Association of immune-related adverse events with the outcomes of immune checkpoint inhibitors in patients with dMMR/MSI-H metastatic colorectal cancer

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ABSTRACT

Background Immune checkpoint inhibitors (ICIs) show a tremendous activity in microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC), but a consistent fraction of patients does not respond. Prognostic/predictive markers are needed. Despite previous investigations in other tumor types, immune-related adverse events (irAEs) have not been well evaluated in patients with MSI-H cancers treated with ICIs.

Methods We conducted an international cohort study at tertiary cancer centers collecting clinic-pathological features from 331 patients with MSI-H mCRC treated with ICIs. Of note, the irAEs were summarized using a 'burden score' constructed in a way that the same score value could be obtained by cumulating many low-grade irAEs or few high-grade irAEs; as a result, the lower the burden the better. Clearly, the irAE burden is not a baseline information, thus it was modeled as a time-dependent variable in univariable and multivariable Cox models.

Results Among 331 patients, irAEs were reported in 144 (43.5%) patients. After a median follow-up time of 29.7 months, patients with higher burden of skin, endocrine and musculoskeletal irAEs (the latter two's effect was confirmed at multivariable analysis) had longer overall survival (OS), as opposed to gastrointestinal, pneumonitis, neurological, liver, renal and other irAEs, which showed an harmful effect. Similar results were observed for progression-free survival (PFS). Based on the results retrieved from organ-specific irAEs, 'aggregated' burden scores were developed to distinguish 'protective' (endocrine and musculoskeletal) and 'harmful' (gastrointestinal, pneumonitis, neurological, hepatic) irAEs showing prognostic effects on OS and PFS.

Conclusions Our results demonstrate that not all irAEs could exert a protective effect on oncologic outcome. An easy-to-use model for ICIs toxicity (burden score of protective and harmful irAEs) may be used as surrogate marker of response.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune-related adverse events (irAEs) have been previously linked to different outcomes in response to immune checkpoint inhibitor (ICI) . However, no existing data in literature explore the association of irAEs with survival outcomes in microsatellite instability metastatic colorectal cancer (MSI mCRC).

WHAT THIS STUDY ADDS

⇒ Through the analysis of a large international cohort of MSI mCRC patients (n=331), we showed that not all irAEs seem to exert a positive prognostic effect on overall survival/progression-free survival in this setting, but rather there are 'protective' irAEs and 'harmful' irAEs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides with a model to aggregate ICI toxicity (burden score of protective and harmful irAEs) that could represent a surrogate clinical marker of response to ICI in MSI mCRC patients.

INTRODUCTION

In a histology-agnostic fashion, Food and Drug Administration (FDA) has approved the use of immune checkpoint inhibitors (ICIs) in solid tumors bearing deficiency in mismatch repair (dMMR) and/or microsatellite instability-high (MSI-H).[1–4] dMMR/MSI-H tumors are characterized by a hypermutated genome and a high load of immunogenic neoepitopes, capable to elicit robust lymphocytic infiltration and upregulation of immune checkpoint molecules, making them vulnerable to ICIs.[5 6]

Table 1 Patients and disease characteristics in the study population

Characteristics	Study population (N=331) n (%)
Age (years)	
Median	60
IQR	(47-70)
Sex	
Female	151 (45.6)
Male	180 (54.4)
ECOG PS	
0	167 (50.5)
≥ 1	164 (49.5)
Primary tumor location	
Right colon	222 (67.1)
Left colon/rectum	109 (32.9)
Primary tumor resection	
Yes	268 (81.0)
No	63 (19.0)
RAS and *BRAF* mutational status	
RAS mutated	103 (31.1)
BRAF mutated	89 (26.9)
All wild-type	127 (38.4)
Unknown	12 (3.6)
Time to metastases	
Synchronous	162 (48.9)
Metachronous	169 (51.1)
Metastatic sites (*N*)	
1	158 (47.7)
>1	173 (52.3)
Previous treatment for metastatic disease	
Yes	260 (78.5)
No	71 (21.5)
Choice of ICI regimen	
Anti-PD-(L)1 monotherapy	239 (72.2)
Anti-PD-1 plus anti-CTLA-4 combo	92 (27.8)

CTLA-4, cytotoxic T-lymphocyte antigen 4; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; PD-(L)1, programmed death- (ligand)1.

