NSCLC avanzato: malattia non-oncogene addicted. La terapia nel paziente anziano

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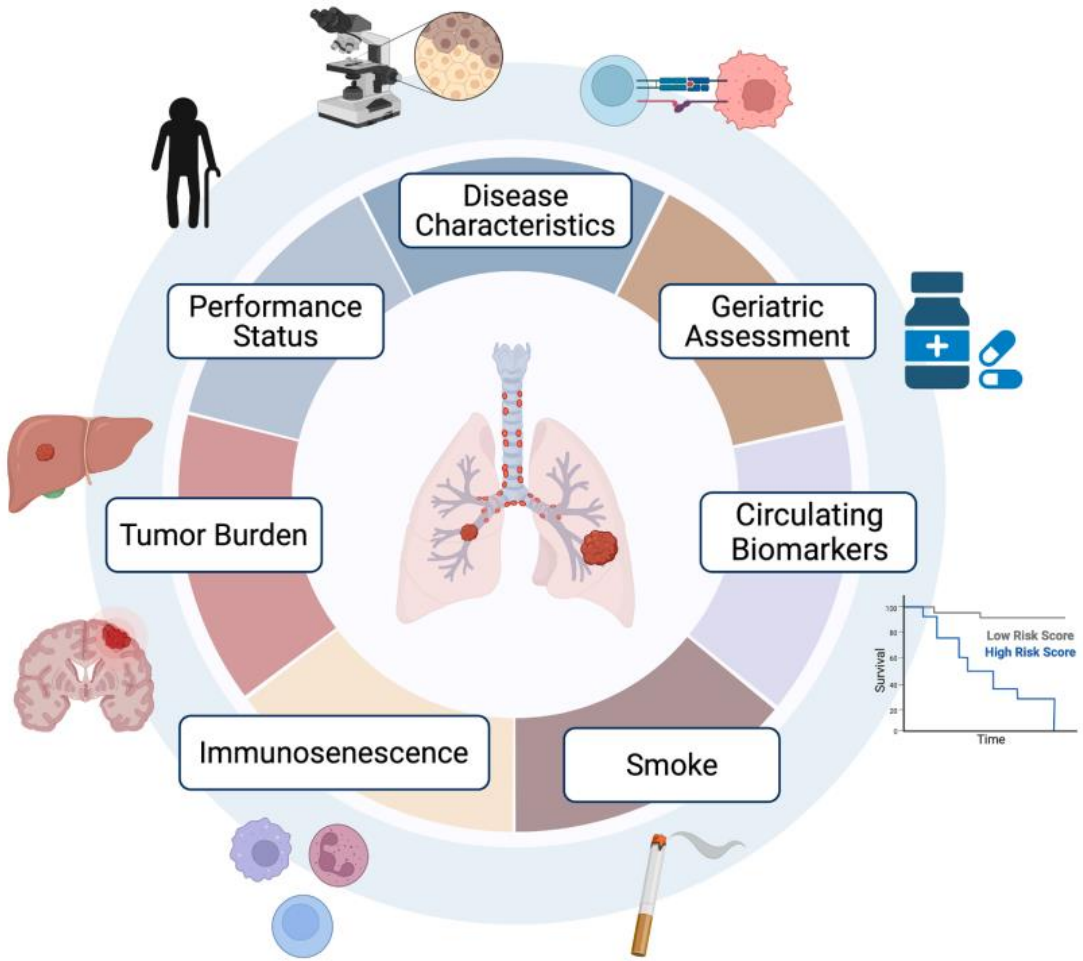
Introduction

- More than 50% of patients with NSCLC are aged above 70 yrs, and almost 10% are 80 yrs or older
- 70 years is currently the most commonly used cut-off for defining patients as elderly, but remember that “chronological age is different from functional age”
- Elderly are under-represented in clinical trials, including those with immune checkpoint inhibitors in non oncogene addicted disease
- Therefore, there is a need for more evidence showing the benefit of immunotherapy, both alone and in combination with chemotherapy/ICIs, in elderly NSCLC patients

Complexity in management of NSCLC in elderly



- They may be treated the same as younger if they have a good performance status and adequate organ funtion
- The multi-organ age-related decline, the burden of comorbidities and the polipharmacy can increase the risk of locoregional and systemic treatment
- G8 and a comprehensive geriatric assessment are useful to better customize the treatment

Tagliamento M, Cancer Treat Rev 2022

SIOG recommendations

- No SIOG guidelines on treatment of lung cancer in elderly were developed, but recommendations only exist

BJC British Journal of Cancer www.nature.com/bjc

REVIEW ARTICLE

Immunotherapy in older patients with non-small cell lung cancer: Young International Society of Geriatric Oncology position paper

Fabio Gomes[1], Melisa Wong[2], Nicolò Matteo Luca Battisti[3], Tiana Kordbacheh[4], Mandy Kiderlen[5], Alastair Greystoke[6] and Andrea Luciani[7]

British Journal of Cancer (2020) 123:874–884; https://doi.org/10.1038/s41416-020-0986-4

