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Cancer Diagnostics and Molecular Pathology

A Challenging Task: Identifying Patients with Cancer of Unknown Primary (CUP) According to ESMO Guidelines: The CUPISCO Trial Experience

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Key Words. Cancer of unknown primary • Diagnosis • Histology • Molecularly guided therapy • Comprehensive genomic profiling • Next-generation sequencing

Abstract

Background. CUPISCO is an ongoing randomized phase II trial (NCT03498521) comparing molecularly guided therapy versus platinum-based chemotherapy in patients newly diagnosed with "unfavorable" cancer of unknown primary (CUP).

Materials and Methods. Patients with an unfavorable CUP diagnosis, as defined by the European Society of Medical Oncology (ESMO), and available cancer tissue for molecular sequencing are generally eligible. Potential patients with CUP entering screening undergo a review involving reference histopathology and clinical work-up by a central eligibility review team (ERT). Patients with "favorable" CUP, a strongly suspected primary site of origin, lack of tissue, or unmet inclusion criteria are excluded.

Results. As of April 30, 2020, 628 patients had entered screening and 346 (55.1%) were screen failed. Screen fails were due to technical reasons (n = 89), failure to meet inclusion and exclusion criteria not directly related to CUP diagnosis (n = 89), and other reasons (n = 33). A total of 124 (35.8%) patients were excluded because unfavorable adeno- or poorly differentiated CUP could not be confirmed by the ERT. These cases were classified into three groups ineligible because of (a) histologic subtype, such as squamous and neuroendocrine, or favorable CUP; (b) evidence of a possible primary tumor; or (c) noncarcinoma histology.

Conclusion. Experience with CUPISCO has highlighted challenges with standardized screening in an international clinical trial and the difficulties in diagnosing unfavorable CUP. Reconfirmation of unfavorable CUP by an ERT in a clinical trial can result in many reasons for screen failures. By sharing this experience, we aim to foster understanding of diagnostic challenges and improve diagnostic pathology and clinical CUP algorithms. ***The Oncologist*** 2021;26:e769–e779

Implications for Practice: A high unmet need exists for improved treatment of cancer of unknown primary (CUP); however, study in a trial setting is faced with the significant challenge of definitively distinguishing CUP from other cancer types. This article reports the authors' experience of this challenge so far in the ongoing CUPISCO trial, which compares treatments guided by patients' unique genetic signatures versus standard chemotherapy. The data presented will aid future decision-

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making regarding diagnosing true CUP cases; this will have far-reaching implications in the design, execution, and interpretation of not only CUPISCO but also future clinical studies aiming to find much-needed treatment strategies.

Introduction

Cancer of unknown primary (CUP) is defined as a histologically confirmed metastatic cancer for which a standardized diagnostic workup fails to identify a definitive site of origin [1–3]. The majority of patients with CUP lack effective therapeutic regimens [3] and display substantial resistance to therapy [4], creating a high unmet need for better treatment. With an ever-evolving landscape of targeted therapies, immunotherapies, and DNA sequencing technologies, the randomized phase II CUPISCO trial (ClinicalTrials.gov identifier: NCT03498521) seeks to compare molecularly-guided therapy and immunotherapy with standard, empirical, platinum-based chemotherapy in patients with CUP [5].

The CUP guidelines of the European Society of Medical Oncology (ESMO) give a detailed recommendation for clinical diagnostic tests that should be performed at first diagnosis to identify the site of origin [3]. These include a histologic work-up with immunohistochemical (IHC) staining, an in-depth medical history, and thorough physical examination and basic blood and biochemical analyses, along with a chest, abdominal, and pelvic computed tomography (CT) scan in all patients. Mammography is also recommended for all women. Dependent on the clinical and IHC picture of metastases, additional tests are required, namely breast magnetic resonance imaging (MRI) in women with axillary lymph node metastases, serum α-fetoprotein, and human chorionic gonadotropin in patients with midline metastatic disease, and serum prostate-specific antigen in men with bone metastases suggestive of prostate cancer. Further tests, including endoscopies, should be performed in a sign, symptom, and laboratory-oriented manner. Accordingly, CUP is a diagnosis of exclusion; if the diagnostic workup does not allow definitive identification of a primary tumor, a CUP diagnosis is maintained [3, 6].

Beyond diagnostic recommendations, the ESMO guidelines offer a definition of distinct "favorable" CUP subsets, which include approximately 15%–20% of patients [3]. There are two scenarios to classify a CUP as favorable: either clinical picture and tissue workup in pathology are highly suggestive of one of a defined set of specific primary tumors that warrant established treatment tailored to this putative site of origin [3], or metastases are amenable to localized treatment with surgery or radiotherapy with curative intent. The remaining 80%–85% of CUP cases are classified as "unfavorable" because of their poor prognosis and are generally recommended empiric chemotherapy (supplemental online Fig. 1). Whereas the primary tumor is enigmatic in some of these unfavorable CUP cases, a putative primary might be assumed in others because of the clinical picture, a specific IHC pattern or the RNA sequencing profile. This putative primary has traditionally been considered a guide for cancer patient management [4, 7–10]. Although site-specific versus empiric treatment has been discussed as beneficial, especially for CUP subsets such as potential renal cell carcinoma (RCC)-CUP and lung-CUP, two recent randomized trials have shown that RNA sequencing-based putative primary prediction, followed by systemic treatment tailored to this putative primary, was not superior to standard empiric chemotherapy [11, 12].

The CUPSICO trial (Fig. 1) is targeting newly diagnosed patients with unfavorable CUP, as defined by ESMO guidelines, with adenocarcinoma or undifferentiated carcinoma histology. Patients with CUP with favorable prognosis subsets, squamous cell carcinomas, and neuroendocrine tumors are excluded from the CUPISCO trial. When starting the study, it became clear that the eligibility process was confronted with the above-mentioned diagnostic difficulties, which were reflected by a substantial screen failure rate. In this article, we describe our experience in identifying "true" unfavorable CUP for the first 628 patients that entered screening for CUPISCO. We report on the clinicopathological challenges associated with diagnosis of unfavorable CUP in the setting of a clinical trial, where more stringent criteria are typically needed for treatment decisions than in daily clinical practice and suggest, based on the ESMO guidelines, refinements of diagnostic algorithms.

