

ORIGINAL RESEARCH

A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients – the ELDERS study

F. Gomes^{1,2*}, P. Lorigan^{1,3}, S. Woolley⁴, P. Foden⁵, K. Burns⁴, J. Yorke^{2,6} & F. Blackhall^{1,3}

¹Medical Oncology Department, The Christie NHS Foundation Trust, Manchester; ²Patient-Centred Research Centre, The Christie NHS Foundation Trust, Manchester; ³Division of Medical Sciences, University of Manchester, Manchester; ⁴Research & Innovation Department, The Christie NHS Foundation Trust, Manchester; ⁵Data Analytics Department, The Christie NHS Foundation Trust, Manchester; ⁶Division of Nursing, Midwifery and Social Work, University of Manchester, Manchester, UK



Available online xxx

Objective: Older cancer patients are underrepresented in the pivotal trials of checkpoint inhibitors (CPIs). This study aimed to investigate the impact of an ageing immune system on CPI-related toxicity and provide evidence for the role of geriatric assessments with CPI.

Methods: The ELDERS study is a prospective observational study with two cohorts: older (70+ years of age) and younger (<70 years of age). Patients with advanced/metastatic non-small-cell lung cancer or melanoma starting single-agent CPI were eligible. The older cohort was assessed for frailty with Geriatric-8 (G8) screening, which when positive (<15 points) was followed by a holistic set of geriatric assessments. Primary endpoint was the incidence of grade 3-5 immune-related adverse events (irAEs).

Results: One hundred and forty patients were enrolled with 43% being pretreated and pembrolizumab represented 92% of treatments on study. The older cohort had a significantly higher comorbidity burden ($P < 0.001$) and polypharmacy ($P = 0.004$). While 50% of older patients had a positive G8 screening, 60% on this frail subgroup had a performance status score of 0 or 1. There was no significant difference in the incidence of irAEs grade 3-5 between older and younger cohorts (18.6% versus 12.9%; odds ratio 1.55, confidence interval 95% 0.61-3.89; $P = 0.353$). Exposure to systemic steroids due to irAEs was numerically longer for older patients (22 versus 8 weeks; $P = 0.208$). A positive G8 screening predicted hospital admissions ($P = 0.031$) and risk of death ($P = 0.01$).

Conclusions: The use of CPI in older patients was not associated with more high-grade toxicity. The G8 screening identified a subgroup with higher risk of AEs and its implementation should be considered in the context of CPI.

Key words: immunotherapy, cancer, toxicity, elderly, ELDERS, G8

INTRODUCTION

Cancer is predominantly a disease of older people^{1,2} and it is estimated that 55% of new cases are diagnosed in people aged 65+ years.³ Older cancer patients are, however, a heterogeneous group and assessing risk–benefit for certain therapeutic strategies can be particularly challenging. Chronological age is often inadequate to reflect functional organ reserves, treatment tolerability and prognosis. Therefore, the incorporation of comprehensive geriatric assessments (CGAs) in oncology is widely advocated.

A CGA is a two-step process with a multidimensional set of geriatric assessments followed by tailored

multidisciplinary interventions to revert or optimise the problems identified. The geriatric assessments include mobility, physical status, nutritional status, psychocognitive status, socioeconomic status, functional capacity for daily life activities, comorbidity burden and polypharmacy.⁴ Ultimately, a CGA has the potential to improve patients' fitness, quality of life, estimate prognosis and risk of treatment toxicity.⁵

In order to identify vulnerable/frail cancer patients who may benefit from a CGA, screening tools such as the Geriatric-8 (G8) have been developed. This screening tool has developed for cancer patients aged 70+ years and consists of eight questions/assessments.^{6,7}

Immunotherapy with checkpoint inhibitors (CPIs) is revolutionising cancer treatment but the age-related remodelling process of the immune system (immunosenescence)⁸ may theoretically affect their efficacy and safety profile. Data on older cancer patients on CPI are encouraging but limited because this group has been under-represented in trials.⁹ This is particularly obvious in non-small-cell lung

*Correspondence to: Dr Fabio Gomes, Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX, UK. Tel: +44-0-161-446-3000

E-mail: fabio.gomes2@nhs.net (F. Gomes).