Patients with dMMR/MSI-H metastatic colorectal cancer (mCRC) represents a small (5% of all cases) but unique subset and derive durable benefit from ICIs. Nevertheless, a significant fraction of patients does not respond, making predictive markers utterly needed. Among putative factors, potentially useful on-treatment clinical factors are the development of immune-related adverse events (irAEs).[2 7–9]

irAEs likely result from cross-reactivity of T cells due to antigens shared between tumor tissue and target organ, although both tumor-intrinsic and tumor-extrinsic factors, such as microbiome or pre-existing autoimmunity, contribute to their generation.[10] Interestingly, ever-growing literature suggests that patients with irAEs may obtain greater clinical benefit from ICI therapy.[11 12] The relationship between irAEs and efficacy is not entirely linear, depending on cancer type, as non-univocal data have been reported in melanoma, and on ICI subtype, since anti-CTLA-4 (cytotoxic T-lymphocyte antigen-4) monotherapy-induced AEs do not correlate with outcomes.[13 14] irAEs characteristics, such as severity, site, whether multiple systems are affected at once, as well as the timing of onset, may also be important players.[11 15–18] Notably, most of the available data correlating the occurrence of irAEs and cancer prognosis are retrospective and may be influenced by immortal time bias and, in particular, data on the role of irAEs specifically obtained in patients with dMMR/MSI-H mCRC are extremely scarce.[19]

Drawing from these considerations, we aimed to dissect irAEs occurring in dMMR/MSI-H mCRC patients treated with ICIs in terms of organ(s) affected and grade of severity, and to investigate the relationship of specific irAEs with the survival outcomes.

PATIENTS AND METHODS
Study population
This was an ambispective, multicenter cohort study including consecutive patients with dMMR/MSI-H mCRC treated at 11 cancer centers with immune-checkpoint inhibitors (ICI), that is, an anti-PD-(L)1 (programmed death (ligand)1) ± an anti-CTLA-4 agent. Mismatch repair and/or MSI status was locally assessed through immunohistochemistry or multiplex PCR, respectively, as per international guidelines.[20] IrAEs were defined as the first AE that occurred after ICI start considered to result from immunological dysfunction, by treating physicians. They were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.

Statistical methods
The study endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as the time interval between date of first ICI administration and first disease progression, relapse or death due to any cause, whichever occurred first. OS was defined as the time interval between date of first ICI administration and death due to any cause. Time was censored at the date of last follow-up (FU) for patients who were still alive for OS, and event-free for PFS.

