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Targeted therapy for older patients with an oncogene driven non-small cell lung cancer: Recommendations from a SIOG expert group

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ABSTRACT

Lung cancer is mostly a disease of aging with approximately half of newly diagnosed patients being 70 years or older. Treatment decisions in this population pose unique challenges because of their heterogeneity with regards to daily functioning, cognition, organ function, comorbidities and polypharmacy, their underrepresentation in clinical trials and the impact of treatment on patient-centered outcomes, particularly in frail patients.

The advent of targeted therapies and immunotherapy has revolutionized the management of advanced non-small cell lung cancer (NSCLC). Molecular profiling has allowed for the identification of actionable genomic alterations and targeted therapies have become standard of care for oncogene-driven NSCLC, significantly improving prognosis and quality of life. However, the data on the efficacy and tolerability of these treatments in older patients remain sparse.

This review, conducted by the International Society of Geriatric Oncology (SIOG) NSCLC task force, examines the available literature on the use of targeted therapies in patients aged 70 years or older with oncogene-driven NSCLC. The task force's expert recommendations aim to guide treatment decisions for older patients with oncogene driven NSCLC.

1. Introduction

Lung cancer is worldwide the most diagnosed cancer and the leading cause of cancer death [1]. With approximately half of newly diagnosed patients aged $\geq$ 70 years, lung cancer is mostly a disease of aging.

Treatment decisions in this older population pose different challenges. Firstly, clinical trials, mainly include younger and fitter patients and therefore there is limited knowledge on pharmacokinetics, pharmacodynamics and the effect of treatments on patient-centered outcomes including function and quality of life (QoL) in (frail) older patients [2,3,4]. Secondly, this population is heterogeneous with regards to frailty, organ reserve, co-morbidities, polypharmacy and patient expectations, implying that a more personalized approach is necessary [5,6].

With the introduction of targeted therapies and immunotherapy, treatment of advanced lung cancer has progressed rapidly [7]. Systematic molecular profiling has identified oncogene-driven non-small cell lung cancer (NSCLC) harboring genomic alterations for which targeted therapies resulted in significantly improvement of prognosis and QoL [8,9]. However, data in older patients including efficacy, tolerability and patient-centered outcomes remain scarce.

The aim of the International Society of Geriatric Oncology (SIOG)

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Table 1
Trials with EGFR tyrosine kinase inhibitors in older patients with EGFR mutant non-small cell lung cancer.

