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Title: Efficacy and safety of immunotherapy in elderly patients with non-small cell lung cancer

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Keywords: Non Small Cell Lung Cancer; Immunotherapy; Elderly; Efficacy; Safety

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Abstract: Objectives Most trials with Immune Checkpoint Inhibitors (ICIs) for Non-Small Cell Lung Cancer (NSCLC) included only small subgroups of patients aged ≥65. As NSCLC is often diagnosed in patients aged ≥70, real-world data about efficacy and safety of immunotherapy (IO) in elderly patients are essential.
Materials and Methods We retrospectively collected data about all patients with advanced NSCLC treated with IO at our Institution between April 2013 and March 2019. The patients were stratified for age as follows: <70 year-old, 70-79 year-old, ≥80 year-old. Chi-square test was used to compare qualitative variables. Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves. Multivariate analyses were performed with Cox model.
Results We reviewed 290 cases, with a median age of 67 (range: 29-89). Patients aged<70, 70-79 and ≥80 year-old were 180, 94 and 16, respectively. Clinical/pathological variables were uniformly distributed across age classes, except for a higher rate of males (p 0.0228) and squamous histology (p 0.0071) in the intermediate class. Response Rate (RR) was similar across age groups (p 0.9470). Median Progression Free Survival (PFS) and Overall Survival (OS) did not differ according to age (p 0.2020 and 0.9144, respectively). Toxicity was comparable across subgroups (p 0.6493). The only variables influencing outcome were performance status (PS) (p<0.0001 for PFS, p 0.0192 for OS), number of metastatic sites (p 0.0842 for PFS, p 0.0235 for OS) and IO line (p<0.0001 for both PFS and OS).
Conclusion Advanced age was not associated to a reduced efficacy of IO in our case series. Furthermore, no toxicity concern emerged even among the eldest pts. To our opinion, ICIs should be considered irrespective of age, provided an optimal PS at baseline. Of note, IO is often the only therapeutic option applicable to these cases considering the toxicity of chemotherapy.

June, 7th 2019

Prof. Rolf Stahel, MD

Editor-in-Chief

Lung Cancer

Dear Editor,

we are pleased to submit the enclosed manuscript entitled "Efficacy and safety of immunotherapy in elderly patients with non-small cell lung cancer" to consider it for publication in *Lung Cancer.*

This is a short report about the performance of immunotherapy in our case series of elderly patients with Non-Small Cell Lung Cancer (NSCLC). In brief, we retrospectively reviewed all the patients treated with Immune Checkpoint Inhibitors (ICIs) at our Institution and we divided them into three age classes: 70, 70-79 and ≥80 year-old. When comparing data of objective response rate, progression free and overall survival, no significant differences were evidenced among these subgroups. Notably, no toxicity concerns emerged even among the eldest patients. Although previous works reported data about the use of ICIs in the elderly, we believe that this large case series, including also a quite large group of cases aged ≥80 year-old, can contribute to increase the knowledge of this topic in the specific field of NSCLC. In particular, the finding that performance status, instead of age, has a strong predictive and prognostic role during immunotherapy emphasizes the need of accurately selecting patients that are best candidate to receive ICIs even at very advanced age.

We confirm that this article has not been published previously and it is not under consideration for publication elsewhere. No funding has been received for its preparation and writing. The described research has been conducted in line with the principles of the Declaration of Helsinki and all the patients signed a written informed consent for the use of personal data. All named authors of this paper have directly participated in the elaboration and writing of the manuscript, and have read and approved the final version submitted. Authors' conflicts of interest are reported in the appropriate section of the manuscript.

We hope that this research will be of interest to your readership. We look forward to your comments regarding our submission. Should you have any concern regarding this article, please do not hesitate to contact us.

On behalf of the authors,

Yours faithfully,

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***Detailed Response to Reviewers**

August 13th, 2019

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Dear "Lung Cancer" Editorial Office,

Dear Reviewer,

Thank you for your comments.

