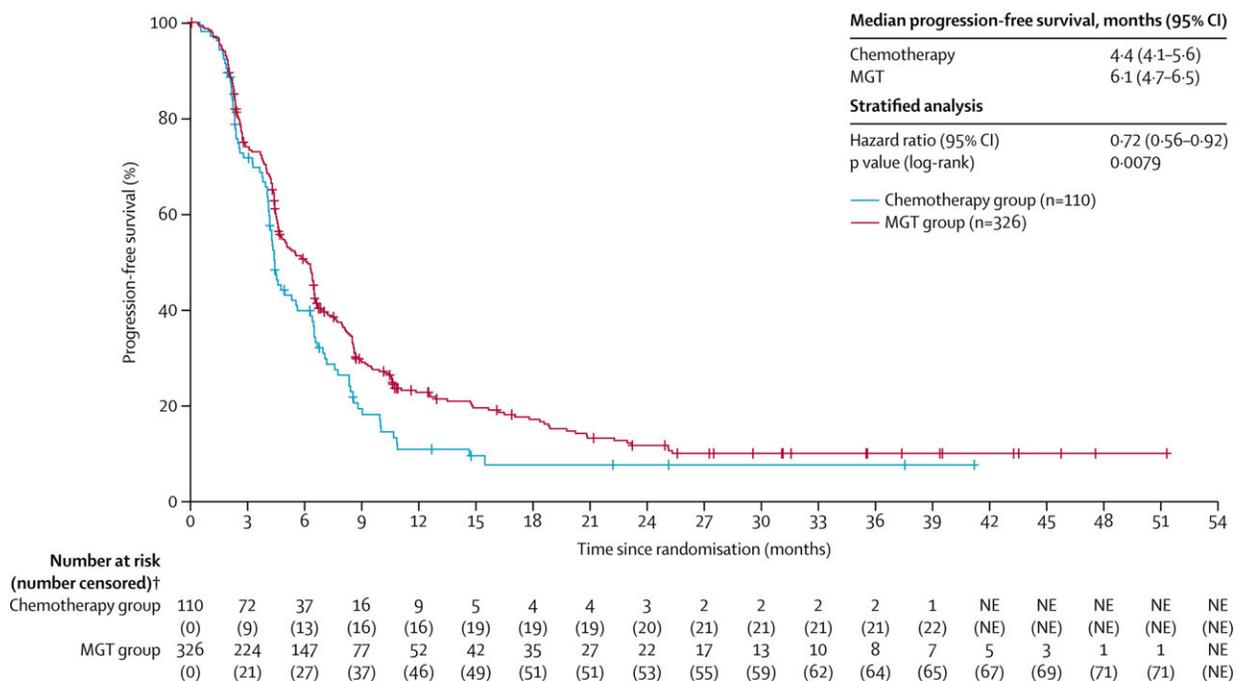


Targeted therapy extends survival in cancers of unknown primary

August 1 2024, by Julia Bird



Progression-free survival in the intention-to-treat population, category 1 patients. Credit: *The Lancet* (2024). DOI: 10.1016/S0140-6736(24)00814-6

If metastases occur in the body, but the original tumor remains undetectable, this is referred to as "cancer of unknown primary" (CUP). But if information on the tissue of origin is missing, neither organ-specific chemotherapy nor targeted drugs are available.

A large international study involving more than 630 patients from 34 countries shows how this phantom cancer can be treated. The results are [published](#) in *The Lancet*. The team led by Professor Dr. Alwin Krämer, examined [cancer cells](#) and genetic fragments in the blood of study participants for known [cancer mutations](#) for which there are already approved drugs available.

The team found these in about a third of CUP patients within the trial. Treatment with the appropriate substance significantly extended the time in which the cancer did not progress and probably also overall survival.

Dr. Krämer is Head of the Clinical Cooperation Unit "Molecular Hematology/Oncology" of the Medical Faculty of Heidelberg University and the German Cancer Research Center (DKFZ), Senior Physician at the Department of Hematology, Oncology and Rheumatology at Heidelberg University Hospital (UKHD) and head of the "Carcinoma of Unknown Primary (CUP)" task force at the National Center for Tumor Diseases (NCT) Heidelberg.

