DiM: Prognostic Score for Second- or Further-line Immunotherapy in Advanced Non–Small-Cell Lung Cancer: An External Validation

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Abstract
No biomarkers, other than programmed cell death ligand 1, have been approved to guide the choice of immunotherapy for non–small-cell lung cancer. We evaluated whether the clinical prognostic score, DiM, could predict outcomes of patients with NSCLC receiving immunotherapy. DiM score could predict outcomes, especially for those with the worst prognosis.

Background: Other than the programmed cell death ligand 1 (PD-L1) value, oncologists have only the clinical characteristics of patients with advanced non–small-cell lung cancer (aNSCLC) to determine candidates for immunotherapy. A clinical prognostic score composed of the Eastern Cooperative Oncology Group performance status, sex, histologic type, stage, platinum-based first-line therapy, and response to first-line therapy has categorized 3 prognostic groups for patients undergoing second-line chemotherapy. We sought to validate the same score for patients with aNSCLC treated with second- or further-line immunotherapy.

Materials and Methods: We collected data from 2 Italian centers. A score was generated to divide patients into 3 prognostic groups: best, score < 5; intermediate, score 5 to 9; and worst, score > 9. Overall survival (OS) and progression-free survival (PFS) were the endpoints.

Results: A total of 347 patients were included for analysis. Their median age was 66 years (range, 30-88 years), most were aged < 70 years (67.5%), 70.7% were men, 79.5% were smokers, and 74.6% had had adenocarcinoma. The Eastern Cooperative Oncology Group performance status was 0 for 23%, 1 for 54.5%, and 2 for 22.5%. Of the 347 patients, 28% were in the best prognosis, 51% in the intermediate, and 21% in the worst prognosis group, respectively. The median OS was 18.0 months for the best, 8.5 months for the intermediate (hazard ratio [HR] vs. best, 1.83; 95% confidence interval [CI], 1.35-2.47; \( P < .001 \)) and 2.6 months for worst (HR vs. best, 5.77; 95% CI, 3.99-8.33; \( P < .001 \)) group. The median PFS was 3.4 months for the best, 3.7 months for the intermediate (HR vs. best, 1.35; 95% CI, 1.03-1.77; \( P = .032 \)), and 1.9 months for the worst (HR vs. best, 2.51; 95% CI, 1.80-3.50; \( P < .001 \)) group. Conclusions: The prognostic score was able to predict the outcomes of patients with aNSCLC who had received immunotherapy. The worst category showed a dismal life expectancy...

A.P. and G.L.R. contributed equally to the present study.

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Prognostic Score for Advanced NSCLC Treated With IO

Introduction

Immune checkpoint inhibitors (ICIs) have significantly changed the therapeutic landscape of advanced non–small-cell lung cancer (aNSCLC).1 Currently, pembrolizumab is the standard of care as first-line therapy for programmed cell death ligand 1 (PD-L1) ≥ 50% NSCLC (KEYNOTE-024).2,3 Nivolumab and pembrolizumab were the first 2 ICIs approved on the basis of the significant improvement in overall survival (OS) compared with docetaxel in patients with pretreated aNSCLC, with both squamous and nonsquamous histologic features.4-6 Atezolizumab is another therapeutic option in the same setting,7 and durvalumab demonstrated activity even in patients with strongly pretreated aNSCLC.8

Despite the improvement in survival, only a limited number of patients will respond to immunotherapy (IO) and even fewer patients will experience a durable response.9 The progression-free survival (PFS) and OS curves in pivotal second-line (2L) studies with nivolumab, pembrolizumab, and atezolizumab showed an overlap in the first months of therapy, demonstrating that most patients will not respond to ICIs, with a non-negligible risk of early clinical failure.4-8 The discovery of predictive and prognostic biomarkers continues to be of great interest.

