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Metabolic interventions to enhance immunotherapy and targeted therapy efficacy in advanced colorectal cancer

Helena Oliveres[1], Marta Cascante[2,3] and Joan Maurel[1,2]

Abstract

Current standard-of-care for metastatic colorectal cancer patients includes chemotherapy and anti-angiogenic or anti-epidermal growth factor receptor for microsatellite stable tumors and pembrolizumab for microsatellite instable tumors. However, despite the available therapies, the prognosis remains poor. In recent years, new drugs combined with immune checkpoint inhibitors have been tested in microsatellite stable metastatic colorectal cancer patients, but the benefit was modest. Here, we review the metabolic interactions between the immune microenvironment and cancer cells. More specifically, we highlight potential correlatives of tumor immune and metabolic features with transcriptomic classifications such as the Consensus Molecular Subtype. Finally, we discuss the unmet need of immune-metabolic signatures and the value of a new signature (IMMETCOLS) for guiding new strategies in metastatic colorectal cancer. We conclude that the field is ready to propose customized strategies for modifying metabolism and improving immunotherapy and targeted therapy efficacy.

Addresses

[1] Medical Oncology Department, Hospital Clinic of Barcelona, Translational Genomics and Targeted Therapeutics in Solid Tumors Group, IDIBAPS, Barcelona, Spain

[2] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Instituto de Salud Carlos III (ISCIII), Madrid, Spain

[3] Department of Biochemistry and Molecular Biomedicine and Institute of Biomedicine (IBUB), Universitat de Barcelona, Barcelona, Spain

Corresponding authors: Cascante, Marta (martacascante@ub.edu); Maurel, Joan (jmaurel@clinic.cat)

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Immunotherapy, Metabolism, Resistance.

Introduction

Metabolism and cancer

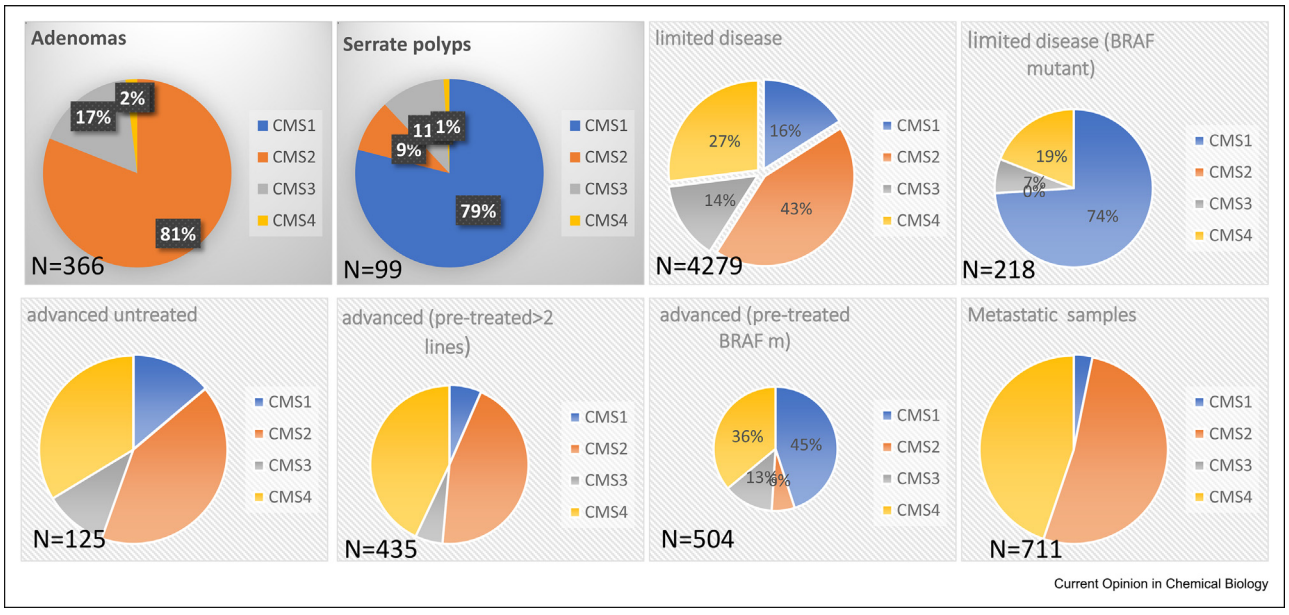
Patient stratification in colorectal cancer: distribution of consensus molecular subtypes in primary samples (early disease, limited disease, advanced disease) and metastatic samples