We modified the text of the manuscript LUNGCANCER-D-19-00747 according to your observations as follows:

 # Reviewer 1:

1) *"I just want to outline the last sentence of the conclusion: <<Of note, IO is often the only therapeutic option applicable to these cases considering the toxicity of chemotherapy>>. I don't think that we can conclude that at the end of this study. The authors should limit their conclusion to the fact that IO should be considered irrespective of age, provided an optimal PS at baseline."*

   Author's response: We agree with this comment. We eliminated the sentence from the revised manuscript.

   REFERENCE IN THE TEXT → page 7, lines 164-167.

2) *"This is the same comment page 5 for this sentence: <<Furthermore, the general fair tolerability of IO renders this treatment option a chance for elderly people, who are often unsuited for chemotherapy due to frailty and comorbidities>>. It is not demonstrated that IO is superior to chemo or even allow to achieve a benefit in a population considered as unsuited for chemo because of frailty and comorbidities."*

   Author's response: Again, we agree with this comment and amended the manuscript consequently.

   REFERENCE IN THE TEXT → pages 3, lines 60-61.

3) *"In the discussion, the authors should oultline the fact that patients were not geriatrically characterized. This is a limit of this study.Concerning the toxicities, the authors should add a sentence explaining that due to its retrospective aspect, perhaps that report of toxicities especilaly of low grades could not have been exhaustive."*

Author's response: We added a paragraph making clear the limitation of the study, particularly referring to the points raised in this comment.

REFERENCE IN THE TEXT → page 7, lines 155-161.

We sincerely believe that these changes bettered our manuscript.

We hope that the result will satisfy your requests and we make ourselves fully available to further changes.

We precise that all the authors approved manuscript adjustments.

Thanking you in advance for your consideration,

Yours sincerely

Dr. Giulia Galli

Highlights

- Data about immunotherapy (IO) in elderly patients with Non-Small Cell Lung Cancer (NSCLC) are few
- We divided our series of NSCLC patients treated with IO as follows: <70 , 70-79, ≥80 year-old
- We found no difference in response rate, progression free survival and overall survival
- The incidence of moderate/severe adverse events was similar in the three subgroups
- We confirm that IO can be a safe and effective option for elderly patients with advanced NSCLC

***Revised manuscript with changes made but not highlighted (i.e. a clean version)**

Efficacy and safety of immunotherapy in elderly patients with non-small cell lung cancer

Giulia Galli[1], Alessandro De Toma[1], Filippo Pagani[1], Giovanni Randon[1], Benedetta Trevisan[1], Arsela Prelaj[1], Roberto Ferrara[1], Claudia Proto[1], Diego Signorelli[1], Monica Ganzinelli[1], Nicoletta Zilembo[1], Filippo de Braud[1], Marina Chiara Garassino[1], Giuseppe Lo Russo[1]

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Funding disclosure

This study did not receive any external funding.

Abstract

*Objective*s Most trials with Immune Checkpoint Inhibitors (ICIs) for Non-Small Cell Lung Cancer (NSCLC) included only small subgroups of patients aged ≥65. As NSCLC is often diagnosed in patients aged ≥70, real-world data about efficacy and safety of immunotherapy (IO) in elderly patients are essential.

Materials and Methods We retrospectively collected data about all patients with advanced NSCLC treated with IO at our Institution between April 2013 and March 2019. The patients were stratified for age as follows: <70 year-old, 70-79 year-old, ≥80 year-old. Chi-square test was used to compare qualitative variables. Survival was estimated with Kaplan-Meier method. Log-rank test was used to compare curves. Multivariate analyses were performed with Cox model.