We analyzed the first occurrence of irAEs, together with the corresponding grade according to the organ affected, and calculated a summary score of organ-specific irAEs burden. This 'burden score' consisted in a simplified
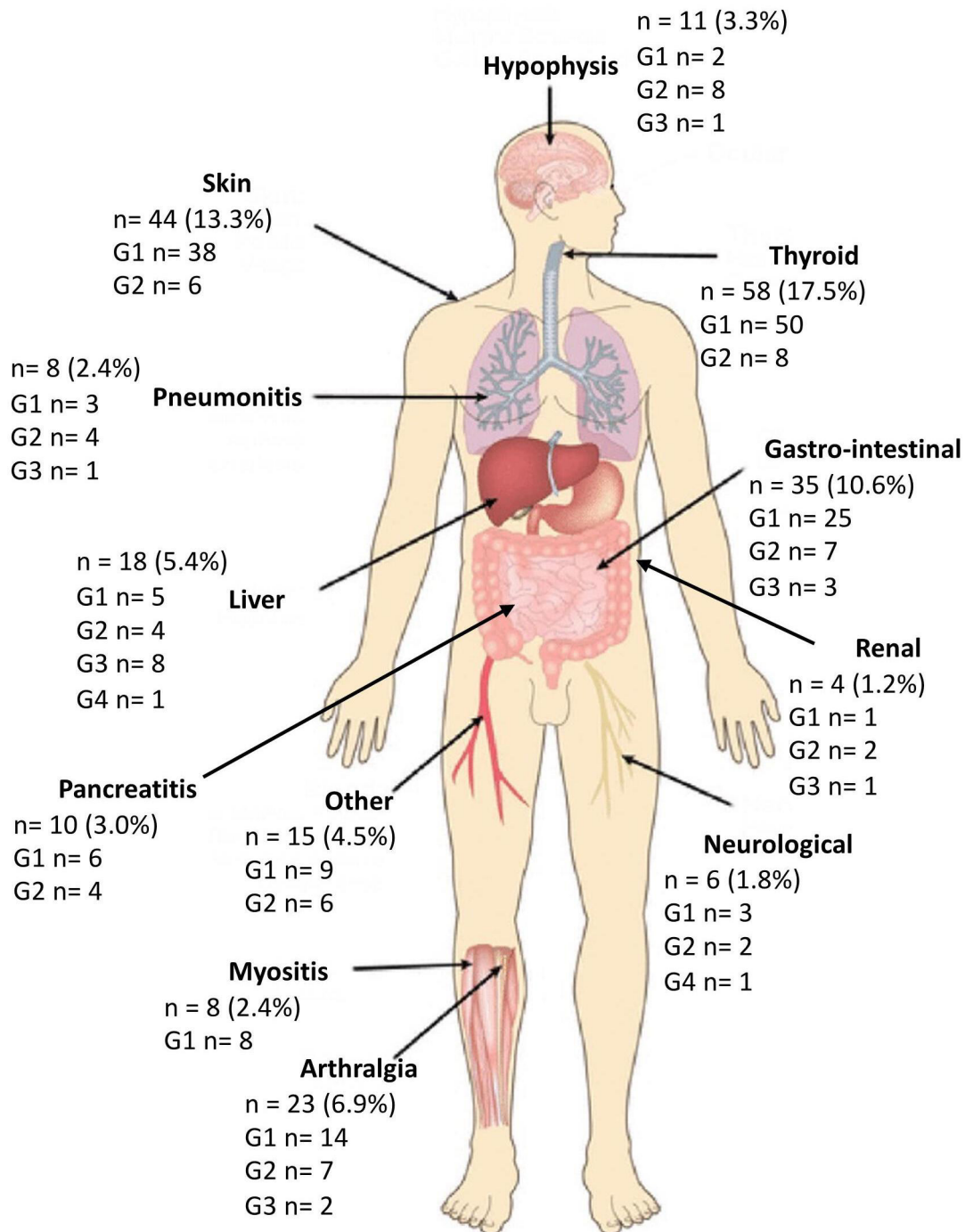
Figure 1 Summary of incidence and severity of immune-related adverse events recorded in the study population.

version of the adverse event burden score proposed by Le-Rademacher *et al*,[21] and was obtained by summing the grade of organ-specific irAEs. Therefore, higher burden score values correlate with higher grade and/or frequency of irAEs, and the same value of the score may be obtained by cumulating many low-grade irAEs or few high-grade irAEs. Univariable and multivariable Cox models were fitted to evaluate the association between the end-points and the organ-specific irAE burdens modeled as time-dependent variables. Several patients and disease characteristics were considered as adjustment factors in

