

Confirmed hepatic progression with falling CEA in metastatic colorectal cancer

Research summary

For this patient, confirmed new colorectal liver metastases should be treated as radiographic disease progression despite stability of the primary tumor and a falling CEA. Do not continue the current cytotoxic regimen unchanged *solely* because CEA is falling. The immediate decision is whether progression is limited to liver lesions that can all be treated locally while the remaining disease is controlled, or whether it warrants a change in systemic treatment. If the finding is enlargement of existing lesions rather than unequivocally new lesions, the formal RECIST 1.1 designation also depends on whether the sum of target-lesion diameters meets the progression threshold, or whether non-target progression is unequivocal; enlargement of an individual lesion alone does not necessarily establish RECIST progressive disease. The description establishes confirmation on a subsequent scan, but not the lesion measurements or the full distribution of metastatic disease needed to make that distinction.

CEA and imaging answer different questions. A falling CEA can be prognostically informative, but it cannot negate demonstrated growth at a metastatic site. Retrospective cohorts document discordance between CEA response and RECIST response, while an analysis of first-line trials shows that lesions within the same patient can have varied responses. Thus, “mixed response” is a useful description of the anatomy of treatment effect, not an alternative RECIST category that converts hepatic progression into disease control. An isolated report of apparent pseudoprogression during bevacizumab treatment illustrates why an unexpected lesion merits imaging review; it does not establish pseudoprogression as a reason to dismiss lesions that remain new or enlarged on subsequent imaging. The **classification** of unequivocally new lesions as progression is highly secure; the best **treatment choice** after progression is more conditional.

If progression is multifocal, extends beyond the liver, cannot be comprehensively treated locally, or is accompanied by loss of clinical benefit, a change in the systemic strategy is favored over continuation of the same cytotoxic backbone. This need not mean stopping every component: in ML18147, continuing bevacizumab *with second-line chemotherapy* after progression on first-line bevacizumab-containing chemotherapy conferred clinical benefit compared with second-line chemotherapy alone. The randomized BEBYP trial also evaluated bevacizumab continuation or reintroduction with a changed second-line backbone. Neither trial demonstrates benefit from simply leaving the **same chemotherapy regimen** in place after confirmed progression. The choice of subsequent treatment depends on the current drugs, previous exposure and toxicity, performance status, and tumor molecular profile—not on the CEA direction

alone.

Alternatively, if comprehensive staging establishes a small number of progressing hepatic sites, sustained control elsewhere, and technical feasibility of treating *all* progressing sites, hepatobiliary multidisciplinary review can consider resection or ablation and a plan to retain effective systemic treatment for the controlled disease. Randomized liver-directed trials support local treatment in selected colorectal liver-metastasis populations, but their eligibility and treatment comparisons differ from chemotherapy-associated oligoprogression; they do not prove that ablating new lesions and continuing an otherwise unchanged regimen is superior to switching regimens. Confidence is therefore high that confirmed unequivocal new lesions must not be disregarded because CEA falls, moderate that non-localizable progression should prompt systemic modification, and lower that local treatment permits safe continuation of this particular regimen.

Bottom line

- **Progression is an imaging determination:** unequivocally new liver metastases constitute RECIST 1.1 progression regardless of primary-tumor stability or CEA decline; growth of existing lesions requires the applicable target-sum or unequivocal non-target assessment. **High certainty for the RECIST definition.**
- **A falling CEA is supportive, not exculpatory:** CEA–imaging discordance occurs in treated metastatic colorectal cancer and cannot override confirmed metastatic growth. **Moderate certainty; observational cohorts.**
- **Describe the distribution, then classify the disease:** stable disease at one site and progressing lesions at another constitute a heterogeneous or mixed anatomical response, but do not themselves establish that progression is *liver-limited oligoprogression*. **Moderate certainty for heterogeneity; trial-database observational analysis.**
- **Do not preserve an ineffective cytotoxic backbone merely because bevacizumab might remain useful:** randomized evidence for bevacizumab beyond progression tested it alongside second-line chemotherapy, not unchanged first-line chemotherapy. **Moderate-to-high certainty for the studied second-line strategy; randomized trials.**
- **Consider continuing effective systemic treatment after complete local treatment only in a selected liver-limited pattern:** establish that every progressing site is treatable and that disease elsewhere remains controlled. This is an individualized option, not a CEA-based exception to progression. **Lower certainty for this exact post-progression strategy; indirect randomized liver-directed evidence and multidisciplinary consensus.**
- **Stop or replace the current systemic approach now when meaningful control cannot be restored:** widespread or rapidly accumulating progression, clinically consequential hepatic growth, or unacceptable toxicity argues against further unchanged treatment; treatment cessation versus

another line depends on fitness and goals of care. **Clinical inference supported indirectly by second-line trials, not a trial of this precise discordant presentation.**

Evidence at a glance

Source	Design	Population (n)	Comparison	Key result	Ref
RECIST 1.1	Response-assessment guideline	Solid-tumor trials; not applicable	New lesions, target lesions and non-target lesions	An unequivocal new lesion establishes progressive disease; target-lesion progression requires an increase of at least 20% in the sum of diameters and an absolute increase of at least 5 mm.	
ESMO, 2026	Clinical practice guideline	Metastatic colorectal cancer; not applicable	Multidisciplinary systemic and locoregional treatment selection	Recommends considering organ and lesion number, prognostic factors, molecular status and CEA in treatment selection [IV, B]; CEA is one factor, not a substitute for imaging.	
EORTC, 2025	Multidisciplinary consensus statement	Colorectal liver metastases; 43 experts	Selection and response assessment for liver-directed treatment	Provides practical consensus recommendations covering imaging, liver-directed treatment selection, response assessment and multidisciplinary care; no comparative treatment effect established.	
ML18147	Randomized phase 3 trial	Metastatic colorectal cancer progressing after first-line bevacizumab plus chemotherapy; 820 enrolled	Second-line chemotherapy plus bevacizumab vs second-line chemotherapy alone	Continuing bevacizumab with second-line chemotherapy produced clinical benefit; the trial did not test continuation of the unchanged first-line backbone.	
ML18147 KRAS subgroup analysis	Prespecified trial subgroup analysis	ML18147 participants; subgroup sizes not stated	Second-line chemotherapy plus bevacizumab vs chemotherapy alone	Median PFS was 6.4 vs 4.5 months in wild-type KRAS (HR 0.61; 95% CI 0.49–0.77) and 5.5 vs 4.1 months in mutant KRAS (HR 0.70; 95% CI 0.56–0.89).	
BEBYP	Randomized phase 3 trial, stopped early	Metastatic colorectal cancer progressing after first-line chemotherapy plus bevacizumab; 185 enrolled	Changed second-line chemotherapy with vs without bevacizumab	Studied continuation or reintroduction of bevacizumab with a second-line regimen , not unchanged chemotherapy after progression.	
CEA–RECIST discordance cohort	Retrospective cohort	First-line palliative chemotherapy for metastatic colorectal cancer (360)	CEA-response categories vs RECIST-response categories	Within RECIST categories, CEA-response patterns were associated with prognosis and subsequent evaluation outcomes; CEA and imaging were not interchangeable.	
Opposite CEA and imaging changes cohort	Observational cohort	Stage IV colorectal cancer receiving systemic therapy (330)	Concordant vs discordant CEA and imaging response	Documented discordant marker and imaging findings after treatment; study-specific CEA categories were not RECIST progression criteria.	