One of the most robust and widely accepted classifications of colorectal cancer (CRC) patients is the Consensus Molecular Subtypes (CMS) classification system [1]. The CMS classification system was developed by an international consortium of experts to facilitate clinical translation and established four groups with distinctive features at the molecular level. *Briefly, CMS1 is associated with immune infiltration, microsatellite instability, and BRAF mutation, the canonical CMS2 is characterized by epithelial cancers with high MYC and WNT activation, CMS3 comprises epithelial tumors with metabolic alterations, and CMS4 is characterized by a mesenchymal subtype with stromal infiltration and TGF-β activation.* CMS is based on the gene expression profile of primary CRC tumors but *its clinical relevance for the prediction of chemotherapy or targeted therapy efficacy has not been demonstrated. We have reviewed the CMS distribution in different situations (*Figure 1).

In tubular adenomas, which represent 80–90% of pre-malignant lesions, *APC* mutations and the CMS2 subtype predominate, whereas *BRAF* mutation and the CMS1 subtype predominate in sessile serrated polyps, which reflects the immune cell abundance of early disease in CMS1.

CMS4 is extremely rare in pre-malignant lesions, suggesting that TGF-β-driven cancer cell mesenchymal support, characteristic of this cluster, is acquired in more advanced stages [2]. In limited disease, CMS1 constitutes between 16% and 20% of cases, CMS2 between 43% and 46%, CMS3 between 10% and 15%, and CMS4 between 25% and 26%. In limited disease, the CMS4 subtype identifies the subgroup with the worst prognosis. In *BRAF* mutant patients, the distribution is different: 81% CMS1, 3% CMS3, and 16% CMS4. An additional classification has been proposed of these patients into two subtypes—BM1 and BM2—that capture additional variations in gene expression profiles within BRAF mutant patients, revealing that such patients with the BM1 subtype (characterized by mesenchymal

Figure 1



In serrate polyps and BRAF mutant patients with limited disease, CMS1 is predominant. In adenomas CMS2 subtype is predominant. In patients with limited disease and untreated metastatic disease, CMS2 and CMS4 are more frequent found. In pre-treated patients with advanced disease and metastatic samples CMS1 and CMS3 are less found.

features) have poor prognosis [3]. In advanced disease, CMS1 identifies the group with the worst prognosis [4,5]. Because CMS1 patients with limited disease have relatively good prognosis, we speculate that metastatic CMS1 patients could display different metabolic tumor microenvironments. Of heavily pre-treated patients, fewer patients have the CMS1 and CMS3 phenotypes, which is in accordance with the poor prognosis in these subsets of patients with advanced disease [6,7]. In *BRAF* mutant patients treated with BRAF and anti-epidermal growth factor receptor (anti-EGFR) inhibitors, the BM2 subtype (characterized by oxidative phosphorylation [OxPhos], cell cycle, glycolysis, and WNT and MYC enhancement) has the worst prognosis [8]. Finally, in metastatic samples, CMS3 and CMS1 subtypes are replaced by CMS2 or CMS4 subtypes [9,10].

Metabolic landscape in colorectal

Common driver mutations induce changes in the fate of glucose and glutamine that differ among preclinical models

Colorectal cancer is characterized by a sequence of mutational events involving APC, RAS and TP53 genes. Lactate, glucose, and glutamine are metabolites with a substantial turnover flux [11]. Therefore, it is understandable that these metabolites would be optimally regulated by common driver mutations. *RAS* mutations [12,13] and WNT signaling [14] increase glycolytic demands. In addition, *APC* and *RAS* mutations increase glutamine efflux and amino acid entry through SLC7A5 transporter [15] and glutamine utilization by aspartate transaminase (GOT1) [16] to feed pyruvate back into the tricarboxylic acid cycle. Although glucose and glutamine are mainly oxidized to produce lipogenic precursors in monolayer cultures, in spheroids, glutamine supports reductive carboxylation to increase OxPhos [17]. Because glucose and glutamine are both essential for cancer and immune cells, metabolic restriction of one of these metabolites increases compensatory programs and nutrients [18].