Results We reviewed 290 cases, with a median age of 67 (range: 29-89). Patients aged<70, 70-79 and ≥80 year-old were 180, 94 and 16, respectively. Clinical/pathological variables were uniformly distributed across age classes, except for a higher rate of males (p 0.0228) and squamous histology (p 0.0071) in the intermediate class. Response Rate (RR) was similar across age groups (p 0.9470). Median Progression Free Survival (PFS) and Overall Survival (OS) did not differ according to age (p 0.2020 and 0.9144, respectively). Toxicity was comparable across subgroups (p 0.6493). The only variables influencing outcome were performance status (PS) (p<0.0001 for PFS, p 0.0192 for OS), number of metastatic sites (p 0.0842 for PFS, p 0.0235 for OS) and IO line (p<0.0001 for both PFS and OS).

Conclusion Advanced age was not associated to a reduced efficacy of IO in our case series. Furthermore, no toxicity concern emerged even among the eldest pts. To our opinion, ICIs should be considered irrespective of age, provided an optimal PS at baseline. Of note, IO is often the only therapeutic option applicable to these cases considering the toxicity of chemotherapy.

Keywords Non Small Cell Lung Cancer; Immunotherapy; Elderly; Efficacy; Safety

Introduction

Non-Small Cell Lung Cancer (NSCLC) is the second most common malignancy worldwide and its incidence increases with age, with about half of the cases diagnosed in people aged ≥70 [1].

In recent years, treatment advances have deeply changed the approach to metastatic NSCLC. In particular, several trials have proved the efficacy of immunotherapy (IO) in first and more advance lines [2]. However, despite the high incidence of NSCLC in the elderly, most trials have excluded such patients from enrolment. Recent retrospective data and some systematic reviews have tried to fill the gap of knowledge about efficacy and safety of IO in the elderly. However, most of them did not focus on a specific disease or included only a small subgroups of cases aged ≥80. Therefore, data are still scant in particular for NSCLC and for patients in the most advanced age class [3].

Given the progressive increase in median age of the global population, and the positive correlation between age and incidence of NSCLC, a deep comprehension of its effects in the elderly in a real-world setting is crucial.

We tried to address this topic, reviewing our Institutional case series of patients with advanced or metastatic NSCLC treated with IO.

Materials and Methods

Data about all consecutive patients with NSCLC treated with ICIs at Istituto Nazionale dei Tumori, Milan, Italy, between April 2013 and March 2019 were collected from Institutional database. All cases with advanced NSCLC receiving at least one administration of IO were considered eligible for the analysis.

Response Rate (RR) was evaluated through Response Evaluation Criteria for Solid Tumors (RECIST) 1.1. Toxicity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0. Performance Status (PS) was defined according to European Cooperative Oncology Group (ECOG) criteria. As PD-L1 status on tumor tissue was evaluated through different tests, it was considered as positive whenever expressed at ≥1% level at Institutional evaluation (with DAKO22C3 kit), or positive at central evaluation for patients enrolled in clinical trials.

For the purpose of the analysis, the patients were stratified according to age at the beginning of IO into three classes: <70 year-old, 70-79 year-old, ≥80 year-old.

Progression Free Survival (PFS) was calculated as the time interval between the first administration of ICI and disease progression or death for any cause, whichever came first. Overall Survival (OS) was calculated as the time interval between the first administration of ICI and death for any cause. Alive patients were right-censored at the time of last contact.

Chi square or Fisher's exact test were used to compare proportions. PFS and OS were estimated through Kaplan-Meier method. Differences between survival curves were analyzed with log-rank test. Cox proportional hazard model was applied for multivariate analysis. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

