Original Article

Frailty and checkpoint inhibitor toxicity in older patients with melanoma

Cheryl P. Bruijnen, MD [1]; José J. Koldenhof, ARNP [1]; Rik J. Verheijden, BSc[1]; Frederiek van den Bos, MD, PhD[2]; Mariëlle H. Emmelot-Vonk, MD, PhD[3]; Petronella O. Witteveen, MD, PhD[1]; and Karijn P. M. Suijkerbuijk, MD, PhD[1]

BACKGROUND: Immune checkpoint inhibitors (ICIs) can cause immune-related adverse events (irAEs) that range from mild to life-threatening. Age itself does not seem to be a predictor for the occurrence of irAEs. It is unknown whether frailty plays a role in the occurrence of irAEs. Therefore, the authors assessed whether irAEs and their sequelae occur more often in frail patients than in fit patients according to the Geriatric 8 (G8) assessment. **METHODS:** Patients with melanoma aged 70 years and older who were about to start ICI therapy and were screened with the G8 assessment were enrolled in this prospective, observational study. Patients were classified by the G8 as either fit or frail. The primary outcome was the occurrence of grade ≥3 irAEs. **RESULTS:** In total, 92 patients were included for statistical analyses, 26 (29%) of whom were classified as frail. Grade ≥3 irAEs occurred in 20% of patients. There was no significant difference in the occurrence of grade ≥3 irAEs between fit and frail patients (17% vs 27%; *P* = .26). Frail patients were admitted to the hospital because of irAEs significantly more often than fit patients (29% vs 54%; *P* = .02) and showed a trend toward increased length of hospitalization (5 vs 8 days; *P* = .06) and more frequent use of immunosuppressants or ICI discontinuation for irAEs (36% vs 58%; *P* = .06). **CONCLUSIONS:** Although frailty appears to be unrelated to the occurrence of severe irAEs, it is an indicator of irAE-related adverse sequelae, such as hospital admission. Screening for frailty can be of added value in the shared decision-making process for older patients who qualify for ICI treatment. ***Cancer* 2022;128:2746-2752**. © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: frailty, Geriatric 8, immune checkpoint inhibitors, immune-related adverse events, melanoma.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have become first-line therapy in advanced stages of different tumor types, such as melanoma, nonsmall cell lung cancer, and renal cell carcinoma.[1-3] With additive evidence of efficacy in distinct subtypes of colon and breast cancer, >40% of patients with cancer are now eligible for checkpoint inhibitors.[4] Consequently, several ICI therapies, such as anti–programmed cell death 1 (anti–PD-1) and anti–programmed cell death ligand 1 (anti–PD-L1), are becoming a common practice for every oncologist.[5,6] In addition to having demonstrated superior efficacy, often with durable clinical benefits in many tumor types, the safety profile of ICI therapy generally compares favorably to that of chemotherapy and targeted therapy.[3,7] Immune-related adverse events (irAEs), the immune-mediated toxicities that occur during ICI therapy, differ from the adverse events (AEs) of other systemic antitumor therapies. AEs can affect multiple organs of the body and mostly do not resolve after discontinuation but require immunosuppressive treatment. IrAEs can be mild, allowing ICI therapy to be continued. Nevertheless, moderate-to-severe irAEs may be associated with severe declines in organ function and quality of life and can even be fatal. Consequently, these toxicities require early detection and proper management.[8] In addition to the discontinuation of ICI therapy, irAE management consists of corticosteroids and other immunosuppressants in case of steroid-refractory irAEs, which can induce significant side effects (especially in older patients), including psychosis, diabetes mellitus, myopathy, and infection.[8]

Because of the favorable safety profile of ICIs, they are considered a tolerable treatment option at an older age.[9,10] Published data do not suggest an increased rate of irAEs with age.[11-13] However, in these trials, patients older than 70 years were consistently underrepresented, and those who were included were in good health, with a good World Health Organization (WHO) performance status (PS) and without substantial comorbidity. Consequently, it seems questionable

whether these results are generalizable to the context of care in daily clinical practice. Thus there is a need to study the occurrence of irAEs in real-world older populations.