Source	Design	Population (n)	Comparison	Key result	Ref
ARCAD lesion-response analysis	Pooled first-line trial-database analysis	Metastatic colorectal cancer (10,551)	Responses of individual lesions at restaging	Varied lesion responses occurred during first-line therapy; lesion-level heterogeneity is not captured by the overall RECIST category.	
Bevacizumab pseudoprogression report	Case report	One patient receiving bevacizumab-containing therapy	Apparent new hepatic lesion vs later imaging course	A suspected new lesion did not enlarge on subsequent imaging during an ongoing radiological response; this does not describe persistently confirmed progression.	
Liver MRI response analysis	Imaging–pathology observational study	Resected colorectal liver metastases after bevacizumab-containing chemotherapy (126 patients)	Contrast-enhanced and diffusion-weighted MRI measures vs pathological response	Investigated imaging features beyond size for identifying pathological response; does not validate CEA as an override of confirmed lesion growth.	
EORTC 40004 (CLOCC)	Randomized liver-directed treatment study	Unresectable colorectal liver metastases (119)	Radiofrequency ablation, with or without resection, plus systemic treatment vs systemic treatment alone	Tested adding local treatment to systemic treatment in selected liver-metastasis patients, not continuation of an unchanged regimen after oligoprogression.	
COLLISION	Randomized phase 3 non-inferiority trial	Small, resectable colorectal liver metastases without extrahepatic metastases; sample size not stated here	Thermal ablation vs surgical resection	Trial stopped early after meeting predefined criteria indicating likely overall-survival non-inferiority, non-inferior local control and fewer adverse events with ablation; applicability to progression on chemotherapy is indirect.	
CAIRO3	Randomized phase 3 trial	Metastatic colorectal cancer without progression after induction CAPOX–bevacizumab (558)	Capecitabine–bevacizumab maintenance vs observation, with planned reintroduction on progression	Evaluated maintenance before progression, not continuation of maintenance or induction despite confirmed new metastases.	

Findings

1. Do confirmed new or enlarging liver lesions constitute RECIST progression despite a stable primary and falling CEA?

Yes. Unequivocally new colorectal liver metastases constitute RECIST 1.1 progressive disease (PD) at the whole-patient level, irrespective of stability of the primary tumour or a falling carcinoembryonic antigen (CEA) concentration. RECIST does not average a progressing metastatic site against a stable primary, and CEA is not part of its radiographic response algorithm. In the clinical situation described, the subsequent scan confirming the liver findings substantially reduces the concern that an initially

suspicious focus represented an equivocal imaging finding. The classification should still be based on the actual images: the decisive question is whether a lesion is unequivocally new and malignant, rather than merely newly conspicuous because of differences in technique, contrast timing or image interpretation.

New lesions and growth of existing lesions are distinct RECIST pathways

A confirmed new metastatic lesion is sufficient for overall RECIST PD without a required increase in the sum of existing target-lesion diameters. Thus, neither a stable primary nor shrinkage at another site can offset an unequivocally new liver metastasis in the RECIST classification. For *enlarging pre-existing* liver lesions, the rule is more specific: target-lesion PD requires an increase of at least 20% in the sum of target-lesion diameters relative to the smallest sum recorded on study, together with an absolute increase of at least 5 mm. Progression of non-target disease instead requires an unequivocal overall worsening of that disease. Growth in one target liver lesion, considered in isolation, must not be relabelled RECIST PD if the target-lesion sum does not meet the specified criteria and there is neither a new lesion nor unequivocal non-target progression.

That distinction is material here because “new or enlarging liver lesions” describes two possible routes to the same assessment, not interchangeable measurement rules. If the confirmed hepatic finding includes an unequivocally new metastasis, whole-patient RECIST PD follows even if every previously selected target lesion remains stable. If the finding consists solely of enlargement of known lesions, their baseline and nadir measurements, target versus non-target designation, and the behaviour of the other measured lesions determine whether formal RECIST PD has occurred. Radiographic stability of the primary supplies information about that site; it is not a competing whole-patient response category.

Measurement reproducibility is particularly relevant when the asserted progression rests on small changes in existing lesions. In an imaging assessment of 29 patients with metastatic colorectal cancer, three radiologists independently selected 138, 101, and 146 metastatic target lesions; variability in relative change with independent selection was 11% for unidimensional measurements. A separate comparison of WHO and RECIST assessments in 48 patients noted that discordance could arise with irregular or asymmetric tumours or measurements near a response threshold. These observations justify careful review of borderline growth, but they do not provide a basis for dismissing a subsequently confirmed, unequivocally new metastasis.

Discordant CEA does not reverse radiographic PD

CEA and imaging can move in opposite directions during systemic treatment. A study of 330 patients with stage IV colorectal cancer explicitly examined discordance between CEA changes and RECIST imaging

findings after systemic therapy; its CEA response categories were study-defined modifications, not alternative RECIST categories. In a retrospective cohort of 360 patients receiving first-line palliative chemotherapy, CEA-response patterns varied within the same RECIST-response categories and carried prognostic information. Conversely, a single-centre analysis of 447 patients reported correlation between the CEA ratio, RECIST imaging change and overall survival. Correlation across a population is compatible with clinically important discordance in an individual: none of these observational analyses establishes that a falling CEA negates unequivocal radiographic progression.

Heterogeneity across lesions provides a further reason not to infer the whole-patient RECIST category from the stable primary. An analysis of patients drawn from 17 first-line metastatic colorectal cancer trials classified individual lesions at first restaging as progressing, responding or stable, and identified varied responses within patients; the investigators explicitly distinguished this lesion-level heterogeneity from conventional RECIST response assessment. In particular, that analysis used a greater than 20% increase in an *individual lesion's* longest diameter to describe a progressing lesion. That research definition must not be substituted for the RECIST 1.1 target-*sum* progression rule.

There is a narrow imaging caveat for treatment involving bevacizumab. A published case described an apparent new liver lesion during bevacizumab-containing treatment that did not enlarge on subsequent imaging while other radiographic findings continued to respond; its authors proposed that the initial finding could have been pseudoprogression. Among 126 patients who underwent hepatic resection after bevacizumab-containing chemotherapy, an imaging study also investigated enhancement and diffusion measurements to identify pathological response not adequately characterised by size-based RECIST. The case concerns an initially apparent lesion whose later course argued against progressive growth, and the resection cohort addresses response characterisation rather than a validated exception for confirmed new metastases. Neither establishes that falling CEA or anti-VEGF-associated imaging changes can override unequivocal hepatic progression confirmed on a subsequent scan. The defensible conclusion is therefore **radiographic PD when a confirmed new liver metastasis is present; for enlargement alone, formal PD only when the applicable RECIST target- or non-target-lesion criterion is met.**

2. When can CEA kinetics be disregarded or used only as supportive evidence in metastatic colorectal cancer?

CEA kinetics should be **supportive, not adjudicative**, when they conflict with adequately characterized serial imaging. A falling CEA can indicate that some CEA-producing disease remains treatment-sensitive, but it cannot establish that every metastatic deposit is controlled. In the described case, the decline should therefore be recorded as a discordant biochemical finding, not used to dismiss the liver findings confirmed on the subsequent scan. RECIST 1.1 bases objective response assessment on lesions rather than substituting a serum marker for imaging; observational cohorts document clinically meaningful

disagreement between CEA-based and imaging-based assessments in metastatic colorectal cancer (mCRC).

