Understanding Evidence and Reimbursement Pathways for Oncology Retreatment: A Cross-country Assessment of Clinical Guidelines and HTA Perspectives

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D'Ausilio, A[1]; Jaiswal, H[2]; Delaitre-Bonnin, C[3]

[1]Thermo Fisher Scientific, Milan, Italy; [2]Thermo Fisher Scientific, Mumbai, India; [3]Thermo Fisher Scientific, Paris, France

Background

- Advances in oncology have improved outcomes for many cancer types, and more people are living after a cancer diagnosis.[1,2] As treatment approaches evolve, retreatment—reusing a therapy after it has been stopped—is being explored in different cancer settings.
- Recent studies and reviews show that evidence for retreatment remains specific to the cancer and treatment context, with questions about patient selection and the strength of evidence still open.[3-5]
- For reimbursement, recent European health technology assessment (HTA) studies report differences between agencies in how they assess evidence such as real-world data and external comparators.[6,7]

Objectives

- To assess how retreatment is addressed in public clinical guidance and HTA documents across selected oncology disease areas in the UK, France, and Germany, and to describe the evidence and criteria reported in those sources.

Methods

- A targeted review examined public clinical guidelines, regulatory information, HTA assessments, reimbursement materials, and published clinical evidence for six selected disease-treatment settings: chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), human epidermal growth factor receptor 2 (HER2)–positive breast cancer, follicular lymphoma (FL), metastatic colorectal cancer (mCRC), and resectable non-small cell lung cancer (NSCLC).
- Sources from the UK, France, and Germany were reviewed. The search covered from September 2020 to September 2026. For each disease area, we recorded whether retreatment was mentioned, the criteria or trigger for restarting treatment, the type of supporting evidence, and whether HTA documents addressed retreatment specifically.
- For this review, retreatment means restarting or reusing a treatment after it has been stopped.
  - We included rechallenge after an intervening treatment when the source described reuse of the same treatment.
  - We did not count ongoing treatment, maintenance, or treatment beyond progression as retreatment unless the source explicitly described it that way.
  - Artificial intelligence (AI)–assisted tools were used to screen and prioritise publications.
  - Researchers reviewed the selected sources and checked the extracted information.

Results

- The terms "restart," "retreatment," and "rechallenge" are not used consistently across all sources.
- Across the six disease areas, clinical guidance addressed retreatment more often than HTA documents (**Table 1** and **Table 2**). Where guidance was available, it generally linked retreatment to a defined clinical situation, such as molecular relapse, prior treatment response, time since treatment, or biomarker status (**Figure 1**).

Table 1. Retreatment Mentioned in Clinical Guidelines or HTAs

Disease	Retreatment Mentioned in Clinical Guidelines	Retreatment Mentioned in HTA
Chronic lymphocytic leukemia	France, Germany, UK	UK
Chronic myeloid leukemia	France, Germany, UK	No
HER2+ breast cancer	No	No
Follicular lymphoma	France, Germany, UK	No
Metastatic colorectal cancer	France, Germany, UK	No
Resectable non-small cell lung cancer	No	No

Abbreviations: HER2 = human epidermal growth factor receptor 2; HTA = health technology assessment

France Germany UK

Table 2. Evidence Supporting Retreatment

Disease	Evidence Supporting Retreatment
Chronic lymphocytic leukemia	Randomised controlled trials; retrospective analysis; real world practice
Chronic myeloid leukemia	Prospective trials; real-world registry data
HER2+ breast cancer	Pooled analysis across 9 clinical trials; real-world multi-institution cohort studies
Follicular lymphoma	Randomised controlled trial; single-arm trial; real-world evidence
Metastatic colorectal cancer	Randomised controlled trials; single arm trial
Resectable non-small cell lung cancer	Randomised controlled trials

Abbreviations: HER2 = human epidermal growth factor receptor 2

Results (cont.)