Materials and Methods

Study Design

CUPISCO is a phase II, randomized, open-label, active-controlled, multicenter trial to assess the efficacy and safety of molecularly-guided therapy based on comprehensive genomic profiling versus platinum-based standard chemotherapy in poor-risk CUP (Fig. 1) [5]. The CUPISCO trial protocol and informed consent form has been approved by more than 30 countries across the globe. Informed consent was obtained from all patients entering the trial. By consenting, patients also agreed to the use of their data for the purpose of publication in the case that they failed screening.

Eligibility Review

The key eligibility criterion for participants in the CUPISCO study is histologically confirmed unfavorable CUP according to ESMO criteria [3, 5]. Eligible patients are required to have a systemic therapy-naive adenocarcinoma or undifferentiated carcinoma, Eastern Cooperative Oncology Group performance status of 0 or 1, and at least one measurable lesion according to the RECIST guideline [5, 13]. In addition to the standardized clinical workup, sites are required to follow the minimum pathology workup outlined in the ESMO guidelines (supplemental online Fig. 2) [3]. Additional assessments to exclude a carcinoma of known origin (e.g., specialized physical examination, endoscopy, imaging, laboratory and blood tests, or additional IHC) can be indicated based on the clinical and pathological picture. Upon completion of local diagnostic workup, samples and patient

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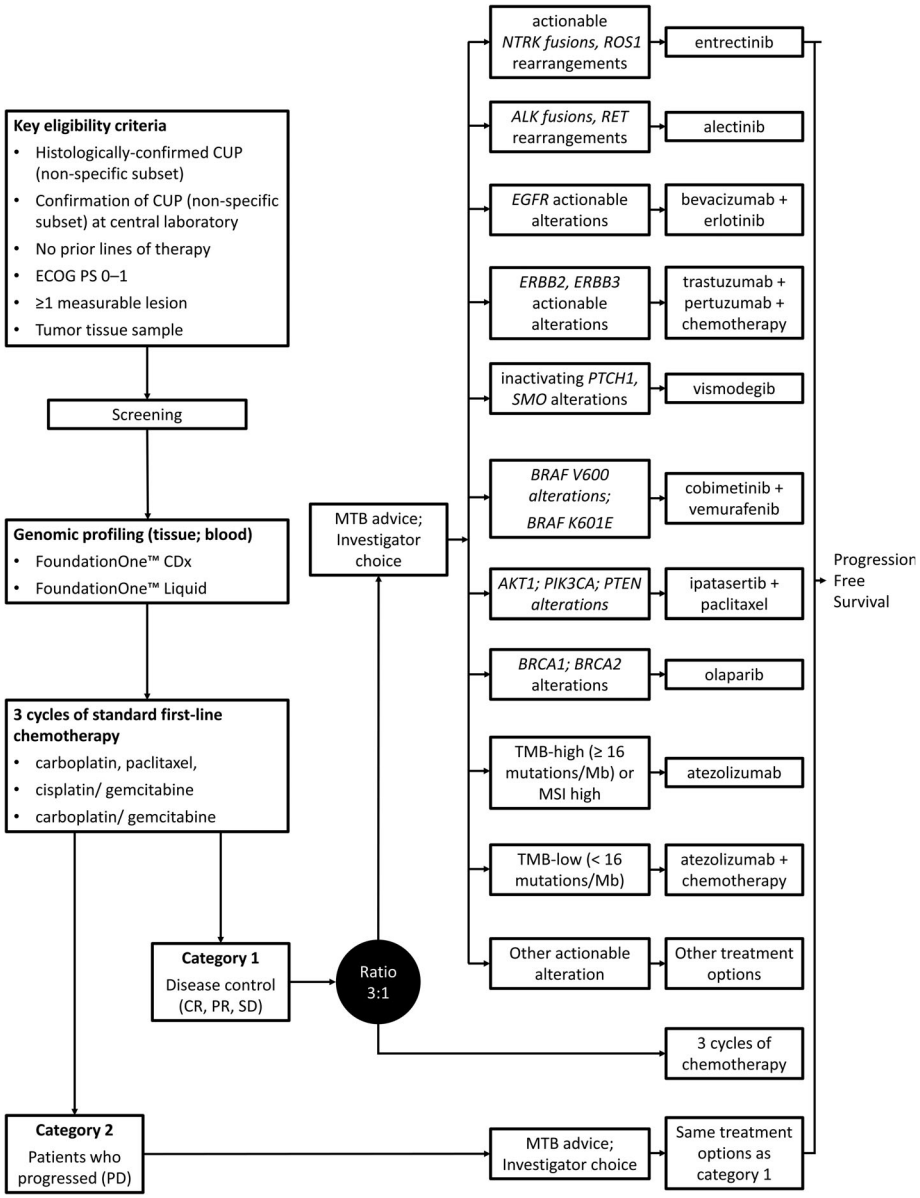

Figure 1. CUPISCO (NCT03498521) study design. A phase II, randomized, open-label, active-controlled, multicenter trial to directly assess whether molecularly guided therapy (MGT), based on comprehensive genomic profiling, is superior to recommended systemic chemotherapy in patients with poor-prognosis CUP who have achieved disease control after receiving three cycles of first-line platinum-doublet induction chemotherapy. Following induction therapy, patients are categorized as either category 1 patients, who achieved disease control (CR, PR, SD), or category 2 patients, who experienced disease progression. Category 1 patients will be randomized and category 2 patients will go directly to targeted therapy (as they progressed on chemotherapy), according to comprehensive genomic profiling and an MTB recommendation. The primary endpoint of the CUPISCO study is progression-free survival in patients who achieved disease control after receiving three cycles of platinum-doublet induction chemotherapy (category 1 patients). The primary comparison is between MGT (pooled) and standard chemotherapy.
Abbreviations: CDx, companion diagnostic; CR, complete response; CUP, cancer of unknown primary; ECOG PS, Eastern Cooperative Oncology Group perfomance status; MSI, microsatellite instability; MTB, molecular tumor board; PD, progressive disease; PR, partial repsonse; SD, stable disease; TMB, tumor mutation burden.

