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Immuno-Oncology

Efficacy and Safety of Immune Checkpoint Inhibitors in Patients with Microsatellite Instability-High End-Stage Cancers and Poor Performance Status Related to High Disease Burden

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Immune checkpoint inhibitors • Microsatellite instability • Mismatch repair deficiency • Performance status • Lazarus response

Abstract

Background. Few real-world series on the efficacy and safety of anti-programmed cell death protein-1(PD-1)/programmed death ligand-1(PD-L1)–based therapy are available in molecularly unselected patients with poor performance status (PS) and specific types of advanced cancers, because such populations are typically excluded from clinical trials due to poor life expectancy and risk of toxicity.

Materials and Methods. This multicenter retrospective case series included patients with microsatellite instability (MSI)-high metastatic cancers with Eastern Cooperative Oncology Group (ECOG) PS of 2 or 3 not related to comorbidities receiving anti-PD-1 with or without anti-CTLA-4 therapy after failure of at least one prior treatment line.

Results. We included 27 patients with six diverse tumor types: colorectal (n = 18), gastric (n = 5), biliary tract, pancreatic, small bowel, and endometrial cancers (n = 1 each). Baseline ECOG PS was 2 (74%) or 3 (26%). Overall response rate was 33%, with six partial and three complete responses. Median time to response was 3.1, months and median duration of response was 16.9 months. Median progression-free survival was 3.4 months (95% CI: 2.3 to not evaluable), and 18-month overall survival was 50.8% (95% confidence interval, 32.7–78.8). Baseline variables were not associated with survival outcomes. ECOG PS 1 was reached by 52% of patients in a median time of 6 weeks, and ECOG PS 0 was reached by 30% of patients in a median time of 10 weeks.

Conclusion. In a high proportion of patients with MSI-high cancers and poor performance status related to end-stage disease, salvage immunotherapy can induce potentially long-lasting "Lazarus responses". Immunotherapy decisions near the end-of-life should be carefully integrated with predictive biomarkers and with palliative care measures in the real-world setting. ***The Oncologist*** 2020;25:803–809

Implications for Practice: In this retrospective cohort study of 27 pretreated patients with microsatellite instability (MSI)-high cancers and Eastern Cooperative Oncology Group performance status of 2 or 3 not related to comorbidities, PD-1/PD-L1-based therapy induced a RECIST response in 33% of patients, with a median duration of 16.9 months, and an improvement of performance status in 52% of patients. MSI-high status can be used in clinical practice as a tumor-agnostic predictive biomarker to select critically ill patients with end-stage cancers for salvage immunotherapy.

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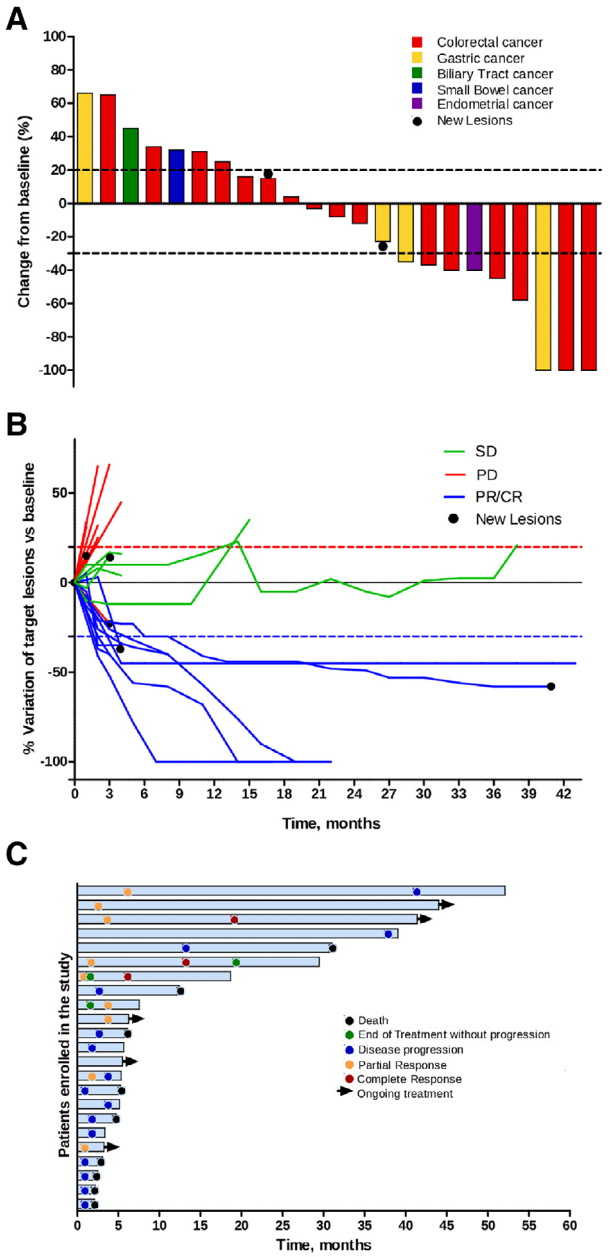
Introduction