TRIALS	AGE ECOG	EFFICACY	TOXICITY
Gefitinib			
Takahashi K, 2014[29] Prospective multicenter phase II (N = 20)	Age: Inclusion: ≥70 Median 79.5; Range 72–90 ECOG: 10 % ECOG 2	ORR 70 % (95 %CI 45.7–88.1) DCR 90 % (95 %CI 68.3–98.7) mPFS 10 mo mOS 26.4 mo	AST/ALT elevation 75 % with 15 % grade 3/4 Rash 90 % Diarrhea 40 % Pneumonitis 5 % (1 patient)
Kashiwabara K, 2021[30] Retrospective monocenter (N = 22)	Age: Inclusion: ≥85 Median 88; Range 85–94 ECOG: 32 % ECOG 3–4	ORR 27 % DCR 63 % mPFS 5.3 mo mOS 12.3 mo	AST/ALT elevation 9 % Rash 9 % Diarrhea 9 % Pneumonitis 9 % (2 patients)
Tateishi K, 2013[31] Retrospective, multicenter (N = 55)	Age: Inclusion: ≥75 Median 81.1; range 75–94 ECOG 12.7 % ECOG 2 3.6 % ECOG 3–4	ORR 72.7 % (95 %CI 59.5–82.9) DCR 92.7 % (95 %CI 82–97.6) mPFS 13.8 mo (95 %CI 9.9–18.8) mOS 29.1 mo (95 %CI 22.4-NA)	ALT/AST elevation 20 % with 7.3 % grade 3/4 Rash 41.8 % Diarrhea 18.2 % Pneumonitis 5.5 % (3 patients)
Uruga H, 2010[32] Retrospective monocenter (N = 9)	Age Inclusion: ≥70 Median 79; Range 73–89 ECOG 11 % ECOG 2 11 % ECOG 3	ORR 66.7 % mPFS 12.9 mo mOS 17.1 mo	ALT/AST elevation 11.1 % Rash 44.4 % Diarrhea 22.2 % No pneumonitis
Maemondo M, 2012[33] Prospective phase II, multicenter (N = 31)	Age: Inclusion: ≥75 Mean 80.3; Range 75–89 ECOG 6 % ECOG 2	ORR 74.2 % (95 %CI 57.9–90.5) DCR 90.3 % mPFS 12.1 mo mOS 33.8 mo	AL/AST elevation 48.4 % Rash 71 % Diarrhea 38.7 % Pneumonitis 3 % (1 patient grade 5)
Corre R, 2018[34] Retrospective, multicenter (N = 114)	Age Inclusion: ≥80 Mean 83.9 28.4 % ECOG 2–3	ORR 63.3 % DCR 78.9 % mPFS 11.9 mo (95 %CI 8.6–14.7) mOS 20.9 mo (95 %CI 14.3–27.1)	Rash 66.7 % Diarrhea 56 %
Kuwako T, 2015[35] Retrospective, multicenter (N = 62)	Age: Inclusion: ≥75 Median 80; Range 75–89 7 pts ECOG 2 (11.3 %); 11 pts ECOG 3–4 (17.7 %)	ORR 61.3 % DCR 83.9 % mPFS 13.2 mo mOS 19.0 mo	ALT/AST elevation 51.6 % with 25.8 % g3/4 Rash 50 % Diarrhea 45.2 % Pneumonitis 4.8 %
Asami K, 2011[36] Prospective phase II (N = 17)	Age: Inclusion ≥ 75; Median 81, Range: 75–88 ECOG: 17 % ECOG 2	ORR 59 % (95 %CI 33–81) DCR 88 % (95 %CI 62–98) mPFS 12.9 mo mOS NR	Rash 47 % Diarrhea 12 % Stomatitis 1 % AST/ALT elevation 41 %
Fujita S, 2012[37] Prospective phase II, open-label, non randomized, multicenter (gefitinib for EGFR mutant) (N = 22 with mutation)	Age: Inclusion ≥ 70; Median 81, Range 71–85 ECOG: No ECOG ≥ 2	ORR 45.5 % (95 %CI 24.4–67.8) DCR 86.4 (95 %CI 65.1–97.1) mPFS 9.7 mo mOS 27.9 %	Rash 63.6 % Diarrhea 27.3 % ALT/AST increase 54.5–63.3 %
Erlotinib			
Inoue Y, 2015[38] Prospective phase II, multicenter (N = 32)	Age: Inclusion: ≥75; Median 80; Range 75–87 ECOG: 3.1 % ECOG 2	ORR 56.3 % (95 %CI 39.4–72) DCR 90.6 % (95 %CI 75.2–97.6) mPFS 15.5 mo (95 %CI 11.2-NR) mOS NR	Rash 81.3 % Diarrhea 50 % Decreased appetite 50 % Stomatitis 12.5 % Pneumonitis 9.4 % TA increase 37.5 %
Miyamoto S, 2020[39] Prospective phase II, multicenter (N = 80) Note: low dose erlotinib 50 mg/day	Age: Median 80, range 49–90 ECOG: 32 % ECOG ≥ 2	ORR 60 % (95 %CI 50.2–69.2) DCR 90 % (95 %CI 82.7–94.9) No difference in ORR between 3 age cohorts (57 %, 71 %, 47 %) mPFS 9.3 mo (95 %CI 7.1–11.4) mOS 26.2 mo (95 %CI 21.9–30.4) The study met its predefined criteria of efficacy on low dose erlotinib	Rash 54 % Diarrhea 27 % Stomatitis 15 % Fatigue 16 % AST/ALT increase 24–30 %
Tsubata Y, 2021[40] Prospective phase II, multicentre (N = 33) Note: starting dose 100 mg	Age: Inclusion ≥ 75 Median 82; Range 75–91 ECOG 18.2 % ECOG 2	ORR 63.6 % DCR 96.9 % mPFS 17.8 mo (95 %CI 15.3–20.3) mOS 26.5 (95 %CI 7.8–45.2)	Rash 72.7 % Diarrhea 30.3 % AST/ALT increase 18.2 % Paronychia 18.2 %