Why a falling CEA may be misleading

CEA is an aggregate signal influenced by tumor secretion as well as tumor burden. It does not identify which lesion produced a change. A decrease driven by a large responding CEA-secreting component could coexist with growth of a smaller component that contributes little to circulating CEA. That explanation is biologically plausible for discordant findings, **not a demonstrated mechanism in this patient**. Lesion-level heterogeneity is well documented: an analysis of patients from first-line mCRC trials classified individual deposits as responding, stable or progressing and found varied responses within individual patients. It did not establish that a particular CEA trajectory can identify the progressing deposits.

Interpretability also depends on whether the cancer produced an elevated, trackable CEA before treatment, the absolute starting concentration, the magnitude and persistence of change, and consistency of assay and sampling conditions. Without that context, the direction of change alone carries limited information. CEA can be influenced by non-tumor factors, so an unexpected result warrants clinical and laboratory interpretation rather than automatic attribution to treatment effect. These qualifications do not require proving that the marker is misleading in this patient; they explain why it cannot overrule confirmed anatomic findings.

The discordance cohorts support this hierarchy, while showing why CEA should not simply be discarded. In a retrospective study of 360 patients receiving first-line palliative chemotherapy, CEA response categories were prognostic within the same RECIST response categories and predicted subsequent assessment outcomes. Those results show that the marker can add risk information *after* imaging has classified response; they do not validate using a falling marker to reverse an imaging classification. A separate study of 330 patients with stage IV colorectal cancer receiving systemic treatment specifically examined opposite CEA and imaging changes. Its investigator-defined biochemical categories were not RECIST categories or validated rules for treatment continuation. The studies also used different CEA-response definitions: the 360-patient cohort defined CEA partial response as a $\geq 50\%$ decrease and CEA progression as a $\geq 50\%$ increase, whereas the 330-patient study treated changes not exceeding 20% of the original CEA level as biochemically stable. Applying either threshold to the unspecified decline in this case would be unjustified.

When serial CEA is useful

Serial CEA is most informative when baseline CEA is elevated and the trajectory is sustained, measured consistently, and interpreted alongside imaging and clinical status. A single-center retrospective analysis of 447 patients whose primary tumor had been surgically treated found that the CEA ratio and RECIST imaging change were each associated with overall survival; concordance at cohort level, however, does not make the measurements interchangeable for an individual with discordant results. A PRODIGE 9 analysis likewise found prognostically distinct CEA trajectories during first-line chemotherapy, including a high-baseline group whose CEA initially decreased before returning to its baseline level. An analysis of CEA-related kinetics after eight weeks proposed prognostic measures for patients with high serum CEA, rather than a rule for overriding radiographic findings.

Prospective work assessing CEA alongside CA19-9 and circulating tumor measures specifically enrolled patients starting chemotherapy with pre-treatment CEA > 5 ng/mL and/or CA19-9 > 30 U/mL. Its applicability to a patient whose baseline CEA may not have been elevated cannot be assumed. Likewise, an observational report suggesting that CEA monitoring might substitute for some CT assessments during a biochemically stable period studied monitoring during first-line treatment; that suggestion should not be extended to adjudicating lesions already confirmed on serial scans. A treatment-monitoring study also found that correlations among CEA, circulating cell-free DNA and imaging-derived tumor load seen before therapy were not maintained consistently under treatment or in later lines.

Apparent contradictions and their limits

CEA can mislead in either direction. Retrospective mCRC reports describe transient *rises* during chemotherapy despite clinical benefit or objective response, including an oxaliplatin-combination series in which four patients (15%, 95% CI 5-31%) met its definition of a treatment-associated surge. Those reports caution against changing treatment solely for an isolated marker rise. They do not establish the converse proposition that a falling CEA excludes progression.

Anti-VEGF treatment introduces a separate imaging consideration: morphologic or diffusion-weighted MRI changes may characterize response of colorectal liver metastases differently from size measurements. Evidence for that proposition includes a study of 126 patients undergoing hepatic resection after bevacizumab-containing chemotherapy and a published bevacizumab-associated pseudoprogression case report. Neither validates CEA decline as a test for distinguishing viable progression from treatment-related imaging appearances. The case report's interpretation depended on subsequent favorable imaging behavior; it is particularly weak grounds for reinterpreting lesions that have enlarged or newly appeared on a subsequent scan.

Thus, CEA should be given little weight **for the specific task of negating confirmed lesion-level change**, while retaining value as a contextual longitudinal marker when its baseline behavior makes it

interpretable. No cited CEA-kinetics study demonstrates that falling CEA, by itself, identifies a subgroup in whom confirmed hepatic progression can safely be treated as biochemical response instead.

3. How should mixed response or liver-limited oligoprogression be distinguished from systemic treatment failure on chemotherapy with or without a VEGF inhibitor?

A mixed response describes **different behavior among disease sites or lesions during the same course of treatment**; it is a pattern of response, not a separate category that establishes why progression has occurred. In this case, the confirmed new or enlarging liver lesions establish a progressing hepatic component, while the primary tumor is radiographically stable. That contrast is insufficient, by itself, to call the pattern *liver-limited oligoprogression*: doing so requires evidence that progression is confined to a limited, anatomically defined set of hepatic lesions and that disease elsewhere remains controlled. It is equally insufficient to infer that every component of the cancer has become resistant to chemotherapy.

Classify the pattern across all disease sites

The useful unit of assessment is the **whole metastatic disease map**, examined lesion by lesion over time, rather than a comparison between the liver and the primary tumor alone. Document which hepatic deposits are new, which pre-existing deposits are growing or stable, whether changes are focal or distributed across the liver, and what has happened at every known extrahepatic site. Review the interval over which those changes developed and the scans used as comparators. Primary-tumor stability establishes only the behavior of the primary; it does not establish control of other metastases.

Lesion-level heterogeneity is a recognized phenomenon in treated metastatic colorectal cancer. An ARCAD analysis examined patients from first-line trials who had multiple baseline lesions and early restaging, classifying individual lesions as progressing, responding, or stable before assessing varied responses within patients. Its lesion-level categories were constructed for that analysis and should not be mistaken for a validated clinical definition of oligoprogression. The study supports describing discordant lesion behavior explicitly rather than collapsing it into “response” or “failure” without an anatomic account. It does not show that a stable primary predicts continued sensitivity of the metastatic deposits, or that every mixed response has the same prognosis.