Figure 1. Retreatment Across Cancer Types

Chronic Lymphocytic Leukemia	Clinical guidance described retreatment as an option for selected patients with relapsed disease. Supporting evidence included a retreatment subgroup from a randomised trial and observational reports. The UK HTA discussion referred to prior treatment, while the reviewed French and German HTA documents provided less detail on retreatment criteria.
Chronic Myeloid Leukemia	Guidance described restarting treatment after loss of a defined molecular response following treatment-free remission, with regular molecular monitoring. Prospective studies reported responses after treatment was restarted. The reviewed HTA documents did not set out a specific restart pathway.
HER2-positive Breast Cancer	Published studies examined reuse of treatment after relapse following earlier therapy, including a Phase II study and retrospective cohort evidence. The reviewed sources provided limited detail on specific retreatment criteria in clinical guidance or HTA documents.
Follicular Lymphoma	Guidance supported retreatment in patients whose disease remained sensitive to anti-CD20 therapy. A treatment-free interval of more than 6 months was used as a key consideration in some sources. Evidence included a randomised comparison of retreatment at disease progression with maintenance treatment. The reviewed HTA documents did not assess retreatment as a distinct question.
Metastatic Colorectal Cancer	Guidance on anti-EGFR rechallenge varied across countries. Some sources described rechallenge for selected patients, with tumour molecular status informing patient selection. Recent European guidance supports assessing circulating tumour DNA for relevant resistance mutations before considering rechallenge.
Resectable Non-small Cell Lung Cancer	The reviewed guidance and HTA documents focused on planned treatment around surgery. We did not identify a specific pathway for restarting treatment after recurrence in the sources reviewed.

Abbreviations: CD20 = cluster of differentiation 20; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; HTA = health technology assessment

Discussion

Figure 2. Key Findings and Evidence Gaps in Retreatment Across Cancer Types

Different Clinical Situations Across Diseases

Retreatment covered different clinical situations across the disease areas reviewed. In CML, treatment may be restarted after molecular relapse during treatment-free remission, with regular monitoring used to identify when to restart. In FL, guidance linked retreatment to whether the disease remained treatment-sensitive and the time since the previous course. In mCRC, rechallenge guidance focused on selecting patients by tumour molecular status. These examples show why retreatment criteria need to be defined for each disease and treatment setting rather than applied across cancers.

Evidence Varies in Design and Maturity

The evidence also varied in design and maturity. For CLL, published evidence included a retreatment subgroup within a clinical trial, alongside observational reports. In FL, a randomised study directly compared retreatment at progression with maintenance. In HER2-positive breast cancer, evidence included a Phase II study and retrospective cohorts. For mCRC, prospective rechallenge studies and newer guidance on circulating tumour DNA have informed patient selection. In resectable NSCLC, the reviewed studies focused on planned perioperative treatment; they did not answer whether treatment should be restarted after recurrence. The strength and purpose of these sources differ, so their results should not be ranked directly across disease areas.

Guidelines versus HTA documents

For evidence development, future studies could report who received retreatment, why treatment was restarted, the length of the treatment-free interval, and the outcomes after restarting. Clear reporting of response, treatment duration, safety, and subsequent therapy would help clinicians and decision-makers interpret the findings. Evidence would also be easier to assess if studies stated whether retreatment involved the same regimen, a modified regimen, or a treatment rechallenge after an intervening therapy.

HTA Documents and Guidelines

Clinical guidelines sometimes described retreatment criteria more clearly than HTA documents. A key consideration is that retreatment may not have been part of the question addressed in an initial HTA assessment, which typically evaluates a treatment for a defined indication and treatment line. Retreatment may be considered later, as evidence and clinical practice evolve, and may therefore fall outside the scope of the original appraisal. This may help explain why many HTA documents did not discuss retreatment specifically. Accordingly, the absence of retreatment-specific language in an appraisal does not, by itself, show that an HTA body rejected retreatment or that it would not be reimbursed in practice.

Future Evidence Development

These findings reflect a targeted review of public sources in the UK, France, and Germany. Some relevant documents or local practices may not have been captured, and guidance may have changed since the search. The review identified patterns in the evidence and reimbursement decisions but cannot establish a causal relationship between them.

Conclusions

- Retreatment is not addressed through a single, cross-indication standard. Its recognition in clinical guidelines and HTA materials varies by disease setting, the evidence available, and the criteria used to select patients. Clear retreatment triggers, monitoring requirements, and evidence on outcomes after reuse may support more consistent assessment. Further prospective evidence and clearer reporting of retreatment outcomes would help inform future clinical guidance and reimbursement decisions.

Contact: anna.dausilio@thermofisher.com

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