PD-L1 expression is the only biomarker approved for use in aNSCLC; however, multiple studies have reported several biologic and technical limitations owing to the temporal changes in PD-L1 expression and its intratumor heterogeneity.9 Conflicting results were described for a proportion of patients who had responded to ICIs with low or negative PD-L1 expression6,10; thus, its negative predictive role has remained suboptimal.9,11 Other than PD-L1 expression, oncologists have only patients’ clinical characteristics to determine whether patients are candidates for ICIs therapy.12-15 Other potential biomarkers have recently been investigated, including the tumor mutation burden, immune score, CD8⁺ tumor-infiltrating lymphocytes, and the immune gene signature, with interesting results.16 However, to date, none of these factors has achieved a definite role in clinical practice.17-19

A crucial factor is also cancer-associated inflammation, which has been correlated with worse outcomes.17,18 Moreover, different peripheral blood parameters have been investigated in various malignancies.11,15 Blood inflammatory biomarkers have been correlated with a low therapeutic response to conventional treatment and a poor prognosis17 and have demonstrated an association with survival outcomes in patients with advanced melanoma receiving ICIs.10,20 Their prognostic role has also been reported in patients with aNSCLC treated with ICIs.22-24 However, few data exist regarding the predictive role of peripheral blood biomarkers in aNSCLC treated with anti–PD-L1 inhibitors.22-28

A clinical prognostic score developed by Di Maio et al29 (the DiM score) consists of the Eastern Cooperative Oncology Group (ECOG) performance status (PS), patient sex, histologic type (ie, squamous, adenocarcinoma, other), stage (IIIB or IV), platinum-based first-line therapy, and response to first-line therapy (ie, complete or partial response, no response). The DiM score was used to categorize patients receiving second-line chemotherapy (CHT) into 3 prognostic groups.29 The score was developed using individual data from 1197 patients enrolled in 9 randomized trials of 2L CHT. Subsequently, the DiM score was externally validated using data from 551 patients enrolled in a randomized phase III trial comparing vinflunine with docetaxel in the same setting, confirming its prognostic importance.30

The aim of the present study was to determine whether the DiM score, developed and validated for patients receiving CHT, would be able to predict the outcomes of patients with aNSCLC receiving second- or further-line IO to identify those patients less likely to respond and to potentially help in the treatment choices.

Materials and Methods

The present study was conducted at the Fondazione IRCCS Istituto Nazionale Tumori of Milan and the IRCCS Oncologico Giovanni Paolo II of Bari, Italy. The present study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice and local ethical guidelines. All enrolled alive patients provided written informed consent.

Study Population

From August 2015 to December 2018, we conducted a retrospective 2-center study of 347 patients with consecutive aNSCLC receiving single-agent anti–PD-L1 inhibitors in 2L or further-line therapy (193 from Milan [C1] and 154 from Bari [C2]).

The eligible patients had fulfilled the following inclusion criteria: a cytologic or histologic diagnosis of aNSCLC and pretreated patients (relapse or stage IIIB-IV) who had received ≥ 1 infusion of an anti–PD-L1 agent as second- or further-line therapy. Patients who had received ICIs within a clinical study were also included. The exclusion criterion was the receipt of IO as first-line therapy or combined with other systemic drugs. The clinical characteristics, including the treatment information from both centers, are reported in Table 1.

Treatment

ICIs were administered intravenously. Nivolumab was initially given at a dose of 3 mg/kg and, later, since May 2018, at a fixed dose of 240 mg every 2 weeks. Pembrolizumab was given at a dose of 2 mg/kg every 3 weeks for patients with PD-L1 expression of ≥ 1%. Atezolizumab was given at a fixed dose of 1200 mg every 3 weeks and durvalumab at a dose of
<table>
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<th>Characteristic</th>
<th>C1 (n = 193; 55.4%)</th>
<th>C2 (n = 154; 44.6%)</th>
<th>C1 + C2 (n = 347; 100%)</th>
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Prognostic Score for Advanced NSCLC Treated With IO

Table 1 Continued

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<tr>
<th>Characteristic</th>
<th>C1 (n = 193; 55.4%)</th>
<th>C2 (n = 154; 44.6%)</th>
<th>C1 + C2 (n = 347; 100%)</th>
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Data presented as n (%), unless otherwise noted. Abbreviations: C1 = center 1 (Milan); C2 = center 2 (Bari); CI = confidence interval; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; IO = immune checkpoint inhibitor; ICI = immune checkpoint inhibitor; ORR = overall response rate; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PS = performance status.

10 mg/kg every 2 weeks. Treatment was continued until disease progression, unacceptable toxicity, withdrawal, or death. Treatment after the occurrence of progressive disease (PD) was permitted if clinical benefit would result according to the clinician’s judgment.

Statistical Analysis

The primary endpoint was OS and its association with the prognostic score to identify potential poor prognostic groups less likely to obtain a favorable outcome with ICIs. OS was calculated from the start of ICI treatment until death or the last follow-up examination.