After the introduction of targeted therapies for patients with oncogene-addicted cancers, some reports described cases of extraordinary activity of these drugs also in terminally ill patients with poor performance status (PS) and critically high disease burden, with rapid improvement of patients' health conditions during the very first days of treatment. The common acknowledgment of such "Lazarus responses" led to a revolution in the treatment decision making for patients who were otherwise candidates only for best supportive care, enabling their access to target therapies at least in presence of predictive biomarkers associated with high chance of treatment response [1].

Few real-world data exist on the role of immune checkpoint inhibitors (ICIs) in patients with Eastern Cooperative Oncology Group (ECOG) PS ≥2 caused by end-stage cancers because this patient population has been excluded from clinical trials, even if bearing ICIs-sensitive tumors (e.g., non-small cell lung cancer with PD-L1 ≥ 50% or skin cancers). The RECIST response to monotherapy with anti-PD-1/PD-L1 agents achieves one of the highest rates (up to 50%) in patients with microsatellite instability (MSI)-high advanced cancers, independently from the primary site of origin [2, 3]. Therefore, MSI could be used as a predictive biomarker to select patients with end-stage cancers for salvage immunotherapy despite poor performance status and reduced life expectancy.

In this study, we aimed at assessing whether anti-PD-1/PD-L1-based therapy can induce "Lazarus responses" and clinically meaningful benefit in patients with MSI-high end-stage cancers and poor performance status.



Materials and Methods

Patients

This study was a retrospective, multicenter, cohort study conducted in four Italian University Hospitals.

Patients with metastatic solid tumors with MSI-high status and receiving an anti-PD-1 monoclonal antibody with or without an anti-CTLA-4 agent were eligible for the study. Inclusion criteria were MSI-high status and mismatch repair deficiency status independently from the primary tumor site of origin, ECOG PS 2 or 3 that had to be clearly related to progressive cancer and not to pre-existing comorbidities as assessed by Charlson Comorbidity Index score ≤ 7 (reflecting presence of up to one mild among 19 considered

Figure 1. (A): Waterfall plot of best tumor response in evaluable patients. The best percentage change from baseline in tumor size by RECIST version 1.1 in all the patients included in the study who received at least one dose of treatment and had at least one evaluable postbaseline tumor assessment. In red, yellow, green, blue and purple are represented patients with colorectal, gastric, biliary tract, small bowe,l and endometrial cancers, respectively, whereas the black dots denote the occurrence of new tumor lesions in presence of stable disease or partial response. Four patients did not undergo a postbaseline tumor assessment for clinical disease progression, one with pancreatic cancer, one with gastric cancer, and two with colorectal cancer. **(B):** Spider plot of RECIST best tumor response and its dynamics. The percentage variation versus baseline of the sum of longest diameters of target lesions for each patient over time. In red, green, and blue are reported patients with PD, SD, and PR or CR as best response, respectively, whereas the black dots denote the occurrence of new tumor lesions in presence of stable disease or partial response. Four patients did not undergo a postbaseline tumor assessment for clinical disease progression. **(C):** Swimmer plot for survival in response-evaluable patients. Overall survival for each patient included in the study who received at least one dose of treatment and had at least one evaluable postbaseline tumor assessment. Red, orange, blue, green, and black dots indicate the occurrence of complete response, partial response, disease progression, end of treatment in absence of disease progression, and death, respectively, whereas black arrows represent the ongoing treatments.
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 1. Patients and tumor characteristics