data are assessed for overall eligibility for CUPISCO by an eligibility review team (ERT), meaning the diagnosis is verified. The process conducted by the ERT includes an assessment of tissue quantity and quality as well as a histology and/or IHC confirmation by the central pathology and medical team and, if needed, the referent oncologist and/or central radiology. Clinical consistency with the ESMO guidelines and the study protocol for the identification of patients with unfavorable CUP is also confirmed. After assessment, eligible patients can be enrolled (Fig. 1).

Results

As of an April 30, 2020, cutoff date, 628 patients had entered the screening process for CUPISCO. At this point, 10 (1.6%) patients were in active screening. Of the

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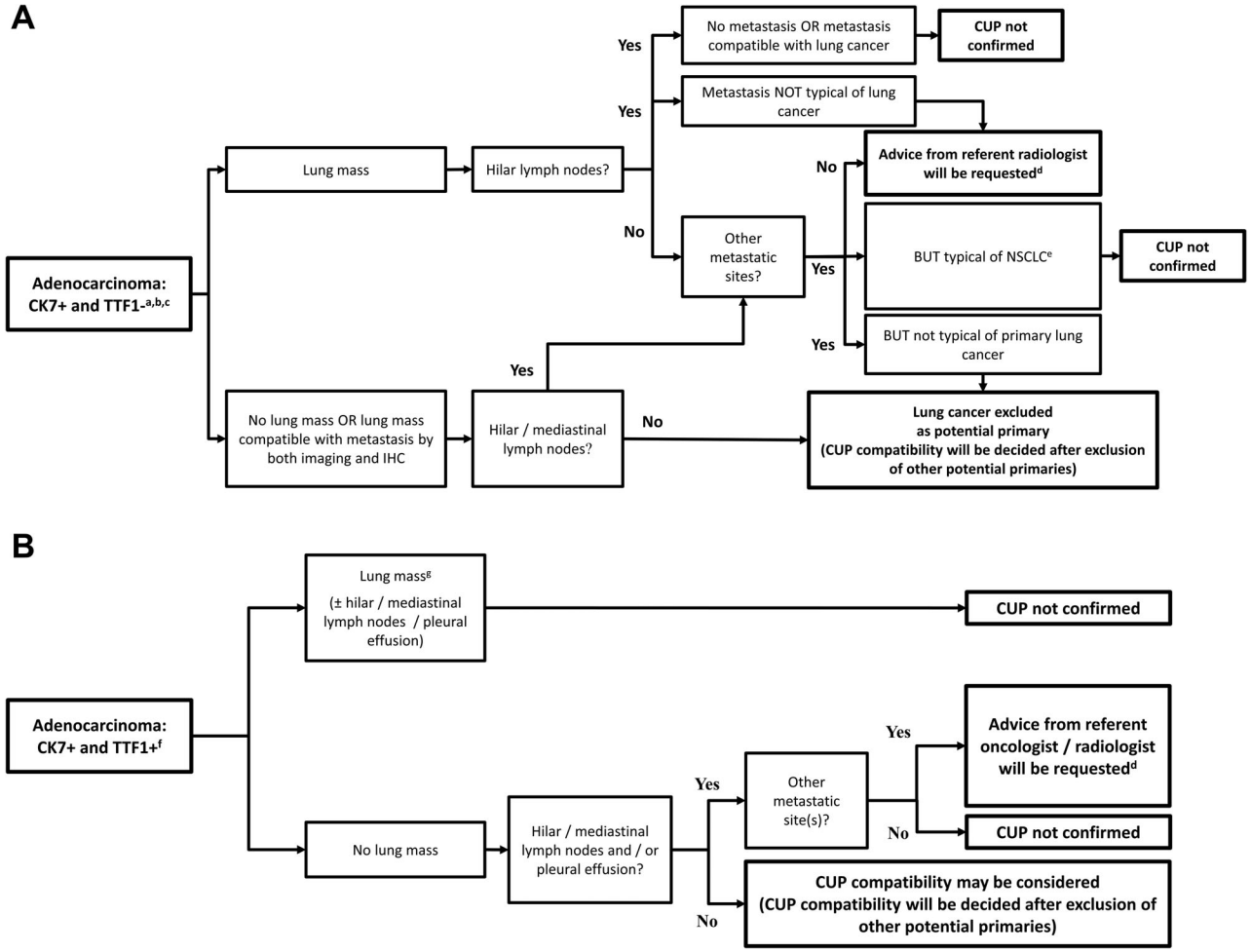

Figure 2. Eligibility review lung algorithm for diagnostic workup in adenocarcinoma that are (**A**) CK7+ and TTF1− and (**B**) CK7+ and TTF1+. [a]Special cases re-reviewed by the reference oncologist and/or radiologist. [b]If imaging is incomplete or of an insufficient quality to comply with this algorithm, better quality and/or additional imaging may be requested by the eligibility review team for medical assessment. [c]Nonspecific profile not excluding lung cancer; may be revisited at time of ''other metastatic sites'' consideration. [d]Escalation to referent experts is triggered by the eligibility review team. Note: All cases may be escalated. Decisions may occur that deviate from the algorithm for case scenarios that were not previously encountered. [e]Brain, bone, liver, adrenal glands, and pleura are the most common sites of metastatic disease [32]. [f]Accepted markers for identification of differentiation toward adenocarcinoma are TTF1 and Napsin A, both of which are approximately 80% sensitive, although TTF1 is easier to assess as a nuclear stain [33]. [g]May be one or more lung masses.
Abbreviations: CK, cytokeratin; CUP, cancer of unknown primary; IHC, immunohistochemistry; max, maximum; NSCLC, non-small cell lung cancer; TTF1, thyroid transcription factor 1.