(*continued on next page*)

Table 1 (*continued*)

TRIALS	AGE ECOG	EFFICACY	TOXICITY
Afatinib			
Imai H, 2018[41] Prospective phase II, multicenter (N = 40)	Age: Inclusion: ≥70; Median 77, Range 70–85 ECOG: 2.5 % ECOG 2	ORR 72.5 % DCR 100 % mPFS 12.9 mo mOS NR	Rash 70 % Diarrhea 77.5 % Stomatitis 42.5 % Pneumonitis 10 %
Mizugaki, 2022[42] Prospective phase II, multicenter (N = 35)	Age: Inclusion ≥ 75; Median 79, Range 75–92 ECOG No ECOG ≥ 2	ORR 80 % DCR 91.4 % mPFS 15.8 mo mOS 29.5 mo	Rash 69.4 % Diarrhea 62.8 % Paronychia 54.3 % Stomatitis 48.6 % Pneumonitis 8.6 %
Kashiwabara K, 2016[43] Retrospective, monocenter (N = 10) Note: low starting dose of 20 or 10 mg!	Age: Median 76; range 49–88 ECOG: All ECOG PS ≥ 2	ORR 11 % DCR 56 % mPFS 3.6 mo mOS 5.8 mo	Diarrhea
Minegishi Y, 2021[44] Prospective, multicentre phase II (N = 38)	Age Inclusion ≥ 75; Median 77.5; range 75–91 ECOG: No ECOG ≥ 2	ORR 75.7 % DCR 89.2 % mPFS 14.2 mo mOS 35.2 mo	Rash 78.9 % Diarrhea 94.7 % Stomatitis 68.4 % Decreased appetite 34.2 % Pneumonitis 13.2 % TA increase 23.7 %
Tanaka H, 2018[45] Phase I, multicentre (N = 15) Dose levels: 20 mg/d, 30 mg/d, 40 mg/d	Age: Inclusion ≥ 75 Median 79; range 75–87 No ECOG ≥ 2	ORR 73.3 % DCR 93.4 % mPFS 22 mo (95 %CI 13.1-NR) The recommended dose for phase II trials was 30 mg/d	Rash 80 % Diarrhea 100 % Stomatitis 33.3 % AST increase 20 %
Brueckl WM, 2023[46] Prospective, non-interventional Post hoc analysis according to age group (N = 152 of which 66 aged ≥ 70)	Age: Median 67; range 38–89 ECOG 4.6 % ECOG ≥ 2	ORR 72 % (95 %CI 57.5–83.8) DCR 96 % (95 %CI 86.3–99.5) mPFS 17.2 mo (95 %CI 11–20.7) mOS 30.4 mo (95 %CI 20.1–39)	Diarrhea 84.8 % Rash 33.3 % Paronychia (22.7 %) Stomatitis (15.2 %)
Dacomitinib			
None			
Erlotinib/bevacizumab			
Aoshima Y, 2021 Phase II, single arm, open-label (N = 25)	Age: Inclusion: ≥75 Median 80; Range 75–89 ECOG: 12 % ECOG ≥ 2	ORR 88 % (95 %CI 74–99) DCR 100 % (95 %CI 88.7–100) mPFS 12.6 mo (95 %CI 8–33.7) mOS NR (95 %CI 34-NR)	Rash 76 % Diarrhea 32 % Paronychia 36 % ALT/AST increase 20 % Stomatitis 19.2 % Proteinuria 28 % Hypertension 16 %
Osimertinib			
Chihara Y, 2022[53] Phase II, single arm, open label (N = 38)	Age: Inclusion ≥ 75 Median 80; Range 75–87 ECOG: 2.6 % ECOG 2	ORR 78.9 % (95 %CI 63.7–88.9) mPFS 15.9 mo (95 %CI 9.8–20.3) mOS NR (95 %CI 29.9-NR)	Fatigue 40 % Rash 42.5 % Dry skin 50 % Paronychia 32.5 % Pruritus 35 %
Yamamoto G, 2021[54] Retrospective (N = 132)	Age: Inclusion ≥ 75 Median 80; Range 75–90 ECOG 14.5 % ECOG ≥ 2	ORR 75.2 % (95 %CI 66.5–82.3) DCR 92.9 % (95 %CI 86.6–96.3) mPFS 19.4 mo (95 %CI15.9–23.9) mOS NR (95 %CI 24.6-NR)	Paronychia 43.9 % Rash 39.4 % Dry skin 38.6 % Anemia 38.6 %
Sakata Y, 2023[55] Retrospective (N = 203)	Age: Inclusion: all ages, <75 vs ≥ 75 ECOG ECOG2 12.6 % in < 75 and 22.1 % in ≥ 75	≥75 vs < 75 group ORR 72.8 % vs 78.3 % DCR 89.4 % vs 89.9 % mPFS 16.9 mo (95 %CI 14.3–20.2) vs 22.1 mo (95 %CI 19.5–26.3) (p = 0.093)	Pneumonitis 20.7 vs 12.8 % (p = 0.020)
Igawa S, 2022[56] Prospective, observational (N = 16)	Age: Inclusion: all Median 78; Range:54–89 ECOG: 88 % ECOG 2 and 12 % ECOG 3	ORR 56.3 % (95 %CI 47.1–78) mPFS 10.5 mo (95 %CI 2.8–18.2)	Rash 44 % Diarrhea 38 % Paronychia 38 %

