Liver transplantation for non-resectable colorectal liver metastases: the International Hepato-Pancreato-Biliary Association consensus guidelines

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Colorectal cancer is a prevalent disease worldwide, with more than 50% of patients developing metastases to the liver. Despite advances in improving resectability, most patients present with non-resectable colorectal liver metastases requiring palliative systemic therapy and locoregional disease control strategies. There is a growing interest in the use of liver transplantation to treat non-resectable colorectal liver metastases in well selected patients, leading to a surge in the number of studies and prospective trials worldwide, thereby fuelling the emerging field of transplant oncology. The interdisciplinary nature of this field requires domain-specific evidence and expertise to be drawn from multiple clinical specialities and the basic sciences. Importantly, the wider societal implication of liver transplantation for non-resectable colorectal liver metastases, such as the effect on the allocation of resources and national transplant waitlists, should be considered. To address the urgent need for a consensus approach, the International Hepato-Pancreato-Biliary Association commissioned the Liver Transplantation for Colorectal liver Metastases 2021 working group, consisting of international leaders in the areas of hepatobiliary surgery, colorectal oncology, liver transplantation, hepatology, and bioethics. The aim of this study was to standardise nomenclature and define management principles in five key domains: patient selection, evaluation of biological behaviour, graft selection, recipient considerations, and outcomes. An extensive literature review was done within the five domains identified. Between November, 2020, and January, 2021, a three-step modified Delphi consensus process was undertaken by the workgroup, who were further subgrouped into the Scientific Committee, Expert Panel, and Transplant Centre Representatives. A final consensus of 44 statements, standardised nomenclature, and a practical management algorithm is presented. Specific criteria for clinico-patho-radiological assessments with molecular profiling is crucial in this setting. After this, the careful evaluation of biological behaviour with bridging therapy to transplantation with an appropriate assessment of the response is required. The sequencing of treatment in synchronous metastatic disease requires special consideration and is highlighted here. Some ethical dilemmas within organ allocation for malignant indications are discussed and the role for extended criteria grafts, living donor transplantation, and machine perfusion technologies for non-resectable colorectal liver metastases are reviewed. Appropriate immunosuppressive regimens and strategies for the follow-up and treatment of recurrent disease are proposed. This consensus guideline provides a framework by which liver transplantation for non-resectable colorectal liver metastases might be safely instituted and is a meaningful step towards future evidenced-based practice for better patient selection and organ allocation to improve the survival for patients with this disease.

Introduction

Liver resection is considered the only potentially curative treatment for patients with colorectal liver metastases.[1] Although the addition of perioperative chemotherapy has resulted in an improvement in disease-free and progression-free survival,[2] palliative chemotherapy is the only option for most patients who present with non-resectable colorectal liver metastases, offering a 5-year overall survival of only 10%.[3] In a bid to increase the proportion of patients with disease amenable to curative resection, more novel resections are being increasingly adopted.[4,5]

The first published series of liver transplantation included two patients with colorectal liver metastases.[6] Although technically successful, the absence of modern chemotherapy agents and an incomplete understanding of disease biology in colorectal cancer ultimately led to it not being adopted for colorectal liver metastases. The use of liver transplantation for metastatic tumours has been controversial, with concerns that the exposure of systemic disease to postoperative immunosuppressive therapy would contribute to increased recurrence and poorer outcomes.[7]

Collective advances in the treatment of colorectal liver metastases and immunosuppression in liver transplantation, as well as the successes in liver transplantation for hepatocellular carcinoma, have reignited interest in liver transplantation for some patients with non-resectable colorectal liver metastases.[8] The first prospective trial evaluating liver transplantation for non-resectable colorectal liver metastases, the SECA-I study, recruited a heterogeneous study cohort and obtained an estimated 5-year survival of 60%.[9] Subsequently, the SECA-II study improved the estimated 5-year survival to 83% by using more stringent selection criteria.[10] Since then, a surge in the

Lancet Gastroenterol Hepatol 2021

Published Online September 7, 2021 https://doi.org/10.1016/S2468-1253(21)00219-3

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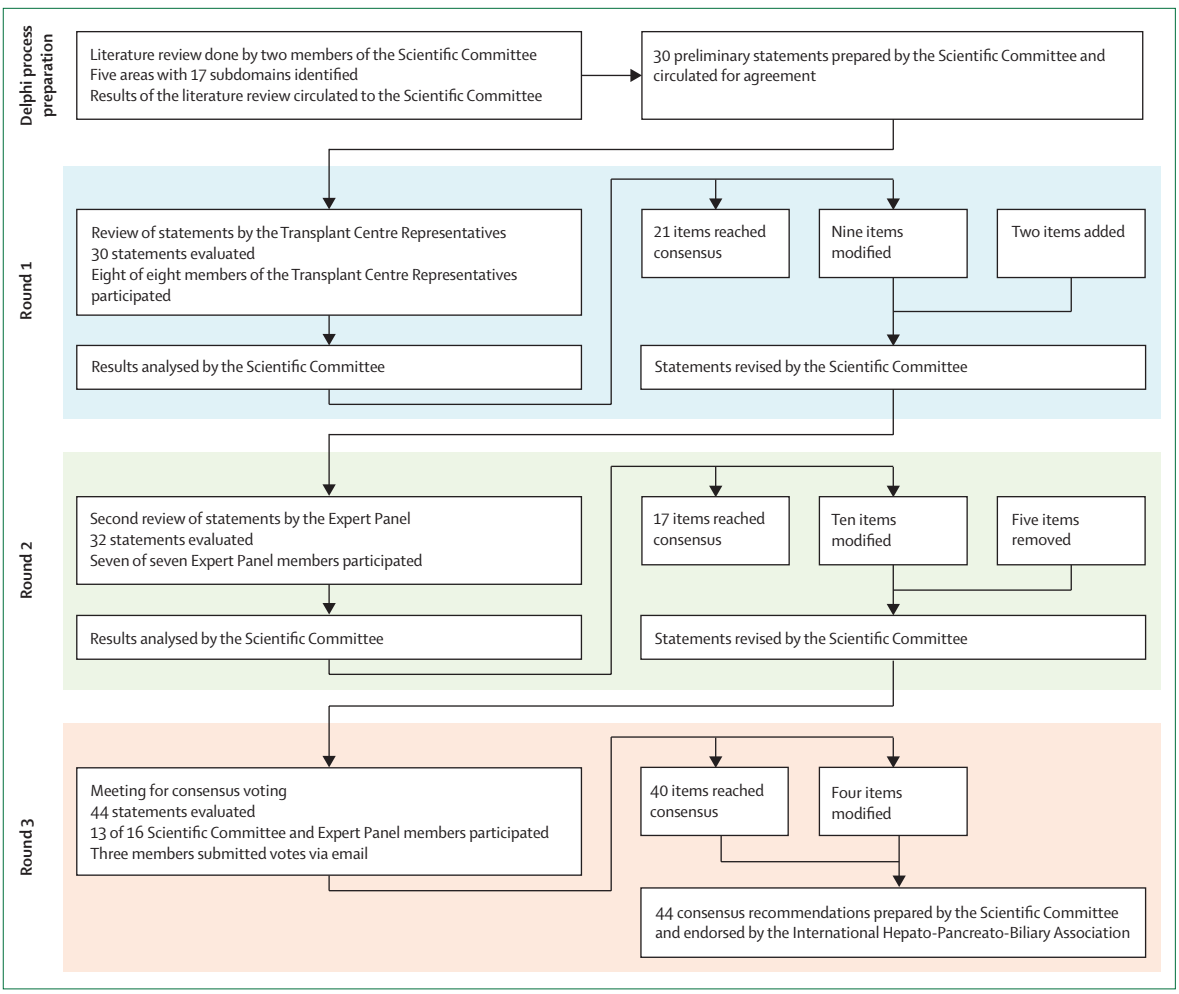