Immune-metabolic subtypes in colorectal cancer

Mesenchymal high glycolytic/low OxPhos phenotype: IMMETCOLS-IMC1 (35%)

IMC1 subtype is characterized by epithelial−mesenchymal transition (EMT) enrichment [19] and upregulation of genes related to glucose metabolism and transport and hexosamine biosynthesis pathway expression [20]. Genes that are particularly upregulated are MCT4 and MCT1. The latter allows cancer cells to utilize lactate to sustain the oxygen consumption rate (OCR) [21] and contributes to PD-1 expression and T-cell exhaustion [22]. Overexpression of lactate dehydrogenase and lactate transporters has also been correlated with enhanced migration and metabolic crosstalk between cancer-associated fibroblasts (CAFs) and metastatic cells at the invasive front,

favored by the acidification of the surrounding extracellular environment [23,24]. In glycolytic cancer cells, lactate is mainly exported to increase the extracellular acidification rate (ECAR) and decrease the OCR and OxPhos, which helps to fuel stromal cells such as myeloid cells [25] and fibroblasts [26] instead of only cancer cells; these stromal cells support cancer cells with alternative nutrients [27,28]. This symbiotic rewiring metabolism, although metabolically intensive for cancer cells, facilitates immune suppression because it impairs CD8 functionality [29], increases Treg presence [30], and promotes M2 polarization [25].

In this cluster, chemotherapy resistance has been associated with both CAF/TGF-β and hypoxia, which converge in hedgehog pathway activation [31]. The contribution of CAFs is supported by a symbiotic relationship in which cancer cells facilitate lactate to CAFs for NF-κB activation and CAFs release paracrine cytokines and chemokines to facilitate EMT and chemotherapy and targeted agent resistance [32,33]. This specific immune-metabolic characteristic has been shown to be associated with resistance to immune checkpoint inhibitors (ICIs) [34,35]. For this.

IMMETCOLS-IMC1 cluster, it has been predicted that the combination of ICIs with MCT1 inhibitors (AZD3965 or diclofenac) would increase sensitivity to ICI-based therapies [20].

Epithelial non-glycolytic phenotype: IMMETCOLS-IMC2 (15%)

The most prominent metabolic feature described for this cluster is the increased expression of genes related to the use of carbon sources other than glucose, key gluconeogenic enzymes, and glutamine transporters [20]. Glutamine, fatty acids, and acetate have emerged as the main alternative fuels for generating ATP in non-glycolytic tumors with functional mitochondria.

Moreover, in non-glycolytic tumors, it has also been reported that overexpression of key gluconeogenic enzymes could help to satisfy the glycolytic intermediate and ribose-5-phosphate needs for cancer cell proliferation. Moreover, using stable isotopic tracer experiments, it has been shown that colon cancer cells with high PCK1 expression use glutamine to generate ribose [36]. It has also been reported that, under glucose deprivation conditions, PCK2 mediates glycerol neogenesis to contribute to the anabolic needs of cancer cells [37]. These non-glycolytic tumors have been associated with acquired resistance to ICIs in melanoma [38] and to intrinsic ICI resistance in melanoma brain metastases [39]. For this cluster, it has been predicted that the targeting of autophagy-related pathways such as chloroquine or metformin can increase ICI efficacy in this cluster [20].