Liver-limited means that the progression is in the liver, not merely that the most conspicuous progression is there. **Oligoprogression** further implies that the progressing component is sufficiently restricted to be distinguished from widespread escape while other disease remains controlled. These are clinical and anatomic judgments; a small total tumor burden is not synonymous with an oligometastatic state, and no

lesion count alone establishes the biology of the disease. A few growing deposits amid otherwise stable sites would support a focal-escape interpretation. Numerous new deposits across liver segments, progression at additional metastatic sites, or repeated emergence of new lesions would instead weigh toward broader systemic treatment failure. The distinction depends on the distribution and trajectory of progression, not on the direction of a tumor marker.

Separate confirmed progression from uncertainty about its extent

Confirmation on a subsequent scan substantially changes the interpretation of the hepatic findings: a transient imaging appearance is a weaker explanation once the lesions persist or enlarge. Nevertheless, defining *how extensive* the progressing component is still requires careful comparison of studies. In an assessment of metastatic colorectal cancer imaging, independent radiologists differed in target-lesion selection and measurement; variability in relative change with independent selection was 11% for unidimensional measurements, 19% for bidimensional measurements, and 22% for volumetric measurements. That measurement issue matters most for borderline enlargement of an existing lesion. It does not convert persistent new hepatic disease into evidence of control.

Anti-VEGF treatment introduces a further interpretive distinction between lesion size and treatment-related morphologic change. Among patients with colorectal liver metastases who subsequently underwent resection after bevacizumab-containing chemotherapy, an MRI study investigated contrast enhancement and diffusion measurements against pathological response, illustrating that size alone may not capture all biologically relevant treatment effects in that selected population. A published bevacizumab-associated pseudoprogression report likewise described an initially concerning hepatic appearance that did not enlarge on later imaging while the patient maintained a radiological response. These observations justify scrutinizing image quality and lesion characteristics when appearances conflict. They do **not** establish pseudoprogression as the explanation for liver lesions confirmed to be new or enlarging on a subsequent scan.

Biological heterogeneity is plausible but should remain an interpretation rather than a diagnosis from the scans. Research on vascular growth patterns in colorectal liver metastases proposes that lesions may differ in their response to antiangiogenic treatment; its mechanistic observations do not provide a validated imaging test for identifying resistant lesions in an individual patient. A reported case of discordant molecular status and differential metastatic-lesion behavior arose during an **anti-EGFR-based** regimen, so it illustrates a possible mechanism of mixed response but cannot establish the mechanism—or treatment implication—under cytotoxic chemotherapy with or without VEGF inhibition here.

The classification with immediate clinical value is therefore precise and conditional: **confirmed hepatic progression with a stable primary, with the extent of metastatic escape determined by complete**

anatomic restaging. If the progressing deposits form a limited hepatic subset against otherwise controlled metastatic disease, “liver-limited oligoprogression” is a defensible description. If progression is multifocal or extends beyond that subset, “mixed response with broader systemic progression” better conveys the pattern. Neither label should be assigned from the stable primary and falling CEA alone; the decisive evidence is the location, number, and serial behavior of *all* lesions.

4. Which findings justify continuing the regimen, modifying the cytotoxic backbone or VEGF inhibitor, or discontinuing therapy now?

The treatment decision is whether the current systemic regimen still controls clinically consequential metastatic disease—not whether it continues to control the primary tumor. With new or enlarging hepatic lesions confirmed on a subsequent scan, a falling CEA and a stable primary do not, by themselves, justify continuing an unchanged regimen indefinitely. CEA–imaging discordance occurs in treated metastatic colorectal cancer, and a retrospective study of patients receiving first-line palliative chemotherapy found that CEA patterns added prognostic information *within* radiographic response categories rather than replacing imaging-based assessment. The immediate choice is therefore between changing the systemic strategy and, in a carefully selected patient, retaining its effective components while addressing a limited site of escape.

When continuation is defensible

Continuation of the current drugs is defensible as a **short, explicitly planned bridge** while the extent of progression, prior treatment exposure, fitness for an alternative regimen, and feasibility of definitive treatment of the progressing deposits are established. It is not a decision to classify confirmed hepatic growth as treatment benefit. A published bevacizumab-associated pseudoprogression report describes a newly apparent hepatic lesion that did not enlarge on subsequent imaging while radiological response continued; that single-case observation cannot justify treating lesions *confirmed to be new or enlarging on a subsequent scan* as pseudoprogression. If review instead identifies a nonmalignant lesion or a technically misleading comparison, the premise of malignant progression changes; repeated, credible enlargement does not warrant successive cycles merely to see whether CEA continues to fall.

Longer continuation of an unchanged systemic regimen is a selective strategy when progression is confined to deposits that can be controlled separately, other disease remains controlled, and the expected benefit of retaining the regimen outweighs its toxicity. That decision requires an actionable plan and reassessment, not a presumption that a stable primary represents systemic control. Trials of maintenance therapy address a different situation: CAIRO3 randomised patients with stable disease or better after induction to capecitabine plus bevacizumab maintenance or observation, with planned

induction-regimen reintroduction at progression. It does not establish that maintenance—or an unchanged induction regimen—should continue after confirmed hepatic progression without an additional intervention. Likewise, the BECOME trial's first-line benefit from adding bevacizumab to mFOLFOX6 in initially unresectable, RAS-mutant liver-limited disease—objective response 54.5% versus 36.7% and median progression-free survival 9.5 versus 5.6 months—does not demonstrate benefit from simply adding bevacizumab to the *same failing backbone* after progression.

When to change the cytotoxic backbone or VEGF strategy

If the growing hepatic disease is not amenable to effective focal control, involves multiple progressing sites, or continues to advance during a deliberate reassessment interval, confirmed progression argues for a different active systemic strategy rather than continuation of the same cytotoxic backbone. Selection depends on which drugs the patient has actually received, prior response and tolerability, performance status, organ function, and tumour molecular profile. None of those treatment-selection features is established by the reported imaging and CEA findings; they must be checked before specifying a replacement regimen. In particular, the history must distinguish an oxaliplatin-based from an irinotecan-based backbone and establish whether a VEGF inhibitor is part of the current treatment.

Changing chemotherapy does not necessarily mean abandoning VEGF inhibition. In the randomised ML18147 trial, patients progressing after first-line bevacizumab plus chemotherapy were assigned second-line chemotherapy with or without continued bevacizumab; the trial supports bevacizumab with a *changed second-line chemotherapy regimen*, not continuation of the ineffective first-line combination unchanged. In its KRAS subgroup analysis, median progression-free survival with bevacizumab plus chemotherapy versus chemotherapy alone was 6.4 versus 4.5 months in KRAS wild-type disease (HR 0.61; 95% CI 0.49–0.77) and 5.5 versus 4.1 months in KRAS-mutant disease (HR 0.70; 95% CI 0.56–0.89). BEBYP also evaluated continuation or reintroduction of bevacizumab *with second-line chemotherapy* after progression on a bevacizumab-containing first line, but it stopped accrual prematurely; it does not resolve whether retaining bevacizumab is preferable to every other antiangiogenic option for an individual patient.