Figure 1: **Flow diagram of the modified Delphi process for the development of consensus guidelines for liver transplantation in non-resectable colorectal liver metastases by the Liver Transplantation for Colorectal liver Metastases 2021 working group**

number of registered trials has fuelled activity in the emerging field of transplant oncology, which involves multiple clinical specialties and the basic sciences. When compared with surgical oncology, transplant oncology is unique in its effect on the allocation of organs as a national resource and the subsequent effect on waiting list mortality. The interdisciplinary nature of the field also necessitates a wide breadth of domain-specific scholarship and expertise to produce optimal outcomes.[11]

As the number of transplants done for patients with non-resectable colorectal liver metastases worldwide increases, there is an urgent need for a consensus approach towards decision making. To address this, the International Hepato-Pancreato-Biliary Association commissioned an international multidisciplinary group of experts to develop consensus guidelines, named the Liver Transplantation for Colorectal liver Metastases 2021 (LT-CoMet 21) working group. The aim of this process was to standardise the nomenclature and define the principles of management for the field. These guidelines will provide a scientific and ethical framework within which future studies can be done to optimise the management of patients with transplantable colorectal liver metastases.

Methods

The LT-CoMet 21 working group was commissioned by the International Hepato-Pancreato-Biliary Association in October, 2020. The consensus process took place between Nov 2, 2020, and Jan 31, 2021, and incorporated a three-step modified Delphi method (figure 1).[12]

Modified Delphi process

In round 1 of the modified Delphi process (figure 1), the preliminary statements were circulated among the Transplant Centre Representatives. The statements were consolidated by the Scientific Committee and revised accordingly before circulation to the Expert Panel in round 2. Revisions were once again consolidated by the

Scientific Committee before the final consensus statements were circulated to the Expert Panel in preparation for the final voting. The consensus meeting took place on Jan 11, 2021, and panel members were given the opportunity to provide comments. For the purposes of the consensus statement, agreement among 70% or more of respondents for each statement was required for consensus.[13]

Findings

Definitions and treatment algorithm

Because of variations in disease presentation, and in the sequencing and goals of chemotherapy, the panel proposed a standardised nomenclature (table 1) and management algorithm (figure 2) to provide clarity in the delivery of care and reporting of outcomes. The final 44 consensus statements are presented in table 2.

	Definitions
Metastatic colorectal cancer	Colorectal cancer that is metastatic to a single or multiple extracolonic sites
Non-resectable colorectal liver metastases	Liver metastases present at diagnosis or after previous resection that cannot be resected with curative intent either by standard, complex (two-stage hepatectomy, ALPPS, and ex-vivo liver resection), or combinatorial (resection combined with ablative strategies) resection
Synchronous liver-only colorectal metastases	Hepatic metastases secondary to colorectal adenocarcinoma that are radiologically (or biopsy) proven before or at the time of diagnosis of primary colorectal cancer[14]
Metachronous liver-only colorectal metastases	Hepatic metastases secondary to colorectal adenocarcinoma that are diagnosed within 1 year (early) or after 1 year (late) of the diagnosis of primary colorectal cancer[14]
Neoadjuvant chemotherapy for liver surgery	Systemic or locoregional therapy given before the liver resection of potentially resectable disease, with the intention of downstaging for curative resection
Bridging therapy to transplantation	Systemic therapy that is administered to patients with non-resectable colorectal liver metastases after the resection of the primary tumour for the evaluation of biological behaviour for consideration for a liver transplantation
Transplantable colorectal liver metastases	Non-resectable colorectal liver metastases with clinicopathological and molecular features associated with a favourable response to bridging therapy to transplantation
Palliative therapy	Systemic therapy or locoregional therapy that is administered with palliative intent

ALPPS=associating liver partition and portal vein ligation for staged hepatectomy.

Table 1: **Proposed standardised nomenclature**

Patient selection

The aim of the selection process was to identify patients with non-resectable colorectal liver metastases with favourable tumour biology who would derive the greatest survival benefit from liver transplantation. The panel reviewed evidence to identify prognostic factors from an array of clinicopathological and molecular features to establish biologically based criteria for patient selection.

Clinico-patho-radiological criteria (statements 1–12)

In accordance with international guidelines, patients with non-resectable colorectal liver metastases being considered for liver transplantation should undergo standard oncological resection of the primary tumour with clear resection margins, including a circumferential resection margin of more than 1 mm for rectal cancer.[15] Patients with a primary tumour histology of undifferentiated adenocarcinoma or signet ring cell carcinoma should be excluded from liver transplantation because these features are associated with worse survival.[16] Extensive lymph node involvement of the primary tumour also predicts poorer survival in patients who have had a resection.[1,17] However, in the absence of nodal recurrence in the extended observation period after late metachronous disease, primary nodal staging becomes of less prognostic relevance. The absence of local recurrence should be confirmed using colonoscopy within 3 months of liver transplantation.