the multivariable models: sex, age, Eastern Cooperative Oncology Group Performance Status, primary tumor sidedness (left, right), primary tumor resection, mutational status (*RAS* mutation, *BRAF* mutation, *RAS,* and *BRAF* wild-type), presence of synchronous metastases, number of metastatic sites (1, >1), presence of bone metastases, lung metastases, peritoneal metastases, brain metastases, nodal metastases, prior adjuvant treatment, prior treatment(s) for metastatic disease, ICI regimen (anti-CTLA-4-based combination or anti-PD-(L)1 monotherapy). To prevent overfitting and obtain reliable
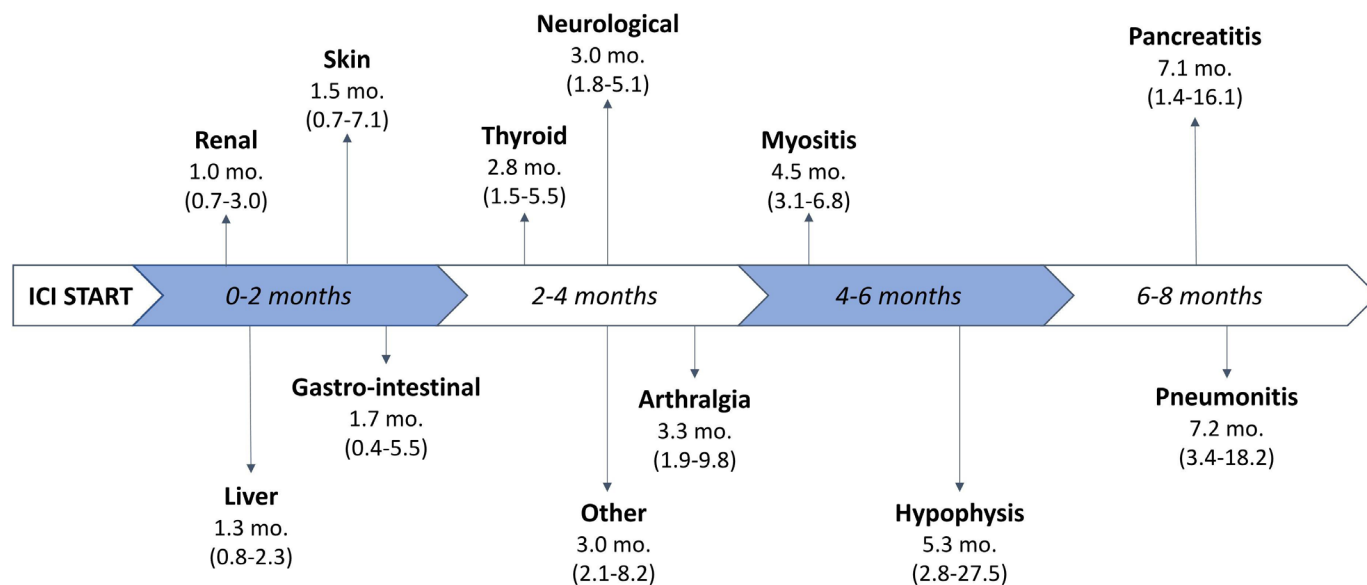
Figure 2 Timeline with median onset-timing (in months, mo.) (IQR) of the different organ-specific irAEs. ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events.

estimates, the adjustment was operated by means of an end-point-specific score beforehand estimated as the linear predictor from a Cox model including all the above listed adjustment factors.

Statistical analyses were conducted using the SAS (version 9.2) and R software programs (http://www.r-project.org/).

RESULTS

Characteristics of study population and description of irAEs

Data of 331 patients with dMMR/MSI-H mCRC receiving with ICIs were retrieved. Median FU time was 29.65 months (IQR, IQR 12.43–44.84). The main patients and disease characteristics are summarized in table 1.