Gomes F, BJC 2020

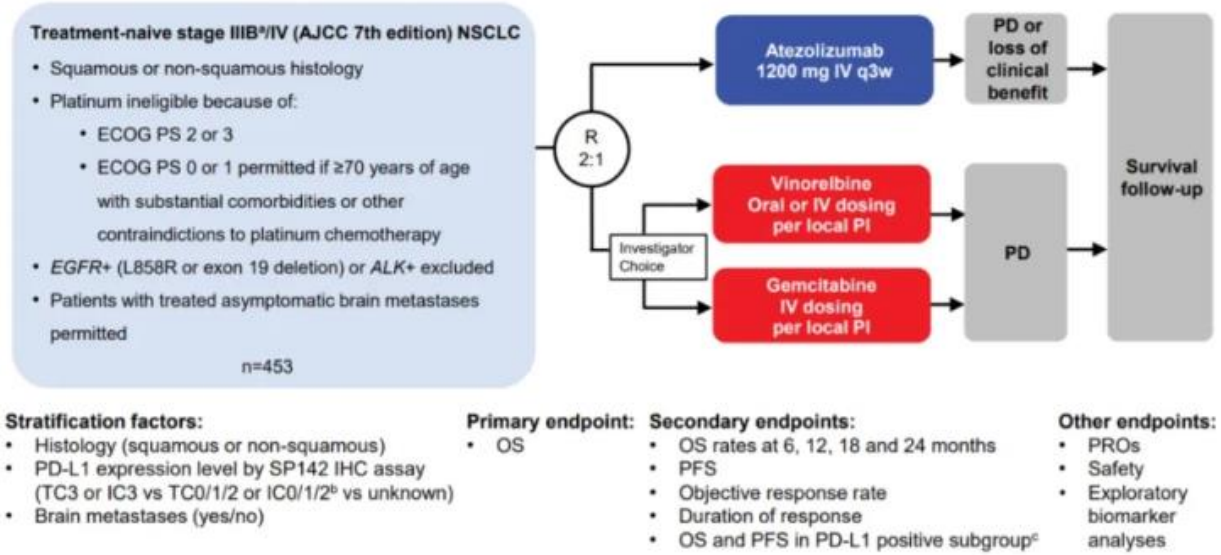
Single agent ICIs for NSCLC in elderly

Study [Ref]	Drug	Setting	Population	Age (Years)	Patients n.	OS HR (95% CI)
CM 017 [34]	Nivolumab vs. Docetaxel	2L	NSCLC squamous, PD-L1 any	<65	152	0.52 (0.35–0.75)
				≥65–75	91	0.56 (0.34–0.91)
				≥75	29	1.85 (0.76–4.51)
CM 057 [35]	Nivolumab vs. Docetaxel	2L–3L	NSCLC nonsquamous PD-L1 any	<65	333	0.81 (0.62–1.04)
				≥65–75	200	0.63 (0.45–0.89)
				≥75	43	0.90 (0.43–1.87)
KN-010 [37]	Pembrolizumab vs. Docetaxel	≥2L	NSCLC, PD-L1 ≥ 1%	<65	604	0.62 (0.52–0.65)
				≥65	429	0.80 (0.64–1.01)
OAK [38]	Atezolizumab vs. Docetaxel	2L–3L	NSCLC, PD-L1 any	<65	453	0.80 (0.64–1.00)
				≥65 yr	397	0.66 (0.52–0.83)
KN-024 [39]	Pembrolizumab vs. standard platinum doublet chemotherapy	1L	NSCLC, PD-L1 ≥ 50%	<65	141	0.60 (0.38–0.96)
				≥65	164	0.64 (0.42–0.98)
KN-042 [40]	Pembrolizumab vs. standard platinum doublet chemotherapy	1L	NSCLC, PD-L1 ≥ 1%	<65	707	0.81 (0.60–1.08)
				≥65	567	0.82 (0.66–1.01)
IMpower110 [42]	Atezolizumab vs. standard platinum doublet chemotherapy	1L	NSCLC, PD-L1 TPS ≥ 50%/TC ≥ 10	<65	102	0.72 (0.44–1.19)
				65–74	80	0.78 (0.45–1.36)
				>74	23	1.03 (0.31–3.48)
EMPOWER-Lung 1 [43]	Cemiplimab vs. standard platinum doublet chemotherapy	1L	NSCLC, PD-L1 ≥ 50%	<65	157	0.66 (0.44–1.0)
				≥65	126	0.48 (0.30–0.66)
IPSOS [44]	Atezolizumab vs. single agent Gemcitabine or Vinorelbine	1L	NSCLC, PD-L1 any	<70	123	0.75 (0.49–1.14)
				70–79	190	0.68 (0.49–0.94)
				≥80	140	0.97 (0.66–1.44)

- As monotherapy, older patients seem to derive the same benefit from ICIs than younger patients with no excess of toxicities