Twitter: [@FabioGomes_Go](https://twitter.com/FabioGomes_Go) (F. Gomes).

2059-7029/© 2020 The Authors. Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

cancer (NSCLC) where the pivotal trials enrolled patients on average 10 years younger than the median age of NSCLC diagnosis.¹⁰ Moreover, the pivotal trials were not designed to address the role of CPI specifically in the older or frail subgroups, nor did they incorporate geriatric assessments. In fact, geriatric assessments were developed in the setting of chemotherapy and surgery, and evidence on their role in the setting of immunotherapy is lacking.

In this context, the ELDERS study is the first prospective study designed with the aim to analyse the safety of CPI in older cancer patients, while also exploring predictive factors and the role of geriatric assessments in this setting.

PATIENTS AND METHODS

Study design

The ELDERS study was a prospective observational study with two age cohorts (1:1): older (aged 70+ years) and younger (aged <70 years). The study recruited patients with advanced/metastatic NSCLC or malignant melanoma. Those identified as eligible by their oncology teams to start single-agent CPI in any treatment line were eligible for this study. All single-agent CPIs were allowed but combination regimens were excluded. The primary endpoint was the incidence of grade 3-5 immune-related adverse events (irAEs). Secondary endpoints included investigating predictive factors for safety outcomes and the role of geriatric assessments with CPIs. Patients were recruited consecutively until each age cohort was full between October 2016 and December 2017 at The Christie NHS Foundation Trust (Manchester). Patients stopped the study due to (i) completing 12 months on study; (ii) consent withdrawal; (iii) CPI discontinuation for disease progression or (iv) death.

The study protocol was approved in the United Kingdom by the National Research Ethics Committee (ref 16/NW/0459) and sponsored by the University of Manchester. All patients provided written informed consent.

Study procedures and assessments

The safety data were collected in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.¹¹ The study-specific assessments were completed at baseline and at 3-monthly reviews (up to 4). Comorbidity and polypharmacy (≥ 5 concomitant medications) were assessed for all patients.¹² The Cumulative Illness Rating Scale adapted for Geriatrics (CIRS-G) measured the comorbidities by organ system.¹³ Geriatric assessments were performed in the older cohort at baseline and repeated at each review. These were based primarily on the G8 screening tool. A positive G8 screening (< 15 points) triggered a set of holistic geriatric assessments (which were then repeated at each subsequent review).⁷ This set of assessments was performed by trained oncologists and nurses and consisted on¹⁴ (i) Beers criteria for potentially inappropriate medications; (ii) Katz and Lawton–Brody scales for functional role on daily life activities; (iii) Holden scale and assessment on recent falls for mobility;

(iv) Mini-Nutritional Assessment for nutrition status; (v) Mini-Mental State Examination for cognition; (vi) Geriatric Depression Scale-15 for psychological status; and (vii) questions on support network and living arrangements for social evaluation.

The study did not include geriatric interventions. Any relevant results were communicated to the treating oncologist and, when appropriate, referrals were made to the primary care physician/community services.

Statistical considerations and analysis

The reported incidence of grade 3-5 irAEs with single-agent CPI varies between 10% and 25%.^{10,15-19} This study hypothesised that CPIs are associated with more grade 3-5 irAEs in older patients and defined that an increase of $> 15\%$ compared with the younger group was clinically significant. A sample size of 140 patients (70 per group) was required to detect a significantly higher incidence from 10% in the younger group to 26% in the older group with an alpha level of 0.05 and 70% power (1-beta), while accounting for two possible study withdrawals.