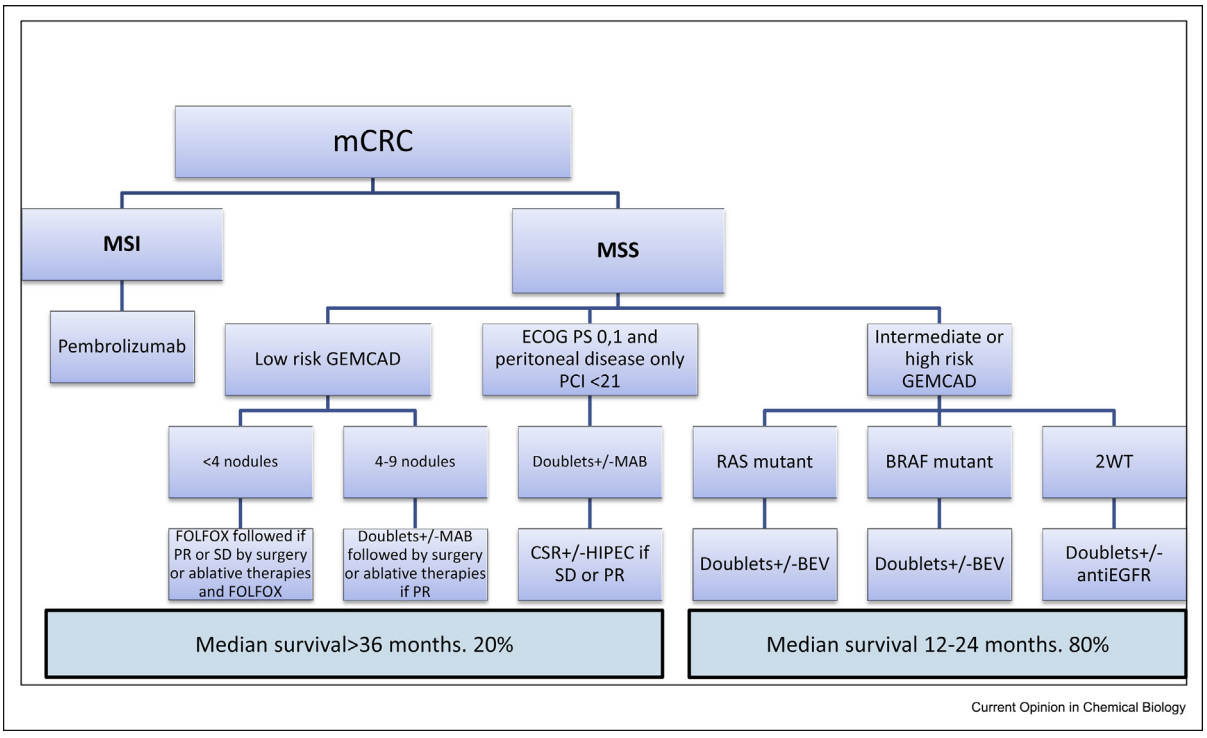
Epithelial high glycolytic/high OxPhos phenotype: IMMETCOLS IMC3 (50%)

Tumors in this cluster are characterized by overexpression of OxPhos, pentose phosphate metabolism, and glucose transport- and metabolism-related genes [20]. The oxidative cancer cell subtype has been reported to fuel OxPhos using lactate and other alternative carbon sources in glucose-depleted environments. Cancer cells that have functional mitochondria and that have acquired high glycolytic capacity will display an advantageous metabolic flexibility and higher adaptability to different microtumor environment challenges (such as an oxygen-abundant/- depleted microenvironment) because they will be able to switch between glycolysis and OxPhos or combine both pathways to optimally satisfy their metabolic needs and thereby support cancer cell proliferation. In addition, high OxPhos and anti-oxidative dependence is associated with chemotherapy resistance [40–42]. This highly activated glycolytic/OxPhos rewiring metabolism has been reported to induce a T-cell immune-excluded phenotype in melanoma patients resistant to ICIs [43]. For tumors in this cluster, it has been hypothesized that OXPHOS inhibitors would increase the efficacy of ICI-based therapies [20].

Standard and emerging targeted therapies in metastatic CRC

CRC represents 12.7% of all new tumors in the European Union. Only a few therapeutic agents have shown efficacy in metastatic disease: fluoropyrimidines, oxaliplatin, irinotecan, anti-EGFR drugs, and anti-angiogenic drugs. In fit patients, they are frequently used in combination. Panitumumab and cetuximab are approved with FOLFOX (fluorouracil, folinic acid, and oxaliplatin) or FOLFIRI (fluorouracil, folinic acid, and irinotecan) doublets as first-line therapy in *RAS* wild-type patients and with FOLFOX, FOLFIRI, or CAPOX (capecitabine and oxaliplatin) in combination with bevacizumab without biomarker restriction. Despite a high response rate (over 50%) in first-line therapy, almost all patients progress in the first 2 years and the current therapy is therefore mainly palliative, except in patients with oligometastatic disease that can be managed with surgery or ablative therapies (Figure 2). Emerging targeted therapies in metastatic CRC (mCRC) are focused on *BRAF* mutant patients, on double (*RAS* and *BRAF* wild-type) HER-2 positive (immunohistochemistry (IHC)3+ or IHC2+ and *in situ* hybridization-positive) patients, and on *KRAS* mutant G12C patients. The efficacy of encorafenib plus cetuximab versus standard therapy (irinotecan-cetuximab) has been established in *BRAF* mutant patients [44] while the efficacy of all other strategies, such as combinations of sotorasib plus panitumumab and adagrasib plus cetuximab in KRAS G12C patients and