With respect to chemotherapy, it is known that age is a predictor of the occurrence of AEs.[14] In addition to age, frailty is also associated with decreased tolerance of chemotherapy.[15] To gain insight into someone's frailty, a geriatric assessment (GA) has been implemented in geriatric oncology. A GA is a multidisciplinary, multidimensional, and systematic assessment and consists of validated scales to identify impairments in the 4 geriatric domains: somatic, functional, nutritional, and psychosocial.[16] Several studies have demonstrated associations between items of the GA and the risk of toxicity during cytotoxic antitumor therapy in older patients.[17,18] Because not all patients are in need of a GA, screening methods have been developed to identify those at risk for adverse health outcomes who may benefit from a GA. Currently, several screening methods are proposed in the International Society of Geriatric Oncology guideline to select patients for a subsequent GA.[19] The Geriatric 8 (G8) is one such screening tool that has specifically been developed for older patients with cancer.[20] The G8 has consistently demonstrated good sensitivity for geriatric impairments.[19] In addition to identifying those patients who will benefit from a GA, there is evidence that the G8 can be used to predict the toxicity of treatment with chemotherapy, radiation therapy, and aromatase inhibitors.[21-24] However, to our knowledge, the predictive value of the G8 for irAEs has never been evaluated in older patients with melanoma. Therefore, the primary objective of the current study was to assess whether irAEs and their sequelae occur more often in patients who are classified as frail using the G8 than in fit patients.

MATERIALS AND METHODS

From January 2016 to January 2021, all patients aged 70 years or older who were diagnosed with melanoma, were about to start with a PD-1 inhibitor (nivolumab or pembrolizumab), and were screened with the G8 were enrolled in this prospective observational study at the University Medical Center Utrecht in the Netherlands. This study included patients with both stage III and stage IV melanoma, as defined by the American Joint Committee on Cancer 2009 classification, 7th edition.[25]

The G8 was completed by the treating physician or nurse practitioner before treatment. The G8 is an 8-item questionnaire that includes 7 items from the 18-item Mini-Nutritional Assessment (MNA) and an age-related item (ages <80, 80-85, or >85 years).[26] The total score ranges from 0 to 17. Patients were classified according to the G8 score as either *fit* (G8 score > 14) or *frail* (G8 score ≤ 14).[20] In case of an impaired G8, the patient could be referred to the geriatrician for a GA.

Baseline patient and tumor characteristics, such as age, WHO PS, tumor stage, and type of PD-1 inhibitor, were extracted from the medical records. Comorbidity was assessed using the Charlson Comorbidity Index, but points for age and malignancy were not included because these involved all patients.[27]

The severity of irAEs was graded according to the Common Terminology Criteria for Adverse Events, version 5.0.[28] The grade of toxicity was determined by the treating physician or nurse practitioner during each treatment cycle and when the patient contacted their treating physician or nurse practitioner temporarily because of irAEs. Our primary end point was a grade ≥3 irAE. Second, we reported the incidence of irAEs that required systemic immunosuppressive treatment, such as steroids, and/or led to treatment discontinuation, and those were labeled *clinically relevant irAEs*. Furthermore, we collected information about emergency department visits and hospital admissions.

The efficacy of ICI treatment in patients with unresectable stage III and IV melanoma was assessed using the best overall response (BOR) on imaging in accordance with RECIST criteria, version 1.1, as determined by the radiologist.[29] The BOR is the best response recorded from the start of treatment until the end of treatment.[29] The objective response rate (ORR) was defined as the percentage of patients with a complete response or a partial response as their BOR. This research was not considered subject to the Medical Research Involving Human Subjects Act by the Institutional Review Board of the University Medical Center Utrecht.

Statistical Analysis

Descriptive analyses were performed to report patient, tumor, and treatment characteristics. For comparisons between fit and frail patients, the χ^2 test or the Fishers exact test was used for nominal and ordinal variables, depending on the sample size of the categories. For continuous variables with a normal distribution, the Student t test was used. In case of nonnormally distributed continuous variables, the Mann-Whitney test was used. Two-sided P values ≤.05 were considered statistically significant. SPSS (Statistical Package for the Social Sciences) version 21.0 was used for the analyses.