Results

A total of 290 cases were identified, with a median age of 67 (range: 29-89). One hundred eighty patients were aged <70, 94 were aged 70-79, 16 were aged ≥80. In the global population there was a slight prevalence of male gender (61.7%), and most patients were current or former smoker at the beginning of IO (80.7%). Tumor histology was non-squamous in 77.6% of cases. PD-L1 was classified as positive in 119 patients, negative in 78; in the remaining cases, the level of expression was unknown. About half of the patients had PS 1, 37.2% had PS 0 and 12.1% had PS 2 at the first administration of ICI. More than 2 sites of distant disease were documented in 166 patients at the beginning of IO. Two hundred five pts received an anti-PD1, 77 an anti-PDL1, 8 an anti-CTLA4 or a combo-IO. ICIs were globally well tolerated, as less than one third of patients developed a toxicity graded ≥2. Most clinical and pathological characteristics were uniformly distributed across age classes, except for gender and histology. In particular, a higher prevalence of male gender and squamous histology was observed in the intermediate age group (70-79 year-old patients). Patient and treatment characteristics are detailed in Table 1.

When stratifying the global population according to age, no toxicity concerns emerged even among the eldest patients. In particular, the incidence of adverse events graded ≥2 was comparable across age groups (35.8% vs 32.7% vs 37.5% for pts aged<70 vs 70-79 vs ≥80 year-old, p 0.6493).

As regards IO efficacy, no differences in Response Rate (RR) emerged between the three classes (21.5% vs 22.3% vs 18.8% for pts aged<70 vs 70-79 vs ≥80 yo, respectively; p 0.9470). Median PFS of the global population was 3.0 months (95%CI 2.57-3.75); median OS was 9.93 months (95%CI 8.26-12-11). Considering age as a continuous variable, the impact of this factor on both PFS and OS was not significant (p 0.1263 and p 0.7077, respectively). Consistently with this finding, the three classes of patients did not show significantly different outcome, median PFS being 2.8 months for patients aged <70, 3.5 months for patients aged 70-79, 2.6 months for patients aged ≥80 (p 0.2020). Corresponding median OS was 9.1 months for patients aged <70, 11.3 months for patients aged 70-79, 9.6 months for patients aged ≥80 (p 0.5154). Results were comparable after stratification for gender (p 0.516 for PFS, p 0.5154 for OS) and histology (p 0.9057 for PFS, p 0.1002 for OS), which were the variables showing an imbalance among age classes. Kaplan-Meier curves for PFS and OS according to age classes are reported in Figure 1 and 2.

At univariate analysis, the variables showing an impact on survival were PD-L1 status (p 0.0026 for PFS, p 0.0242 for OS), ECOG PS (p<0.0001 for PFS and OS), number of metastatic sites (p 0.0019 for PFS, p 0.0006 for OS) and IO line (p<0.0001 for PFS, 0.0006 for OS). Multivariate analysis confirmed an independent role on PFS for ECOG PS and IO line, on OS for ECOG PS and number of metastatic sites. Results of univariate and multivariate analyses are reported in Table 2 and 3.

Discussion

Pre-clinical data have shown that aging can induce measurable changes in some functions of systemic immunity. In particular a progressive and global remodelling of immune functions during aging involving both innate and adaptive immunity, known as immunosenescence, may potentially predict benefit from IO in NSCLC patients [4]. Mice experiments have also proved that elderly animals have a reduced variability of T cell populations, a slower lymphocyte proliferation after antigen stimulation and a reduced cytokine

secretion [5]. Furthermore, after exposure to IO, elderly mice have an increased risk of severe immune-related adverse events than young controls, due to uncontrolled release of pro-inflammatory mediators [6].

Nonetheless, data on cancer patients are less clear. Therefore, some reviews and meta-analyses have been performed with the purpose of pooling data from clinical trials. Such works have generally focused on different tumors (NSCLC, urothelial carcinoma, prostate cancer, melanoma) and compounds (nivolumab, pembrolizumab, combined IO). Their results have been concordant in showing a PFS benefit also for elderly patients treated with IO, while there was a trend towards a higher Hazard Ratio (HR) in OS as compared to younger patients, in particular for nivolumab and for NSCLC. No data have supported the suspicion of an increased incidence of toxicity among elderly patients [7].