618 (98.4%) that completed screening, 272 (44%) were confirmed as unfavorable CUP cases by the ERT and were enrolled into the trial, whereas 346 (56.0%) patients had been screen failed (Table 1) because of unmet inclusion criteria (supplemental online Fig. 3). Gender and age distribution were similar in the enrolled and screen failed cohorts (supplemental online Table 1). Screen failure rates were comparable between countries (data not shown).

Of the 346 screen failures, 89 (25.7%) constituted technical failures related to tissue quantity or quality insufficient for CUP confirmation by the ERT and sequencing; 89 (25.7%) did not meet study-specific inclusion criteria that were unrelated to CUP diagnosis, such as laboratory results (e.g., high bilirubin levels), physical preconditions (e.g., known liver disease: hepatitis), and physical performance status; 11 (3.2%) qualified for a rescreening after an initial screen failure (e.g., because of an old [>4 months] initial biopsy specimen); and 33 (9.5%) patients were screen failures for other reasons (e.g., patient withdrawal, physical condition, or death; Table 1).

Table 1. Summary of screening failures

Screening failures	*n* = 346
Failure due to the lack of confirmation of adeno- or poorly differentiated CUP	124
Technical failures (e.g., insufficient quality or quantity of tissue, errors in data reporting)	89
Failure to meet inclusion criteria, unrelated to CUP diagnosis	89
Other reasons (urgent treatment needed, withdrawal by patient or death)	33
Rescreening of individual	11

Abbreviation: CUP, cancer of unkown primary.

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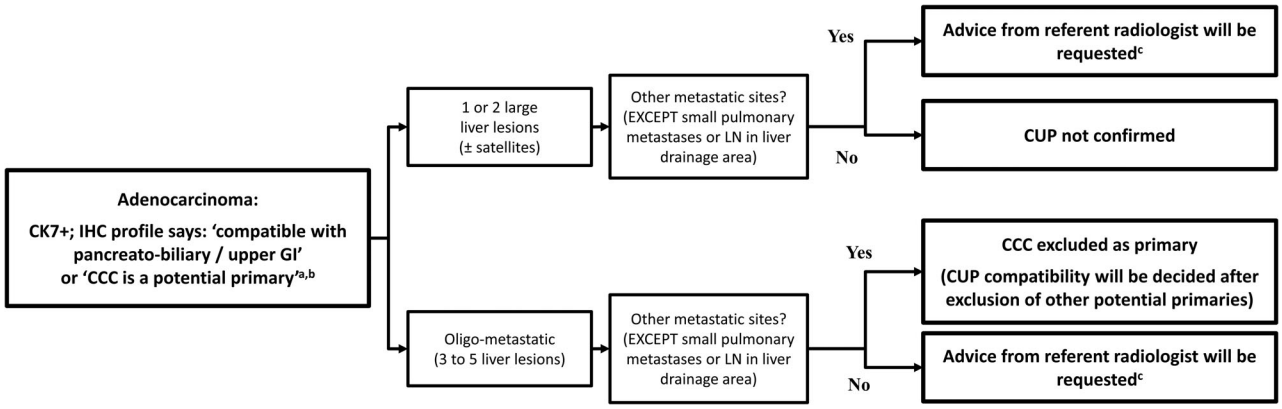

Figure 3. Eligibility review intrahepatic cholangiocellular carcinoma (iCCC) algorithm for diagnostic workup. [a]Pancreato-biliary histology is compatible with CUP; however, iCCCs should be ruled out with help from referent radiologist. [b]MRI may be requested by the eligibility review team to provide more specific assessment of disease. [c]Escalation to referent experts is triggered by the eligibility review team.
Abbreviations: CCC, cholangiocellular carcinoma; CK, cytokeratin; CUP, cancer of unknown primary; GI, gastrointestinal; IHC, immunohistochemistry; LN, lymph node.

Diagnosis of unfavorable adeno- or poorly differentiated CUP could not be confirmed by the ERT in 124 (35.8%) cases and were excluded (Tables 1, 2). In these cases, the unfavorable CUP diagnosis was rejected by the ERT on the grounds of pathology alone in 46 (37.1%) cases, with the remaining 78 (62.9%) rejected because of a combination of pathology, radiology and clinical presentation (e.g., imaging, endoscopy, physical examination). In view of the high screen failure rate and the strong desire to thoroughly substantiate our decisions, we expanded the pathologic and immuno-histologic workup beyond those outlined by ESMO (Table 3).

Cases Not Compatible with Study Inclusion Criteria Because of the Histologic Subtype (Squamous or Neuroendocrine Histology or Favorable CUP Subtype)

Among screen failures related to central pathology review, 31 (25%) patients were excluded because of histologic subtype (squamous cell carcinomas and neuroendocrine tumors [NETs]) and the diagnosis of a favorable CUP subgroup. Of the 10 (8%) squamous cell carcinomas (p40+, p63 +, CK5/6+), 1 was keratinizing and 9 showed a non-keratinizing, poorly differentiated morphology, five of which showed strong block-type positivity for p16-IHC as a surrogate marker for a human papillomavirus infection. A confirmed neuroendocrine histology (NET, G2, and G3) with characteristic synaptophysin and/or chromogranin A staining was found in 10 (8%) cases. Eight biopsies were from the liver and two from an intraabdominal lesion. Eleven patients (8.8%) were excluded because of a colorectal IHC signature (CK7−, CK20+, CDX2+) representing a favorable CUP subgroup.