TABLE 1. Baseline Characteristics

Variable	No. of Patients (%)			*P*
	Total, N = 92	Fit Patients, n = 66	Frail Patients, n = 26	
Sex				.18
Men	56 (61.0)	43 (65.0)	13 (50.0)	
Women	36 (39.0)	23 (35.0)	13 (50.0)	
Age at diagnosis: Median ± SD, y	76.0 ± 4.6	75.0 ± 3.6	79.0 ± 58	.02
WHO PS				.00
0	25 (27.0)	24 (36.0)	1 (4.0)	
1	55 (60.0)	34 (52.0)	21 (81.0)	
2	8 (9.0)	4 (6.0)	4 (15.0)	
Unknown	4 (4.0)	4 (6.0)	0 (0.0)	
BMI: Median ± SD, kg/m^2	25.4 ± 3.8	25.6 ± 4.0	25.1 ± 2.8	.27
CCI				.80
0	40 (44.0)	28 (42.0)	12 (46.0)	
1	31 (34.0)	21 (32.0)	10 (39.0)	
2	16 (17.0)	12 (18.0)	4 (15.0)	
≥3	5 (5.0)	5 (8.0)	0 (0.0)	
Melanoma stage[a]				
III				.31
IIIA	2 (2.0)	2 (3.0)	0 (0.0)	
IIIB	13 (14.0)	10 (15.0)	3 (12.0)	
IIIC	24 (26.0)	18 (27.0)	6 (23.0)	
IV				.06
IV M1a	11 (12.0)	8 (13.0)	3 (12.0)	
IV M1b	11 (12.0)	10 (15.0)	1 (4.0)	
IV M1c	31 (34.0)	18 (27.0)	13 (50.0)	
Brain metastases	5 (5.0)	3 (5.0)	2 (7.0)	.59
LDH >ULN [250 U/L]	19 (21.0)	11 (17.0)	8 (30.0)	.17
Type of immune checkpoint inhibitor				.64
Pembrolizumab	60 (65.0)	44 (67.0)	16 (61.0)	
Nivolumab	32 (35.0)	22 (33.0)	10 (39.0)	

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; G8, Geriatric 8; LDH, lactate dehydrogenase; SD, standard deviation; ULN, upper limit of normal; WHO PS, World Health Organization performance status.
[a]Staging was determined according to the American Joint Committee on Cancer staging manual (7th edition).

RESULTS

In total, 92 patients aged 70 years or older were enrolled in this study. Baseline patient characteristics are presented in Table 1. The median age was 76 years (range, 70-89 years). Fifty-three patients were diagnosed with a stage IV melanoma. Sixty-six patients (71%) had a G8 score >14 and were classified as fit, and 26 patients (29%) had a G8 score ≤14 and were classified as frail. In the majority of the frail patients (62%), a GA was performed. Fit patients were significantly younger and had a better WHO PS at baseline compared with frail patients. Other baseline characteristics did not differ statistically significantly between fit and frail patients. At the date of analysis, the median follow-up was 11.0 months (range, 1.0-53.0 months).

Immune-Related Adverse Events

Eighteen patients (20%) experienced grade ≥3 irAEs. There was no statistically significant difference in the occurrence of grade ≥3 irAEs between fit patients and frail patients (17% vs 27%; *P* = .26) (Table 2). Clinically relevant irAEs requiring immunosuppressants and/or leading to treatment discontinuation occurred in 39 patients (42%), including 24 fit patients (36%) and 15 frail patients (58%; *P* = .06). The clinically relevant irAEs mostly consisted of arthralgia or myalgia (n = 8), pneumonitis (n = 7), colitis (n = 5), and hepatitis (n = 5).

The frequency of discontinuation of ICI therapy did not differ between fit and frail patients, and there were no significant differences in reasons for discontinuation (toxicity, progression, or response) (Table 2). The duration of steroid use did not differ significantly between the 2 groups.

No patient died because of an irAE. The median time to the occurrence of grade ≥3 irAEs and to the occurrence of clinically relevant irAEs was 4 months for both groups (range, 1.1-6.9 and 3.2-4.8 months, respectively).