The phase 2 trial "CUPISCO" is registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03498521) (NCT03498521).

Searching for properties of tumor cells against which suitable weapons already exist

In up to 5% of cancers, no primary tumor can be detected, which massively limits the treatment options for the majority of those affected. Patients receive non-specific chemotherapy and thus only achieve an average survival time of less than one year.

"There have been few new findings on CUP syndrome in recent decades," says Professor Krämer. "Studies have only shown that

therapies based on molecular analyses to determine the tissue of origin are no more successful than standard chemotherapy.

"We took a different, [primary tumor](#)-agnostic approach and looked for molecular characteristics of the tumor cells—more precisely, the underlying gene mutations—that have already proven to be effective targets in other types of cancer and for which targeted drugs are available.

A total of 636 patients were included in the study at more than 150 participating clinics. All patients were newly diagnosed with unfavorable subtype CUP. Initially, all patients received three cycles of non-specific standard chemotherapy.

The participants in whom the cancer was temporarily halted in this way were then randomly divided into two groups: 110 patients received a further three cycles of standard chemotherapy as a control group. Of the remaining 326 patients, those in whom the scientists found 1 of 12 selected target mutations were then given the appropriate drug.

If none of the sought-after mutations were present, a so-called immune checkpoint inhibitor was given in addition to the chemotherapy, which does not have a targeted effect but stimulates the body's own cancer defenses. During the average two-year follow-up period, the study physicians examined how long the cancer did not progress under the respective [therapy](#) and when it resumed its growth. There were no differences in the severity of the side effects.

About a third of patients benefited from targeted therapy

"The comparison between the group with mutation-targeted therapy and

the [control group](#) is particularly interesting from a medical point of view," says Prof. Krämer. The difference in the time until the cancer became active again was just under four months on average—eight months for targeted therapy and four months for standard therapy.

"In some of the patients with targeted therapy, the cancer had not progressed any further even at the time of the final evaluation. It is therefore possible that the disease will remain under control in the longer term if there is a good response to the therapy," says Krämer.

"Based on our results, I assume that around a third of patients could benefit from targeted therapy and gain additional months to years of disease-free survival. In patients with suitable genetic changes in the cancer cells, this treatment is clearly superior to standard therapy."

The follow-up period of the study continues, so that definitive figures on overall survival will also be available in around a year's time.

The CUPISCO study is not only the largest intervention study of its kind for cancer of unknown primary. In response to the complex patient recruitment process of the CUPISCO trial, the scientists centralized and [published](#) in 2022 the globally very heterogeneous diagnostic criteria for CUP syndrome into a new guideline for the diagnosis, differential diagnosis and treatment of this tumor entity.

Also new is the proof that the genetic analysis of fragments of the tumor [genetic material](#) from blood samples is as reliable as corresponding examinations of tissue samples itself in patients with CUP. "This evidence is extremely important, as [tumor biopsies](#) often do not provide enough tissue material for all the necessary analyses, especially in CUP syndrome," says Krämer.

"For targeted treatment, as we have now successfully carried out in our

study, we are therefore dependent in many cases on liquid biopsy, i.e., tumor genetic analysis from the blood. In order to improve the care of CUP patients in the future, this method should be approved along with the tissue-based tests already available for CUP diagnostics."

Results have already been incorporated into European guidelines

Based on the results of the CUPISCO study, the scientists conclude that all patients with newly diagnosed CUP syndrome should undergo a genetic analysis of the tumor genome either on tumor biopsy material or a liquid biopsy in order to identify targeted [treatment options](#).

This recommendation for tumor genetic analysis and subsequent targeted treatment of [patients](#) with CUP syndrome was recently included in the newly formulated European guidelines for mutation analysis and precision medicine treatment of advanced tumor diseases and was [published](#) in the *Annals of Oncology*.

More information: Alwin Krämer et al, Molecularly guided therapy versus chemotherapy after disease control in unfavourable cancer of unknown primary (CUPISCO): an open-label, randomised, phase 2 study, *The Lancet* (2024). [DOI: 10.1016/S0140-6736\(24\)00814-6](https://doi.org/10.1016/S0140-6736(24)00814-6)

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