Patients were evaluable for all study analysis from start of CPI throughout the active study period (up to 12 months from enrolment). Predictive factors for key safety outcomes (incidence of grade 3-5 irAEs, hospital admission and hotline use) along with prognostic factors for risk of death were explored considering disease and patient characteristics (such as data from geriatric assessments). Descriptive and inferential statistical analysis were performed including univariable and multivariable analyses. Several statistical tests were used to explore correlations according to the type of variable. For all the statistical tests, a two-sided *P*-value was used and < 0.05 indicated statistical significance.

RESULTS

A total of 140 patients were eligible and successfully enrolled. Sixteen patients were ineligible after registration because a combination regimen was started ($n = 11$), the treatment plan was cancelled ($n = 4$) or due to early stage disease ($n = 1$). The median follow-up time was 6.3 months (8.5 and 5.9 months for the older and younger cohorts, respectively; $P = 0.398$). Fifty-two patients (37%) completed the planned 12 months on study. For those who stopped the study earlier, a majority (85%) stopped due to disease progression with CPI being discontinued. Consequently, while all 140 patients completed the baseline assessment, completion of the 3-monthly clinical reviews (up to 4) reduced over time. In the older cohort, 77%, 54%, 46% and 39% of patients completed the first, second, third and fourth reviews, respectively. In the younger cohort, 64%, 47%, 40% and 36% of patients completed the first, second, third and fourth reviews, respectively.

Patient characteristics

The older cohort had a significantly higher incidence of polypharmacy ($P = 0.004$) and comorbidity burden

Table 1. Baseline patient and disease characteristics			
	Older cohort (n = 70)	Younger cohort (n = 70)	P value
Age			
Median (range), years	75 (70-91)	62 (43-69)	<0.001
Sex			
Male, n (%)	41 (58.6)	44 (62.9)	0.604
Female, n (%)	29 (41.4)	26 (37.1)	
Performance status			
0, n (%)	18 (25.7)	26 (37.2)	0.166
1, n (%)	33 (47.1)	33 (47.1)	
2, n (%)	19 (27.2)	11 (15.7)	
Body mass index			
Median (range)	25.8 (17.2-40.7)	25.2 (18.0-43.6)	0.612
Comorbidity (CIRS-G/CIRS)			
Total score, median (range)	11 (2-22)	7 (0-18)	<0.001
Any grade 3 or 4, n (%)	54 (77.1)	39 (55.7)	0.008
Con meds			
Median (range)	5 (1-14)	4 (0-14)	0.007
Polypharmacy (≥ 5), n (%)	43 (61.4)	26 (37.1)	0.004
Type of cancer			
Melanoma, n (%)	33 (47.1)	31 (44.3)	0.734
NSCLC, n (%)	37 (52.9)	39 (55.7)	
TNM stage ^a			
III, n (%)	11 (15.7)	5 (7.1)	0.279
IV M1a, n (%)	16 (22.9)	17 (24.3)	
IV M1b-c, n (%)	43 (61.4)	48 (68.6)	
Number of metastatic organ sites			
Median (range)	2 (0-6)	2 (0-6)	0.999
≥ 3 , n (%)	17 (24.3)	18 (25.7)	0.845
Brain metastasis			
Present, n (%)	4 (5.7)	10 (14.3)	0.091
LDH			
Median (range)	466 (268-2829)	463 (145-2062)	0.848
Above normal range, n (%)	9 (12.9)	13 (18.6)	0.353
CPI			
Pembrolizumab, n (%)	66 (94.3)	63 (90.0)	0.784
Ipilimumab, n (%)	2 (2.9)	4 (5.8)	
Nivolumab, n (%)	1 (1.4)	1 (1.4)	
Atezolizumab, n (%)	0 (0.0)	1 (1.4)	
Durvalumab, n (%)	1 (1.4)	1 (1.4)	
Line of systemic treatment			
First, n (%)	43 (61.4)	37 (52.9)	0.593
Second, n (%)	24 (34.3)	28 (40.0)	
Third or more, n (%)	3 (4.3)	5 (7.1)	

CIRS(-G), Cumulative Illness Rating Scale (-Geriatrics); Con meds, concomitant medication; CPI, checkpoint inhibitor; LDH, lactate dehydrogenase; NSCLC, non-small-cell lung cancer.