Figure 2



Algorithm for patients with metastatic colorectal cancer (mCRC). MSI microsatellite instability; MSS microsatellite stability; ECOG PS Eastern Cooperative Oncology Group Performance Status; LDH Lactate Dehydrogenase; ULN upper limit of normal; PCI Peritoneal Cancer Index; GEMCAD Spanish Multidisciplinary Group on Digestive Cancer; MAB Monoclonal antibody; WT wild type; FOLFOX infusional fluorouracil, leucovorin, and oxaliplatin; PR partial response; SD stable disease; CSR Cytoreductive surgery; HIPEC Hyperthermic IntraPeritoneal Chemotherapy; BEV bevacizumab; EGFR Epidermal growth factor receptor. GEMCAD score. Segui et al., Ann Oncol 2020 Volume 31Suppl 4. Low risk GEMCAD: only liver disease with less than 10 nodules and ECOG PS0-1 and LDH<1.5ULN. Intermediate risk GEMCAD: liver metastases only ≥10 nodules or multiorgan spread and ECOG PS 0–1 and LDH<1.5 ULN. High GEMCAD risk: ECOG PS 2 or/and LDH>1.5ULN.

trastuzumab-deruxtecan in HER-2-positive patients, has been observed in phase II trials with relatively low numbers of patients [45–47]. Despite the relatively high activity in terms of the response rate, the median progression-free survival (PFS) with all of these strategies ranges from 4.2 months to 6.9 months. Currently, all of these combinations are being evaluated in phase III trials as first-, second-, and third-line therapy for advanced CRC (Table 1).

Importantly, less than 10% of treated patients remain progression free at the 12-month follow-up, which suggests that intrinsic and acquired resistance mechanisms exist. For example, in patients treated with adagrasib, acquired KRAS mutations, as well as bypass mutations and oncogenic fusions, contribute to acquired resistance [48]. Although the combination of sotorasib and cetuximab [49] shows high efficacy and MEK/glycolysis inhibition against colorectal cell lines and xenograft murine models, the metabolic rewiring patterns associated with resistance are unclear. Indeed, an increase in OxPhos with prioritization of alternative nutrients such as pyruvate and palmitate has been reported in surviving cancer cells subjected to RAS deprivation [50]. It would be valuable to address these mechanisms of resistance, especially in tumors that rely on high OxPhos.

Strengths and weaknesses in the design of clinical trials for ICIs in mCRC

Microsatellite unstable and microsatellite stable patients exhibit profound biological differences that are associated with ICI compound efficacy, as was elegantly demonstrated in a seminal study [51]. Microsatellite unstable patients have a high response rate with ICIs (ranging from 34%–69%), with a 2-year PFS of up to 50% in untreated [52] and pre-treated [53] mCRC patients. This impressive activity has been confirmed in a phase III study comparing pembrolizumab and chemotherapy as first-line therapy [54]. Regrettably, as shown in Table 2, none of the combinations used in phase II trials with ICIs and other preclinical candidate compounds in microsatellite stable mCRC patients achieved a minimum threshold (less than a 20% response rate and less than a 20% 1-year PFS). Despite these poor phase II data, these combinations were developed in phase II

Table 1

Clinical trials with new targeted therapies in metastatic colorectal cancer.

Trial	N. patients	Design/L	Drug	Biomarker	BOR%	1y PFR%	Primary end-point*
Fakih, 2022 [46]	62	II/>2	Sot	KRAS G12C	10	15	BOR
Yaeger, 2022 [47]	44	II/>2	Ada	KRAS G12C	19	15	BOR
Yaeger, 2022 [47]	32	II/>2	Ada/Cet	KRAS G12C	46	24	BOR
Kopetz, 2019 [44]	665	III/≥2	Enc/Cet vs Iri/Cet	BRAF V600E	20 vs 2	10 vs 10	OS
Siena, 2021 [45]	53	II/>2	DS-8201	HER2+	45	NR	BOR
Kopetz, 2021	870	III/1	Enc/Cet/CHT vs Enc/Cet vs CHT	BRAF V600E			PFS
CodeBreak 300	153	III/>2	Sot/Pan vs IC	KRAS G12C			PFS
CRYSTAL-10	420	III/2	Enc/Cet vs CHT	KRAS G12C			OS PFS
DESTINY CRC-03	120	IIR/2	DS-8201 vs CHT	HER2+			BOR
MOUNTAINEER-03	400	III/1	Tra/Tuc/FOLFOX vs FOLFOX	HER2+			PFS

N; number. L; Line of therapy. Sot; Sotorasib. Ada; Adagrasib. Enc; Encorafenib. Cet; Cetuximab. Iri; Irinotecan. DS-8201; Trastuzumab deruxtecan. CHT; Tra; Trastuzumab. Tuc; Tucatinib. Chemotherapy. Pan; Panitumumab. BSC; Best supportive care. IC; Investigator's Choice. BOR; Best overall response. PFR; Progression free rate. OR; Objective Response. Overall Survival; OS. Overall Response Rate; ORR.