The secondary endpoints were PFS and its association with the prognostic score. PFS was calculated from the date of the first ICI administration until PD, death from any cause, or the last follow-up visit for patients alive without PD. The Kaplan-Meier method was used to calculate the median PFS (mPFS) and median OS (mOS) with the 95% confidence intervals (CIs) and to generate survival curves for PFS and OS according to the 3 risk categories. The median follow-up period was calculated using the inverted Kaplan-Meier technique. The log-rank test (Mantel-Cox) was used to evaluate statistically significant differences in PFS and OS, which was defined as the $P < .05$ level. The prognostic score was computed using the scoring system presented in Table 2. Similar to previous studies, patients were divided into 3 groups using cutoff scores well balanced along the range of values: best prognosis, score < 5; intermediate prognosis, score 5 to 9; and worst prognosis, score > 9. A Cox proportional hazard model was used to compare the 3 categories. The concordance C-index was calculated using the model proposed by Pencina and D’Agostino to measure the power of the discriminations. All statistical analyses were performed using the SPSS program, version 25.0 (IBM Corp, Armonk, NY) and R, version 3.5.1 (R Foundation, Vienna, Austria).

Response Evaluation

The radiologic assessments consisted of a baseline total body computed tomography scan. Computed tomography scans were subsequently performed every 3 to 4 cycles or whenever PD was clinically suspected.

The tumor response was assessed using the Response Evaluation Criteria in Solid Tumors, version 1.1. The overall response rate (ORR) was defined as the sum of the complete and partial responses and the disease control rate as the sum of the complete and partial responses and stable disease. Patients with PD for whom clinical benefit would be maintained according to the clinician’s judgment could receive treatment after PD and were considered to have stable disease if PD had not been confirmed.

Results

Patient Characteristics

A total of 347 patients with aNSCLC who had received an anti–PD-L1 inhibitor as 2L or further-line therapy were included in the present analysis. The patient characteristics are summarized in Table 1. Of the 347 patients, 246 were men (70.7%) and 276 were smokers (79.5%). The median age was 66 years (range, 30-88 years), and 113 patients (32.5%) were aged > 70 years. The median ECOG PS was 1 (range, 0-1), with 22.5% patients having an ECOG PS of 2. The histologic subtype was adenocarcinoma in 65.4%, squamous cell in 23.1%, and other in 3.1%. At baseline, bone, liver, and brain metastases were present in 38.3%, 19.6%, and 18.4% of the patients, respectively. Two thirds of the patients (64.3%) had received ICIs as 2L therapy, and 124 patients had received anti–PD-L1 inhibitors as third-line or further therapy.

General Response and OS Outcomes

All 347 patients included in the present study were assessable for the survival analysis. At the data cutoff point (December 2018), 306 patients (88%) had experienced PD and 260 patients had died.
(75%). Overall, after a median follow-up of 29 months (95% CI, 25.2-34.6 months), the mPFS was 3.1 months (95% CI, 2.6-3.5 months) and the mOS was 7.6 months (95% CI, 5.7-9.5 months). The ORR and disease control rate were 16.2% (95% CI, 12.6%-20.4%) and 44.1% (95% CI, 39.0%-49.4%), respectively.

**Prognostic Index**

The index score was assigned and calculated using the proposed scoring system from previous reports by Di Maio et al.\(^{29,30}\) (Table 2). The patients were separated into 3 categories. Of the 347 patients, 96 (27.7%) had had a low score (< 5, best category), 178 (51.3%) had had a score of 5 to 9 (intermediate category), and 73 (21%) had had a high score (> 9, worst category).

**Survival Results Among the 3 Groups**

The mOS was 18.0 months (95% CI, 11.1-24.8 months) for the best group, 8.5 months (95% CI, 6.6-10.3 months) for the intermediate group, and 2.6 months (95% CI, 1.8-3.4 months) for the worst group. The Kaplan-Meier curves for the 3 prognostic groups are shown in Figure 1. We used the Cox hazard model to describe the differences between the intermediate and best prognosis groups (hazard ratio [HR], 1.83; 95% CI, 1.35-2.47; \(P < .001\)) and worst and best prognosis groups (HR, 5.77; 95% CI, 3.99-8.33; \(P < .001\)). The C-index of the model for OS was 0.67 (95% CI, 0.63-0.70).