^a American Joint Committee on Cancer (AJCC) 7th edition TNM for lung cancer/melanoma.

measured by the CIRS total score ($P < 0.001$). The incidence of grade 3-4 comorbidities was significantly higher in the older cohort (77% versus 56%; $P = 0.008$). The most commonly affected systems in the younger cohort were the respiratory and vascular, whereas those in the older cohort were the vascular and musculoskeletal. All other patient and disease characteristics were similar (Table 1).

Geriatric assessments were completed in all patients in the older cohort. Thirty-five older patients (50%) had a positive G8 screening (<15 points) and all but one were identified at the baseline assessment. The exception was a patient identified at the first 3-monthly review, due to CPI toxicity which aggravated a pre-existing mild musculoskeletal autoimmune disease. The remaining patients with negative screening (fit subgroup) at baseline remained negative at the subsequent reviews. Those with a positive screening (frail subgroup) were overall older ($P = 0.056$),

had a worse performance status ($P < 0.001$), a higher comorbidity burden ($P = 0.001$) and more polypharmacy ($P = 0.001$). Yet, there were no differences in cancer burden (tumour stage, number of metastatic sites and lactate dehydrogenase level). Twenty-one patients (60%) within this frail subgroup would be classed as fit if based solely on the standard performance status assessment of 0 or 1.

Following a positive geriatric screening, all these 35 patients completed a holistic set of geriatric assessments, which was repeated at each subsequent review (Figure 1). Apart from comorbidity and polypharmacy, the most commonly affected component was the capacity to perform activities of daily living in 66% of patients (Figure 2). All these patients had issues performing instrumental activities of daily living, such as shopping and cooking, but 17% of them also reported limitations with basic activities, such as eating or going to the toilet. Considering those with at least

