, a benefit of chemotherapy plus immunotherapy over standard chemotherapy alone has not been universally found in other cancers, and additional predictive biomarkers are needed to assist in the selection of patients with CUP who can benefit from the addition of immunotherapy.[24,26–28]

Although CUPISCO was not designed to statistically analyse individual cohorts, the response to MGTs appeared to be highly diverse and the individual target mattered. An improved outcome in the MGT group was observed in patients receiving atezolizumab monotherapy (in patients with tumour mutational burden-high or microsatellite instability-high), vemurafenib plus cobimetinib (in patients with *BRAF V600* alterations or *K601E*), or pemigatinib (in patients with *FGFR1, FGFR2,* or *FGFR3* alterations). We observed that these cohorts had consistently longer progression-free survival, overall survival, and time to deterioration in self-rated health and general wellbeing quality of life; however, further investigation is needed.

The results of the CUPISCO trial suggest that early CGP by tissue-based or liquid-based testing, or both, and incorporation of MGT into the treatment armamentarium of first-line therapy improves progression-free survival in patients with CUP. Given the overall poor prognosis of unfavourable CUP and the high risk of rapid clinical deterioration of patients with this malignancy, the window of opportunity for MGT might otherwise be missed. Accordingly, incorporation of CGP into first-line therapy is also supported by the limited success of earlier

	Molecularly guided therapy (n=312)	Chemotherapy (n=101)
Total number of adverse events	3069	550
Total patient deaths	185 (59%)	58 (57%)
Patients with at least one of the following (first occurrence)		
Adverse events		
Total patient-years at risk	22·3	4·7
Number of adverse event onsets observed	295	89
Adverse event rate per 100 patient-years at risk	1324 (1172·9 to 1475·1)	1908·8 (1512·3 to 2305·4)
Adverse events leading to withdrawal from treatment		
Total patient-years at risk	212	22
Number of adverse event onsets observed	76	17
Adverse event rate per 100 patient-years at risk	35·9 (27·8 to 43·9)	77·3 (40·6 to 114·1)
Adverse event leading to dose modification or interruption		
Total patient-years at risk	104·3	15·7
Number of adverse event onsets observed	197	50
Adverse event rate per 100 patient-years at risk	188·9 (162·5 to 215·3)	318·6 (230·3 to 406·9)
Serious adverse events		
Total patient-years at risk	202·5	25·2
Number of adverse event onsets observed	112	13
Adverse event rate per 100 patient-years at risk	55·3 (45·1 to 65·5)	51·5 (23·5 to 79·5)
Serious adverse events leading to withdrawal from treatment		
Total patient-years at risk	251·2	26·5
Number of adverse event onsets observed	23	1
Adverse event rate per 100 patient-years at risk	9·2 (5·4 to 12·9)	3·8 (−3·6 to 11·2)
Serious adverse events leading to dose modification or interruption		
Total patient-years at risk	227·4	25·5
Number of adverse event onsets observed	57	8
Adverse event rate per 100 patient-years at risk	25·1 (18·6 to 31·6)	31·4 (9·6 to 53·1)
Related adverse events		
Total patient-years at risk	39·7	6·5
Number of adverse event onsets observed	267	84
Adverse event rate per 100 patient-years at risk	672·9 (592·2 to 753·7)	1286·4 (1011·3 to 1561·5)
Related adverse events leading to withdrawal from treatment		
Total patient-years at risk	213·4	22
Number of adverse event onsets observed	68	17
Adverse event rate per 100 patient-years at risk	31·9 (24·3 to 39·4)	77·3 (40·6 to 114·1)
(Continued from previous column)		
Related adverse events leading to dose modification or interruption		
Total patient-years at risk	130·1	16·2
Number of adverse event onsets observed	163	47
Adverse event rate per 100 patient-years at risk	125·3 (106·1 to 144·6)	290·5 (207·5 to 373·6)
Related serious adverse events		
Total patient-years at risk	232·9	25·7
Number of adverse event onsets observed	54	7
Adverse event rate per 100 patient-years at risk	23·2 (17·0 to 29·4)	27·2 (7·1 to 47·4)
Adverse events with fatal outcome†		
Total patient-years at risk	257·3	26·5
Number of adverse event onsets observed	13	0
Adverse event rate per 100 patient-years at risk	5·1 (2·3 to 7·8)	0 (NE to NE)
Grade 3–5 adverse events		
Total patient-years at risk	127·5	17·2
Number of adverse event onsets observed	194	44
Adverse event rate per 100 patient-years at risk	152·1 (130·7 to 173·5)	255·9 (180·4 to 331·6)
Related grade 3–5 adverse events		
Total patient-years at risk	160·9	18
Number of adverse event onsets observed	146	37
Adverse event rate per 100 patient-years at risk	90·7 (76·0 to 105·5)	205·3 (139·1 to 271·4)