As a secondary endpoint, we evaluated the PFS for the 3 categories. The mPFS was 3.4 months (95% CI, 2.1-4.7 months), 3.7 months (95% CI, 3.2-4.2 months), and 1.9 months (95% CI, 1.5-2.2 months) for the best, intermediate, and worst category, respectively. The Kaplan-Meier curves for PFS are shown in Figure 2. The Cox model showed that the difference was statistically significant between the intermediate and best groups (HR, 1.35; 95% CI, 1.03-1.77; \(P = .032\)) and worst and best groups (HR, 2.51; 95% CI, 1.80-3.50; \(P < .001\)).

**Multivariate Analysis of OS**

A multivariate analysis of the OS for the overall population was performed. The multivariate analysis included the following baseline patient characteristics: age, sex, smoking status, pack-years, ECOG PS, histologic type, stage, liver, brain, or bone metastases, use of ICIs as 2L or further-line therapy, platinum-based first-line therapy, and ORR at first-line therapy (Table 3). Only the ECOG PS (0 vs. 2: HR, 0.14; 95% CI, 0.092-0.213; \(P < .0001\); 1 vs. 2: HR, 0.33; 95% CI, 0.23-0.45; \(P < .0001\)), presence of liver metastases at baseline (HR, 1.73; 95% CI, 1.27-2.36; \(P = .001\)), and smoking status expressed in pack-years (HR, 0.71; 95% CI, 0.53-0.96; \(P = .026\)) were confirmed as relevant prognostic factors.

**Results Stratifying the Model by Institution**

To identify differences between the 2 institutions, we implemented separated survival analyses for OS and PFS for C1 and C2. The mOS was 7.6 months (95% CI, 5.4-9.9 months) and 7.5 months (95% CI, 4.4-10.6 months), respectively, for C1 and C2 (\(P = .761\)). The mPFS was 2.2 months (95% CI, 1.9-2.6 months) and 3.8 months (95% CI, 2.6-3.5 months), respectively, for C1 and C2 (\(P = .005\)). The Kaplan-Meier curves for PFS and OS are shown in Supplemental Figures 1 and 2 (in the online version).
Discussion

In the present analysis, we found that the DiM prognostic score, initially developed and validated for patients with aNSCLC receiving 2L CHT, also performed well for patients receiving ICIs, allowing for the identification of patients with a good prognosis and a subgroup of patients with a very short life expectancy.

In recent years, IO has changed the survival of patients with aNSCLC, significantly prolonging the mOS and offering an interesting possibility of obtaining a long-term benefit for a few subjects. Nonetheless, only a small percentage of patients (18%-20%) will respond to ICIs as 2L therapy, with a mPFS of ~2 to 4 months.4-8

The identification of prognostic and/or predictive clinical factors and biomarkers remains a crucial topic. The early identification of those with and without a response to ICIs will be decisive in the attempt to avoid inadequate treatment and optimize the use of drugs in clinical practice, sparing unnecessary toxicity and costs. The identification will also be essential to detect those patients who might experience detrimental effects from hyper-PD.35-37 Different clinical factors are currently under investigation, including ECOG PS, patient age, smoking status, hyponatremia, use of steroids and antibiotics, and the presence of liver, bone, and brain metastases. However, no consensus has been reached regarding the benefit of ICIs for these patients.38,39

In both studies by Di Maio et al29,30 of the development and validation of the DiM score, the patients were classified into 3 survival groups: best, intermediate, and worst prognosis categories. Their findings led to the identification of a subset of patients (worst category) with a poor prognosis. For the latter patients, the mOS was < 4 months. Although the finding represents prognostic, and not predictive, information, the investigators concluded that the possibility of benefiting from active treatment was very small for this category of patients.29,30

To indirectly compare our cohort of patients treated with ICIs with the patients who had received 2L CHT, we performed an external validation of the score in the same setting. Therefore, we speculated that if the score was successfully validated in our series of patients who had been treated with ICIs, these results could confirm its prognostic role.

The validation of the DiM score in the present 347 patients treated with ICIs also allowed us to perform an indirect comparison between patients who had received CHT and those who had been treated with ICIs.