Montrone M, J Clin Med 2023

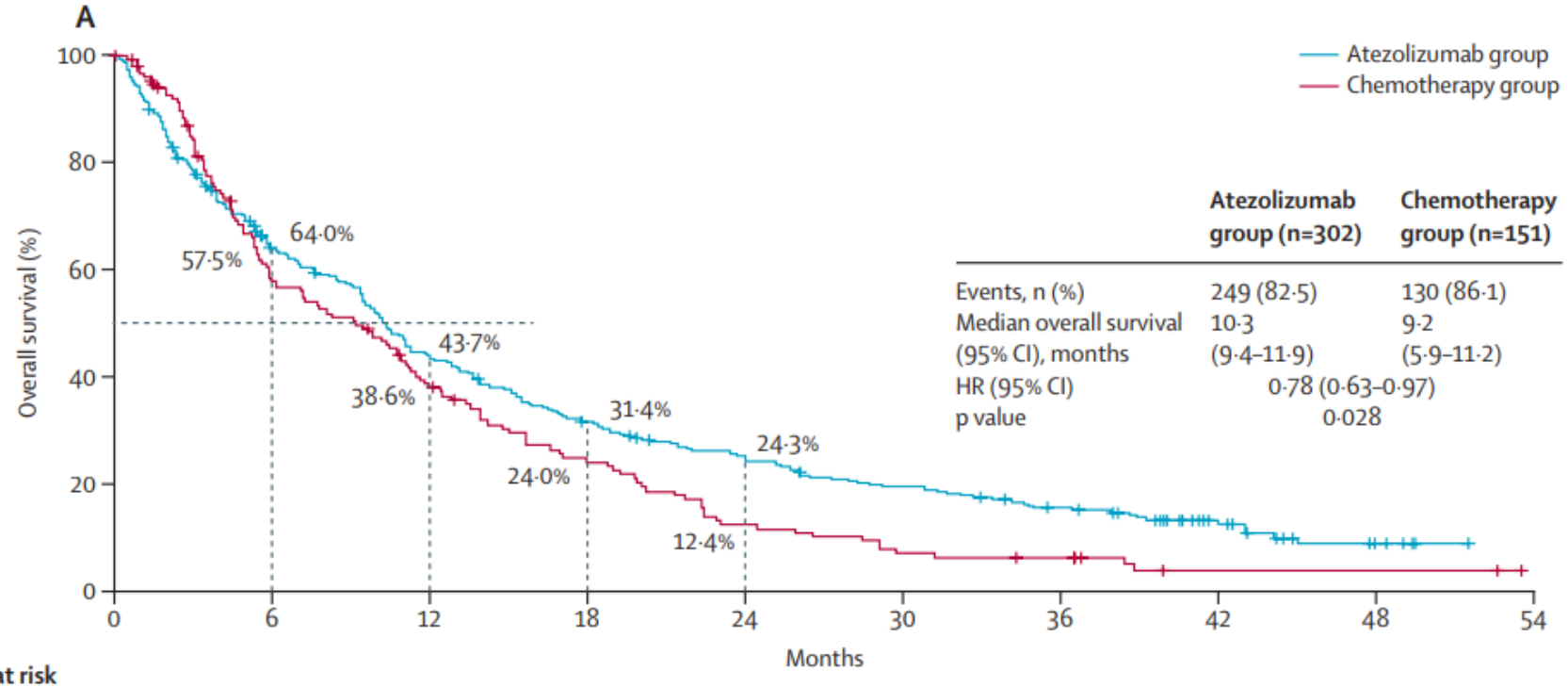
IPSOS study



	Atezolizumab (n=302)	Chemotherapy (n=151)
Age, years	75·0 (69·0–81·0)	75·0 (68·0–80·0)
Age group		
≥80 years	97 (32%)	43 (28%)
70–79 years	125 (41%)	65 (43%)
<70 years	80 (26%)	43 (28%)
Eastern Cooperative Oncology Group performance status score		
0 or 1	56 (19%)	19 (13%)
2	228 (75%)	116 (77%)
3	18 (6%)	16 (11%)
Ongoing medical conditions per patient	6·0 (3·0–9·0)	5·0 (3·0–8·0)
Patients with ≥1 ongoing medical condition	293 (97%)	146 (97%)
Respiratory, thoracic, and mediastinal disorders	198 (66%)	96 (64%)
Vascular disorders	179 (59%)	84 (56%)
Metabolism and nutrition disorders	155 (51%)	86 (57%)
Cardiac disorders	106 (35%)	51 (34%)
Musculoskeletal and connective tissue disorders	100 (33%)	54 (36%)
General disorders and administration site conditions	96 (32%)	54 (36%)
Gastrointestinal disorders	97 (32%)	30 (20%)

Lee SM, Lancet 2023

IPSOS study



	Atezolizumab group (n=302)	Chemotherapy group (n=151)
Events, n (%)	249 (82·5)	130 (86·1)
Median overall survival (95% CI), months	10·3 (9·4–11·9)	9·2 (5·9–11·2)
HR (95% CI)	0·78 (0·63–0·97)	
p value	0·028	

Number at risk (number censored)										
Atezolizumab group	302 (0)	180 (16)	122 (17)	86 (19)	64 (22)	50 (23)	37 (26)	17 (40)	5 (48)	0 (53)
Chemotherapy group	151 (0)	80 (11)	52 (13)	31 (15)	16 (15)	9 (15)	7 (16)	2 (19)	2 (19)	0 (21)

B

	Events/patients, n/N	Median overall survival, months	Events/patients, n/N	Median overall survival, months	HR (95% CI)
All patients	249/302	10·3	130/151	9·2	0·78 (0·63–0·97)
Age					
≥80 years	87/97	9·9	36/43	9·7	0·97 (0·66–1·44)
70–79 years	105/125	10·3	58/65	6·1	0·68 (0·49–0·94)
<70 years	57/80	11·9	36/43	9·8	0·75 (0·49–1·14)