A recent work have addressed the topic of IO in the elderly in the real-world, analyzing a cohort of squamous NSCLC patients enrolled in Italian nivolumab expanded access program. The authors have divided the patients into three groups: <65, 65-75 and >75 year-old. No differences in RR and PFS could be observed among the classes, while OS was shorter for the eldest patients as a likely consequence of comorbidities leading to death from other causes. IO was well tolerated across all age groups. The authors concluded that nivolumab appears as a safe and effective second line treatment for elderly patients with squamous NSCLC in a real-life setting [8].

Furthermore, a pooled analysis of three studies comparing pembrolizumab to chemotherapy (Keynote 024, Keynote 042 and Keynote 010) has been recently presented. Data about almost 400 NSCLC patients aged >75 have shown that IO improved OS also in the eldest cohort of the trials, irrespective of line of therapy and PD-L1 cutoff (>1% vs >50%). Elderly patients treated with IO experienced less adverse events than those receiving chemotherapy; toxicity of pembrolizumab was similar to that reported in the younger cohort of the trials [9].

In our case series, we chose to stratify the patients using different age cutoffs. Our purpose was to evaluate safety and efficacy of IO in a cohort of patients with a considerably older age than that included in most trials. Although the group of the eldest patients was quite small, we could not evidence any difference in RR, PFS and even OS. A numeric trend towards a longer survival of the intermediate class was observed, but

it was likely an effect of the small number of cases in each group. However, these slight differences were not significant. Indeed, the performance of IO was fair also for patients aged ≥80, with results that are comparable to those reported in clinical trials. Notably, a safe toxicity profile was confirmed in our case series across all age groups. This result is particularly relevant considering that literature data are scarce for patients aged ≥75 and even ≥80. A report of four patients aged >90 treated successfully and safely with IO have been recently published, but, at the best of our knowledge, this is the largest case series of NSCLC patients aged ≥80 treated with ICIs [10].

This study presents some limitation. First of all, the only estimate of patients' global functioning we could evaluate was ECOG performance status. Patients were not evaluated through a comprehensive geriatric characterization and no standardized geriatric scales were applied. This surely impairs the possibility of generalize data and compare them with other case series from different Institutions. Secondarily, the retrospective nature of the analysis may have implied an under-report of adverse events and reduced the reliability of toxicity grading.

Given such limitation, however, this single Institution experience confirms a satisfactory safety and toxicity profile of IO in elderly patients. On the contrary, a poor PS appears as a strong negative predictive and prognostic factor during treatment with ICIs. This underlines the importance of considering PS, instead of age, when evaluating patients potentially candidate to IO. Therefore, a comprehensive evaluation of each cancer patient in advanced age, with the cooperation of a specialist in geriatric medicine, considering the whole medical picture and the global functioning besides the age, should be performed when deciding if a patient is candidate or not to receive active treatment.

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***Revised manuscript highlighting changes made**

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Funding disclosure

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Abstract

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Conclusion Advanced age was not associated to a reduced efficacy of IO in our case series. Furthermore, no toxicity concern emerged even among the eldest pts. To our opinion, ICIs should be considered irrespective of age, provided an optimal PS at baseline. Of note, IO is often the only therapeutic option applicable to these cases considering the toxicity of chemotherapy.

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Introduction

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Given the progressive increase in median age of the global population, and the positive correlation between age and incidence of NSCLC, a deep comprehension of its effects in the elderly in a real-world setting is crucial. ~~Furthermore, the general fair tolerability of IO renders this treatment option a chance for elderly people, who are often unsuited for chemotherapy due to frailty and comorbidities.~~

We tried to address this topic, reviewing our Institutional case series of patients with advanced or metastatic NSCLC treated with IO.