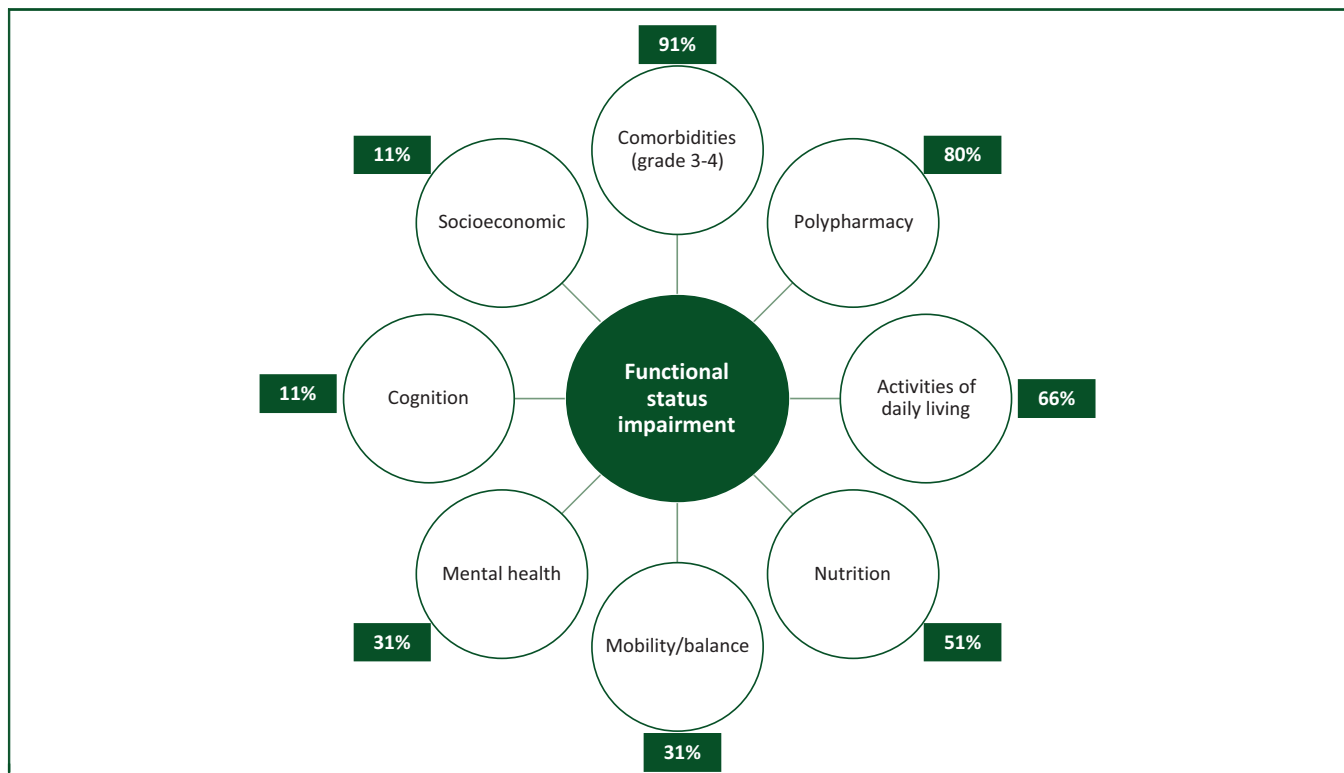


Figure 1. Geriatric assessment components linked with functional status impairment (older cohort with a positive Geriatric-8 screening, $n = 35$).

two sets of holistic geriatric assessments completed in two different timepoints throughout the study (23/35), a total of 19 patients (83%) were either stable or had an improvement in the affected component(s) where issues were identified. Any potential geriatric interventions directed at affected components occurred outside of the study protocol/site and their impact was not evaluable on this study.

Safety analysis

The incidence of grade 3-5 irAEs (primary endpoint) was not significantly higher in the older cohort compared with the younger cohort [18.6% versus 12.9%; odds ratio 1.55, confidence interval (CI) 95% 0.61-3.89; $P = 0.353$]. There was one case of toxic death (grade 5), which occurred in the older cohort and caused by pneumonitis. The incidence of any grade irAEs was not significantly higher in the older cohort (60% versus 51.4%; odds ratio 1.41, CI 95% 0.69-2.92; $P = 0.395$). The profile of irAEs was identical between both cohorts (Figure 2). The duration of exposure to systemic steroids (due to any grade irAEs) was numerically longer in the older cohort [median of 22 weeks (CI 95% 9.5-34.5) versus 8 weeks (CI 95% 5.3-10.7); $P = 0.208$]. No differences were observed in the incidence of non-irAEs or treatment discontinuation rate. Whereas older patients had a numerically higher use of the hotline telephone services (63% versus 50%, $P = 0.125$), the hospital admission rates were similar and, in most cases, due to non-irAEs (Table 2).

Considering the entire study population, no patient-related factors (age, performance status, body mass index, comorbidity burden and polypharmacy) or cancer burden

factors (TNM stage, lactate dehydrogenase level and number of metastatic sites) were predictive for key safety outcomes (incidence of irAE grade 3-5, hospital admissions and hotline use) in multivariate analysis. However, a higher comorbidity score and polypharmacy were associated with an increased risk of death ($P = 0.04$ and $P = 0.03$, respectively).

The role of geriatric assessments

Considering the older cohort, a positive G8 screening was a predictor for hospital admissions ($P = 0.031$) in multivariate analysis. Among those with positive screening (frail subgroup), only 32% of admissions were treatment related. The remaining admissions were due to other non-irAEs (such as infections, thrombotic events, falls, pain), whereas for those with a negative screening (fit subgroup), 58% of admissions were treatment related. A positive G8 screening was also associated with higher risk of death ($P = 0.01$). For those who completed the holistic set of geriatric assessments, no signal was identified, suggesting that one particular impaired component determined a higher risk for safety outcomes or a worse prognosis.