Characteristic	*n* = 27 (%)
Age, median (IQR), yr	52 (43–63)
Gender, *n* (%)	
Female	12 (44)
Male	15 (56)
ECOG PS, *n* (%)	
2	20 (74)
3	7 (26)
Lynch syndrome, *n* (%)	
No	10 (59)
Yes	7 (41)
NA	10
Charlson Comorbidity Index score, *n* (%)	
6 (no comorbidities)	21 (78)
7 (one mild comorbidity)	6 (22)
Previous lines of therapy, *n* (%)	
Median (range)	2 (1–5)
1	9 (33)
2	13 (48)
>2	5 (19)
Primary tumor site of origin, *n* (%)	
Colorectal cancer	18 (66)
Left-sided	6 (22)
Right-sided	12 (44)
Gastric cancer	5 (18)
Biliary tract cancer	1 (4)
Pancreatic cancer	1 (4)
Small bowel cancer	1 (4)
Endometrial cancer	1 (4)
Primary tumor resected, *n* (%)	
No	8 (30)
Yes	19 (70)
Synchronous metastases, *n* (%)	
No	8 (30)
Yes	19 (70)
Number of metastatic sites, *n* (%)	
1	14 (52)
2	6 (22)
>2	7 (26)
Specific sites of metastases, *n* (%)	
Liver	5(18)
Lung	3 (11)
Peritoneum	12 (44)
Lymph nodes	16 (59)
Bone	4 (15)
Baseline LDH (U/L), *n* (%)	
Median (IQR)	334 (234–385)
Low (≤median)	14 (52)
High (>median)	13 (48)
Baseline lymphocytopenia (<LLN), *n* (%)	
No	16 (59)
Yes	11 (41)
Baseline neutrophil-to-lymphocyte ratio, *n* (%)	
Median (IQR)	5.5 (3.1–10.4)
≥5	15 (55)
≥10	8 (30)
Baseline hypoalbuminemia (<3 g/dL), *n* (%)	
No	11 (41)
Yes	16 (59)
Type of treatment received, *n* (%)	
Nivolumab	18 (67)
Nivolumab plus ipilimumab	6 (22)
Pembrolizumab	3 (11)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; IQR, interquartile range; LDH, lactic acid dehydrogenase; LLN, lower limit of normal; NA, not available.

comorbid diseases as previously reported [4]), at least one previous treatment line for metastatic disease, and presence of measurable disease. During immunotherapy, tumor assessments with computed tomography (CT) or magnetic resonance imaging scans were performed at baseline and every 8–9 weeks (depending on the treatment schedule) until disease progression. Radiological evaluations could have been anticipated based on decisions of the treating physicians in case of clinical progression. MSI status was confirmed by both polymerase chain reaction and immunohistochemistry, each assessed locally. The primary outcome measure was overall response rate (ORR) according to RECIST 1.1 criteria. Secondary outcome measures were clinical benefit rate, time-to-response and duration of response, progression-free survival (PFS), overall survival (OS), rate of ECOG performance status recovery, and safety. This study was approved by institutional review board of Fondazione IRCCS Istituto Nazionale dei Tumori (INT 117/15), and each patient signed a written informed consent.

Statistical Analysis

Descriptive statistics were used to summarize patients and disease characteristics. The Kaplan-Meier method was used for survival analyses to estimate PFS and OS, time to response, and duration of responses. Univariable Cox models were used to test interactions between variables. All analyses were performed using GraphPad version 5.02, SAS (version 9.1) and R software.

Results

Among 203 patients with MSI-high solid tumors referring to the participating hospitals between June 1, 2015, and July 30, 2019, 27 fulfilled inclusion criteria as detailed in the supplemental online Figure 1. One-hundred seventy-four patients (84%) were excluded because their PS was <2, whereas two