Lee SM, Lancet 2023

IPSOS study

	Atezolizumab (n=302)	Chemotherapy (n=151)	Difference in overall survival rates	Stratified hazard ratio (95% CI)
Overall survival, months	10·3 (9·4 to 11·9)	9·2 (5·9 to 11·2)	..	0·78 (0·63 to 0·97)
6-month rate	64% (58·6 to 69·5)	58% (49·4 to 65·7)	6·5% (−3·3 to 16·3)	..
12-month rate	44% (37·9 to 49·4)	39% (30·5 to 46·7)	5·1% (−4·9 to 15·0)	..
18-month rate	31% (26·0 to 36·8)	24% (16·8 to 31·2)	7·4% (−1·6 to 16·5)	..
24-month rate	24% (19·3 to 29·4)	12% (6·7 to 18·0)	11·9% (4·4 to 19·5)	..
Progression-free survival, months	4·2 (3·7 to 5·5)	4·0 (2·9 to 5·4)	..	0·87 (0·70 to 1·07)
12-month rate	20% (15·0 to 24·3)	14% (8·3 to 20·0)	..	..
24-month rate	9% (5·5 to 12·2)	2% (0·0 to 3·7)	..	..
Objective response				
Objective response	51 (17%; 12·8 to 21·6)	12 (8%; 4·2 to 13·5)	..	..
Complete response	4 (1%)	0	..	..
Partial response	47 (16%)	12 (8%)	..	..
Stable disease	122 (40%)	73 (48%)	..	..
Progressive disease	67 (22%)	36 (24%)	..	..
Non-evaluable	14 (5%)	12 (8%)	..	..
Missing	48 (16%)	18 (12%)	..	..
Duration of response				
Number of responders	51	12	..	..
Median (95% CI), months	14·0 (8·1 to 20·3)	7·8 (4·8 to 9·7)	..	..

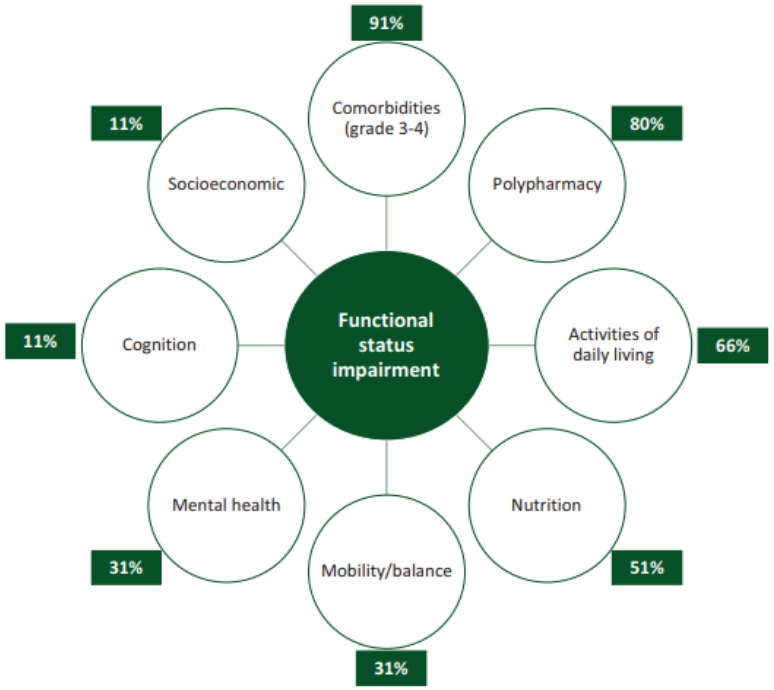
	Atezolizumab (n=300)	Chemotherapy (n=147)
All-grade adverse events	275 (92%)	143 (97%)
Treatment-related	171 (57%)	118 (80%)
Grade 3–4 adverse events	136 (45%)	71 (48%)
Treatment-related	49 (16%)	49 (33%)
Deaths	35 (12%)	13 (9%)
Treatment-related deaths	3 (1%)	4 (3%)
Serious adverse events	146 (49%)	53 (36%)
Treatment-related	35 (12%)	23 (16%)
All-grade adverse events of special interest	102 (34%)	27 (18%)
Grade 1–2	79 (26%)	24 (16%)
Grade 3–4	20 (7%)	3 (2%)
Deaths	3 (1%)	0
All-grade adverse event of special interest requiring use of corticosteroids	34 (11%)	7 (5%)
Adverse events leading to discontinuation of study drug	39 (13%)	20 (14%)
Adverse events leading to modification or interruption of study drug	96 (32%)	71 (48%)

- The median age of pts was 75 years (31% were ≥80 years) and 83% had ECOG PS 2–3.
- Thus, IPSOS provides new insights into the benefits of atezolizumab in a NSCLC population who are older, frail, or have substantial comorbidities

Lee SM, Lancet 2023

Safety of single-agent ICIs in elderly: ELDERS study

- Prospective observational study including pts with metastatic NSCLC (> 50%)
- The use of single-agent CPI in older cancer patients was not associated with a higher incidence of high grade immune toxicity; the G8 screening identified a subgroup with higher risk of AEs