Patients who present with non-resectable colorectal liver metastases or develop it after resection might both be considered for liver transplantation. Sequential resection techniques such as the two-stage hepatectomy and associating liver partition and portal vein ligation for staged hepatectomy (ie, ALPPS) have expanded the pool of surgical candidates. These approaches can result in R0 resections with good survival in patients with initially unresectable disease, hence resection should still be done where possible.[4,18] There is little evidence to support liver transplantation for patients with resectable colorectal liver metastases.

The diagnostic accuracy of contrasted liver MRI or fine-cut triphasic liver CT, or both, for colorectal liver metastases after systemic therapy is well established, and therefore is recommended for assessing the resectability of non-resectable colorectal liver metastases in patients before liver transplantation.[19] The development of extrahepatic metastases is a sign of disseminated disease and a poor prognostic marker in metastatic colorectal cancer.[20] A fluorine-18-fluorodeoxyglucose PET-CT scan enables the detection of extrahepatic disease not characterised by CT alone and should be used to exclude such patients.[21] Although there is little evidence to support routine intraoperative nodal sampling before liver transplantation,[22] it should be considered when clinical suspicion is high and preoperative PET imaging is inconclusive. Patients found to have lymph node-positive disease should be excluded from liver transplantation.

There is growing evidence to support the use of PET-CT in evaluating the biological behaviour of colorectal liver metastases.[23,24] Metabolic tumour volume and total lesion glycolysis on pre-transplant PET-CT are independent predictors for survival after transplant.[25,26] The panel agreed that the consideration of metabolic tumour volume and total lesion glycolysis in tandem with the response to systemic therapy provides a better reflection of biological activity than an absolute cutoff of hepatic tumour burden quantified by the size and number of lesions.

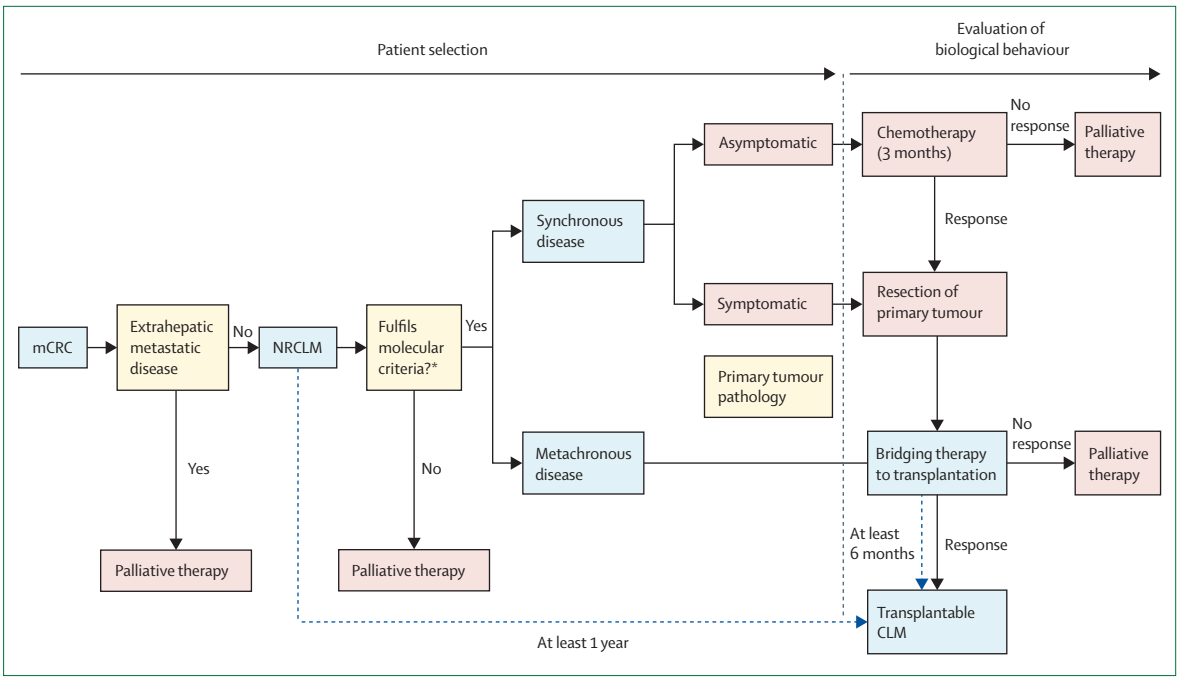

Figure 2: **Proposed management algorithm**
CLM=colorectal liver metastases. mCRC=metastatic colorectal cancer. NRCLM=non-resectable CLM. *No *BRAF* V600E mutation, microsatellite stable, and mismatch repair proficient.

Molecular prognostic markers (statements 13–17)

Interrogation of the molecular landscape of colorectal cancer has yielded insights into the crucial mutations underlying its pathogenesis.[27,28] Mutations in the *BRAF* gene are present in approximately 8% of patients with metastatic colorectal cancer, and are associated with a reduction in disease-free survival and overall survival after both liver resection and liver transplantation.[16,29–31] However, median overall survival in patients with non-V600 *BRAF*-mutant metastatic colorectal cancer (60·7 months) is significantly longer than that for patients with V600 *BRAF*-mutant metastatic colorectal cancer (11·4 months) and for those with wild-type *BRAF* metastatic colorectal cancer (43·0 months).[32] Hence, the panel opted to exclude patients with *BRAF* V600E-mutated metastatic colorectal cancer. Although *RAS* mutations are associated with inferior survival in patients with colorectal liver metastases undergoing resection,[33,34] their prognostic value in patients undergoing liver transplantation has not yet been clearly proven. Molecular analyses have revealed no significant differences in genetic alterations between primary and secondary colorectal cancer tumours,[35] hence the molecular profiling of either the primary tumour or secondary metastases is deemed acceptable.

Data from cohorts of patients with resected colorectal liver metastases have suggested that other genetic mutations, such as concomitant *APC* and *PIK3CA* mutations or *TP53* with *RAS* mutations, are also poor prognostic factors.[36,37] Multi-gene mRNA panels to predict overall survival have also been shown to outperform standard clinical risk scores.[38] The further interrogation of tissue-based and circulating biomarkers, such as cell-free DNA, should be pursued to improve prognostication and to aid in predicting the behaviour of secondary hepatic lesions.