After an oxaliplatin-based regimen, an irinotecan-based regimen with an appropriate antiangiogenic agent may be considered if the patient can tolerate it. The randomised VELOUR result, as reported in a treatment review, found median overall survival of 13.5 months with aflibercept plus FOLFIRI versus 12.06 months with placebo plus FOLFIRI (HR 0.817, $P = 0.0032$), and median progression-free survival of 6.9 versus 4.67 months (HR 0.758, $P < 0.0001$). These data support an eligible later-line treatment option; they do not establish that a VEGF inhibitor should be switched solely because CEA and imaging disagree. Nor should first-line bevacizumab efficacy, or cross-trial comparisons among bevacizumab, aflibercept and ramucirumab, be read as proof that one VEGF strategy rescues confirmed progression while the cytotoxic backbone is left unchanged.

When to stop treatment now

Discontinue or withhold the **current regimen now**, rather than give another routine cycle, when its hepatic disease is clearly advancing and there is no credible plan to control that progression, or when toxicity, deteriorating functional status, organ dysfunction, or a treatment-related contraindication makes further dosing unsafe. “Stop the current regimen” should not be conflated with “stop all anticancer treatment”: a patient fit for another effective line may need a prompt switch, whereas one unable to benefit safely from further systemic treatment needs a different goals-of-care decision. If an invasive procedure is contemplated, the VEGF-inhibitor component also requires a separate peri-procedural safety assessment. The reported falling CEA does not settle any of these choices; the decisive additional findings are the full distribution and pace of radiographic progression, the exact treatment already given, treatment tolerance, and whether all clinically important progressing disease can be addressed without sacrificing control elsewhere.

5. When does liver-directed therapy allow ongoing systemic treatment rather than an immediate regimen change?

Liver-directed treatment can permit continuation of a systemic regimen after confirmed hepatic progression **only when the progressing disease can be treated comprehensively and disease outside the planned treatment field remains controlled**. The rationale is to eradicate a limited site of escape while retaining treatment that may still be controlling disease elsewhere. It is a selected, multidisciplinary strategy—not evidence that the progressing liver lesions remain sensitive to the current chemotherapy, and not a reason to continue the regimen unchanged while a local-treatment plan is deferred. An EORTC multidisciplinary consensus addresses liver imaging, selection for liver-directed treatment and response assessment as linked decisions.

Selecting a credible local-treatment strategy

The pivotal question is whether an experienced hepatobiliary team can treat **every site of hepatic progression**, with an acceptable functional liver remnant or an adequate ablative margin, while establishing the extent and management of any extrahepatic disease. Review should establish the number, size and distribution of the progressing lesions; their relation to major vessels and bile ducts; background liver function and treatment-associated liver injury; whether previously treated sites have failed locally; and whether the primary tumour or other metastases require treatment. A stable primary tumour alone does not establish that all disease outside the liver is controlled.

Resection is appropriate when complete clearance is technically and physiologically feasible; thermal ablation may be preferable for suitable small lesions, including when parenchymal preservation matters. The phase 3 COLLISION trial compared ablation with resection in selected patients with **ten or fewer** colorectal liver metastases measuring ≤ 3 cm, no extrahepatic metastases and Eastern Cooperative Oncology Group performance status 0–2. It stopped early after prespecified criteria indicated a high likelihood of non-inferior overall survival, non-inferior local control and fewer adverse events with ablation. Those results inform *how* eligible small liver metastases may be treated locally. Because the trial compared local modalities rather than continuation versus change of chemotherapy after hepatic escape, it does not establish that ablation rescues a progressing systemic regimen.

Local treatment also needs a defined systemic-treatment plan. If complete clearance is feasible, a short procedural interruption followed by reassessment and, where appropriate, resumption of the previously useful regimen is different from declaring the regimen effective against the escaped lesions. If conversion to complete clearance is the objective, resectability should be revisited during systemic treatment rather than waiting for further radiographic progression; prolonged chemotherapy can itself complicate liver-directed treatment. Prior VEGF-inhibitor exposure must be incorporated into operative timing and wound-healing assessment.

What combined-treatment trials establish—and what they do not

Randomised evidence supports combining liver-directed treatment with systemic therapy in *selected liver-metastasis populations*, but it is indirect for confirmed oligoprogression on an ongoing cytotoxic regimen. In the EORTC 40004/CLOCC programme, patients with unresectable colorectal liver metastases were assigned to systemic treatment with or without radiofrequency ablation, with resection permitted for suitable lesions. An account of the trial reported median progression-free survival of **16.8 months with chemotherapy plus ablation versus 9.9 months with chemotherapy alone**. The trial's comparison was addition of local treatment to a treatment strategy, not ablation followed by continuation of a cytotoxic backbone already failing at a documented liver site. Thus, it supports considering comprehensive local control alongside systemic treatment; it cannot quantify the benefit of preserving this patient's current regimen after progression.

Nor does evidence that an effective *initial* regimen can convert liver-limited disease to resectability answer the post-progression question. In the BECOME randomised trial, patients with initially unresectable **RAS-mutant, liver-limited** metastases received first-line mFOLFOX6 with or without bevacizumab. Objective response was **54.5% versus 36.7%**, median progression-free survival **9.5 versus 5.6 months**, and median overall survival **25.7 versus 20.5 months**, respectively. These are first-line conversion outcomes, not evidence for keeping mFOLFOX6 after confirmed hepatic progression.

Choice of local modality also matters. Resection or ablation can target discrete lesions for complete clearance. Stereotactic radiotherapy may be considered when a lesion is unsuitable for either, subject to normal-liver and adjacent-organ constraints. Hepatic arterial infusion and other intra-arterial approaches are principally specialised options for more extensive liver-dominant disease; they should not be assumed equivalent to complete eradication of a few progressing lesions. In particular, a synthesis of first-line radioembolisation trials found improved liver-specific control but **no overall-survival benefit** and more severe adverse events when selective internal radiotherapy was added to chemotherapy. Improved hepatic control alone therefore does not prove that ongoing systemic therapy can safely be left unchanged.

For the present decision, liver-directed treatment creates a defensible route to retaining the regimen if complete treatment of the confirmed progressing lesions is feasible, assessment shows no other sites escaping treatment, the current drugs remain tolerable, and the team specifies how treatment will be interrupted, resumed and reassessed. If hepatic disease cannot be comprehensively controlled, if progression extends beyond the planned local field, or if prompt reassessment reveals further escape, local treatment is unlikely to compensate for systemic resistance. The strongest local-therapy trials support intervention in carefully selected liver-metastasis populations; none directly tests liver-directed therapy plus *unchanged cytotoxic chemotherapy, with or without a VEGF inhibitor*, against an immediate regimen change in patients presenting with confirmed hepatic oligoprogression.

Guidelines

Response classification and treatment choice are distinct decisions. RECIST 1.1 classifies an unequivocal new malignant lesion as progressive disease, irrespective of stability elsewhere or a falling serum marker. Enlargement of an existing target liver lesion, by contrast, does not automatically establish RECIST progression: target-lesion progression is assessed from the sum of target-lesion diameters, whereas progression of non-target disease requires unequivocal worsening. When a putative new lesion is equivocal, RECIST permits continued assessment until its status is clarified; confirmation establishes progression at the earlier assessment. The stipulated confirmation of new or enlarging hepatic lesions therefore warrants review of *which* RECIST criterion is met, but a stable primary and falling CEA cannot negate an unequivocal new metastasis.