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

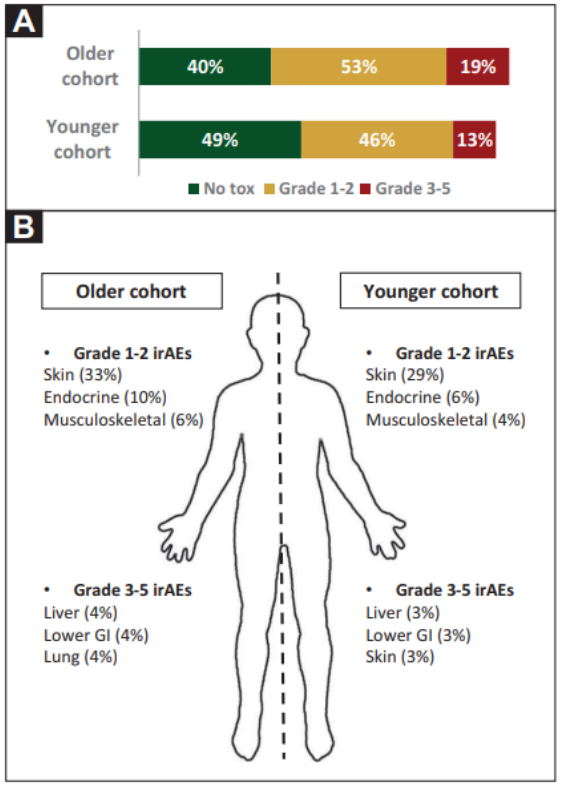


Table 2. Summary of safety data

	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

Gomes F, ESMO Open 2021

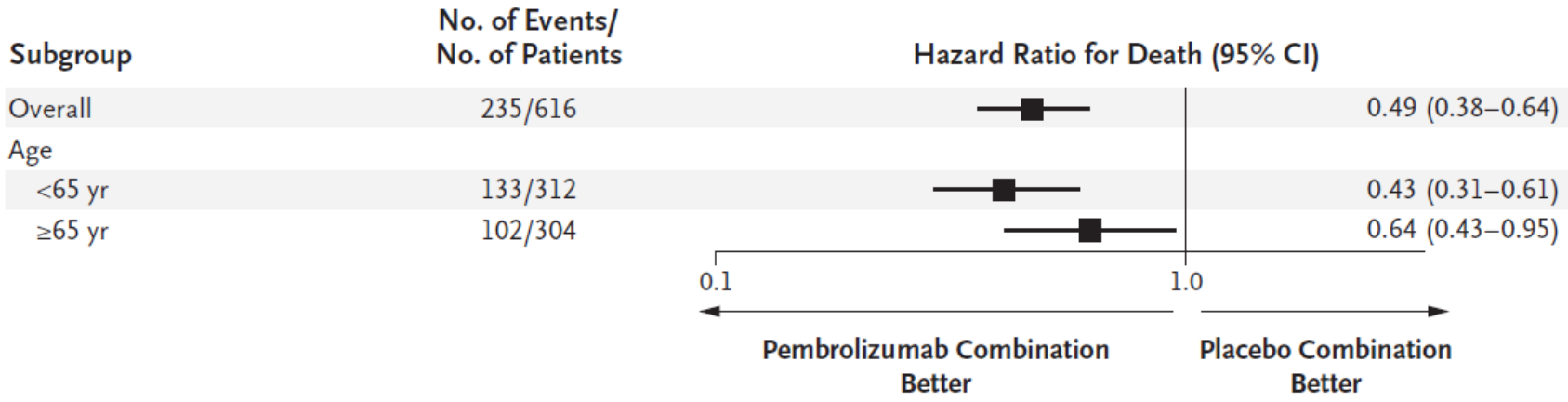
ICIs-based combinations for NSCLC in elderly

Study [Ref]	Drug	Setting	Population	Age (Years)	Patients n.	OS HR (95% CI)
KN-189 [45]	Pembrolizumab + Platinum-Pemetrexed vs. Platinum-Pemetrexed	1L	NSCLC, PD-L1 any	<65	312	0.49 (0.37–0.65)
				≥65	304	0.72 (0.54–0.97)
KN-407 [46]	Pembrolizumab + Carboplatin-(Nab)Paclitaxel vs. Carboplatin-(Nab)Paclitaxel	1L	NSCLC, PD-L1 any	<65	254	0.52 (0.34–0.80)
				≥65	305	0.74 (0.51–1.07)
EMPOWER-Lung 3 [47]	Cemiplimab + Platinum doublet chemotherapy vs. Platinum doublet chemotherapy	1L	NSCLC, PD-L1 any	<65	278	0.57 (0.40–0.81)
				≥65	188	0.88 (0.56–1.37)
IMpower131 [48]	Atezolizumab + Carboplatin-(Nab)Paclitaxel vs. Carboplatin-(Nab)Paclitaxel	1L	NSCLC squamous, PD-L1 any	<65	326	0.89 (0.68–1.15)
				65–74	279	0.84 (0.63–1.13)
				75–84	77	0.74 (0.45–1.23)
IMpower150 [49]	Atezolizumab + Carboplatin-Paclitaxel + Bevacizumab vs. Carboplatin-Paclitaxel + Bevacizumab	1L	NSCLC nonsquamous, PD-L1 any	<65	441	0.83 (0.65–1.04)
				65–74	281	0.72 (CI, 0.54–0.97)
				75–84	72	0.97 (0.58–1.62)
CM 227 [50]	Nivolumab + Ipilimumab vs. standard platinum doublet chemotherapy	1L	NSCLC, PD-L1 ≥ 1%	<65	406	0.72 (0.55–0.93)
				65–74	306	0.85 (0.64–1.13)
				≥75	81	0.95 (0.56–1.62)
CM 227 [50]	Nivolumab + Ipilimumab vs. standard platinum doublet chemotherapy	1L	NSCLC, PD-L1 < 1%	<65	205	0.70 (0.50–0.97)
				65–74	136	0.61 (0.40–0.63)
				≥75	32	0.65 (0.25–1.68)
CM 9LA [51]	Nivolumab + Ipilimumab + 2 courses chemotherapy vs. standard platinum doublet chemotherapy	1L	NSCLC, PD-L1 any	<65	354	0.64 (0.5–0.82)
				65–74	295	0.78 (0.59–1.02)
				≥75	70	1.04 (0.63–1.72)