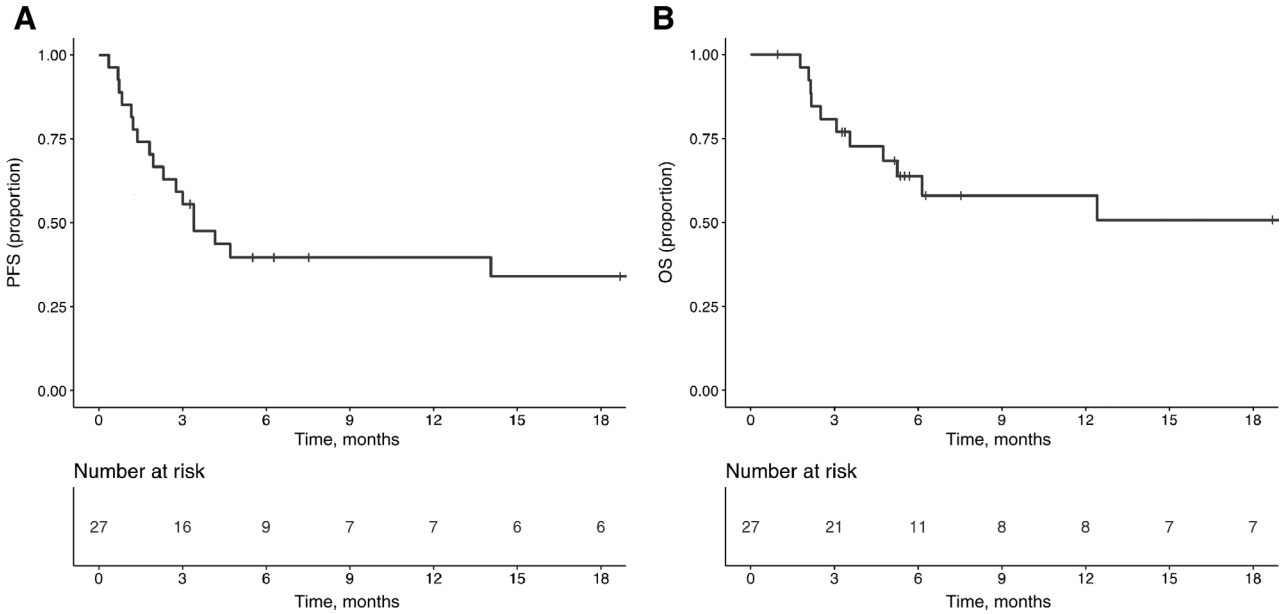


Figure 2. Survival analysis. Progression-free survival and overall survival curves in the overall study population are illustrated in **(A)** and **(B)**, respectively.
Abbreviations: OS, overall survival; PFS, progression-free survival.

patients with PS ≥2 were excluded because they did not receive an anti-PD-1–based treatment because of rapid clinical deterioration. The final study population included patients with six diverse tumor types: colorectal (*n* = 18), gastric (*n* = 5), biliary tract, pancreatic, small bowel, and endometrial cancers (*n* = 1 each). Patients' demographics, disease characteristics, and type of therapy received are shown in Table 1. A brief description of each patient's main reasons leading to poor performance status, coupled with significant baseline CT scan imaging, is reported in the supplemental online Results. The median treatment duration was 2.7 months (interquartile range [IQR], 1.4–5.9). Among 22 patients who discontinued the treatment, the reasons for permanent discontinuation were disease progression (*n* = 19), adverse events (*n* = 2), and patient or physician decision (*n* = 1).

ORR was 33% (9/27) (95% confidence interval [CI], 17–54), including six partial responses (PR) and three complete responses (CRs). Clinical benefit rate (CR + PR + stable disease) was 52% (14/27; 95% CI, 32–71). No cases of pseudoprogression were observed. Four patients did not receive at least one postbaseline tumor reassessment because of rapid clinical progression (one pancreatic cancer, one gastric cancer, and two colorectal cancers); in 24 patients for whom the tumor response was evaluated according to RECIST1.1, the graphs showing best responses and their dynamics are depicted in Figure 1. Median time to response was 3.1 months (range, 1.8–6.8), and median duration of response was 16.9 months (range, 1.3–40.9).

The data cutoff date for the analyses was November 10, 2019. At the time of analysis, 19 PFS and 12 OS events were observed, respectively. The median follow-up duration was 18.7 months (IQR, 5.5–41.4). Median PFS was 3.4 months (95% CI, 2.3 to not evaluable) and 18-month OS rate was 50.8% (95% CI, 32.7–78.8; Fig. 2). The main prognostic baseline variables did not influence PFS and OS outcomes (Table 2). Two patients experienced improved PS and RECIST PR after an initial phase characterized by PS worsening due to persistence of critically high disease burden ("delayed Lazarus responses" depicted in supplemental online Fig. 2).

An ECOG PS 1 was reached by 52% (14/27) of patients, with a median time of 6 weeks (range, 3–16). An ECOG PS 0 was reached by 30% (8/27) of patients, with a median time of 10 weeks (range: 6–76). The dynamics of ECOG PS variation are depicted in Figure 3.