The ESMO clinical practice guideline treats CEA as one factor in metastatic colorectal cancer treatment selection alongside the number of involved organs and lesions, prognostic scores, time to metastases, BRAF and mismatch-repair status, and nodal pathology; this recommendation is graded **[IV, B]**. It also states that locoregional treatment can remain an option in selected patients with resectable metastatic

disease, graded **[IV, B]**. Neither recommendation makes a favorable CEA trajectory grounds for overriding confirmed radiographic progression or requires that every instance of progression prompt immediate abandonment of all components of systemic therapy. The older liver-resection guideline is more guarded about the marker's role: it calls the case for routine serial CEA measurements unproven (**category of evidence III; strength of recommendation C**). These positions differ in emphasis, not in the hierarchy of evidence for an established new lesion: CEA may inform assessment and selection, but does not replace anatomical evaluation.

EORTC's multidisciplinary consensus addresses baseline imaging, selection for liver-directed therapies, response assessment and follow-up in colorectal liver metastases. Its relevance here is to place a potentially treatable hepatic site of progression before a liver multidisciplinary team, rather than equate a mixed radiographic pattern with either global regimen failure or permission to continue unchanged. The treatment decision remains conditional on the extent of progression, whether all progressive deposits can be controlled locally, disease outside the liver, procedural feasibility, and the effectiveness and tolerability of the systemic treatment at other sites. Evidence supporting these options does not create a guideline exception to the RECIST designation of progression.

Certainty and limitations

Certainty is high for the response-classification principle and appreciably lower for the best treatment after that classification. RECIST 1.1 supplies explicit, reproducible rules for unequivocal new lesions and target- versus non-target-lesion progression. Its application still depends on image quality, comparable examinations and correct lesion attribution. In a study of 29 patients with metastatic colorectal cancer, independent radiologists selected different metastatic targets; with independent selection, variability in relative change was 11% for **unidimensional measurements**, illustrating why a marginal size change alone needs careful review. A published case of apparent bevacizumab-associated hepatic pseudoprogression shows that imaging appearances can occasionally mislead, but a single case in which subsequent imaging supported continued response cannot establish a general strategy of treating confirmed new or enlarging malignant lesions as non-progression. In the stated setting, repeat-scan confirmation substantially narrows that concern without making every enlarging lesion, considered in isolation, RECIST progression.

Evidence on CEA is predominantly prognostic and observational, not evidence that treatment should be continued when imaging documents progression. A retrospective analysis of **360** patients receiving first-line palliative chemotherapy found that CEA-response categories conveyed prognostic information within RECIST-response categories. A separate study enrolled **330** patients with stage IV colorectal cancer to examine discordant CEA and imaging findings. Analyses of first-line treatment, including PRODIGE 9, associate CEA trajectories with prognosis. Correlation at a population level is compatible with an

individual patient having radiographically progressive deposits while CEA falls; none of these analyses randomised patients with that discordance to continue versus change chemotherapy. Accordingly, falling CEA can support an interpretation that some disease remains treatment-sensitive, but cannot establish that the progressing liver lesions are controlled.

Mixed response has a firmer descriptive basis than it has a treatment algorithm. An analysis drawing on **10,551 patients** in the ARCAD database examined lesion-level response heterogeneity among participants in first-line metastatic colorectal cancer trials; it distinguishes varied lesion behavior from a single patient-level RECIST category. Trial populations and lesion-based definitions, however, do not identify which patient with newly confirmed hepatic progression benefits from retaining an otherwise active regimen. Nor can stability of the primary alone establish liver-limited oligoprogression: that designation requires assessment of *all* metastatic sites and whether the progressive sites are sufficiently limited for complete local treatment.

Randomised evidence supports two relevant strategies, but each addresses a different population from the precise decision at hand. In **ML18147**, patients progressing after first-line bevacizumab-containing chemotherapy were assigned second-line chemotherapy with or without continued bevacizumab; the trial supports maintaining VEGF inhibition **with a changed chemotherapy regimen**, not continuing an ineffective cytotoxic backbone unchanged solely because CEA is falling. BEBYP similarly studied bevacizumab continuation or reintroduction alongside second-line chemotherapy after progression; its early termination limits precision. Conversely, CAIRO3 randomised **558 patients** who had *stable disease or better* after induction to maintenance capecitabine–bevacizumab or observation, with planned reintroduction on progression. It informs de-escalation before progression, not maintenance of the same regimen despite confirmed progression.

Liver-directed evidence also requires separation of local-control benefit from proof of the proposed *sequencing* strategy. CLOCC compared ablation, with or without resection, plus systemic therapy against systemic therapy alone in patients with unresectable colorectal liver metastases; it was not a trial confined to patients developing a few progressive liver deposits while other disease remained controlled on their current regimen. COLLISION compared thermal ablation with resection for selected small, resectable liver metastases and stopped early after meeting predefined criteria favoring non-inferiority and fewer adverse events with ablation. It helps inform the choice of local modality, not whether the same systemic drugs should continue through oligoprogression. Thus, retaining a tolerable regimen while definitively treating a few hepatic escape lesions is a biologically and clinically coherent **individualised option**, not a strategy directly established by these trials.

For the immediate decision, the evidence is strongest against letting falling CEA reclassify confirmed hepatic progression as disease control. It supports changing the cytotoxic regimen when progression is not amenable to complete local control, while allowing that a VEGF inhibitor may remain part of a *new line*

in an appropriate patient. It supports multidisciplinary consideration of local treatment when progression is genuinely limited and treatable, but does not prove that continuing the unchanged systemic regimen after that treatment improves survival over switching it. The distinction between those paths rests on whole-body disease assessment, technical feasibility, prior treatment and toxicity—not the direction of CEA alone.

Clinical reasoning

1. Frame the decision. This patient has metastatic colorectal cancer treated with cytotoxic chemotherapy, with or without a VEGF inhibitor. The primary tumor is radiographically stable, CEA is falling, and new or enlarging liver lesions have been confirmed on a subsequent scan. The immediate decision is whether those hepatic findings warrant continuing the present regimen unchanged, treating a limited site of escape while retaining it, or changing systemic treatment. The first standard is radiographic response assessment, not the direction of CEA. Under RECIST 1.1, an unequivocal new malignant lesion establishes progressive disease irrespective of stability elsewhere. Enlargement of an existing lesion requires more care: target-lesion progression depends on the change in the **sum** of target-lesion diameters from its nadir, meeting both a $\geq 20\%$ relative increase and an ≥ 5 mm absolute increase; progression of non-target disease must be unequivocal. Growth of one lesion, without those findings, does not automatically establish formal RECIST progressive disease. The clinical decision may nevertheless turn on convincing, serially documented growth of metastases even when a report does not provide the measurements needed to assign a formal RECIST category.