Carcinoma Cases Not Compatible with CUP Because of Proof or Strong Evidence of a Likely Primary Tumor

After additional IHC and clinical and radiological correlation, the ERT felt that the primary tumor had been effectively identified to discard a diagnosis of CUP in 80 (64.5%) patients with a confirmed carcinoma. Nineteen (15.3%) patients were deemed compatible with a diagnosis of a primary lung neoplasm according to histopathology and the clinical presentation (Fig. 2). To assess the morphology of lung lesions and discriminate between putative primary versus lung metastases, seven of these cases were escalated to our reference radiologist. Overall, one case was diagnosed as an adenoid cystic carcinoma of the lung and 18 cases were classified as non-small cell lung cancer (NSCLC) rather than CUP, with 12 (9.6%) positive for cytokeratin 7 (CK7), thyroid transcription factor 1 (TTF1), and Napsin A. Three of these cases showed a false negative result for TTF1 in the local pathology workup and tested strongly TTF1-positive in the central laboratory workup. Six cases were positive for CK7 and confirmed negative for TTF1 and Napsin A but were clinically compatible with metastatic lung cancer (Fig. 2). Two patients had to be excluded based on a histologic and clinical picture compatible with a salivary gland neoplasm, and one patient was excluded with a primary thyroid neoplasm. A young female patient with severe pleural effusions, a paravertebral mass, and pleural infiltration was classified as having a NUT carcinoma, an aggressive, poorly differentiated carcinoma defined by the presence of a NUTM1-rearrangement. The biopsy showed small- to intermediate-sized cells with a monomorphic appearance, nuclei with granular to coarse chromatin, and strong positivity for NUT (speckled nuclear positivity) (supplemental online Fig. 4).

After careful review, seven (5.7%) patients with presumed pancreatic hepatobiliary origin were classified as intrahepatic cholangiocellular carcinoma (iCCC), four of them after an escalation to reference radiology (Fig. 3). Another eight (6.5%) patients were deemed compatible with a primary tumor in the pancreas, seven with pancreatic ductal adenocarcinoma and one with acinic cell carcinoma. In seven (5.7%) patients, a CUP exclusion was made based on the diagnosis of a gastrointestinal primary tumor, three gastric carcinomas, two colorectal, and two appendix carcinomas presenting with a pseudomyxoma peritonei. One liver biopsy and one lung biopsy were classified as

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hepatocellular carcinoma by morphology and confirmed by IHC (arginase-1 positivity).

In total, nine (7.3%) cases were classified metastatic breast cancer. Two patients were found to be hormone receptor (estrogen, progesterone)-positive, one patient had a metaplastic carcinoma, and six presented with metastatic triple-negative breast cancer (TNBC) based on pathology, imaging, and clinical workup (e.g., axillary/internal mammary chain lymph node positive or positive breast cancer history). Eight (6.5%) patients were excluded based on a diagnosis compatible with a female reproductive organ primary tumor (two uterine, six adnexa). Six (4.8%) of these patients were screen failed because of a serous carcinoma (high-grade) histology and marker profile (strong positivity for CK7, Pax8, WT1, and p53 plus estrogen receptor positivity in 4 cases) with masses in the gynecological tract or abdominal cavity. As per ESMO guidelines, peritoneal adenocarcinomatosis of a serous papillary histological type (no distinction between low- or high-grade) belongs to the favorable-risk CUPs, and these patients are not eligible. Patients with such a histology and marker profile can only be eligible when no mass in the abdominal cavity is found (e.g., to rule out primary peritoneal serous carcinoma).

Recently, two publications presented data suggesting that 4%–5% of patients with CUP show IHC profiles consistent with metastatic renal cell carcinoma (mRCC) [14, 15] in the absence of renal cancer imaging. We excluded eight (6.5%) patients based on histomorphology, IHC profile (Pax8, Pax2, CD10, Racemase, RCC, CAIX, TFE3, TFEB), and compatibility with RCC in contrast-enhanced CT/MRI imaging. Another six patients with a suspicious IHC profile did not present with a renal mass after careful clinical workup and high-resolution CT/MRI and were confirmed as eligible for the CUPISO trial. An additional six (4.8%) patients were excluded as a primary tumor in the bladder or ureter was found after IHC profiles were suggestive of a urinary system tumor. In two male patients, a prostate adenocarcinoma was confirmed and both showed a negative IHC stain for prostate-specific antigen (PSA), but the morphology was indicative and the IHC for prostate-specific membrane antigen (PSMA) was positive. Additional makers such as PSMA and NKX3-1 (homeobox protein) are highly recommended to be included in the workup, as it is known that PSA can be negative in poorly differentiated metastatic prostate cancer [16].

Cases Not Compatible with CUP Because of Noncarcinoma Entities in Central Review

In total, 13 (10.5%) cases were classified as noncarcinoma entities. Seven (5.7%) patients screen failed because of the diagnosis of a malignant soft tissue tumor. Soft tissue tumors that show cytokeratin positivity can easily be misdiagnosed as carcinoma; in four (3.2%) of the cases, additional molecular testing was performed to confirm the diagnoses and guide further treatment (Table 4). Two male patients (age 18 and 56) presented with an intraabdominal mass compatible with a desmoplastic small round cell tumor (supplemental online Fig. 5). Two other male patients (age < 20 and > 70) presented with a malignant myoepithelial neoplasm (malignant myoepithelioma). The younger patient presented with a 9-cm primary tumor in the right forearm metastatic to pectoral lymph nodes,

Table 2. Details of screening failures due to lack of confirmation of adeno- or poorly differentiated CUP