DISCUSSION

The ELDERS study was a negative superiority study, finding no evidence that the incidence of grade 3-5 irAEs with CPI was higher in older cancer patients. While the study was designed to identify a clinically meaningful difference in high-grade toxicity for older patients, there was a limitation in its scope at a 15% difference and in the study power to

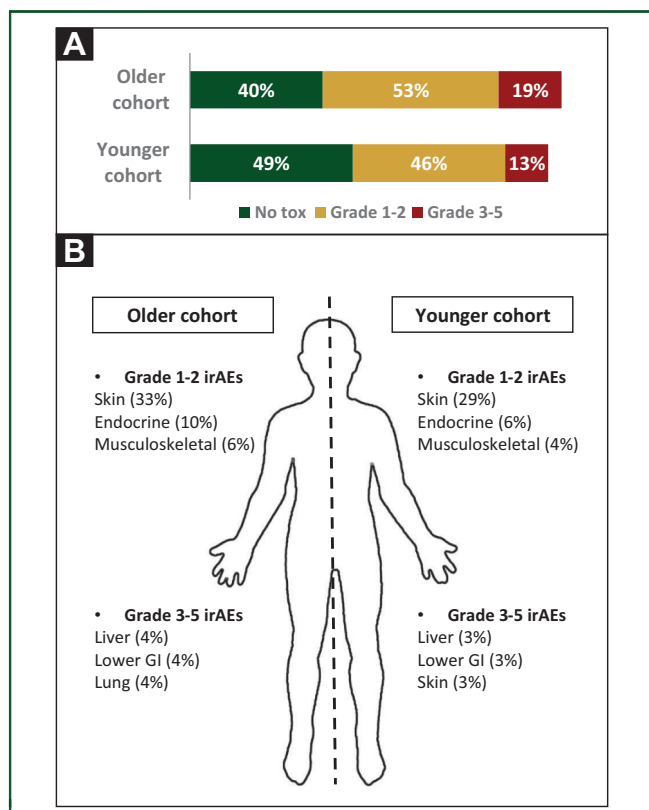


Figure 2. Distribution of immune-related toxicity. (A) Cumulative incidence of toxicity grading per age cohort; (B) incidence of the most common toxicities per grade and age cohort. GI, gastrointestinal; irAEs, immune-related adverse events; tox, toxicity.

detect it. Yet, looking beyond the incidence of high-grade toxicity, the management of immune toxicity can be more challenging in older patients. The use of systemic steroids or other immunomodulators, particularly if used for long periods, may have significant consequences. It may lead to decompensation of pre-existing diseases and iatrogenic events such as corticosteroid-induced psychosis, diabetes mellitus worsening, infections caused by atypical pathogens, myopathy and pathologic fractures. Therefore, we may underestimate the impact of irAEs particularly in the more vulnerable and older patients.

Similarly, a recent study²⁰ focusing on a large cohort of patients on single-agent CPI included in a pharmacovigilance registry did not find evidence of a higher risk of grade 3-5 toxicity in older patients. However, it did find a higher incidence of grade 2-4 toxicity which was driven by grade 2 toxicity and such patients had more often multiple toxicities. This highlights the risks and challenges beyond high-grade toxicity.

Chronological age has limited value to predict safety outcomes or prognosis, and standard fitness assessments, such as performance status, are less reliable to assess the functional level of older patients.²¹ This highlights the importance of implementing geriatric assessments to better select older patients according to treatment tolerance and care outcomes. The fact that the study cohorts were defined exclusively based on a chronological age cut-off is debatable. However, the 70 years cut-off was defined based on