The stable primary and falling CEA describe different aspects of disease behavior; neither cancels hepatic progression. “Mixed response” is a useful description of discordant behavior across sites, **not** a RECIST category that permits progressive lesions to be scored as stable disease. Lesion-level heterogeneity has been documented in patients receiving first-line metastatic colorectal cancer treatment, whereas RECIST assigns a patient-level response. For this patient, stability of the primary alone does not establish that all non-hepatic disease is controlled: a complete restaging review must determine the distribution and trajectory of every known site.

2. Match the evidence to the decision. Studies of CEA–imaging discordance in metastatic colorectal cancer support using CEA as a contextual or prognostic measure, rather than as an override of imaging. A retrospective analysis of 360 patients receiving first-line palliative chemotherapy found that CEA response patterns carried prognostic information within RECIST response categories; its study-defined CEA categories were not an alternative radiographic progression standard. Another cohort of 330 patients specifically examined opposing CEA and imaging changes after systemic therapy. CEA trajectories also correlated with prognosis in an analysis of patients receiving first-line chemotherapy in PRODIGE 9. Those observations make the falling marker worth recording and checking against prior values, but they do not

demonstrate that continued treatment controls confirmed enlarging metastases.

Imaging itself must be read critically. In a study of 29 patients with metastatic colorectal cancer, independent target-lesion selection by radiologists produced 11% variability in relative unidimensional measurement change. Antiangiogenic treatment can also alter the appearance of colorectal liver metastases in ways incompletely represented by size-only criteria; an imaging–pathology study evaluated enhancement and diffusion changes after bevacizumab-containing chemotherapy. A published bevacizumab-treated case initially thought to have a new lesion subsequently showed no increase in that lesion and continued radiographic response. That case justifies careful review of a *questionable* new finding; it does not justify discounting this patient's new or enlarging lesions merely because CEA falls, particularly when the finding has persisted or enlarged on a subsequent scan. Confirmed serial progression is materially different from a single equivocal image.

3. Weigh the choices and their risks. The clearest potential harm of leaving treatment unchanged is allowing resistant hepatic disease to expand while a favorable marker trend offers false reassurance. The harm of changing treatment prematurely is loss of a regimen that may still control other disease, exposure to new toxicity, and possible disruption of a feasible liver-directed plan. Thus the consequential distinction is **limited, completely treatable hepatic escape versus broader failure of disease control**—not whether the primary tumor remains stable. Oligoprogression means a limited number of progressing deposits during otherwise effective systemic treatment; it cannot be inferred from the word “liver” alone. Assess the number, size, location and rate of growth of hepatic lesions, the behavior of other metastases, and whether all progressing sites can be eradicated with an acceptable functional liver remnant or another suitable local modality. Colorectal oligometastatic reviews distinguish oligoprogression during active therapy from other limited-metastasis states and emphasize selection for local treatment rather than lesion count in isolation. EORTC multidisciplinary consensus addresses imaging, selection for liver-directed treatment and response assessment as linked decisions.

Randomized evidence supports local treatment in selected colorectal liver-metastasis populations, but it does **not** directly test continuing an unchanged, demonstrably failing chemotherapy backbone after oligoprogression. In the CLOCC comparison, radiofrequency ablation, with or without resection, was added to FOLFOX with or without bevacizumab for unresectable limited liver metastases, rather than applied specifically after escape on the same regimen. A reported median progression-free survival of 16.8 months with chemotherapy plus ablation versus 9.9 months with chemotherapy alone describes that trial population, not this patient's expected result. In COLLISION, thermal ablation was compared with resection for selected small, resectable colorectal liver metastases in patients without extrahepatic metastases; it informs **how** suitable deposits might be treated locally, not whether systemic progression should be ignored. Likewise, the BECOME randomized trial found, in initially unresectable RAS-mutant *liver-limited* disease, an objective response rate of 54.5% with first-line mFOLFOX6 plus bevacizumab versus 36.7% with mFOLFOX6 alone, and median progression-free survival of 9.5 versus 5.6 months.

These are treatment-selection data for a defined first-line population, not a rationale for adding bevacizumab alone to an ineffective regimen without reassessing the cytotoxic backbone.

4. Work through the systemic alternatives. If hepatic progression is multifocal, rapidly accumulating, technically unsuitable for complete local control, or accompanied by progression at other sites, favor changing the systemic strategy rather than administering more cycles of the identical failing regimen because CEA is falling. The next backbone depends on what the patient has actually received and tolerated: an oxaliplatin-based regimen commonly gives way to an irinotecan-based option, or the reverse, with subsequent choices conditioned by prior exposure, molecular profile, performance status and treatment goals. None of those patient-specific details is established here. If the regimen includes bevacizumab, progression does not by itself mean that VEGF inhibition must end. In the randomized ML18147 trial, continuing bevacizumab **with second-line chemotherapy**, rather than second-line chemotherapy alone, provided clinical benefit after first-line bevacizumab-containing treatment. Its KRAS subgroup analysis reported median progression-free survival of 6.4 versus 4.5 months with bevacizumab plus chemotherapy versus chemotherapy in KRAS wild-type disease (HR 0.61; 95% CI 0.49–0.77), and 5.5 versus 4.1 months, respectively, in KRAS-mutant disease (HR 0.70; 95% CI 0.56–0.89). BEBYP also evaluated bevacizumab continuation or reintroduction **alongside a second-line backbone**. “Bevacizumab beyond progression” must not be misread as evidence for leaving the entire first-line combination unchanged despite ongoing growth.

Conversely, an apparently modest, localized escape does not require reflex discontinuation of *all* effective systemic treatment. If comprehensive staging shows the remaining disease is controlled and a liver team can completely address the progressing deposits, local treatment followed by a defined plan for systemic treatment and early reassessment is reasonable. Whether that plan retains, pauses, de-escalates or changes the backbone should reflect its control of untreated sites and the requirements of surgery, ablation or radiotherapy—not CEA alone. Maintenance trials such as CAIRO3 randomized patients who had **stable disease or better after induction**, with planned reintroduction on progression; their maintenance results cannot be transferred without qualification to lesions progressing on the current treatment. If a VEGF inhibitor is being administered, procedural planning must also account for wound-healing and other treatment-related risks; an operative plan may call for a treatment hold, which is different from declaring VEGF inhibition permanently ineffective.

5. Decide and act. Do **not** continue the present regimen unchanged solely because the primary is stable and CEA is falling. First, have the radiologist and treating team review the baseline, nadir and serial scans lesion by lesion: identify unequivocal new metastases, measure target-lesion sums where appropriate, assess non-target disease, and establish whether the hepatic change is isolated. Liver-focused imaging can resolve treatment-related morphology or define anatomy for intervention, but should answer a specific staging or local-treatment question rather than indefinitely postpone a decision. Record the assessment as radiographic progression when RECIST criteria are met; describe the stable primary and

falling CEA separately as discordant findings. If enlargement is convincing but formal target-sum criteria are not met, document both the RECIST classification and the clinically important site-specific growth instead of conflating them.