Most patients (78.5%) received at least one previous treatment line for advanced disease before ICI start. Eventually, 72.2% patients were treated with anti-PD-(L)1 monotherapy, while the remaining patients (27.8%) received anti-CTLA-4-based combination therapy. At censoring time for this study, a total of 122 patients (36.8%) experienced progressive disease (PD). Overall, 144 patients (43.5%) experienced at least one irAE (any grade and site). A detailed description of irAEs according to organ affected and grade of severity can be found in figure 1. Most common adverse effects were hypo- or hyper-thyroidism (n=58; 17.5%), skin toxicity (n=44; 13.3%) and gastrointestinal disorders (n=35; 10.6%). We grouped together less frequent irAEs, such as anemia, infusion reactions, xeropthalmia, under the category 'other'. Most irAEs were reported as <G3. Of note, no lethal (G5) irAE was registered in our cohort. Among the patients who experienced at least 1 irAEs, toxicity was managed through supportive treatment in 83 patients (57.6%), while steroid therapy was required in 51 (35.4%). In 10 patients (6.9%), irAEs led to drug cessation (3 due to

gastrointestinal, 2 due to neurological, 2 due to renal, 2 due to hepatic irAEs, and 1 due to pneumonitis). Mean prednisone-equivalent dosage of steroid therapy was 62.8 mg/day (IQR 25–82.5). A table with the summary of the patients who required steroid treatment for specific irAE(s) can be found in online supplemental material. Median time to onset of toxicity (figure 2) was shortest for renal (1.0 months, IQR, 0.7–3.0), liver (1.3 months, IQR 0.8–2.3), skin (1.5 months, IQR 0.7–7.1), and gastrointestinal (1.7 months, IQR 0.4–5.5) irAEs. Other toxicities generally presenting within 4 months from ICI start date were thyroid, other, neurological irAEs and arthritis. Late immune-related toxicities included myositis, hypophysitis, pancreatitis, and pneumonitis. A visual representation of median onset timing of organ-specific irAEs can be found in figure 2.

Association of irAEs with survival outcomes

Higher burden of any irAEs was not significantly associated with OS (HR 0.89; 95% CI CI 0.53 to 1.48; p=0.582) nor with PFS (HR 1.27; 95% CI 0.82 to 1.96; p=0.068).

This led us to perform an in-depth analysis of association between survival outcomes and organ-specific irAEs burden. To build the organ-specific burden score, we grouped together myositis and arthralgia as musculoskeletal irAEs, thyroiditis and hypophysitis as endocrine irAEs, and colitis and pancreatitis as gastrointestinal irAEs.[22]

At univariable analysis (table 2), the higher burden of skin, endocrine, and musculoskeletal irAEs had a protective effect on OS, whereas higher burden of gastrointestinal, pneumonitis, neurological, liver, renal, and other irAEs had a detrimental effect on OS.

At multivariable analysis (table 2), adjusting for patients' and disease characteristics, higher burden of endocrine and musculoskeletal irAEs had a protective effect on OS, whereas higher burden of skin, gastrointestinal,

Table 2 Cox proportional hazards regression models for OS and PFS in the entire study population according to organ-specific irAEs

Organ-specific irAEs	OS				PFS			
	Univariable model		Multivariable model		Univariable model		Multivariable model	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Gastrointestinal	1.15 (0.80 to 1.65)	0.438	1.33 (0.87 to 2.03)	0.189	1.27 (0.94 to 1.72)	**0.113**	1.30 (0.92 to 1.84)	0.141
Skin	0.84 (0.44 to 1.61)	0.601	1.16 (0.64 to 2.11)	0.628	1.49 (0.96 to 2.31)	0.078	1.81 (1.18 to 2.27)	**0.006**
Endocrine	0.46 (0.24 to 0.88)	**0.019**	0.43 (0.21 to 0.89)	**0.023**	0.78 (0.51 to 1.17)	0.223	0.76 (0.50 to 1.16)	0.207
Pneumonitis	1.92 (0.97 to 3.84)	0.063	1.41 (0.73 to 2.72)	0.304	1.78 (0.88 to 3.60)	0.108	1.50 (0.76 to 2.97)	0.241
Neurological	1.39 (0.87 to 2.22)	0.163	1.64 (1.03 to 2.60)	**0.036**	1.28 (0.80 to 2.04)	0.296	1.63 (1.04 to 2.56)	**0.032**
Musculoskeletal	0.29 (0.08 to 1.08)	0.066	0.22 (0.06 to 0.88)	**0.032**	0.79 (0.44 to 1.44)	0.449	0.56 (0.28 to 1.11)	0.098
Liver	1.38 (1.02 to 1.86)	**0.034**	1.53 (1.11 to 2.10)	**0.009**	1.38 (1.06 to 1.80)	**0.018**	1.52 (1.15 to 2.01)	**0.004**
Renal	1.20 (0.56 to 2.54)	0.641	1.19 (0.52 to 2.70)	0.683	1.02 (0.48 to 2.15)	0.960	1.02 (0.45 to 2.30)	0.958
Other	1.25 (0.62 to 2.54)	0.537	1.15 (0.57 to 2.32)	0.701	1.42 (0.77 to 2.60)	0.258	1.45 (0.79 to 2.66)	0.225