Montrone M, J Clin Med 2023

Elderly in KN 189 study

Characteristic	Pembrolizumab Combination (N=410)	Placebo Combination (N=206)
Age		
Median (range) — yr	65.0 (34.0–84.0)	63.5 (34.0–84.0)
<65 yr — no. (%)	197 (48.0)	115 (55.8)



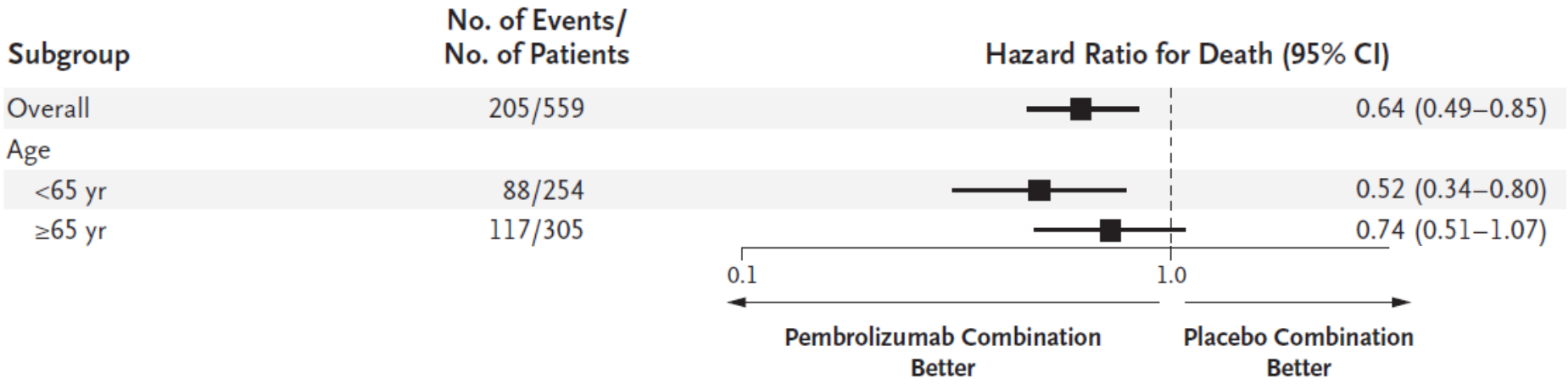
- No data are available on elderly subgroup, but patients aged ≥ 65 yrs showed OS benefit from combination similar to that reported by patients < 65 yrs

- Similarly, no data on toxicity outcomes in older patients were published

Ghandi L, NEJM 2018

Elderly in KN 407 study

Characteristic	Pembrolizumab Combination (N=278)	Placebo Combination (N=281)
Age		
Median (range) — yr	65 (29–87)	65 (36–88)
<65 yr — no. (%)	127 (45.7)	127 (45.2)

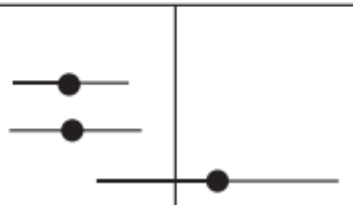


- Elderly patients did non report any statistically significant benefit in OS
- No age-specific data on toxicity are available

Paz-Ares L, NEJM 2018

Elderly in CM 9LA study

	Nivolumab plus ipilimumab with chemotherapy (two cycles)		Chemotherapy		Unstratified hazard ratio for death (95% CI)
	Events/ patients	Median overall survival, months (95% CI)	Events/ patients	Median overall survival, months (95% CI)	
Age, years					
<65	92/176	15·6 (13·4-NR)	125/178	10·7 (9·1-13·2)	0·61 (0·47–0·80)
≥65–75	70/148	19·4 (15·5-NR)	95/147	11·9 (9·0-14·1)	0·62 (0·46–0·85)
≥75	28/37	8·5 (5·6-13·5)	22/33	11·5 (5·8-19·2)	1·21 (0·69–2·12)