Arrange prompt multidisciplinary review if *all* progressing sites might be resected or ablated. If complete local control is not plausible, move toward an appropriate next systemic regimen without waiting for CEA to rise. If it is plausible, formulate the local intervention and systemic plan together, including the intended reassessment scan and a clear trigger for changing treatment if additional lesions emerge. Monitor radiographic disease distribution, symptoms, functional status, liver function and treatment toxicity alongside serial CEA; the marker is supportive, not the stopping or continuation rule.

6. Check what could change that action. The essential checks are the exact current drugs and prior lines; whether a VEGF inhibitor is actually being given; the number and distribution of progressing lesions; extrahepatic disease behavior; resectability or ablatability; hepatic reserve; performance status; treatment toxicities and contraindications; and molecular findings relevant to a subsequent systemic choice. A biopsy is most consequential if lesion identity remains in doubt or tissue findings would change treatment; falling CEA alone is not a reason to biopsy every radiographically convincing metastasis. The recurrent pitfalls are treating CEA decline as proof of whole-body control, calling any small increase in an individual diameter RECIST progression, treating one equivocal anti-VEGF imaging change as definite failure, or invoking pseudoprogression after serial confirmation of worsening lesions. Equally important is not interpreting a stable primary as evidence that unreported metastatic sites are stable.

Illustrative scenario: Restaging shows a solitary growing liver metastasis, all other known deposits remain controlled, and a liver multidisciplinary team judges complete ablation feasible. The lesion still represents progression if RECIST new-lesion criteria are met. Local treatment with a planned systemic-treatment decision and close imaging reassessment may preserve a useful regimen; the rationale is verified control elsewhere and complete treatment of the escape site, **not** the falling CEA.

Illustrative scenario: The same treatment and falling CEA are present, but restaging instead shows several enlarging deposits distributed through the liver that cannot all be treated definitively. This change in the extent and treatability of hepatic progression shifts the balance toward changing the systemic backbone now. If the patient has been receiving bevacizumab and remains eligible for it, VEGF inhibition can still be considered with the next-line chemotherapy; continuing bevacizumab is distinct from continuing the unchanged failing combination.

What this means in practice

Treat the confirmed liver findings as evidence of progression, not as a response rescued by the CEA trend. An unequivocally new malignant liver lesion establishes progressive disease under RECIST 1.1 regardless of stability elsewhere. For enlargement of existing lesions alone, formal RECIST progression depends on the change in the sum of target-lesion diameters from nadir, or unequivocal progression of non-target disease; growth of one lesion need not, by itself, meet the patient-level threshold. The subsequent scan confirmation in this case makes a transient imaging discrepancy a less persuasive reason to continue treatment unchanged. Falling CEA remains potentially informative about disease elsewhere, but it does not negate an established new metastasis or establish control of the enlarging hepatic disease. Discordance between CEA and RECIST has been documented in metastatic colorectal cancer, and CEA kinetics are prognostic rather than a replacement for anatomical assessment when the two conflict.

Do not equate a stable primary with control of the metastatic compartment. “Mixed response” describes heterogeneity between lesions, not a separate RECIST category that overrides progression. Lesion-level response heterogeneity has been observed across first-line metastatic colorectal cancer trials. In this case, stability is established for the primary and progression for the liver; response at other metastatic sites cannot be inferred. Before deciding that treatment has failed *systemically*, review all measurable and non-measurable disease on comparable scans, including the number, distribution and pace of progressing liver lesions. Reproducibility matters particularly for borderline size changes: independent lesion selection produced variability in relative unidimensional change in a metastatic colorectal cancer imaging study. That caveat is less applicable to unequivocal malignant lesions persisting or enlarging on a subsequent scan. A published bevacizumab-associated pseudoprogression account illustrates why an initially ambiguous hepatic image can merit review, but a case report cannot justify disregarding confirmed progression.

The default decision is to change the ineffective systemic strategy, not to continue the identical regimen solely because CEA is falling. If hepatic progression is multifocal, rapid, or accompanied by progression elsewhere, continued treatment with the same cytotoxic backbone offers no established rationale for controlling the advancing disease. Select the next regimen according to the actual current drugs, prior exposure, performance status, toxicity, molecular profile and treatment goals. If the current treatment includes bevacizumab, changing the chemotherapy backbone does **not** necessarily require abandoning VEGF inhibition: the randomized ML18147 trial tested bevacizumab with *second-line chemotherapy* after progression on bevacizumab-containing first-line treatment, and BEBYP also evaluated bevacizumab continuation or reintroduction with a changed second-line regimen. These trials support a conditional option to retain bevacizumab in an appropriate subsequent regimen; they do **not** establish benefit from simply continuing the same failing chemotherapy–bevacizumab combination. Conversely, stopping bevacizumab for a contraindication or planned invasive procedure is a distinct safety decision, not proof that all systemic therapy should stop.

Make an exception to immediate backbone change only for a credible, actionable liver-limited pattern. If comprehensive restaging shows that progression is confined to a small number of hepatic sites while disease elsewhere remains controlled, obtain hepatobiliary multidisciplinary review for complete local treatment. Resection or ablation may address the progressing deposits while permitting continued systemic control of the remaining disease; feasibility depends on lesion location, whether *all* relevant sites can be treated, functional liver reserve and operative risk. The COLLISION randomized trial informs selection between ablation and resection for small, resectable and ablatable colorectal liver metastases, but did not randomize patients with oligoprogression on an otherwise beneficial chemotherapy regimen to local treatment plus unchanged chemotherapy versus an immediate systemic switch. Likewise, CLOCC compared local ablation plus systemic treatment with systemic treatment alone in selected unresectable liver metastases, rather than testing that specific beyond-progression decision. Liver-directed treatment therefore provides a defensible *conditional* route to continuing an otherwise useful regimen, not a reason to label hepatic progression “stable disease” or to defer reassessment indefinitely. A stable primary alone does not establish liver-limited disease.

Open questions

The central unresolved treatment question is whether ablating or resecting **confirmed hepatic oligoprogression while maintaining the same cytotoxic regimen** improves survival, quality of life or time to a necessary systemic change compared with changing the regimen promptly. The relevant randomized evidence establishes roles for selected liver-directed treatments and for bevacizumab with a *new* chemotherapy backbone after progression; neither comparison directly answers that question. A pragmatic randomized trial should enroll patients with centrally confirmed colorectal liver oligoprogression during chemotherapy, document control of every other disease site, and compare complete local treatment followed by continuation of the current systemic regimen against a standard next-line systemic regimen. Overall survival, time to further progression, treatment toxicity, quality of life and the proportion ultimately receiving complete local treatment would distinguish genuine preservation of an effective strategy from merely postponing a needed change.

There is also no validated CEA trajectory that reliably identifies patients whose confirmed progressing liver lesions can safely be observed on unchanged chemotherapy. Studies linking CEA kinetics with prognosis or subsequent imaging outcomes do not demonstrate that a falling value predicts benefit from continuing a regimen *after* anatomical progression. A prospective study with serial, centrally reviewed site-specific imaging and prespecified CEA analyses could test whether any marker pattern adds useful discrimination once the extent and pace of hepatic progression are known. Until then, the decision in this case turns on the radiographic progression, full metastatic restaging and feasibility of complete local control—not on the favorable direction of CEA.