After starting the ICI, 34 patients (37%) visited the emergency department. Numerically, more frail patients (50%) visited the emergency department because of irAEs compared with fit patients (32%), although the difference was not statistically significant (*P* = .10).

TABLE 2. Summary of Immune-Related Adverse Events

Variable	Total, N = 92	Fit Patients, n = 66	Frail Patients, n = 26	P
No. of grade ≥3 irAEs (%)	18 (20.0)	11 (17.0)	7 (27.0)	.26
Clinically relevant irAE, n (%)	39 (42.0)	24 (36.0)	15 (58.0)	.06
Requiring immunosuppressants	8 (9.0)	5 (8.0)	3 (12.0)	
Discontinuation ICI	8 (9.0)	5 (8.0)	3 (12.0)	
Both	23 (25.0)	14 (21.0)	9 (35.0)	
Type of clinically relevant irAE: No. (%)				
Hepatitis	5 (7.0)	3 (6.0)	2 (8.0)	
Nephritis	3 (4.0)	0 (0.0)	3 (13.0)	
Colitis	5 (7.0)	3 (6.0)	2 (8.0)	
Pneumonitis	7 (9.0)	4 (8.0)	3 (13.0)	
Cholangitis	2 (3.0)	1 (2.0)	1 (4.0)	
Dermatitis	1 (1.0)	0 (0.0)	1 (4.0)	
Arthralgia/myalgia	8 (10.0)	7 (13.0)	1 (4.0)	
Hypophysitis	2 (3.0)	2 (4.0)	0 (0.0)	
Diabetes mellitus	1 (1.0)	0 (0.0)	1 (4.0)	
Neurologic toxicity	3 (4.0)	3 (6.0)	0 (0.0)	
No. of ICI discontinuations (%)	68 (74.0)	48 (73.0)	20 (77.0)	.68
Due to toxicity	32 (35.0)	21 (32.0)	11 (42.0)	.34
Due to progression	24 (26.0)	19 (29.0)	5 (19.0)	.35
Due to ongoing response	36 (39.0)	26 (39.0)	10 (39.0)	.93
Duration of steroid use: Median [95% CI], wk	41 [33-49]	40 [31-50]	37 [29-45]	.56
No. of emergency department visits (%)	34 (37.0)	21 (32.0)	13 (50.0)	.10
No. of emergency department visits: Median/min-max	0/0-5	0/0-5	0.5/0-5	.13
No. of hospital admissions (%)	35 (36.0)	19 (29.0)	14 (54.0)	.02
Due to toxicity	21 (23.0)	10 (15.0)	11 (42.0)	<.01
No. of hospitalizations: Median/min-max	0/0-3	0/0-3	1/0-2	.02
Duration of hospitalization: Median/min-max, d	6/2-38	5/2-30	8/4-38	.06
Time to grade ≥3 irAEs: Median [95% CI], mo	4.0 [1.1-6.9]	2.0 [0.0-5.1]	5.0 [1.6-8.4]	.97
Time to clinically relevant irAE: Median [95% CI], mo	4.0 [3.2-4.8]	4.0 [2.5-5.5]	4.0 [2.6-5.4]	.73

Abbreviations: CI, confidence interval; G8, Geriatric 8; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; max, maximum; min, minimum.

TABLE 3. Efficacy of Immune Checkpoint Inhibitor Therapy in Patients With Stage IV Melanoma

	No. of Patients (%)			
Variable	Total, N = 53	Fit Patients, n = 41	Frail Patients, n = 12	P
Best objective response				.16
Complete response	7 (14.0)	6 (18.0)	1 (6.0)	
Partial response	21 (42.0)	12 (35.0)	9 (56.0)	
Stable disease	11 (22.0)	10 (29.0)	1 (6.0)	
Progressive disease	11 (22.0)	6 (18.0)	5 (31.0)	
Clinically relevant irAE	26 (49.0)	16 (42.0)	11 (65.0)	.12
Grade ≥3 irAE	12 (23.0)	7 (19.0)	5 (29.0)	.42

Abbreviations: G8, Geriatric 8; irAE, immune-related adverse event.