In the last decade, immunotherapy has revolutionised the treatment of multiple cancer types.[39,40] At present, immunotherapy is approved for use in patients with colorectal cancer with high microsatellite instability and deficient DNA mismatch repair.[41,42] An interim analysis of the CheckMate 142 trial showed a 60% overall response rate in patients with high microsatellite instability and deficient DNA mismatch repair metastatic colorectal cancer at approximately 20 months.[43] Given the concern for a high allograft rejection rate associated with the administration of immunotherapy after solid organ transplantation,[44] these patients would not be eligible for palliative immunotherapy for disease recurrence post-transplantation. Thus, considering the notable results of immunotherapy for patients with high microsatellite instability or deficient DNA mismatch repair metastatic colorectal cancer and the risk of graft rejection that precludes these patients from receiving immunotherapy after liver transplantation, at present such patients should be excluded from liver transplantation for non-resectable colorectal liver metastases.

Evaluation of biological behaviour

Because clinico-patho-radiological markers and molecular features provide only a static approximation of disease

	Statement
(A) Patient selection	
Clinico-patho-radiological criteria	
Statement 1 (primary tumour)	Standard oncological resection of the primary tumour with clear resection margins, including a circumferential resection margin of at least 1 mm for patients with rectal cancer, should be done
Statement 2 (primary tumour)	Primary tumour histology of undifferentiated adenocarcinoma and signet ring cell carcinoma are poor prognostic factors and are an exclusion for liver transplantation for non-resectable colorectal liver metastases
Statement 3 (primary tumour)	Nodal disease of N2 of the primary tumour is a relative exclusion criteria for liver transplantation for non-resectable colorectal liver metastases. For patients with late metachronous non-resectable colorectal liver metastases, in the absence of nodal recurrence, it is less likely that the nodal stage of primary might be of prognostic relevance
Statement 4 (hepatic metastases)	Patients who present with non-resectable colorectal liver metastases, or who develop non-resectable colorectal liver metastases in the setting of recurrence after resection, might be considered for liver transplantation
Statement 5 (hepatic metastases)	There is little evidence to support the use of liver transplantation for resectable disease
Statement 6 (hepatic metastases)	Initial resectability of hepatic metastases should be evaluated by contrasted liver MRI or fine-cut triphasic liver CT, or both
Statement 7 (hepatic metastases)	Where a ^{18}F-FDG PET-CT scan is available, metabolic tumour volume and total lesion glycolysis could be evaluated for the assessment of tumour metabolic activity. Patients with a metabolic tumour volume of >70 cm^3 and total lesion glycolysis of >260 g should be excluded
Statement 8 (hepatic metastases)	There is no clear evidence to exclude patients from liver transplantation for non-resectable colorectal liver metastases on the basis of the initial number and size of lesions present before the initiation of systemic therapy. Caution should be taken in patients with multifocal disease or lesions that are large in size, or both, because these are associated with poorer outcomes
Statement 9 (extrahepatic metastases)	There is no evidence to support liver transplantation in patients with non-resectable colorectal liver metastases who initially present with or subsequently develop extrahepatic or extracolonic metastases
Statement 10 (extrahepatic metastases)	High resolution CT thorax is recommended to rule out pulmonary metastases
Statement 11 (extrahepatic metastases)	^{18}F-FDG PET-CT is recommended to rule out extrahepatic metastatic disease and is important on follow-up during bridging chemotherapy to transplantation for the evaluation of a response in metastases. An initial scan before the commencement of chemotherapy would allow an assessment of evolution
Statement 12 (extrahepatic metastases)	Systematic intraoperative nodal sampling before liver transplantation should be considered when clinical suspicion is high and preoperative PET imaging is inconclusive
Molecular criteria	
Statement 13	Analysis of the primary tumour or hepatic metastases, or both, for *BRAF* and *RAS* mutations as well as microsatellite instability and mismatch repair status is mandatory
Statement 14	Patients with *BRAF* V600E mutation should not be considered for liver transplantation
Statement 15	*RAS* mutation is a negative prognostic factor but not a contraindication to liver transplantation for non-resectable colorectal liver metastases. Patients with *RAS* mutations can be considered if other favourable biological factors are present
Statement 16	Because of the favourable results with immunotherapy for patients with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer, at present such patients should not be considered for liver transplantation
Statement 17	Further molecular profiling of solid lesions and circulating biomarkers is strongly recommended to be done within research trials
(B) Evaluation of biological behaviour	
Bridging therapy to transplantation	
Statement 18	Patients should have had least one line of fluorouracil-based, oxaliplatin-based, or irinotecan-based chemotherapy, with response observed for at least 6 months
Statement 19	Matched targeted therapy might be considered in patients with specific molecular subtypes or actionable mutations
Statement 20	Prehabilitation should be considered for potential candidates with non-resectable colorectal liver metastases for liver transplantation at the same time as undergoing bridging therapy to transplantation to reduce the risk of complications associated with sarcopenia after liver transplantation
Assessment of response and observation time	
Statement 21	Radiological or biochemical evidence, or both, of progressive disease observed when receiving bridging therapy for transplantation is a contraindication to liver transplantation
Statement 22	Radiological imaging together with measurement of CEA concentration should be done at regular intervals of 2–3 months to evaluate the response
Statement 23	Where possible, resection should be considered in patients with liver metastases that are responsive to therapy
Statement 24	Radiological response to chemotherapy should be assessed by CT imaging using the RECIST criteria (with or without Chun criteria) where: (1) a complete response, a partial response of at least 30%, or stable disease with a response using Chun criteria are suggestive of a favourable biology; or (2) a progressive disease is a contraindication to liver transplantation
Statement 25	Biochemical response to chemotherapy should be assessed by measurement of CEA where: (1) CEA >80 µg/L with an increasing trend is a contraindication, and (2) CEA >80 µg/L with a decreasing trend is a relative contraindication in which liver transplantation might be considered in the presence of other favourable biological factors
Statement 26	Response to bridging therapy to transplantation should be observed for at least 6 months, with an interval from diagnosis of non-resectable colorectal liver metastases of at least 1 year

(Table 2 continues on next page)