P values <0.05 are highlighted in bold
irAEs, immune-related adverse events; OS, overall survival; PFS, progression-free survival.

pneumonitis, neurological, hepatic, renal, and other irAEs had a detrimental effect on OS.

Based on the above results, we built 'aggregated' burden scores of protective (endocrine and musculoskeletal) and harmful (gastrointestinal, pneumonitis, neurological, liver) irAEs. This aggregation was based on the prognostic effect of organ-specific burden scores at multivariable analysis, and determined by HRs direction (<1 protective, >1 harmful), HR magnitude (<0.83 for protective and >1.2 for harmful events) and/or p value (<20%). The aggregated burden scores showed very strong prognostic effect at multivariable analysis (protective burden score HR 0.36; 95% CI 0.19 to 0.66; p=0.001; harmful burden score HR 1.46; 95% CI 1.19 to 1.79; p<0.001).

At univariable analysis (table 2), higher burden of endocrine and musculoskeletal irAEs had a protective effect on PFS, whereas higher burden of gastrointestinal, skin, pneumonitis, neurological, hepatic, renal and other irAEs had a detrimental effect on PFS.

At multivariable analysis (table 2), higher burden of endocrine and musculoskeletal irAEs had a protective effect on PFS, whereas higher burden of gastrointestinal, skin, pneumonitis, neurological, hepatic, renal and other irAEs had a detrimental effect on PFS. As for OS, we built 'aggregated' burden scores of protective (endocrine and musculoskeletal) and harmful (gastrointestinal, skin, pneumonitis, neurological, liver) irAEs. The adjusted model including these aggregated burden scores showed a stronger effect of protective (HR 0.68; 95% CI 0.47 to 0.98; p=0.04) than harmful (HR 1.49; 95% CI 1.26 to 1.76; p<0.001) burden score.

Finally, we assessed whether a different management of irAEs (ie, either supportive therapy alone or steroid therapy or ICI discontinuation) could result in significantly different outcomes (online supplemental material 2). Median PFS was not reached for patients who discontinued ICI, 71.3 months for those treated with supportive therapy alone and 38.9 months for those who required steroids as well, however, these were not statistically significant (p=0.53). Instead, mOS was not reached for all three groups of patients (p=0.49). Notably, no significant differences in terms of PFS and OS were observed in these three subgroups of patients.

DISCUSSION

This multicenter cohort study is the largest study evaluating the association between irAEs and survival outcomes in a large international dataset of over 300 dMMR/MSI-H mCRC patients treated with ICIs. Our results show that different organ-specific irAEs may selectively exert 'protective' or 'harmful' effects.

These results are particularly relevant in light of the unmet need of developing prognostic and predictive factors to improve clinical stratification of patients with dMMR/MSI-H mCRC treated with ICI.[2 23 24] Indeed, despite the introduction of ICI has dramatically improved the prognosis of these patients, with

some of them achieving long-term benefit, there is yet a relevant proportion of patients displaying primary or acquired resistance.[7 23 25–27]