Table 3 summarizes the frequency and severity of treatment-related toxicities. Grade ≥ 3 adverse events were reported in 11% (3/27) of patients, accounting for colitis, hepatitis, and pancreatitis (*n* = 1 each). No treatment-related deaths were reported.

Discussion

The introduction of ICIs led to seismic changes in the treatment of several tumor types. In patients with advanced cancers, reduced life expectancy, and poor PS related to high disease burden, the use of anti-PD-1/PD-L1 agents may be justified by their favorable toxicity profile and their long-term effectiveness in specific patients' subgroups. However, several concerns may be raised due to the time (at least weeks) needed to induce tumor responses and the high burden of immunosuppression related to cachexia, systemic inflammation, and dependence on supportive corticosteroids.

Specifically, critically ill patients with poor PS are excluded from immunotherapy trials, whereas few and small real-world series on the efficacy and safety of anti-PD-1/PD-L1-based therapy are available in ECOG PS 2 patients with molecularly unselected advanced melanoma, non-small cell lung cancer, and urothelial carcinoma [5–7].

Specifically, in patients with end-stage MSI-high cancers and poor life expectancy, the potential occurrence of "Lazarus response" to ICIs poses a great challenge because of the expected high response rate to treatment and the long-

Table 2. Univariate Cox proportional hazards regression models for PFS and OS

	PFS		OS	
Characteristic	**HR (95% CI)**	***p* value**	**HR (95%CI)**	***p* value**
Age	1.01 (0.98–1.04)	.435	1.00 (0.97–1.04)	.992
Gender		.337		.846
Female	ref		ref	
Male	1.62 (0.60–4.35)		1.12 (0.35–3.59)	
ECOG PS		.409		.184
2	ref		ref	
3	1.51 (0.57–4.04)		2.20 (0.69–7.06)	
Previous lines of therapy		.354		.759
1	ref		ref	
≥2	2.73 (0.33–22.8)		1.08 (0.66–1.75)	
Primary tumor site of origin		.449		.692
Colorectal	ref		ref	
Noncolorectal	1.46 (0.55–3.87)		0.76 (0.20–2.89)	
Synchronous metastases		.993		.623
No	ref		ref	
Yes	1.01 (0.38–2.68)		0.75 (0.23–2.39)	
Primary tumor resected		.482		.953
No	ref		ref	
Yes	0.70 (0.26–1.91)		1.04 (0.28–3.93)	
Number of metastatic sites		.941		.801
1	ref		ref	
>1	1.04 (0.42–2.55)		0.86 (0.27–2.73)	
Liver metastases		.451		.466
No	ref		ref	
Yes	1.62 (0.46–5.66)		1.77 (0.38–8.22)	
Lung metastases		.988		.877
No	ref		ref	
Yes	1.01 (0.23–4.48)		0.85 (0.11–6.73)	
Peritoneal metastases		.985		.844
No	ref		ref	
Yes	1.01 (0.39–2.63)		1.12 (0.35–3.59)	
Bone metastases		.402		.545
No	ref		ref	
Yes	1.72 (0.48–6.08)		1.62 (0.34–7.64)	
Lymph nodal metastases		.528		.452
No	ref		ref	
Yes	0.75 (0.30–1.85)		0.64 (0.20–2.04)	
Baseline LDH		.557		.823
Low	ref		ref	
High	1.32 (0.53–3.27)		1.14 (0.36–3.61)	

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; LDH, lactic acid dehydrogenase; OS, overall survival; PFS, progression-free survival; ref, reference.

lasting survival predicted by MSI-high status and reported in clinical trials [2, 3, 8–16], which are counteracted by the treatment-related costs and potential toxicities. Albeit limited by its retrospective nature and small sample size, our real-world study showed that the outcomes and safety of anti-PD-1/PD-L1-based therapy in critically ill patients with MSI-high advanced cancers are similar to those reported by clinical trials conducted in eligible patients with ECOG PS 0 or 1 [2, 8, 12–14, 16]. Notably, the chance of achieving complete or long-lasting responses was not negligible despite the limited life expectancy. Baseline prognostic variables did not significantly influence the patients' outcomes,