Significantly more frail patients were admitted to the hospital because of irAEs compared with fit patients: 11 patients (42%) versus 19 patients (29%; $P \geq .01$). In addition, the median duration of hospitalization was nonsignificantly longer for the frail patients (8 vs 5 days; $P = .06$).

Treatment Efficacy in Patients With Stage IV Melanoma

The efficacy of ICIs was assessed in 53 patients who had stage IV melanoma only (Table 3). The majority of these patients were classified as fit according to the G8 (n = 41; 77%) and 12 patients (23%) were classified as frail.

The ORR was 56% (28 patients; 21 partial responses and 7 complete responses). Furthermore, 10 patients had stable disease as their best response. There were no statistically significant differences in the ORR between fit and frail patients (ORR, 53% vs 62%, respectively). At the time of analysis, 28 patients had progressive disease, as shown in Table 3.

DISCUSSION

In this prospective cohort study among patients with stage III and IV melanoma aged 70 years and older who received treatment with anti–PD-1 monotherapy, we observed no difference between grade ≥3 irAEs in fit and frail older patients. Nevertheless, frail patients more often experienced irAE-related sequelae, such as hospitalization, and tended to have an increased length of hospitalization. These results could be of value when counseling frail patients for ICI treatment.

With 20% grade ≥3 irAEs identified in this study, our data confirm findings from randomized controlled trials (which enrolled younger patients) demonstrating that the occurrence of grade ≥3 irAEs ranged from 9%

to 22% and that older age itself was not associated with a higher risk of irAEs.[7,30-33] Also, our observed efficacy was comparable to that reported in another real-world data study.[34-36] Therefore, chronological age alone should not cause physicians to withhold ICI treatment from older patients.

However, grade ≥3 irAEs are not the only irAEs of which one should be aware when treating older patients using ICIs. Grade <3 irAEs can result in treatment discontinuation and hospitalization, and they possibly may affect either functional status and quality of life, or treatment with immunosuppressants, or both, especially in frail patients. In our study, almost one-half of patients (42%) experienced such a *clinically relevant irAE*; and, in 35% of patients, toxicity led to treatment discontinuation. In the literature, the percentage of ICI treatment discontinuation in older patients because of toxicity is inconsistent and varies between 14% and 63%.[37-41] Studies directly comparing ICI tolerance between younger and older patients generally described more frequent discontinuation of ICI treatment because of toxicity in older patients, although this difference was not always statistically significant.[37,40,42]

We identified only 1 other study that assessed the relation between an impaired G8 and the occurrence of irAEs. Kubo et al retrospectively studied the safety of ICI in 95 patients aged 75 years and older who had nonsmall cell lung cancer and retrospectively calculated a modified G8 using data from the medical records and excluding patients with a WHO PS of 3. Those authors concluded that an impaired, modified G8 was not associated with more grade ≥2 irAEs.[43] This result is in line with our findings, although their study population differed from ours with respect to tumor type and age group.

Although the G8 was developed as a frailty screening tool to select patients who could benefit from a GA, it was not intended to be a predictive tool. The association between an impaired G8 and the occurrence of AEs was previously demonstrated for antitumor treatments other than ICI, such as chemotherapy, radiation, and aromatase inhibitors.[21-24]

The association between frailty assessed by instruments other than the G8 and the occurrence of irAEs has been explored in small studies. A small, retrospective study in 28 patients did not find an association between impairments in GA domains and the occurrence of irAEs.[44] Another study assessed whether frailty, defined by a GA or, lacking a GA, defined as having a WHO PS ≥3, a Charlson Comorbidity Index score ≥11, and/or falls in the prior 6 months, was associated with the occurrence of irAEs of any grade. The authors did not find a statistically significant difference, however, and that study was also limited by a small study population (n = 51).[39]

We found that frailty according to the G8 was associated with more hospital admissions because of irAEs and with an increased length of hospitalization. Gomes et al also described an impaired G8 as a predictor for hospital admissions in patients treated with ICIs, although only 32% of those hospital admissions were irAE-related.[37] Apparently, frailty does not influence the occurrence of an irAE; however, when an irAE occurs, it more often leads to hospital admission in frail patients compared with fit patients. This supports the finding that the management and impact of all irAEs, irrespective of grade, can be more challenging in frail patients. Further illustrating this point, Gomes et al also demonstrated that older patients had a longer duration of exposure to systemic steroids used to treat irAEs.[37] Our study indicated that frailty was not associated with a longer duration of steroid treatment.