Failure due to the lack of confirmation of adeno- or poorly differentiated CUP	*n* = 124
Cases not compatible with study inclusion criteria due to the histologic subtype	31
Squamous cell carcinoma	10
Neuroendocrine tumor	10
Colorectal signature (CK20+, CDX2+, CK7−)	11
Carcinoma cases not compatible with CUP due to proof or strong evidence pointing towards a likely primary tumor	80
Lung cancer	19
TTF1/Napsin A positive	12
TTF1/Napsin A negative	6
Adenoid cystic carcinoma	1
NUT carcinoma	1
Salivary gland	2
Thyroid carcinoma	1
Gastrointestinal tract	7
Gastric cancer	3
Colorectal/appendix cancer	4
Pancreatic cancer	8
Pancreatic ductal adenocarcinoma	7
Acinic cell carcinoma	1
Intrahepatic cholangiocellular carcinoma	7
Hepatocellular carcinoma	2
Breast carcinoma	9
Triple-negative breast cancer	6
Hormone receptor positive	2
Metaplastic breast carcinoma	1
Urinary system	14
Renal cancer	8
Bladder	5
Ureter	1
Prostate cancer	2
Female reproductive organs	8
Uterine	2
Adnexa	6
Cases not compatible with CUP because of noncarcinoma entities in central review	13
Mesothelioma	3
Lymphoma (classical Hodgkin lymphoma)	1
Sarcoma	7
Desmoplastic small round cell tumor	2
Malignant myoepithelioma	2
Sarcoma NOS	2
Osteosarcoma	1
Melanoma	2

Abbreviations: CK, cytokeratin; CUP, cancer of unkown primary; NOS, no special type; TTF1, thyroid transcription factor 1.

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Table 3. CUPISCO immunohistochemistry work-up recommendations: Proposed modifications to the ESMO 2015 guidelines

Primary markers	Potential additional markers[a]
CK7−/CK20−	
Hepatocellular carcinoma	Arginase1, HepPar1[b]
Renal cell carcinoma[a]	Pax8, Pax2, RCC, racemase, CD10, TFE3
Prostate cancer	PSA[b], PSMA, NKX3-1
Squamous cell carcinoma	CK5/6, p63, p40
CK7+/CK20−	
Lung, thyroid cancer	TTF1[b], Napsin A[b], Thyreoglobulin [b], SMARCA4
Salivary gland[a]	Epithelial component: EMA; myoepithelial component: p63, S100, calponin, SMA; useful: GATA3 (e.g., salivary duct carcinoma – AR+, Her2+)
Breast	GATA3, Sox 10, mammaglobin, BRST2, ER[b], PgR[b]
Endometrial, cervical	PAX8, ER[b], PgR[b]
Ovarian	PAX8 (general), WT1, p53, ER (high-grade serous carcinoma), HNF-1beta (clear cell carcinoma)
Pancreatobiliary	CDX2[b], CK19, SMAD4, CK17
CK7−/CK20+	
Colorectal carcinoma	CDX2[b], SATB2
Merkel cell carcinoma	Synaptophysin,[b] chromogranin A[b]
CK7+/CK20+	
Urothelial	GATA3, p63
Upper GI/pancreatobiliary	CDX2[b], CK19, SMAD4, CK17
Noncarcinoma entities	
Melanoma screen	Sox10, S100[b] > Melan A, HMB45[b]
Mesothelioma screen	CK5/6, calretinin, WT-1, BerEP4 (−)
Germ cell tumor screen	SALL4 > OCT3/4[b] > CD30, AFP, B-HCG[b]
Sex cord-stroma tumor screen	Inhibin, Melan A, Calretinin
Adrenocortical neoplasm screen	SF1, Melan A, inhibin, Synaptophysin

[a]Depending on histology and clinical contex.
[b]Markers part of ESMO guidelines.
Abbreviations: AFP, alpha-fetoprotein; B-HCG, beta human chorionic gonadotropin; ; CDX-2, homeobox-Protein CDX-2; CK, cytokeratin; EMA, epithelial membrane antigen; ER, estrogen receptor; ESMO, European Society of Medical Oncology; GI, gastrointestinal; Hep Par-1, hepatocyte paraffin 1; HNF, hepatocyte nuclear factor; PgR, progesterone receptor; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; WT-1, Wilms' tumor protein 1.

Table 4. Soft tissue cases with cytokeratin expression

Entity	Clinical features	Pathology features
Desmoplastic small round cell tumor	Primarily affects children and young adults, male predominance, usually widespread abdominal/peritoneal mass	Histology: sharply outlined nests of small, round cells surrounded by a prominent desmoplastic stroma. Immunohistochemistry: positive for cytokeratins, EMA, desmin, WT1 (only when antibody binds to the C-terminus); negative for myogenin, MYOD1. Molecular pathology: characteristic recurrent translocation t(11;22)(p13;q12) resulting in a fusion between the *EWSR1* (22Q12.2.) and *WT1* (11p13)
Myoepithelial carcinoma (malignant myoepithelioma)	Wide age range (peak in young to middle-aged adults; median age 40 years); equal gender distribution; found in limbs, limb girdles, trunk, rarely in bone, visceral organs, skin, and head and neck	Histology: wide morphological spectrum of cytological and architectural (trabecular, reticular, nested, solid) heterogeneity. Immunohistochemistry: positive for cytokeratins (>90%), S100, EMA (□60%), GFAP (□50%), SOX10 (□80%), calponin (□90%), SMA (□60%), desmin (□20%), subset for p63; negative for SMARCB1 (subset shows loss). Molecular pathology: subset shows rearrangement in *EWSR1*, *PLAG1*, *FUS*

Abbreviations: EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein.

whereas the elderly patient had a-23 cm mass described in the retroperitoneum. Both patients had an atypical fluorescence in situ hybridization (FISH) result for the *EWSR1* break apart probe (supplemental online Fig. 5). Given that myoepithelial tumors are more common in the pediatric or younger adult population, the molecular confirmation of the diagnosis was particularly crucial for the older patient. An Archer FusionPlex Sarcoma Panel revealed a *EWSR1-POU5A1* rearrangement that confirmed the rectified diagnosis of a malignant myoepithelial tumor/malignant myoepithelioma. It should be pointed out that this procedure was beyond the standard workup detailed in the study protocol, in which only IHC and FISH are specified as additional tests. A tumor in the bone of a young male patient (<20 years) was compatible with an osteosarcoma based on imaging and local biopsy assessment, and two other patients were diagnosed with a sarcoma not otherwise specified, as the sample was immediately shipped back for further workup in the local institution and was not further classified by the central lab. Other noncarcinoma diagnoses were two cases of melanoma and three pleural mesotheliomas, one representing a biphasic subtype. Finally, we diagnosed one patient with classic Hodgkin lymphoma presenting in the liver.