Materials and Methods

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Chi square or Fisher's exact test were used to compare proportions. PFS and OS were estimated through Kaplan-Meier method. Differences between survival curves were analyzed with log-rank test. Cox proportional hazard model was applied for multivariate analysis. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

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At univariate analysis, the variables showing an impact on survival were PD-L1 status (p 0.0026 for PFS, p 0.0242 for OS), ECOG PS (p<0.0001 for PFS and OS), number of metastatic sites (p 0.0019 for PFS, p 0.0006 for OS) and IO line (p<0.0001 for PFS, 0.0006 for OS). Multivariate analysis confirmed an independent role on PFS for ECOG PS and IO line, on OS for ECOG PS and number of metastatic sites. Results of univariate and multivariate analyses are reported in Table 2 and 3.

Discussion

Pre-clinical data have shown that aging can induce measurable changes in some functions of systemic immunity. In particular a progressive and global remodelling of immune functions during aging involving both innate and adaptive immunity, known as immunosenescence, may potentially predict benefit from IO in NSCLC patients [4]. Mice experiments have also proved that elderly animals have a reduced variability of T cell populations, a slower lymphocyte proliferation after antigen stimulation and a reduced cytokine

secretion [5]. Furthermore, after exposure to IO, elderly mice have an increased risk of severe immune-related adverse events than young controls, due to uncontrolled release of pro-inflammatory mediators [6].

Nonetheless, data on cancer patients are less clear. Therefore, some reviews and meta-analyses have been performed with the purpose of pooling data from clinical trials. Such works have generally focused on different tumors (NSCLC, urothelial carcinoma, prostate cancer, melanoma) and compounds (nivolumab, pembrolizumab, combined IO). Their results have been concordant in showing a PFS benefit also for elderly patients treated with IO, while there was a trend towards a higher Hazard Ratio (HR) in OS as compared to younger patients, in particular for nivolumab and for NSCLC. No data have supported the suspicion of an increased incidence of toxicity among elderly patients [7].

A recent work have addressed the topic of IO in the elderly in the real-world, analyzing a cohort of squamous NSCLC patients enrolled in Italian nivolumab expanded access program. The authors have divided the patients into three groups: <65, 65-75 and >75 year-old. No differences in RR and PFS could be observed among the classes, while OS was shorter for the eldest patients as a likely consequence of comorbidities leading to death from other causes. IO was well tolerated across all age groups. The authors concluded that nivolumab appears as a safe and effective second line treatment for elderly patients with squamous NSCLC in a real-life setting [8].

Furthermore, a pooled analysis of three studies comparing pembrolizumab to chemotherapy (Keynote 024, Keynote 042 and Keynote 010) has been recently presented. Data about almost 400 NSCLC patients aged >75 have shown that IO improved OS also in the eldest cohort of the trials, irrespective of line of therapy and PD-L1 cutoff (>1% vs >50%). Elderly patients treated with IO experienced less adverse events than those receiving chemotherapy; toxicity of pembrolizumab was similar to that reported in the younger cohort of the trials [9].

In our case series, we chose to stratify the patients using different age cutoffs. Our purpose was to evaluate safety and efficacy of IO in a cohort of patients with a considerably older age than that included in most trials. Although the group of the eldest patients was quite small, we could not evidence any difference in RR, PFS and even OS. A numeric trend towards a longer survival of the intermediate class was observed, but

it was likely an effect of the small number of cases in each group. However, these slight differences were not significant. Indeed, the performance of IO was fair also for patients aged ≥80, with results that are comparable to those reported in clinical trials. Notably, a safe toxicity profile was confirmed in our case series across all age groups. This result is particularly relevant considering that literature data are scarce for patients aged ≥75 and even ≥80. A report of four patients aged >90 treated successfully and safely with IO have been recently published, but, at the best of our knowledge, this is the largest case series of NSCLC patients aged ≥80 treated with ICIs [10].

This study presents some limitation. First of all, the only estimate of patients' global functioning we could evaluate was ECOG performance status. Patients were not evaluated through a comprehensive geriatric characterization and no standardized geriatric scales were applied. This surely impairs the possibility of generalize data and compare them with other case series from different Institutions. Secondarily, the retrospective nature of the analysis may have implied an under-report of adverse events and reduced the reliability of toxicity grading.