The current study has several limitations. First, the small number of patients restricted the use of statistical analyses for identifying predictive factors of the occurrence of irAEs in older patients. With a larger sample size, a study with the goal of developing a prediction model for irAEs in older patients could be developed to explore the predictive value of individual factors incorporated into the G8 for irAEs and their sequelae. An irAE-risk stratification would help clinicians council their patients in the selection of the most appropriate treatment strategy and would provide opportunities to discuss advanced care planning when treatment is withheld. Second, only 29% of our patients were classified as frail according to the G8 score, which was lower than anticipated because most published evidence suggests percentages between 50% and 80%.[45] This is most likely because of the selection of patients treated with ICIs. Another explanation of our low rate of frail patients is the that the G8 involves multiple items about nutritional status. Almost one-half of our population consisted of patients with stage III melanoma who were receiving anti–PD-1 in the adjuvant (curative) setting. The nutritional status in this patient group is possibly better than in patients who have advanced disease, resulting in an unimpaired G8 and a classification as fit. Finally, most of the frail patients in this study underwent a GA, and a GA could lead to GA-based interventions, which may have influenced treatment outcomes.

The strength of our study is that this is the first study to prospectively assess the occurrence of irAEs in the elderly with a high risk of frailty according to the G8 in patients with melanoma. In addition to assessing the

occurrence of grade ≥3 irAEs, we also focused on the incidence of irAEs requiring immunosuppressants and/or leading to treatment discontinuation, hospital admissions, and visits to the emergency department

In conclusion, this study provides insufficient evidence that frailty, according to the G8, is associated with a higher occurrence of grade ≥3 irAEs. Nonetheless, the increased incidence of hospital admission because of irAEs in the frail group suggests that the impact of irAEs is greater in frail patients. Although frailty itself was not statistically associated with the occurrence of irAEs, providing insight into a patient's risk of frailty can aid in identifying those frail older patients with a higher risk of hospital admissions and a higher risk of the occurrence of irAEs requiring treatment with immunosuppressants and/or leading to discontinuation. Therefore, implementation of the G8 for older patients undergoing ICI treatment is feasible and should be considered. Ultimately, insight into a patient's frailty serves as a guide in making individualized treatment decisions.

FUNDING SUPPORT

CONFLICT OF INTEREST DISCLOSURES

AUTHOR CONTRIBUTIONS

Cheryl P. Bruijnen: Conceptualization, data curation, formal analysis, interpretation of the results, drafting of the article, and critically reviewing or revising the article for important intellectual content. **José J. Koldenhof:** Conceptualization, data curation, interpretation of the results, and critically reviewing or revising the article for important intellectual content. **Rik J. Verheijden:** Formal analysis, interpretation of the results, and critically reviewing or revising the article for important intellectual content. **Frederiek van den Bos:** Data analysis, interpretation of the results, drafting of the article, and critically reviewing or revising the article for important intellectual content. **Mariëlle H. Emmelot-Vonk:** Interpretation of the results and critically reviewing or revising the article for important intellectual content. **Petronella O. Witteveen:** Interpretation of the results and critically reviewing or revising the article for important intellectual content. **Karijn P. M. Suijkerbuijk:** Conceptualization, interpretation of the results, drafting of the article, and critically reviewing or revising the article for important intellectual content.

REFERENCES

1. Beaver JA, Theoret MR, Mushti S, et al. FDA approval of nivolumab for the first-line treatment of patients with BRAFV600 wild-type unresectable or metastatic melanoma. *Clin Cancer Res*. 2017;23:3479-3483. doi:10.1158/1078-0432.CCR-16-0714

2. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301. doi:10.1056/NEJMoa1716948

3. Motzer RJ, Tanner NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277-1290. doi:10.1056/NEJMoa1712126

4. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. *JAMA Netw Open*. 2019;2:e192535. doi:10.1001/jamanetworkopen.2019.2535

5. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379:2108-2121. doi:10.1056/NEJMoa1809615

6. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18:1182-1191. doi:10.1016/S1470-2045(17)30422-9

7. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16:375-384. doi:10.1016/S1470-2045(15)70076-8

8. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical practice guideline. *J Clin Oncol*. 2018;36:1714-1768. doi:10.1200/jco.2017.77.6385

9. Barlesi F, Garon EB, Kim DW, et al. Health-related quality of life in KEYNOTE-010: a phase II/III study of pembrolizumab versus docetaxel in patients with previously treated advanced, programmed death ligand 1-expressing NSCLC. *J Thorac Oncol*. 2019;14:793-801. doi:10.1016/j.jtho.2019.01.016

10. Larkin J, Minor D, D'Angelo S, et al. Overall survival in patients with advanced melanoma who received nivolumab versus investigator's choice chemotherapy in CheckMate 037: a randomized, controlled, open-label phase III trial. *J Clin Oncol*. 2018;36:383-390. doi:10.1200/JCO.2016.71.8023

11. Elias R, Morales J, Rehman Y, Khurshid H. Immune checkpoint inhibitors in older adults. *Curr Oncol Rep*. 2016;18:47. doi:10.1007/s11912-016-0534-9

12. Bastiaannet E, Battisti N, Loh PK, et al. Immunotherapy and targeted therapies in older patients with advanced melanoma; Young International Society of Geriatric Oncology review paper. *J Geriatr Oncol*. 2019;10:389-397. doi:10.1016/j.jgo.2018.06.009

13. Freeman M, Weber J. Subset analysis of the safety and efficacy of nivolumab in elderly patients with metastatic melanoma. *J Immunother Cancer*. 2015;3(suppl 2):P133. doi:10.1186/2051-1426-3-S2-P133

14. Hurria A, Mohile S, Gajra A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *J Clin Oncol*. 2016;34:2366-2371. doi:10.1200/JCO.2015.65.4327

15. Gajra A, Klepin HD, Feng T, et al. Predictors of chemotherapy dose reduction at first cycle in patients age 65 years and older with solid tumors. *J Geriatr Oncol*. 2015;6:133-140. doi:10.1016/j.jgo.2014.12.002

16. Stuck AE, Siu AL, Wieland GD, Rubenstein LZ, Adams J. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet*. 1993;342:1032-1036. doi:10.1016/0140-6736(93)92884-V

17. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. *Ann Oncol*. 2005;16:1795-1800. doi:10.1093/annonc/mdi368

18. Bruijnen CP, van Harten-Krouwel DG, Koldenhof JJ, Emmelot-Vonk MH, Witteveen PO. Predictive value of each geriatric assessment domain for older patients with cancer: a systematic review. *J Geriatr Oncol*. 2019;10:859-873. doi:10.1016/j.jgo.2019.02.010

19. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Ann Oncol*. 2015;26:288-300. doi:10.1093/annonc/mdu210

20. Bellera CA, Rainfray M, Mathoulin-Pelissier S, et al. Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol*. 2012;23:2166-2172. doi:10.1093/annonc/mdr587

21. Stokoe JM, Pearce J, Sinha R, Ring A. G8 and VES-13 scores predict chemotherapy toxicity in older patients with cancer. *J Geriatr Oncol*. 2012;3(suppl 1):S81. doi:10.1016/j.jgo.2012.10.096

22. Middelburg JG, Mast ME, de Kroon M, et al. Timed Get Up and Go Test and Geriatric 8 scores and the association with (chemo-)radiation therapy noncompliance and acute toxicity in elderly cancer patients. *Int J Radiat Oncol Biol Phys*. 2017;98:843-849. doi:10.1016/j.ijrobp.2017.01.211

23. Baitar A, Van Fraeyenhove F, Vandebroek A, et al. Geriatric screening results and the association with severe treatment toxicity after the first cycle of (radio)chemotherapy. *J Geriatr Oncol*. 2014;5:179-184. doi:10.1016/j.jgo.2013.12.004

24. Dottorini L, Catena L, Sarno I, et al. The role of Geriatric screening tool (G8) in predicting side effect in older patients during therapy with aromatase inhibitor. *J Geriatr Oncol*. 2019;10:356-358. doi:10.1016/j.jgo.2018.10.007

25. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27:6199-6206. doi:10.1200/JCO.2009.23.4799

26. Vellas B, Villars H, Abellan G, et al. Overview of the MNA—its history and challenges. *J Nutr Health Aging*. 2005;10:456-463; discussion 463-465.

27. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-383.

28. National Cancer Institute. Common Terminology Criteria for Adverse Events. Accessed July 9, 2021. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40

29. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247. doi:10.1016/j.ejca.2008.10.026

30. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2014;372:320-330. doi:10.1056/nejmoa1412082

31. Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:1480-1492. doi:10.1016/S1470-2045(18)30700-9

32. Weber JS, Hodi FS, Wolchok JD, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. *J Clin Oncol*. 2017;35:785-792. doi:10.1200/JCO.2015.66.1389

33. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378:1789-1801. doi:10.1056/nejmoa1802357

34. van Zeijl MCT, Haanen JBAG, Wouters MWJM, et al. Real-world outcomes of first-line anti-PD-1 therapy for advanced melanoma: a nationwide population-based study. *J Immunother*. 2020;43:256-264. doi:10.1097/CJI.0000000000000334

35. Shah KP, Song H, Ye F, et al. Demographic factor associated with toxicity in patients treated with anti-programmed cell death-1 therapy. *Cancer Immunol Res*. 2020;8:851-855. doi:10.1158/2326-6066.CIR-19-0986

36. Betof AS, Nipp RD, Giobbie-Hurder A, et al. Impact of age on outcomes with immunotherapy for patients with melanoma. *Oncologist*. 2017;22:963-971. doi:10.1634/theoncologist.2016-0450

37. Gomes F, Lorigan P, Woolley S, et al. A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients—the ELDERS study. *ESMO Open*. 2021;6:100042. doi:10.1016/j.esmoop.2020.100042

38. Ibrahim T, Mateus C, Baz M, Robert C. Older melanoma patients aged 75 and above retain responsiveness to anti-PD1 therapy: results of a retrospective single-institution cohort study. *Cancer Immunol Immunother*. 2018;67:1571-1578. doi:10.1007/s00262-018-2219-8

39. Archibald WJ, Victor AI, Strawderman MS, Maggiore RJ. Immune checkpoint inhibitors in older adults with melanoma or cutaneous malignancies: the Wilmot Cancer Institute experience. *J Geriatr Oncol*. 2020;11:496-502. doi:10.1016/j.jgo.2019.07.005

40. Baldini C, Martin Romano P, Voisin AL, et al. Impact of aging on immune-related adverse events generated by anti–programmed death (ligand) PD-(L)1 therapies. *Eur J Cancer*. 2020;129:71-79. doi:10.1016/j.ejca.2020.01.013

41. Nebhan CA, Cortellini A, Ma W, et al. Clinical outcomes and toxic effects of single-agent immune checkpoint inhibitors among patients aged 80 years or older with cancer: a multicenter international cohort study. *JAMA Oncol*. 2021;7:1856-1861. doi:10.1001/jamaoncol.2021.4960

42. de Glas NA, Bastiaannet E, van den Bos F, et al. Toxicity, response and survival in older patients with metastatic melanoma treated with checkpoint inhibitors. *Cancers (Basel)*. 2021;13:2826. doi:10.3390/cancers13112826

43. Kubo T, Watanabe H, Ninomiya K, et al. Immune checkpoint inhibitor efficacy and safety in older non-small cell lung cancer patients. *Jpn J Clin Oncol*. 2020;50:1447-1453. doi:10.1093/jjco/hyaa152

44. Welaya K, Loh KP, Messing S, et al. Geriatric assessment and treatment outcomes in older adults with cancer receiving immune checkpoint inhibitors. *J Geriatr Oncol*. 2020;11:523-528. doi:10.1016/j.jgo.2019.05.021

45. Baitar A, Kenis C, Moor R, et al. Implementation of geriatric assessment-based recommendations in older patients with cancer: a multicentre prospective study. *J Geriatr Oncol*. 2015;6:401-410. doi:10.1016/j.jgo.2015.07.005