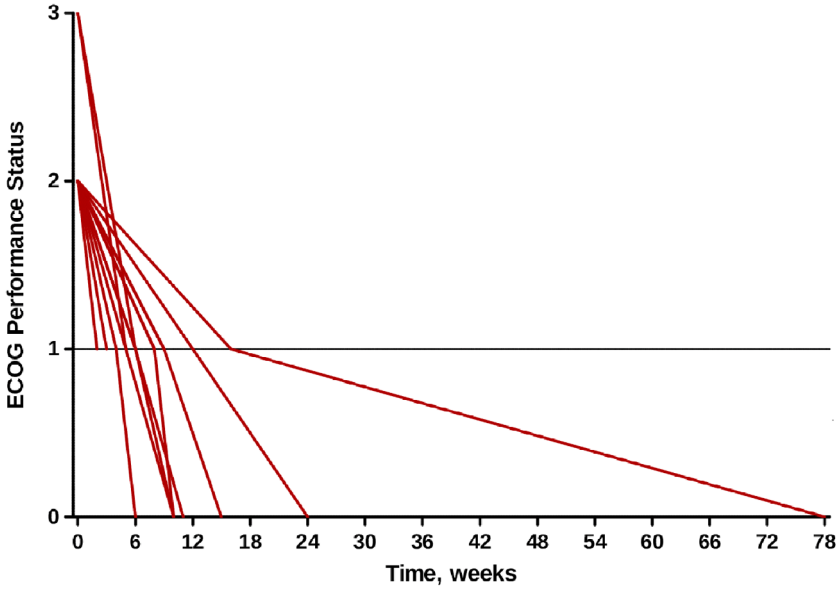


Figure 3. Spider plot for dynamic clinical response by means of ECOG performance status.
Illustrates the dynamic of variation of ECOG performance status from baseline during treatment in patients who achieved a clinical benefit in terms of improvement of performance status.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 3. Incidence of adverse events

Adverse event	G1–2, *n* (%)	G3, *n* (%)	G4, *n* (%)
Fatigue	9 (33)	0	0
Pruritus	6 (22)	0	0
Hypothyroidism	5 (18)	0	0
Mucositis	4 (14)	0	0
Diarrhea	2 (7)	1 (3)	0
Alanine aminotransferase increased	0	1 (3)	0
Aspartate aminotransferare increased	0	1 (3)	0
Amylase increased	0	1 (3)	0
Lipase increased	0	1 (3)	0

which may have been mostly related to the treatment efficacy in the end-of-life setting shared by the target population. However, some pretreated patients with rapidly progressive cancers may miss the chance to receive ICIs because of rapid PS deterioration, and, therefore, when included in the intention-to-treat population of clinical trials, such critically ill populations may contribute to worsening expected outcomes compared with those observed in retrospective real-world datasets. Finally, even if no new and critical safety signals emerged in our frail patients' population, early deaths due to progressive disease may have masked the development of potential toxicities.

Because anti-PD-1/PD-L1 agents are not directly targeted on the bulk of tumor cells and their mechanism of action is based on profound modifications of the host immune response, responses may be delayed, occurring after the first radiological reassessment, and may not be accompanied by a sudden improvement of symptoms and PS. In line with this observation, in the Checkmate-142 trial conducted in pretreated patients with MSI-high metastatic colorectal cancer [14], the upper limit of the IQR of the time to response to nivolumab was 3.2 months, meaning that a quarter of patients achieved a RECIST response after at least 3 months of treatment. When physicians decide to administer immunotherapy in presence of a short life expectancy, the lack of an immediate improvement of health conditions during the first courses of treatment, as usually shown for targeted agents, may lead to early treatment discontinuation, even if cases of "delayed Lazarus response" may occur the real-world setting.

Conclusion

MSI-high status could be used in the clinical practice as a tumor-agnostic predictive biomarker to select patients with poor PS and end-stage cancers for salvage immunotherapy. Our study may prompt future investigations on ICIs in other patients' subgroups with ECOG PS >1 and high chance of response, such as those with skin cancers, PD-L1 positive (≥50%) non-small cell lung cancer, and hyper- or ultramutated cancers [17]. In these critically ill but molecularly selected populations, anti-PD-1/PD-L1–based therapy might be a potentially effective and low-toxicity option as opposed to best supportive care or other standard treatments with lower risk-benefit ratio, although larger real-world data or dedicated clinical trials are warranted in this setting.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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