Given such limitation, however, this single Institution experience confirms a satisfactory safety and toxicity profile of IO in elderly patients. On the contrary, a poor PS appears as a strong negative predictive and prognostic factor during treatment with ICIs. This underlines the importance of considering PS, instead of age, when evaluating patients potentially candidate to IO. ~~Considering that elderly patients commonly present comorbidities that can contra-indicate the prescription of chemotherapy or increase the risk of severe toxicity with cytotoxic treatment, IO could often become the only applicable treatment option for these cases.~~ Therefore, a comprehensive evaluation of each cancer patient in advanced age, with the cooperation of a specialist in geriatric medicine, considering the whole medical picture and the global functioning besides the age, should be performed when deciding if a patient is candidate or not to receive active treatment.

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***Conflict of Interest Statement (Word document)**

Conflict of interest statement

CP declares travel accommodations and honoraria with MSD International GmbH, BMS, Eli Lilly. DS declares travel accommodations and honoraria with AstraZeneca, MSD International GmbH, BMS. FdB provided consultation, attended advisory boards and/or provided lectures for the following organizations, from whom received honoraria or education grants: Amgen, AstraZeneca, Boehringer-Ingelheim, BMS, Eli Lilly, F. Hoffmann-La Roche, Ignyta, Merck Sharp and Dohme, Merck Serono, Novartis, Pfizer. MCG declares personal financial interests with the following organizations: AstraZeneca, MSD International GmbH, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Eli Lilly, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda; she also declares Institutional financial interests with the following organizations: Eli Lilly, MSD, Pfizer (MISP), AstraZeneca, MSD International GmbH, BMS, Boehringer Ingelheim Italia S.p.A, Celgene, Ignyta, Incyte, Inivata, MedImmune, Novartis, Pfizer, Roche, Takeda, Tiziana, Foundation Medicine; at the end, she has received research funding from the following organizations: AIRC, AIFA, Italian Moh, TRANSCAN. GLR declares travel accommodations and honoraria with AstraZeneca, MSD International GmbH, BMS, Eli Lilly. All other authors have no relevant conflicts of interest to disclose.

Tables

Table 1. Patient and treatment characteristics with Chi square test.

	Age <70, N[1] (%)	**Age 70-79, N[1] (%)**	**Age ≥80, N[1] (%)**	**Total**
Gender				
Male	102 (56.7)	63 (67.0)	14 (87.5)	179 (61.7)
Female	78 (43.3)	31 (33.0)	2 (12.5)	111 (38.3)
		p 0.0228		
Smoking status				
Current/former smoker	144 (80.0)	78 (83.0)	12 (75.0)	234 (80.7)
Never smoker	36 (20.0)	16 (17.0)	4 (25.0)	56 (19.3)
		p 0.4879		
Histology				
Squamous NSCLC[2]	31 (17.2)	32 (34.0)	2 (12.5)	65 (22.4)
Non-squamous NSCLC[2]	149 (82.8)	62 (66.0)	14 (87.5)	225 (77.6)
		p 0.0071		
PD-L1 status				
Positive	69 (38.4)	43 (45.7)	7 (43.8)	119 (41.0)
Negative	58 (32.2)	16 (17.0)	4 (25.0)	78 (26.9)
Unknown	53 (29.4)	35 (37.3)	5 (31.2)	93 (32.1)
		NA		
PS[3] ECOG				
0	74 (41.1)	32 (34.0)	2 (12.5)	108 (37.2)
1	88 (48.9)	47 (50.0)	12 (75.0)	147 (50.7)
2	18 (10.0)	15 (16.0)	2 (12.5)	35 (12.1)
		p 0.1153		
N[1] of metastatic sites				
1	74 (41.1)	44 (46.8)	6 (37.5)	124 (42.8)