	Statement
(Continued from previous page)	
Sequencing of treatment in patients with synchronous non-resectable colorectal liver metastases	
Statement 27	In patients presenting with synchronous non-resectable liver metastases with an asymptomatic primary tumour: (1) systemic therapy is administered (as per current practice) with assessment at a maximum interval of every 3 months for treatment response. For primary rectal tumours, preoperative (chemo) radiotherapy is to be given according to current practice. If there is favourable response, proceed with primary surgery if considering liver transplantation; and (2) a favourable biological response to bridging therapy to transplantation should be observed for at least 6 months before consideration for liver transplantation. If progressive disease is observed on therapy, then the goals of care would become palliative
Statement 28	In patients presenting with synchronous non-resectable colorectal liver metastases with a symptomatic primary requiring surgical resection: (1) surgical resection of the primary tumour, and (2) a favourable biological response to bridging therapy to transplantation should be observed for at least 6 months before the consideration of liver transplantation. If progressive disease is observed on therapy, then goals of care would become palliative
Multidisciplinary teams	
Statement 29	Selection of potential patients with non-colorectal liver metastases for tests and ultimately consideration for liver transplantation should be done by a multidisciplinary team including colorectal surgeons, hepatobiliary and liver transplantation surgeons, oncologists, transplant hepatologists, radiologists, and pathologists
(3) Graft selection and allocation	
Organ allocation and waitlist prioritisation	
Statement 30	The decision regarding the type of graft used for liver transplantation for non-colorectal liver metastases should be made ideally at the national organ allocation level or at least by the transplant centre. National organ availability, waiting list mortality, and centre-specific post-operative outcomes after liver transplantation should be considered
Expanding the deceased donor pool	
Statement 31	Extended criteria donor grafts might be considered for patients with non-colorectal liver metastases
Statement 32	Novel perfusion technologies in resuscitating discarded livers for liver transplantation in non-colorectal liver metastases might be considered in centres with experience in this technology, ideally within a prospective controlled trial
Statement 33	Novel surgical techniques, such as deceased donor RAPID and living donor RAPID, show promise for expansion of the donor pool; however, long-term oncological outcomes are unclear
Living donor liver transplantation for non-colorectal liver metastases	
Statement 34	Living donor liver transplantation in the setting of non-colorectal liver metastases should be done in centres with perioperative and long-term recipient and donor outcomes that are acceptable by international benchmarks, preferably within a prospective controlled trial. The morphology of the living donor graft (including graft-to-recipient weight ratio, vascular and biliary anatomy, steatosis, and future liver remnant) should meet the safe acceptable criteria of the transplanting centres
Organ allocation for re-transplantation	
Statement 35	Re-transplantation for early graft failure with standard donation after brain death grafts might be considered in accordance with national or centre-specific organ allocation criteria for liver transplantation. Where these criteria are not met, re-transplantation with extended criteria or living donor grafts might be considered on the basis of centre expertise. This practice might therefore vary between countries and regions worldwide
(4) Recipient considerations	
Immunosuppression	
Statement 36	The principle of immunosuppression in this setting is to minimise exposure to calcineurin inhibitors
Statement 37	Induction: interleukin 2 receptor antagonist (eg, basiliximab) induction with or without steroids accompanied by calcineurin inhibitor (eg, tacrolimus at C_{min} 6–8 ng/mL for the first month) and an antiproliferative immunosuppressant (eg, mycophenolate mofetil at 1–2 g daily) is considered safe
Statement 38	Maintenance: based on centre experience, calcineurin inhibitor therapy should be replaced with an mTOR inhibitor (eg, everolimus or sirolimus) within 4–6 weeks from transplantation or calcineurin inhibitor therapy can be slowly reduced (eg, to C_{min} 3–4 ng/mL for tacrolimus) for long-term maintenance with the addition of an mTOR inhibitor
Statement 39	In patients requiring chemotherapy during follow-up, immunosuppression should be modified accordingly
Prevention and management of recurrent disease	
Statement 40	There is little evidence to recommend the routine use of adjuvant chemotherapy after liver transplantation for non-colorectal liver metastases
Statement 41	Isolated pulmonary recurrence post-liver transplantation should be considered for resection
Statement 42	The use of systemic therapy should be reserved for the management of multi-site recurrence and disseminated disease. Caution should be taken in future trials in this area given the potential toxicity of chemotherapy in patients for perioperative transplant
Outcomes	
Statement 43	Liver transplantation for non-colorectal liver metastases should aim for a 5-year survival of more than 50% to justify the risk, resources, and cost of the intervention. Survival should be better than the survival on palliative chemotherapy alone
Statement 44	Patients undergoing liver transplantation for non-colorectal liver metastases should be entered into a clinical trial or a prospective international registry

CEA=carcinoembryonic antigen. RAPID=resection and partial liver segment 2–3 transplantation with delayed total hepatectomy.

Table 2: **Consensus statements on liver transplantation for colorectal liver metastases**

biology, further evaluation of biological behaviour using the response to systemic therapy is necessary to select patients for liver transplantation.

Bridging therapy to transplantation (statements 18–20)

First-line therapy with combinations of fluoropyrimidines, oxaliplatin, and irinotecan with or without biological therapies such as anti-VEGF or anti-EGFR therapy, have markedly improved survival in patients with metastatic colorectal cancer.[45–50] Although the role of neoadjuvant chemotherapy in resectable colorectal liver metastases is unclear, its use in borderline resectable liver-only metastatic colorectal cancer is well established.[51] Pre-transplantation exposure to systemic therapy is essential for several reasons. First, this exposure allows an attempt at conversion therapy, because patients with initially unresectable colorectal liver metastases who are successfully down-staged and resected have a 5-year overall survival of more than 40%.[52] Second, the administration of bridging therapy enables clinicians to avoid liver transplantation in patients with early disease progression, a known predictor of poor overall survival.[53] Lastly, good disease control when on systemic therapy and subsequently during the chemotherapy-free window before liver transplantation is crucial, because the timing of receiving a liver transplant graft from a deceased donor might be unpredictable. The panel agreed that the response to bridging therapy should be observed for at least 6 months, and the development of progressive disease after more than three lines of chemotherapy reflects aggressive biology outside of what would be acceptable to consider for liver transplantation.