Table 2. Summary of safety data

	Older cohort (n = 70)	Younger cohort (n = 70)	P value
irAEs incidence			
irAEs any grade, n (%)	42 (60.0)	36 (51.4)	0.395
irAEs grade 3-5, n (%)	13 (18.6)	9 (12.9)	0.353
Toxic death, n (%)	1 (1.4)	0 (0.0)	0.999
CPI discontinuation (toxicity related)			
n (%)	13 (18.6)	10 (14.3)	0.494
Immunosuppressants use (PO/IV)			
Steroids, n (%)	20 (28.6)	17 (24.3)	0.565
Median duration, weeks (range)	22 (1-32)	8 (1-52)	0.208
Infliximab, n (%)	1 (1.4)	1 (1.4)	0.999
Mycophenolate, n (%)	2 (2.9)	2 (2.9)	0.999
AEs incidence			
AEs grade 3-5, n (%)	19 (27.1)	16 (22.9)	0.558
Hospital admission			
n (%)	34 (48.6)	35 (50.0)	0.866
Hospital admission causes			
irAE related, n (%)	14 (20.0)	10 (14.3)	0.369
Other causes, n (%)	27 (38.6)	25 (35.7)	0.726
Hospital hotline use			
n (%)	44 (62.9)	35 (50.0)	0.125

CPI, checkpoint inhibitor; irAEs, immune-related adverse events; IV, intravenous; PO, per os.

the population in which the G8 screening tool was validated along with other studies implementing geriatric assessments.^{7,14}

While no predictive factors for irAEs were identified in this study, a positive G8 screening (frail subgroup) was a predictor of hospital admission. However, most admissions were not CPI related, instead cancer and comorbidity related. Moreover, a positive G8 screening was prognostic for risk of death, along with comorbidity burden and polypharmacy. Ultimately, half of the older cohort screened positive but this rate was lower than anticipated, as most published evidence suggests a rate of around 70%.^{7,22} This highlights a study limitation concerning a possible selection bias favouring fit patients. However, this may have been partially driven by limitations in the access to CPI, which in the case of the NSCLC population is only approved for public funding in the UK for patients with performance status score of 0 or 1.

For those patients who underwent a holistic set of geriatric assessments following a positive G8 screening, the problems identified might have been unnoticed otherwise. The most commonly identified issues were nutritional and the role function impairments on daily living activities, similarly to the published literature.²³ This study was, however, limited on the physical assessment component, where muscle strength assessments such as the handgrip and the time-up-and-go test are strongly recommended but were not implemented, because the study's assessments were mostly questionnaire based. Importantly, a formal CGA requires the implementation of both these geriatric assessments and targeted interventions. While the scope of this study was the assessment phase, several subsequent interventions were performed yet outside the study protocol via referrals to community services. Ultimately, the

study was not designed to evaluate the impact of such interventions, only the value of implementing the assessments. Moreover, the results of these assessments were not meant to influence treatment decisions, as patients were identified for the study after a treatment decision was made.

Lastly, there is no universally accepted set of geriatric assessments and interventions. Thus, it is reasonable that each hospital/practice selects those more useful and feasible to deliver within their own setting. In this study, over 95% of cases with a positive G8 screening occurred at baseline, suggesting that if there is no suspicion of frailty, then it is less likely this will develop during single-agent CPI. Therefore, focusing geriatric assessments mainly at the start of CPI may be a reasonable approach if resources are limited.

In conclusion, the use of single-agent CPI in older cancer patients was not associated with a higher incidence of high-grade immune toxicity. Nonetheless, the impact of immune toxicity, even lower grade, on this subgroup of patients may be more challenging due to their comorbidity burden and reduced organ function. Therefore, while age in itself may not play a role, the overall patient fitness does and the G8 screening tool was able to identify those vulnerable/frail older patients with a higher risk of hospital admission and higher risk of death. Its implementation for patients undergoing CPI treatment is feasible in a busy clinical practice and should be considered. This, however, should be implemented with an intention to offer holistic geriatric assessments. While not all aspects contributing to a patient's frailty may be reverted with interventions, in most cases there is room for optimisation with the support of a multidisciplinary team. Ultimately, as new combination regimens with CPI make their way into our everyday standard of care, appropriate selection of older cancer patients is paramount.