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Discussion

The currently recruiting CUPISCO study aims to address the high unmet need for new therapeutic approaches in patients with newly diagnosed unfavorable adeno- or undifferentiated carcinoma CUP by offering molecularly guided therapy based on NGS sequencing and comparing the efficacy and safety of this approach versus standard platinum-containing chemotherapy. Whereas other trials enroll patients according to tumor entities or specific biomarkers, the CUPISCO trial employs a novel standard of eligibility review by having a centralized and extended pathology, as well as a clinical, review according to current published ESMO guidelines. Among the first 628 patients screened so far, a remarkably high rate of screen failures (56%) has been observed. Hereby, the three major reasons for screen failures have been failure to meet inclusion criteria irrespective of CUP diagnosis, lack of sufficient tissue for molecular analyses, and failure to confirm CUP diagnosis in the central eligibility process. A certain dropout rate due to failure to meet inclusion criteria is expected in any clinical trial. Screen failure from lack of sufficient tumor tissue for mandatory molecular workup is also a common problem and highlights the future potential of liquid biopsies. However, the high failure rate to confirm the diagnosis of CUP at central review in the CUPISCO trial is specific to CUP and documents the need for improved diagnostic strategies in general, moving beyond the specifics of this trial. It is for this reason we have specifically focused on this group of screen failures. Our study demonstrates that a uniform definition of CUP remains challenging, as it constitutes a clinicopathologic syndrome that includes a wide range of histological and clinical presentations [17]. To our judgement, the eligibility process of the CUPISCO trial reveals the uncertainties inherent to CUP diagnosis and teaches several lessons regarding the definition of CUP in general. A thorough morphology and immuno-pathologic workup together with the clinical picture allows the identification of cases falsely interpreted as unfavorable adeno- or undifferentiated carcinoma CUP and classifies them into three groups (I–III).

(I) Cases Not Compatible with the Study Inclusion Criteria Because of the Histologic Subtype, Either by Squamous or Neuroendocrine Histology (NET) or Favorable CUP Subtype

In this group, the IHC profile alone led to tumor classification and trial exclusion. All the squamous cell carcinomas were initially classified as poorly differentiated carcinomas. To avoid the misinterpretation of a squamous cell carcinoma, especially when poorly differentiated and non-keratinizing, markers such as p40, p63, and CK5/6 are crucial. Despite histomorphological clues, 10 NET (G2 and G3) cases were misinterpreted as poorly differentiated adenocarcinoma or carcinomas because of the lack of neuroendocrine markers (n = 9) performed or false negative results (n = 1). As NETs can present with a heterogenous morphology, neuroendocrine markers should be considered early in CUP workups, and synaptophysin is recommended by the CUPISCO trial ERT as the most reliable neuroendocrine marker, followed by chromogranin. Lack of awareness of inclusion and exclusion criteria or incomplete local pathology workup recommended by the ESMO guidelines led to the screening and exclusion of the favorable CUP subgroup cases (colorectal signature: CK7−, CK20+, CDX2).

(II) Carcinoma Cases Not Compatible with CUP Because of Proof, or Strong Evidence, of a Likely Primary Tumor

In this group, it became evident that interpretation of clinical and radiological findings regarding the distinction between CUP and known primaries varies significantly between treating physicians. Although these discrepancies are rather academic outside of clinical trials as long as the likely primary guides treatment, they are crucially important in a trial setting in which the integrity of the study population is paramount. In the following sections, we discuss the most frequent, controversial clinical constellations within CUPISCO and the algorithms we implemented to consistently distinguish between CUP and known primary cancers. The distinction between CUP and NSCLC ranked first on the list of contentious cases. Regarding this differential diagnosis, an IHC phenotype with expression of CK7, TTF1, and Napsin A; the detection of a lung mass and hilar/mediastinal lymph nodes; and a metastatic pattern involving pleura, liver, brain, bone, and adrenals point toward NSCLC. Accordingly, we have incorporated all these criteria in an algorithm shown in Figure 2. However, TTF1+ staining in a metastatic setting does not prove a primary origin in the lung [18, 19]. Therefore, when combined with a clinical and radiological picture that was fully incompatible with lung cancer or another primary site, the patient was deemed eligible for the study. Conversely, approximately 20% of poorly differentiated adenocarcinomas of the lung are TTF1 negative [20]. Therefore, CK7+ cases with clinical features suggestive of lung cancer should be classified as NSCLC regardless of TTF1 and Napsin A negativity, as suggested in the algorithm. The relevance of lung cancer as a differential diagnosis to CUP is in line with CUP autopsy series, where lung primaries have been identified in as many as 27% of patients [10]. As TTF1 negativity can cause difficulties in the proper diagnosis of lung cancer, additional markers are needed. A useful marker is SMARCA4, as the more aggressive TTF1-negative lung cancers frequently show loss in the IHC because of a genomic alteration in the SMARCA gene [21, 22]. The second-most frequent differential diagnosis was that between CUP with hepatic metastases and iCCC, which was particularly challenging in CK7+ adenocarcinoma cases in which the IHC profile does not discriminate between both diagnoses. Here, assessment of imaging criteria suggestive of iCCC including a single large liver mass, capsule retraction, cholestasis, venous infiltration, heterogenous contrast enhancement, and peripheral washout by reference radiology was decisive [23, 24]. The algorithm for the demarcation of CUP versus iCCC accordingly incorporates imaging as major decision criterion (Fig. 3). Another important differential diagnosis involves the distinction of CUP and RCC, given that effective treatment of advanced RCC with several targeted agents and immune checkpoint inhibitors has no overlap with empiric platinum-based chemotherapy