In patients with metastatic colorectal cancer, sarcopenia is likely to develop both from malignancy and as a result of chemotherapy.[54–56] Patients undergoing bridging therapy to transplantation are at a high risk of developing sarcopenia given the extended duration of treatment. Pre-transplantation sarcopenia is associated with many poor outcomes after liver transplantation.[57–60] The panel therefore recommended a pre-transplantation assessment of sarcopenia to identify patients who might benefit from prehabilitation.[61,62]

Assessment of response and observation time (statements 21–26)

Assessment of response to systemic therapy in solid tumours is typically quantified by radiological changes in tumour size according to the Response Evaluation Criteria in Solid Tumors (RECIST).[63] However, RECIST underestimates the response to therapies that have a cytostatic rather that cytotoxic mechanism of action.[64] The Chun criteria uses specific morphological changes within liver metastases to predict the pathological response to chemotherapy, and has been shown to outperform RECIST.[65–67] Hence, the Chun criteria was recommended for the quantification of the response in patients with stable disease according to RECIST.

Carcinoembryonic antigen (CEA) concentration is closely related to disease activity in colorectal cancer. Although a pre-transplant CEA of more than 80 µg/L is a negative prognostic marker,[9] the trend in the response to therapy was agreed by the panel to be more prognostic. Non-invasive biomarkers, such as cell-free DNA, are being studied extensively for their role in monitoring therapeutic responses and predicting clinical outcomes in metastatic colorectal cancer.[68–73] Further validation in patients with non-resectable colorectal liver metastases receiving bridging therapy to transplantation will be necessary before these biomarkers can be applied to predict survival after liver transplantation.

International guidelines recommend an optimal assessment interval of 2 months for a response to chemotherapy in metastatic colorectal cancer.[15] Because a protracted observation time before liver transplantation for non-resectable colorectal liver metastases is reported to be a good prognostic factor,[9] the panel recommended that a favourable response to bridging therapy should be observed for at least 6 months, with an interval of at least 1 year from the diagnosis of non-resectable colorectal liver metastases (figure 2).

Sequencing of treatment in patients with synchronous non-resectable colorectal liver metastases (statement 27–28)

Synchronous presentation of the primary colorectal tumour and liver metastases is reflective of a poorer disease biology and inferior survival.[74,75] The current treatment approach in synchronous non-resectable colorectal liver metastases depends on whether or not the primary tumour is symptomatic. Patients with non-resectable colorectal liver metastases who are symptomatic typically undergo surgical resection of the primary tumour followed by palliative chemotherapy,[14] whereas patients who are asymptomatic would receive palliative chemotherapy because there is little survival benefit to upfront resection of the primary tumour.[76]

The removal of all macroscopic extrahepatic disease before liver transplantation is essential for patients undergoing liver transplantation for secondary liver tumours. Hence, in patients with a symptomatic primary tumour and non-resectable colorectal liver metastases under consideration for liver transplantation, the primary tumour is first resected and bridging therapy to transplantation is commenced for the evaluation of biological behaviour. For asymptomatic disease, chemotherapy is initiated, and resection of the primary tumour is only undertaken if there is a favourable response according to the criteria described earlier. Given the more aggressive biology associated with synchronous disease, a further assessment of biological behaviour should be undertaken by assessing the response to bridging therapy to transplantation (figure 2). It is essential that patients are appropriately counselled that this treatment course might not lead to eventual transplantation.

Multidisciplinary teams (statement 29)

The multidisciplinary management of patients with colorectal liver metastases has been shown to improve the consistency and continuity of care, and is an independent predictor of overall survival.[77–81] Transplant oncology for non-resectable colorectal liver metastases lies at the intersection of colorectal surgery, hepatobiliary surgery, liver transplant surgery, transplant hepatology, oncology, radiology, pathology, and basic science. Therefore, an expert multidisciplinary team approach is of utmost importance in the management of patients with non-resectable colorectal liver metastases to have the most desirable outcome.

Graft selection and allocation

Organ allocation and waitlist prioritisation (statement 30)

The allocation of a small number of donor organs for liver transplantation is an ethical challenge, where it is often difficult to reach an agreement on what policies constitute a fair outcome (ie, distributive justice). Decision makers therefore rely on a fair process, using frameworks such as the Accountability for Reasonableness, to guide organ allocation and waitlist prioritisation.[82]

In accordance with the ethical principle of utility, which incorporates beneficence and non-maleficence,[83] this stringent patient selection process aims to identify patients with non-resectable colorectal liver metastases who would derive the most survival benefit from liver transplantation. As in other malignant indications for transplantation, prioritisation is then based on the stratification of survival benefit. In hepatocellular carcinoma, this process is done through morphological-based criteria, such as the Milan, University of California San Francisco, or Tokyo criteria,[84–86] which incorporate both tumour size and number by the so-called Metroticket concept.[87] In transplantable colorectal liver metastases, it is probable that biologically based criteria, as described earlier, will enable accurate prognostication and prioritisation.

National organ allocation policies, such as the so-called sickest-first approach based on the Model for End-stage Liver Disease (MELD) score,[88] aim for an equitable distribution of resources in keeping with the principle of justice. The inclusion of patients with malignant indications on the transplantation waiting list will invariably result in tension between the principles of utility and justice, because these patients have preserved liver function and are unlikely to be prioritised compared with patients with end-stage liver disease. In some countries, patients with hepatocellular carcinoma are therefore allocated MELD concession points to increase their waitlist priority.[89] A similar practice might have to be applied to allow for the inclusion and prioritisation of patients with transplantable colorectal liver metastases on national waiting lists.

Expanding the deceased donor pool (statements 31–33)

In countries with a shortage of donor organs, patients with non-resectable colorectal liver metastases might be precluded from liver transplantation in favour of standard indications. One solution to this is the use of extended criteria donors. Given their healthy liver function and the absence of portal hypertension, patients with colorectal liver metastases are more likely to tolerate a graft from an extended criteria donor than the typical patient with end-stage liver disease. Although there were initial concerns in patients with hepatocellular carcinoma regarding the effect of complications associated with grafts from extended criteria donors (eg, ischaemic cholangiopathy) on quality of life, outcomes have since improved, thus supporting the use of marginal grafts from both donation after brainstem death and donation after circulatory death.[90]

Novel surgical techniques to expand the donor pool are also crucial. Normothermic machine perfusion technologies have increased the use of previously non-transplantable livers, as highlighted in the results of the VITTAL study, where 70% of perfused discarded livers were transplanted with good survival outcomes.[91,92] In addition, resuscitation by machine perfusion significantly reduced the incidence of biliary complications in grafts from extended criteria donors, making this an attractive resource in expanding the donor pool in centres with the required expertise.[92]