≥2	106 (58.9)	50 (53.2)	10 (62.5)	166 (57.2)
	p 0.6034			
ICI[4] class				
Anti-PD1	120 (66.7)	72 (76.6)	13 (81.3)	205 (70.7)
Anti-PDL1	53 (29.4)	21 (22.3)	3 (18.8)	77 (26.5)
Combo-IO[5] or other	7 (3.9)	1 (1.1)	0 (0)	8 (2.8)
	p 0.1459			
Toxicity graded ≥2				
Yes	48 (26.7)	26 (27.7)	6 (37.5)	80 (27.6)
No	132 (73.3)	68 (72.3)	10 (62.5)	210 (72.4)
	p 0.8636			
Total	180 (62.1)	94 (32.4)	16 (5.5)	290 (100)

Table 2. Univariate and multivariate analysis for PFS and OS.

	PFS[6] (months)				**OS[7] (months)**			
	Median	*95%CI*		*p value*	*Median*	*95%CI*		*p value*
Gender								
Male	2.93	2.43	3.75	0.5168	9.57	6.97	12.10	0.5154
Female	2.99	2.34	5.13		9.93	7.83	15.17	
Smoking status								
Never smoker	2.99	1.91	5.49	0.4254	11.32	5.07	20.69	0.6830
Current/former smoker	3.16	2.57	3.82		10.23	8.26	13.39	
IO[5] agent								
Anti-PD1	2.99	2.57	3.82		9.08	7.43	11.32	
Anti-PDL1	3.31	2.01	5.62	0.0631	11.25	7.53	17.76	0.4688
Anti-CTLA4 or combo-IO[5]	2.16	1.25	3.56		14.21	3.16	24.18	

Histology								
Squamous NSCLC[2]	3.19	2.34	4.64	0.9429	7.83	5.23	11.32	0.1053
Non-squamous NSCLC[2]	2.90	2.43	3.82		10.26	8.29	13.49	
PD-L1 status								
Positive	4.44	3.13	6.65	**0.0026**	9.08	5.92	13.22	**0.0242**
Negative	2.57	1.91	3.72		13.52	9.57	24.44	
	HR	*95%CI*		*p value*	*HR*	*95%CI*		*p value*
	0.754	0.526	1.054	0.0964	0.727	0.489	1.078	0.1128
PS[3] **ECOG**								
0	5.49	3.75	7.83		21.91	13.39	24.44	
1	2.63	2.17	3.26	**<0.0001**	7.57	5.13	10.26	**<0.0001**
≥2	1.88	1.45	2.60		2.67	1.52	5.13	
	HR	*95%CI*		*p value*	*HR*	*95%CI*		*p value*
	1.610	1.236	2.097	**0.0004**	2.347	1.705	3.231	**<0.0001**
N[1] **of metastatic sites**								
1	3.82	2.99	5.13	**0.0019**	13.39	9.64	21.91	**0.0006**
≥2	2.57	2.10	2.83		7.76	5.43	10.23	
	HR	*95%CI*		*p value*	*HR*	*95%CI*		*p value*
	1.337	0.950	1.882	0.0959	1.689	1.136	2.539	**0.0098**
Line of IO[5]								
1	6.81	4.18	11.25		22.01	12.11	NR	
2	2.63	2.30	3.26	**<0.0001**	7.76	5.43	9.93	**0.0006**
≥3	1.92	1.84	2.99		8.59	5.23	13.39	
	HR	*95%CI*		*p value*	*HR*	*95%CI*		*p value*
	1.345	1.084	1.669	**0.0070**	1.151	0.888	1.492	0.2890

Table legend

[1] Number

[2] Non-Small Cell Lung Cancer

[3] Performance Status

[4] Immune Checkpoint Inhibitor

[5] Immunotherapy

[6] Progression Free Survival

[7] Overall Survival