Table 2

Clinical trials with immune checkpoint inhibitors in mCRC.

Trial	N. patients	Design/Line (L)	Drug	BOR%	1y PFR%	HR[a]	% 2y OS[a]	mOS[a]
MSI								
Lenz, 2022 [52]	45	II/1L	Ipi/Niv	69	76	-	-	-
Overman, 2018 [53]	119	II/≥2L	Ipi/Niv	55	71	-	-	-
Andre, 2020 [54]	307	III/1L	Pem vs CHT	44 vs 33	55 vs 37	0.60 (0.45–0.8)	48.3 vs 18.6	*NR vs 36.7*
MSS								
Eng, 2019 [55]	363	III/≥2L	Ate vs Ate/Cob vs Reg	2 vs 5 vs 2	<10	1 (0.73–1.38)	<5	*7.1 vs 8.9 vs 8.5*
Chen, 2020 [56]	*180*	*IIR/>2L*	*Dur/Tre vs BSC*	*1 vs 0*	*NE*	*0.72 (0.54–0.9)*	*<10*	*6.6 vs 4.1*

MSS; Microsatellite stable. MSI; Microsatellite unstable. L; line. Ipi; Ipilimumab. Niv; Nivolumab. Pem; pembrolizumab. Reg; regorafenib. Ate; Atezolizumab. Cob; Cobimetinib. Dur; Durvalumab. Tre; Tremelimumab. BSC; Best supportive care. BOR; Best overall response. HR; Hazard ratio. PFR; Progression free rate. Y; year. mOS; median overall survival. NR; Not reached. NE: not evaluated.
[a] Only in randomized studies.

randomized trials and phase III trials with disappointing results [55,56]. We believe that, in highly immunosuppressive tumors such as those of microsatellite stable mCRC patients, optimal biomarker selection would be appropriate to improve on current results.

Conclusions

Currently, there are no customized (immune signature-based) strategies for the development of new combinations with ICIs in mCRC. There are multiple caveats that jeopardize ICI combination development in mCRC. First, there is no predefined activity cut-off in phase II trials to pursue to phase III trials. Usually, ICI combinations have been proposed for testing efficacy in multiple tumor types. In addition, response rates between 10% and 20% with ICI combinations were considered promising for phase III trial development. *We propose that only phase II trials with response rates between 30% and 40% and* 12-month *progression-free rates exceeding 30% be evaluated in phase III trials.* Second, there are no reliable biomarkers for selecting the optimal patients for new combinations. We propose customized metabolic interventions with MCT1/4 inhibitors (e.g., AZD3965 or diclofenac) combined with ICIs for the IMC1 cluster and OxPhos inhibitors with ICIs for the IMC3 cluster. These combinations should probably be implemented in phase I or II trials before the development of phase III trial in mCRC patients.

Author contributions

Conceptualization, JM and MC; Data curation, HO, JM, and MC; Funding acquisition, JM and MC; Investigation, HO, JM, and MC; Resources, JM and MC; Supervision, JM and MC; Writing, reviewing, and editing, HO, JM, and MC. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Joan Maurel reports a relationship with Sirtex Medical Inc that includes: consulting or advisory. Joan Maurel reports a relationship with Pierre Fabre SA that includes: consulting or advisory. Joan Maurel reports a relationship with Shire that includes: consulting or advisory. Joan Maurel reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Joan Maurel reports a relationship with Bayer AG that includes: consulting or advisory. Joan Maurel reports a relationship with Servier Monde that includes: consulting or advisory. Joan Maurel reports a relationship with Sanofi that includes: consulting or advisory. Joan Maurel reports a relationship with Roche that includes: consulting or advisory. Joan Maurel reports a relationship with Advance Medical that includes: consulting or advisory. Joan Maurel has patent licensed to P5020EP00.

Data availability

Data will be made available on request.

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** of outstanding interest

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