The resection and partial liver segment 2–3 transplantation with delayed total hepatectomy (RAPID) technique has been performed using grafts from both deceased and living donors with good outcomes.[93] Because the use of left lateral grafts from deceased donors might deprive paediatric or small adult recipients on the waiting list of a liver, a national or regional consensus regarding the allocation of split grafts to patients with non-resectable colorectal liver metastases should be obtained. Despite good perioperative outcomes, the long-term oncological outcomes of the RAPID technique are unclear, with concerns regarding leaving the tumour in-situ in the presence of circulating hypertrophic growth factors during immunosuppression.[94]

Living donor liver transplantation for non-resectable colorectal liver metastases (statement 34)

The key limitations of using grafts from deceased donors include an effect on waiting list mortality (the percentage of patients on the waiting list who die waiting for a transplant increases because of longer waiting times because of the reduced number of grafts available from deceased donors) and the difficulty in matching the optimal timing for liver transplantation with a chemotherapy-free window. Living donor liver transplantation circumvents these issues, but at the expense of risk to the living donor.[95] A minimum survival benchmark for living donor liver transplantation for oncological indications has been previously suggested to be important in preventing compassionate liver transplantation for patients beyond the standard criteria.[96,97] Equally important considerations include the experience and

outcomes of the transplanting centre doing living donor liver transplantation. In the initial consensus statements, strict cutoffs for graft-to-recipient weight ratio, steatosis, and future liver remnant were described. Although a cutoff for a graft-to-recipient weight ratio of more than 0·8% was initially set, large living donor liver transplantation centres have reported good outcomes, with graft-to-recipient weight ratios as low as 0·6%.[98] Hence, in view of the wide range of experience between centres, the panel recommended that centres doing these transplantations should meet internationally accepted outcomes, operate within the centres' standard donor and recipient selection criteria, and enrol patients in prospective trials.

The living donor RAPID approach is an alternative to deceased donor RAPID that reduces the potential effect on waiting list mortality resulting from the allocation of a split left lateral graft to a patient with non-resectable colorectal liver metastases. Although the risk to the living donor for a left lateral segmentectomy for donation is marginally lower than that of a standard left or right hepatectomy,[93] there might be additional risk conferred to the recipient by a more morbid second stage hepatectomy as well as the oncological effects of leaving metastatic disease in a patient who is immunocompromised, as mentioned earlier.[99]

Organ allocation for re-transplantation (statement 35)

The panel does not recommend re-transplantation for recurrent hepatic metastases because this is reflective of disseminated disease and associated with a poor prognosis.[100] However, the decision to offer re-transplantation for early graft failure (ie, primary non-function or hepatic artery thrombosis) is an ethical dilemma.

For hepatocellular carcinoma beyond the standard criteria, an international consensus concluded that "based on utility, justice, and equity, they did not support re-transplantation for patients who were beyond the standard eligibility criteria, because these patients would not have qualified for [deceased donor liver transplant] in the first place".[97] Although non-resectable colorectal liver metastases are a non-standard oncological indication for liver transplantation, some series[9,10] have shown similar outcomes to non-malignant indications. Therefore, a national or regional consensus regarding the access to standard grafts donated after brainstem death for both the primary transplant and re-transplantation for graft failure should be obtained before commencing transplant activity for transplantable colorectal liver metastases. In the absence of a surplus of standard grafts donated after brainstem death, expertise by the liver transplant team (surgeons and hepatologists, etc) with non-standard deceased donor liver transplantation, such as grafts from extended criteria donors, or living donor liver transplantation, might expand the donor pool for re-transplantation. In countries or centres doing liver transplantation for non-resectable colorectal liver metastases where re-transplantation will not be offered, it is essential that recipients and potential living donors are counselled appropriately on the risk, benefits, and possible outcomes.[101,102]

Recipient considerations

Immunosuppression (statements 36–39)

The panel found little evidence to recommend specific immunosuppression strategies in patients undergoing liver transplantation for non-resectable colorectal liver metastases, with data mostly extrapolated from literature on recurrent hepatocellular carcinoma after liver transplantation.[103–105] Post-transplantation immunosuppressive therapy aims to prevent graft rejection at the same time as minimising side-effects, such as calcineurin inhibitor-induced kidney injury,[104] as well as the risk of developing recurrent and de-novo malignancies.[106] However, because graft rejection requiring treatment with T-cell depleting antibodies or pulsed steroids is associated with an increased risk of cancer recurrence, minimising calcineurin inhibitor exposure to reduce the risk of calcineurin inhibitor-induced kidney injury should not be pursued at the expense of episodes of graft rejection.[107]

The combination of mTOR inhibitors with a low-dose calcineurin inhibitor have resulted in similar rejection rates to calcineurin inhibitor monotherapy at the same time as lowering rates of kidney injury.[108] Their combined use has also shown reduced recurrence and improved overall survival after liver transplantation for hepatocellular carcinoma.[109,110] The panel recommended the use of either a calcineurin inhibitor that is gradually tapered with the addition of an mTOR inhibitor or a calcineurin inhibitor with a swap to an mTOR inhibitor after 4–6 weeks to minimise the risk of wound healing complications associated with mTOR inhibitors.[111]

Prevention and management of recurrent disease (statements 40–42)

The addition of perioperative chemotherapy to liver resection has significantly improved progression-free survival.[46,112] 6 months of perioperative systemic therapy is currently recommended for patients with resectable colorectal liver metastases undergoing surgical resection.[14,113] Patients with transplantable colorectal liver metastases will have received at least 6 months of bridging systemic therapy before transplantation. Given the slow growth of recurrent disease,[100] the absence of a proven overall survival benefit from additional adjuvant therapy, and the risk of chemotoxicity in patients who are immunosuppressed, the routine use of adjuvant chemotherapy is not recommended.

In non-resectable colorectal liver metastases treated by liver transplantation, although recurrence is common with an overall 1-year disease-free survival of less than 40%,[114] durable survival after relapse has been shown with a 3-year overall survival of 73%.[10] This survival is probably explained by slow-growing lung metastases,

Search strategy and selection criteria

24 experts from the fields of liver transplantation, hepatobiliary surgery, oncology, hepatology, and bioethics were invited to participate in the consensus process. For the modified Delphi consensus process, experts were allocated into three groups based on our selection criteria (appendix): (1) the Scientific Committee, (2) the Expert Panel, and (3) the Transplant Centre Representatives. The role of the Scientific Committee was to identify the main areas in need of consensus, do a systematic review, and formulate the initial consensus statements. The Expert Panel evaluated the proposed statements. The Transplant Centre Representatives were leaders of medium-sized to large-sized transplant programmes whose role was to assess the statements based on the feasibility of operationalisation. The Scientific Committee and the Expert Panel were involved in the final voting process. The Scientific Committee identified five areas (patient selection, evaluation of biological behaviour, graft selection, recipient considerations, and outcomes) consisting of 17 subdomains that were in need of consensus decisions (appendix). This framework was used to guide an extensive review of the literature.