Data are total patient-years at risk, number of adverse event onsets observed, and adverse event rate per 100 patient-years at risk (95% CI), unless otherwise specified. This table includes adverse events started on or after the first dosing date in the treatment period to the end of the adverse event reporting period (last dosing date +90 days for the atezolizumab and atezolizumab plus chemotherapy cohorts; +30 days for other cohorts), and adverse events started before the first dosing date in the treatment period and ongoing or ending after the first dosing date in the treatment period with a worsening in grade. Total patient-years at risk is the sum over all patients of the time intervals (in years) from the first dosing date in the treatment period to the onset date of the first occurrence of the adverse event (or the end of the adverse event reporting period for patients without adverse event). 95% CIs for rates were constructed using the exact method. NE=not evaluable. *The safety population included all patients who received at least one dose of any study drug. †Two fatal adverse events occurred in patients treated with atezolizumab (one fatal adverse event was related to atezolizumab treatment in combination with gemcitabine and concurrent illness [medical history of this patient included probable upper respiratory infection], and one was related to atezolizumab only, and possibly related to underlying pathology, paraneoplastic aetiology, and evacuatory paracentesis).

Table 2: **Safety summary for category 1 patients in the safety population* adverse events adjusted for patient-years at risk**

precision oncology trials such as MOSCATO[29] and SHIVA,[30] which included only patients with heavily pretreated, advanced cancers. Moreover, a next-generation sequencing study including patients with CUP has shown that, because of interim worsening of

performance status, MGT could be implemented in only very few patients, highlighting the benefit of the approach used in CUPISCO (ie, treating patients with chemotherapy while awaiting next-generation sequencing results).[31] As CUP can be viewed as a tissue-agnostic paradigm metastatic malignancy, CUPISCO's results could also have implications for other cancer types, which is supported by data published by Matsubara and colleagues, who observed a clinical benefit of CGP in patients with previously untreated metastatic or recurrent solid tumours.[32]

No major safety signals were raised during the study. Overall, the incidence rate of adverse events in the MGT group was similar or lower than in the chemotherapy group, except for serious adverse events leading to treatment discontinuation and adverse events with fatal outcomes. These findings are notable given that chemotherapy was administered for a short, fixed duration (three to six cycles for most patients), whereas MGT was administered for prolonged periods (until loss of clinical benefit). However, despite the differing administration times, quality of life was similar in both groups. Furthermore, adverse events observed during MGT were generally manageable, because the therapies included were already used in clinical practice and their safety profiles are well understood.

With the aim of providing proof-of-concept for the inclusion of broad molecular profiling in routine clinical practice to inform treatment strategies for patients with CUP, several MGTs from different pharmaceutical companies were used in CUPISCO, with per-protocol allowance of additional groups with new MGTs upon emerging evidence within an adaptive study design. Accordingly, entrectinib, pemigatinib, and ivosidenib cohorts were added while the trial was ongoing. Following on from the CUPISCO results, further refining and researching this approach will be important because multiple new effective treatments for molecular targets previously thought not to be targetable (eg, *KRAS*) as well as novel molecular diagnostics are being developed. Future analysis of the CUPISCO category 2 patient cohort, which received MGT after progression on induction chemotherapy, will further shed light on whether upfront MGT improves outcomes compared with targeted treatment after progression on chemotherapy.