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traditionally used for CUP. Of note, RCCs were found as primary tumors in approximately 5% of patients with CUP by autopsy [10]. Nonclear cell histologies with a large proportion of unclassified RCCs seem predominant in CUP [15]. After initiating the CUPISCO trial, two publications suggested that approximately 4%–5% of CUPs show morphology and IHC consistent with mRCC in the absence of a kidney lesion [14, 15] The authors claim that patients with CUP-mRCC should be considered for RCC-specific therapy. Contrast-enhanced CT/MRI is the imaging modality of choice in the diagnosis of RCC and has a median sensitivity of 88% [25]. As the treatment approaches in mRCC and CUP differ, a pathological and radiological workup is crucial for such patients. Therefore, in tumors morphologically suggestive of mRCC, we recommend additional IHC for RCC subtypes and contrast-enhanced CT/MRI scanning.

The differential diagnosis between CUP and breast cancer with distant metastases was also a recurring eligibility issue throughout the trial, with nine patients excluded as metastatic breast cancer after ERT analysis. We recommend that hormone receptor expression is suggestive of metastatic breast cancer and should be treated accordingly. However, some receptor positivity can also be seen in nonmammary and nongynecological tumors such as lung, skin adnexa, and others, warranting a full clinical workup [26]. Markers supportive of a TNBC diagnosis include GATA3 and SOX10, whereas androgen receptor, mammaglobin, BRST2, and NYBR1 are less reliable [27, 28]. None of these markers are recommended in the current CUP ESMO guidelines [3]. GATA3 is regularly used by pathologists to screen for breast and urothelial tumors. Given that metastatic TNBC can be a challenging diagnosis, we recommend a broader IHC panel together with MRI of the breast, which is established as the most sensitive method for breast cancer detection.

By the very nature of diagnostic procedures mandatory for inclusion into CUPISCO (including patient history physical examination, basic laboratory tests, CT/MRI imaging of chest, abdomen and pelvis, and additional tests like endoscopies mandated by the central eligibility team upon clinical suspicion), all diagnostic requirements of the ESMO criteria were routinely fully met, or even overfulfilled in many cases. This highlights that the screen failures were typically not attributable to a lack of diagnostic tests or a lower socioeconomic status of the respective county [29] but rather to a discrepant interpretation of clinical and histological findings and divergent judgements on the concept of CUP. This trial has exposed the need to refine and further standardize the diagnosis of CUP, particularly for clinical trials, in which the integrity of the study population as a "true" CUP cohort is paramount. To make the diagnosis of CUP more objective [9], we have therefore developed specific diagnostic algorithms and recommendations using radiology and pathological criteria for lung (Fig. 2) and cholangiocellular carcinoma (Fig. 3), as well as cancer of mammary origin (breast; supplemental online Fig. 6), salivary gland cancer (supplemental online Fig. 7), renal cell carcinoma (supplemental online Fig. 8), and serous carcinoma (supplemental online Fig. 9) in a CUP scenario. These algorithms consist of suggested modifications to the existing ESMO guidelines. On the one hand, they could improve the ability to efficiently select patients with "true" CUP in future CUP trials. On the other hand, they should characterize patients with "false" CUP, who might benefit from treatment according to the identified respective tumor entity, which was hopefully administered in patients screen failed for CUPISCO. The algorithms will obviously need to be tested for their feasibility and practicability in future CUP trials, although by the very nature of CUP, the accuracy of diagnostic decisions will never be properly cross-validated.

(III) Cases Not Compatible with CUP Because of Noncarcinoma Histology in Central Review

Soft tissue tumors that show positivity for cytokeratins can represent a pitfall and easily be misinterpreted as carcinoma, especially as these types of neoplasms are extraordinarily rare. Helpful in the diagnostic workup is the clinical presentation with age, location of the lesions, and a basic pathology workup using pan-cytokeratin, S100, smooth muscle actin, desmin, and CD34. A lack of cytokeratin staining should question a diagnosis of carcinoma and lead to the consideration of a noncarcinoma entity such as melanoma, lymphoma, or mesenchymal neoplasms.

Conclusion

Revision of CUP diagnoses by central eligibility review helped to identify the primary cancer in many cases. This could be achieved by the scrutiny of second assessment itself and by additional clinical tests and central IHC workup, which proved particularly helpful to identify rare entities overlooked by primary pathologists. Having implemented and enforced the central eligibility review by both reference pathology and a clinical eligibility team from the very start of the CUPSICO trial, we truly believe in the integrity of our study cohort as a "true" CUP cohort. Having initially underestimated the uncertainties of CUP diagnosis, the study team pushed early on to formalize the decision process and to educate investigators.

Beyond the CUPISCO trial itself, its eligibility process has demonstrated that even when adhering to a centralized process and following established guidelines [3], the diagnosis of CUP, being a diagnosis of exclusion, remains challenging [9, 10, 30, 31]. CUP ESMO guidelines [3] were designed to guide real-world treatment decisions and not to define unfavorable CUP as a target population for clinical trials. The CUPISCO trial shows a need for additional detailed consensus diagnostic guidelines for CUP trials to allow harmonization of study populations and spare trial eligibility teams the burden of turning down patients after prolonged screening processes. The current trial also shows that the correct diagnosis of CUP is a multidisciplinary effort between oncologists, pathologists, and radiologists.

When ordering diagnostic tests in patients with suspected CUP, oncologists and pathologists should balance ordering too few versus too many tests. Concerns of overdiagnosing are reinforced by two recent randomized CUP trials, which showed no benefit of gene expression

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profiling-based site-specific treatment versus standard platinum-based chemotherapy [11, 12]. The implementation of diagnostic algorithms could aid a more efficient histopathology workup, as the tissue is often limited, and assist in making timely diagnoses without over-burdening the patient.

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