The results from our study have demonstrated that the use of the DiM score allowed for patient distribution into 3 survival categories for the patients who had received 2L ICI therapy. The C-index for OS was good (0.670), indicating satisfactory discrimination using the 3 risk categories. Specifically, patients within the worst prognosis group had the shortest mOS and mPFS at 2.6 and 1.9 months, respectively. It is probable that these patients would respond poorly to any anticancer therapy and that best supportive care could be the best choice for them. The differences in mPFS between the 2 centers participating in the present analysis might be explained by the differences in the timing of the radiologic assessments, which was longer in C2 compared than in C1. Similar to the results from other reports,22,23,38,39 our results highlighted the negative prognostic role of ECOG PS 2 for patients with aNSCLC and treated with ICIs.
The treatment of patients with a poor ECOG PS with ICIs has remained an argument of clinical debate. However, patients with a poor ECOG PS have a poor prognosis and, thus, are less likely to benefit from ICIs, probably owing to their ineffective immune system and fewer functional lymphocytes. However, ongoing prospective trials are assessing the efficacy of ICIs (ClinicalTrials.gov identifiers, NCT02733159 and NCT02879617) in patients with a poor ECOG PS, which should help to better define the role of ICIs in this setting. Because these drugs have been characterized by a favorable toxicity profile, many clinicians could be tempted to consider many patients who would have been excluded from CHT as being eligible for ICI therapy. Thus, after approval of ICIs in clinical practice in the setting of advanced urothelial cancer, the initiation of ICIs near the end of life significantly increased for patients with a poor PS although their use did not significantly change for patients with good PS. Again, in our study, the multivariate analysis results confirmed ECOG PS as a prognostic factor, suggesting that this important factor drives OS.

Patient sex is 1 of the factors included in the DiM prognostic score. Traditionally, in the CHT era, several analyses showed that men will have slightly worse results than those of women. Nevertheless, a recently reported meta-analysis of trials testing ICIs reported a significant interaction between ICI efficacy and sex, with worse outcome for women, probably resulting from a high occurrence of driver mutations. However, another recent meta-analysis that included 23 randomized trials of ICI-treated patients did not reported differences when stratified by sex.

Usually, patients with squamous cell NSCLC and especially those with rare histotypes (large cell neuroendocrine carcinoma, mixed and undifferentiated carcinoma) will have a poor prognosis compared with those with adenocarcinoma. Despite its negative prognostic role, patients with the squamous histologic type seemed to benefit highly from ICI treatment, as did patients with adenocarcinoma. However, for those with rare histologic subtypes, the role of ICI treatment remains unclear.

In the study by Di Maio et al of patients treated several years previously, patients who had received first-line platinum-based therapy had worse outcomes with 2L therapy. However, it is difficult to apply these findings to patients treated with ICIs, considering that, currently, most patients will receive first-line platinum-based CHT. However, the response to previous therapies seemed to correlate with the response to ICIs in a retrospective analysis.

Ideally, the identification of predictive factors could improve decision making in clinical practice. With all the limitations of our indirect comparison, the improving of OS with ICI treatment for patients with aNSCLC was found when we compared the mOS for those in the best and intermediate categories in our present series compared with the patients who had received CHT in the original development of the DiM score (18.0 vs. 12.9 months and 8.5 vs. 6.9 months for the best and intermediate categories, respectively). Thus, when we compared the worst category results (4.0 vs. 2.6 months), the ICIs performed worse in terms of OS compared with CHT, possibly owing to the detrimental effect of ICIs in this group of patients. However, the patients included in the present analysis were treated in clinical practice, which probably allowed for the inclusion of some patients, who, because of poor PS, were excluded from the clinical trials of docetaxel used for the development of the DiM score. This could partially explain the worse outcome of the worst category in the present series. Consequently, our indirect comparison did not allow for a robust definition of the absolute benefit associated with ICIs in the different prognostic groups. Furthermore, it is important to emphasize that the score remains prognostic, rather than predictive. Finally, despite the poor outcomes, we cannot exclude that ICIs are also associated with activity and efficacy in the group of patients with the worst prognosis. However, the absolute outcomes in that group have undoubtedly been poor, and an honest and serious reflection is required on the cost-effectiveness of treatment with ICIs for these patients.

In addition to clinical factors, multiple inflammatory markers have recently been investigated as possible prognostic and predictive biomarkers owing to their easy accessibility and limited testing costs.
The role of peripheral immune cells, through routine blood parameters, was recently studied in patients treated with ICIs. The neutrophil/lymphocyte ratio (NLR) has been the most studied because it better reflects the balance between protumor and anti-tumor activity of the host immune system. Both Jiang et al. and Cao et al. reported that a greater baseline and post-treatment NLR was associated with poor PFS and OS.