CUPISCO succeeded in its aim of demonstrating the feasibility of a CGP-based and molecular tumour board-based large-scale clinical trial. Tissue material is scarce in CUP because a primary tumour is missing, and in metastatic malignancies, tumour samples are frequently taken by needle biopsy only. Moreover, the scarce material is often used for extensive immunohistochemical analyses for tissue-of-origin determination. Therefore, liquid next-generation sequencing is important to support as many patients as possible, especially considering the number of treatment decisions based on liquid next-generation sequencing in this study and the high rate of ineligibility during the screening period (partly due to lack of tissue). For cases where blood and tissue samples led to treatment decision discrepancies, the tumour fraction in liquid biopsies was one of the major determinants in deciding whether the results from liquid or tissue biopsies were prioritised or taken into account. Ultimately, the investigator made the final treatment decision for the patient.

Considerable efforts, including an elaborate eligibility process with reference pathology and oncology, were done in CUPISCO to include only patients with true CUP and to exclude other cancers. The rate of ineligibility during the screening period due to confirmation of a non-CUP diagnosis at central review based on the 2015 ESMO CUP guidelines[7] was high (39%). Therefore, ESMO CUP guidelines were updated to include central pathology work-up according to state-of-the-art diagnostic methods and novel differential diagnostic algorithms during CUPISCO.[3,33] These algorithms will help to better define this disease entity.[3]

Limitations of the study include the open-label design, the investigator assessment of progression-free survival, and the modest progression-free survival improvement in the MGT group compared with chemotherapy. In terms of generalisability CUPISCO specifically included patients with unfavourable, non-squamous CUP, who account for 80% of all CUP cases. The generalisability of CUPISCO could also depend on location: CGP could be readily available in some countries or centres, but not in others. Randomly assigning patients who had disease control after three cycles of chemotherapy might have selected for the more favourable patients in the unfavourable CUP subset (76% of enrolled patients). Analysis of the CUPISCO category 2 patient cohort, which received MGT after progression on induction chemotherapy, will also shed light on this question. Finally, ancestry was not taken into account in CUPISCO, but tumour mutational burden-high has been shown to be significantly associated with improved outcomes only in European ancestries[34] and merits validation in non-European ancestry populations. Ancestry-aware, tumour-only tumour mutational burden calibration and ancestry-diverse biomarker studies are crucial to ensure that existing disparities are not exacerbated in precision medicine.

CUP is a heterogenous disease, which most likely includes cases derived from many different tissues of origin. Indeed, improved progression-free survival of patients in the MGT group might at least in part be related to a mix of various specific cancers containing different targetable alterations being subsumed as CUP despite a rigorous study-eligibility process. This makes CGP even more important and relevant in cases where a primary cancer cannot be identified. Future analyses will aim to identify, by DNA methylation profiling, tissue-of-origin from CUPISCO participants from whom leftover tumour biopsy material is available, as part of

the trial's translational analysis plan, and correlate tissue-of-origin with mutational profiles and response to the respective treatment. Along the same lines, in contrast to earlier studies,[11,12] a current trial now suggests that gene expression-profiling-based, tissue-of-origin identification with subsequent primary site-directed therapy might after all be able to improve survival compared with platinum-based chemotherapy in patients with CUP.[35] As research into CUP diagnosis, molecular characterisation, and therapy has gained momentum, additional trials are necessary to establish the best therapy for each patient.

In conclusion, CUPISCO demonstrated the value of including CGP in the initial diagnostic work-up to inform treatment decisions for patients with newly diagnosed, unfavourable CUP by means of tissue or liquid biopsies, or both, thus expanding treatment options for these patients. On the basis of these results, we recommend that CGP is performed at initial diagnosis for patients with unfavourable CUP.

Contributors

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Data sharing

For more on **Roche's criteria** for eligible studies see https://vivli.org/members/ourmembers/

For more on **Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents** see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm

Qualified researchers may request access to individual patient-level data through the clinical study data request platform.

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