The PubMed database was searched with no language limitations from Jan 1, 1990 until October 31, 2020. Multiple searches were performed using the search terms "colorectal liver metastases", "colorectal cancer" and "liver transplantation". Only papers published in English were reviewed. Relevant articles from resection in colorectal liver metastases and liver transplantation for hepatocellular carcinoma were identified by authors and reviewed where appropriate. Full texts of relevant studies were retrieved and reviewed for eligibility. All retrieved references were circulated among the panel members. Based on the results of the review, 30 preliminary statements were discussed and agreed upon by the Scientific Committee.

which account for most recurrences after liver transplantation for non-resectable colorectal liver metastases,[100] where up to 40% are occult metastases that were retrospectively identified to have already been present at time of transplantation.[115] Pulmonary metastases in patients transplanted for non-resectable colorectal liver metastases do not grow faster than those in patients without a transplant with non-immunosuppressed rectal cancer,[115] suggesting that their growth is not accelerated by immunosuppression. Hence, small pulmonary lesions can be observed until they reach a size where radical resection is feasible. The panel strongly advocated for the aggressive management of isolated extrahepatic recurrences post-liver transplantation because aggressive management is associated with good survival outcomes.

Recurrence of disease within the liver after liver transplantation is rare and is mostly observed in the setting of disseminated disease and multisite recurrence.[100] This pattern is distinctly different to what is observed after liver resection for colorectal liver metastases, where despite a similar overall rate of relapse, up to 45% of those who relapse have hepatic first-site recurrences.[116] In patients post-liver transplantation for non-resectable colorectal liver metastases who develop hepatic recurrence, the median overall survival is 14 months and such patients should therefore be managed with palliative intent.[100] Chemotherapy has been safely administered in patients with transplanted non-resectable colorectal liver metastases for up to 90 months with no reports of graft loss.[117] However, more data on the tolerability, safety, and efficacy of systemic therapy for recurrent disease in this population is still needed.

Outcomes (statements 43–44)

A post-transplant 5-year overall survival of 50% has been proposed as an ethically justifiable starting point to consider transplantation for patients with end-stage liver disease.[118] This cutoff would capture the most up-to-date 5-year survival rate of 50% according to a 2020 published systematic review and pooled analysis in liver transplantation for non-resectable colorectal liver metastases.[119] Encouragingly, in patients who underwent liver transplantation after 2005, the 5-year survival rate increased to more than 65%, reflecting the effect of an improved selection criteria.[119] Liver transplantation has been shown to be cost-effective compared with modern oncological treatment in patients with low-risk colorectal liver metastases.[120]

The standard-of-care for patients with non-resectable colorectal liver metastases at present is palliative systemic therapy, and liver transplantation should improve on this survival to be ethically justifiable. Comparison of liver transplantation with palliative chemotherapy in a matched cohort from the NORDIC VII study showed a 5-year overall survival of 56% compared with 9% in patients starting first-line chemotherapy.[120] However, the data did not include modern chemotherapy, which is associated with a response rate of up to 80%, with approximately 60% of patients amenable to resection after treatment.[121] As systemic therapy options continue to evolve, it will be necessary to compare liver transplantation with modern era systemic and locoregional options within prospective and ideally randomised controlled trials.

Conclusion

Trials evaluating liver transplantation for non-resectable colorectal liver metastases have shown good outcomes in well selected patients, and this has sparked an exponential increase in the number of patients transplanted for this indication worldwide. When compared with treatment approaches in surgical oncology, transplant oncology is faced with two unique challenges. First, the scarcity of organs mandates a particularly stringent selection process, because the survival benefit from liver transplantation is derived as the risk is accrued by the living donor or transplant waiting list. Second, a wider breadth of expertise spanning multiple disciplines is required to produce optimal outcomes.

Where the criteria for selection of patients with hepatocellular carcinoma for transplantation is currently based on morphology, it is likely that the selection and prioritisation of patients with non-resectable colorectal liver metastases will be based on biology. We recognise the stimulating ongoing work in this field and emphasise the importance of international registries and future prospective trials in elucidating biological prognostic factors to improve the stratification of risk. As survival

outcomes for liver transplantation in well selected patients with non-resectable colorectal liver metastases improve, it is foreseeable that non-resectable colorectal liver metastases might become a standard indication for liver transplantation in the future, and strategies for prioritising these patients against those with other malignant and non-malignant indications for liver transplantation must be devised.

We have established a set of standardised nomenclature and criteria for patient selection and evaluation of biological behaviour before the consideration of liver transplantation for non-resectable colorectal liver metastases. This consensus guideline provides a framework by which liver transplantation for non-resectable colorectal liver metastases can be safely instituted and is a meaningful step towards future evidenced-based practice for better patient selection and organ allocation to improve survival for patients with this disease.

Contributors

GKB, CAC, and RA contributed to the formal analysis of the data from the consensus process for the paper. GKB, CAC, PL, JH, KJH, PT, CEC, SD, P-DL, RA, and DFM contributed to the conceptualisation, formal analysis of the data from the consensus process, and writing of the original draft. GKB, CAC, PL, MDM, RWL, JH, KJH, PT, CEC, SD, P-DL, PM, JI, SGI, FP, JS, AG, KMo, DFM, WPY, ACYC, CCW, GS, MH, KMe, and IC contributed to the design of the study methods. GKB and CAC contributed to the project administration and visualisation of figures. All study aspects were supervised by RA. All authors reviewed and edited the final manuscript.

Declaration of interests

PT receives honoraria from Astellas Pharma Europe, outside the current study. GS receives research grants from Bayer and Roche, and consulting fees from Astrazeneca, Novartis, and Roche, outside the current study. RA receives honoraria for symposia from Merck Serono and Sanofi, outside the current study. All other authors declare no competing interests.

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