The assessment of different biomarkers in a single predictive or prognostic score could allow for the identification of patients who will have a survival benefit from ICIs. Many immune-based scores were studied using clinical characteristics and blood biomarkers, such as iSEND (immunotherapy, sex, ECOG, NLR, delta NLR). ALI (advanced lung cancer inflammation index), LIPI (lung immune prognostic index), SII (systemic inflammation index), and AISI (aggregate index of systemic inflammation). All these scores included the NLR and most had included lactate dehydrogenase and the ECOG PS. Similar to our study, they identified different predictive or prognostic groups that were significantly associated statistically with a progressively worse PFS or OS. As confirmed in our multivariate analysis, the presence of baseline liver metastases and heavy smoker status (≥ 40 pack-years) have a relevant association with a worse prognosis. In the present analysis, our aim was to validate the prognostic role of the DiM score for patients receiving IO. However, liver metastases and smoking status were not among the factors evaluated for the development of the DiM score. However, the prognostic ability in this setting could be improved by including additional clinical and biologic factors. This was recently demonstrated in another study from our group. A score termed EPSillon was created and then validated, which included 5 different prognostic parameters (i.e., NLR, lactate dehydrogenase, smoking status, ECOG PS, and liver metastases).

A major limitation of our study, just as for other recent studies that have tried to propose prognostic or predictive scores in patients treated with ICIs, was its retrospective nature, without a control group of patients who had not received ICIs. A control arm is necessary to assess the real predictive role of a marker or score. Moreover, the present study lacked the PD-L1 status of the patients included in the present analysis because, for some patients receiving ICIs within the expanded access program, PD-L1 tests were not required, especially in the beginning. Thus, its correlation with clinical factors was impossible. Moreover, when we compared the population between the 2 centers, some statistically significant differences were found. For example, in C1, more women had been included compared with C2. This was probably because the smoking-related incidence of lung cancer in women increased in northern Italy (C1) compared with that in southern Italy (C2). This could also be the reason for treating more patients with stage III in C2 than in C1. Another difference was found among the patients with ECOG PS 2, which was more often present. This was probably because of the more accurate selection of patients within clinical trials (more frequent in C1) compared with those included in the Expanded Access Program (more frequent in C2). Adenocarcinoma was more common in C1 than in C2, probably because more female patients were included in C1 with a younger median age (65 vs. 67 years). The latter could also be the reason patients presented with more central nervous system, liver, and bone metastases at baseline before treatment using ICIs.

Finally, to the best of our knowledge, the present study is the first to apply a score originally developed for patients receiving CHT to a series of patients receiving IO to allow for an indirect comparison between these 2 treatments in different prognostic groups. Given the simple use, this score could be readily integrated into routine clinical practice, helping clinicians in decision-making.

Conclusions

The DiM score, generated using data from patients treated with 2L CHT, is also able to predict the prognosis of patients treated with ICIs. We recognize that, given the absence of a control group, its value remains prognostic, rather than predictive, for the efficacy of IO. However, these results showed that patients within the worst category (poor clinical factors) had a short absolute life expectancy and probably would not benefit from any active systemic therapy, regardless of the treatment type. Reasonably, for this subset of patients, best supportive care could be the best choice. Regardless, integrating a composite biomarker (clinical and laboratory factors with molecular and PD-L1 status) is necessary for these patients, because the use of ICIs could even have a detrimental effect.

Clinical Practice Points

- The development of prognostic or predictive biomarkers of the response to IO continues to be a great interest.
- The use of a combination of biomarkers, rather than that of a single biomarker alone, could be a useful tool in decision making.
- DiM (a clinical prognostic score) was previously validated in patients who had received 2L CHT.
- The use of the DiM score was able to divide patients treated with 2L IO into 3 prognostic groups (best, intermediate, worst).
- The patients in the worst prognostic group did not benefit from IO or CHT; thus, best supportive care might be the best choice for these patients.

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**Supplemental Data**

Supplemental figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.jclcc.2020.01.005.

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Supplemental Data

Supplemental Figure 1  Kaplan-Meier Curve of Progression-free Survival (PFS) for Center 1 and Center 2
Supplemental Figure 2: Kaplan-Meier Curves of Overall Survival (OS) for Center 1 and Center 2

Kaplan-Meier for OS

Center
- C1
- C2
- C1-censored
- C2-censored

Overall Survival (%) vs. OS (months)