ACKNOWLEDGEMENTS

The authors thank Katie Baker for assisting in the operational delivery of the study.

FUNDING

None declared.

DISCLOSURE

The authors have declared no conflicts of interest.

REFERENCES

- Extermann M. Interaction between comorbidity and cancer. *Cancer Control*. 2007;14:13-22.
- Kendal WS. Dying with cancer: the influence of age, comorbidity, and cancer site. *Cancer*. 2008;112:1354-1362.
- NIH-SEER. *Cancer of Any Site — Cancer Stat Facts*; 2019. Available at: <https://seer.cancer.gov/statfacts/>. Accessed January 8, 2021.
- Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol*. 2007;25:1824-1831.
- Mohile SG, Dale W, Somerfield MR, Hurria A. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO Guideline for Geriatric Oncology Summary. *J Oncol Pract*. 2018;14:442-446.
- Soubeyran P, Bellera CA, Gregoire F, et al. Validation of a screening test for elderly patients in oncology. *J Clin Oncol*. 2008;26:20568.
- Soubeyran P, Bellera C, Goyard J, et al. Validation of the G8 screening tool in geriatric oncology: the ONCODAGE project. *J Clin Oncol*. 2011;29:9001.
- Nikolich-Zugich J. The twilight of immunity: emerging concepts in aging of the immune system. *Nat Immunol*. 2018;19:10-19.
- Kanesvaran R, Cordoba R, Maggiore R. Immunotherapy in older adults with advanced cancers: implications for clinical decision-making and future research. *Am Soc Clin Oncol. Educ Book*. 2018;38:400-414.
- Gomes F, Tay R, Chiramel J, Califano R. The role of targeted agents and immunotherapy in older patients with non-small cell lung cancer. *Drugs Aging*. 2018;35:819-834.
- National Cancer Institute. CTCAE files. Available at: <https://evs.nci.nih.gov/ftp1/CTCAE/About.html>; 2019. Accessed January 8, 2021.
- Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. 2017;17:230.
- Miller MD, Paradis CF, Houck PR, et al. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. *Psychiatry Res*. 1992;41:237-248.
- Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32:2595-2603.
- Daste A, Domblides C, Gross-Goupil M, et al. Immune checkpoint inhibitors and elderly people: a review. *Eur J Cancer*. 2017;82:155-166.
- Chiarion Sileni V, Pigozzo J, Ascierto PA, et al. Efficacy and safety of ipilimumab in elderly patients with pretreated advanced melanoma treated at Italian centres through the expanded access programme. *J Exp Clin Cancer Res*. 2014;33:30.
- Friedman CF, Horvat TZ, Minehart J, et al. Efficacy and safety of checkpoint blockade for treatment of advanced melanoma (mel) in patients (pts) age 80 and older (80+). *J Clin Oncol*. 2016;34:10009.
- Popat S, Ardizzoni A, Ciuleanu T, et al. 1266 - Nivolumab in previously treated patients with metastatic squamous NSCLC: results of a European single-arm, phase 2 trial (CheckMate 171) including patients aged ≥ 70 years and with poor performance status. *Ann Oncol*. 2017;28(suppl_5):v460-v496 [Abstract].
- Middleton G, Barrie C, Barone G, et al. 4342 - Pembrolizumab in performance status 2 patients with non-small-cell lung cancer (NSCLC): results of the PePS2 trial. *Ann Oncol*. 2018;29(suppl_8):viii493-viii547 [Abstract].
- 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.
- Jolly TA, Deal AM, Nyrop KA, et al. Geriatric assessment-identified deficits in older cancer patients with normal performance status. *Oncologist*. 2015;20:379-385.
- Kenis C, Bron D, Libert Y, et al. Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Ann Oncol*. 2013;24:1306-1312.
- Caillet P, Canoui-Poitrine F, Vouriot J, et al. Comprehensive geriatric assessment in the decision-making process in elderly patients with cancer: ELCAPA study. *J Clin Oncol*. 2011;29:3636-3642.