- Patients ≥ 75 yrs did not derive a benefit from experimental treatment

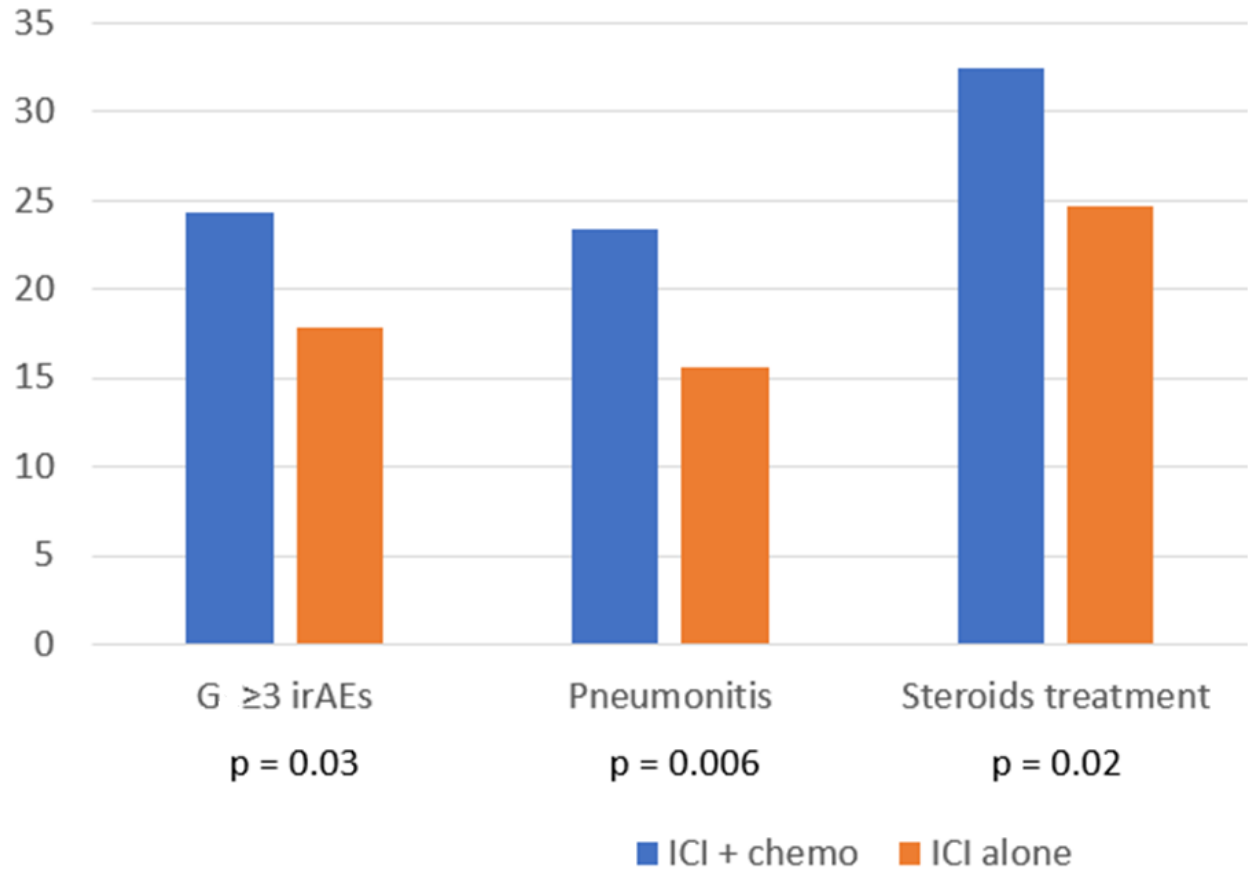
Paz-Ares L, Lancet Oncol 2021

Safety of ICIs-based combinations in elderly

- Unfortunately, aged-specific safety data are not available at this time concerning trials with combination chemotherapy plus ICIs or combination of ICIs

- A recent multicenter retrospective study enrolled 1245 pts aged ≥ 75 yrs with IIIB-IV stage, receiving ICI+chemo, ICI alone or chemo alone as first line