So far, no clear data have been specifically provided for patients with dMMR/MSI-H mCRC. Studies investigating the association between irAEs and outcomes of patients treated with ICI focused only on other types of ICI-sensitive cancers and were not conclusive. There is indeed conflicting evidence regarding the prognostic impact of irAEs, depending on timing of onset, severity or organ(s) affected, and ICI regimen used, for example, anti-PD-(L)1 monotherapy, anti-CTLA-4 agents alone or anti-CTLA-4-based combination therapy.[11–14 17 18] Furthermore, the immortal time bias may have influenced earlier data on correlation between irAE and ICI efficacy: patients with toxicities may appear to have longer survivals simply because they must survive long enough to experience them, while patients dying shortly after ICI start do not have enough time to develop irAEs, eventually falsely inflating their positive prognostic effect.[28 29] Current evidence overall suggests that the occurrence of irAEs as a whole should not be categorized as exclusively protective or detrimental and that immortal time bias has to be considered.

Based on these premises, we first dissected irAEs occurring in our population in terms of grade and site of origin, and then we built organ-specific irAEs burden scores modeling them as time-dependent variables to minimize the potential risk of survivor bias.

After adjusting for patients' and disease characteristics at multivariable analyses, the only events that appeared to have a protective effect on OS were endocrine and musculoskeletal irAEs, while all the others (such as skin, gastrointestinal, pneumonitis) all had a detrimental effect on both OS and PFS.

The prognostic relevance of protective and harmful irAEs emerged more clearer in the analysis of 'aggregated' burden scores, that showed very strong prognostic effect for both at multivariable analysis for OS and a stronger effect of protective than harmful burden score at multivariable analysis for PFS.

Our results are in part in line with the previously published data regarding the positive association of endocrine and rheumatological (including arthralgia and arthritis) toxicities with ICI efficacy.[30–33] On the contrary, the association of cutaneous irAEs with a negative effect on OS and PFS was not expected, since the opposite observation was previously made.[15 34–36] We should consider that most of these previous results were shown in different disease setting (ie, advanced melanoma), where different specific cutaneous toxicities may arise. Specifically, the skin toxicity that was strongly associated to high response rates is vitiligo, but this specific skin irAE was rather uncommon in our population (which presented mainly with rash).[37 38] Similar to cutaneous irAEs, gastrointestinal irAEs have been previously associated with better outcomes, while

they demonstrated to be harmful in our dataset.[36] This discordance could be attributed, again, to different settings: our dataset was made up of advanced CRC patients with accompanying gastrointestinal morbidity, and this could potentially blur this association and diminish ICI effects.

However, development of irAEs and the reason why different organ-specific irAEs are related to different outcomes remain unsolved questions and a controversial topic. A leading hypothesis for irAEs generation is tissue cross-reactivity but differences in immunogenomics may play as well a role.[39–41] Further studies are needed to elucidate biological mechanisms behind organ-specific irAEs and to potentially dissociate pharmacological effects of ICIs from their unwanted toxicities.

We must acknowledge that our study has some limitations, first represented by the retrospective and heterogeneous nature of our study cohort. Furthermore, it could be argued that higher grade organ toxicities, that is, hepatic and renal irAEs, are more often associated with serious adverse events and could be life-threatening themselves or compromise subsequent treatments, thus worsening prognosis. However, there was no lethal irAE (G5) in our cohort and most irAEs were graded as <3. Additionally, more serious toxicities could require steroid or immunosuppressive therapy, potentially dampening the efficacy of ICIs.[42–44] However, the use of steroid therapy was equally distributed in both subgroups identified by 'harmful' and 'protective' irAEs. Notably, we were also able to show that PFS and OS were not worsened by the use of steroid therapy or by the permanent discontinuation of ICIs because of irAEs.

In conclusion, through a joint effort between multiple international institutions, we went further into understanding the prognostic impact of irAEs and developed an easy-to-use model to aggregate ICI toxicity (burden score of protective and harmful irAEs) that may be used as surrogate marker of response to ICI in dMMR/MSI-H mCRC patients. Further analyses of completed and ongoing randomized controlled trials are required to validate our findings and to properly integrate organ-specific irAEs as prognostic indicators in clinical practice.

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