- Median OS was 20 mos in ICI+chemo vs 19.8 mos in ICI alone



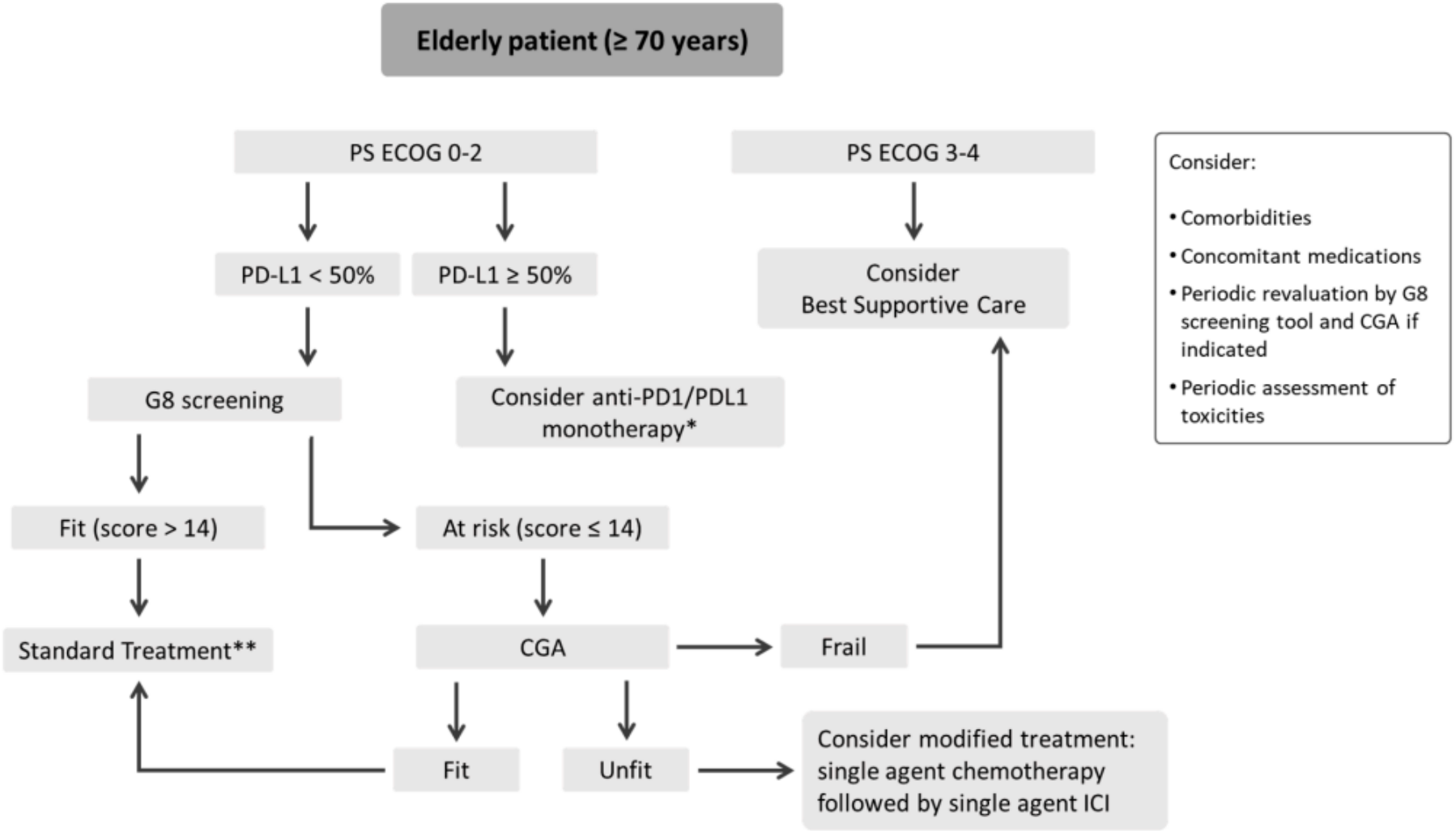
Uematsu M, Abstract ASCO 2023

Ongoing studies in elderly

Study	Population	Study design	Treatment arms	Primary endpoint
NCT03977194 (ELDERLY)	Patients with stage IIIB-IV NSCLC aged 70 to 89 years	Phase 3 randomized	Carboplatin AUC 6 day 1 + paclitaxel 90 mg/m^2 day 1, 8, 15 every 4 weeks alone (A) or with atezolizumab 1200 mg q3w (B)	OS
NCT03975114 (MILES-5)	Patients with untreated stage IIIB-IV NSCLC aged $\geq$ 70 years	Phase 2 randomized	(A) Standard chemotherapy followed at progression by durvalumab 1500 mg q4w. (B) Durvalumab 1500 mg followed at progression by chemotherapy. (C) Combination immunotherapy with durvalumab 1500 mg + tremelimumab 75 mg q4w (4 cycles) followed at progression by chemotherapy	12-month OS
NCT04533451	Patients with untreated stage IV or recurrent lung adenocarcinoma	Non-randomized, allocation at oncologist's choice	Pembrolizumab 200 mg q3w or 400 mg every 42 days alone (A) or with carboplatin AUC 5 and pemetrexed 500 mg/m^2 q3w (B)	Incidence of grade $\geq$ 3 AEs
NCT03345810 (DURATION)	Patients with metastatic NSCLC aged $\geq$ 70 years and/or with a Charlson-Comorbidity-Index > 1 and/or ECOG PS > 1 not eligible to platinum-doublet	Phase 2 randomized	(A) CARG-Score $\leq$ 3: Carboplatin AUC 5 day 1 + nab-Paclitaxel 100 mg/m2 day 1, 8 q3w. (B) CARG-Score $\leq$ 3: Carboplatin AUC day 1 + nab-Paclitaxel 100 mg/m^2 day 1, 8 q3w (2 cycles) followed by durvalumab 1125 mg q3w (2 cycles) and durvalumab maintenance 1500 mg q4w. (C) CARG-score > 3: vinorelbine 30 mg/m^2 day 1,8 (2 cycles) or gemcitabine 1000 mg/m^2 day 1, 8 (2 cycles) q3w followed by durvalumab 1125 mg q3w (2 cycles) and durvalumab maintenance 1500 mg q4w. (D) CARG-score > 3: vinorelbine 30 mg/m^2 day 1,8 or gemcitabine 1000 mg/m2 day 1, 8 q3w	Incidence of grade $\geq$ 3 treatment-related AEs

Tagliamento M, Cancer Treat Rev 2022

Ideal therapeutic algorithm for NSCLC in elderly



* G8 screening should be done also in patients with PD-L1 TPS ≥ 50%

** Chemotherapy plus immunotherapy should be considered.
The association of double ICIs plus chemotherapy should be carefully evaluated, given the loss of survival benefit in patients older than 75 years

Montrone M, J Clin Med 2023

Take home messages

- Elderly patients must not be excluded from ICIs +/- chemo treatment just for chronological age
- Oncologists should routinely use G8 and perform a CGA when required
- We need data from prospective studies to better define the role of immunotherapy alone or in combination with chemo in elderly patients

Thanks for your attention!