N = Number; ECOG: Eastern Cooperative Oncology Group performance status; ORR: Objective Response Rate; DCR: Disease Control Rate, mPFS: median Progression Free Survival; mOS: median Overall Survival; mo: months; HR: Hazard Ratio; CI: confidence Interval.

NSCLC task force is to review available literature on targeted therapy in older patients, defined as ≥ 70 years, with advanced, oncogene driven NSCLC and formulate expert recommendations.

2. Questions

This review addresses four clinical questions concerning advanced oncogene-driven NSCLC in older patients: 1) What is the incidence of specific genetic alterations in this population, considering other confounding factors including smoking, sex and race? 2) What is the efficacy of targeted therapies in this population? 3) What is the toxicity in this population? 4) What are the available data for other outcomes including QoL and functional status?

The present review includes the following oncogene drivers in

NSCLC: Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), ROS proto-oncogene 1 receptor (ROS1), v-Raf murine sarcoma viral oncogene homologue B1 (BRAF), Rearranged during transfection (RET), Mesenchymal Epithelial Transition (MET) exon 14, Neutrophic Tyrosine Kinase Receptor Kinase (NTRK) and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue kinase (KRAS) G12C.

3. Methods

SIOG formed a multidisciplinary task force to formulate expert recommendations for the treatment of advanced oncogene driven NSCLC in older patients.

The recommendations were developed using a systematic review in Pubmed and Web of Science in March 2024 by L.D. Search details as well as in- and exclusion criteria are listed in Appendix 1.

Members of the task force provided a critical review and formulated expert recommendations.

4. Results

4.1. EGFR mutated NSCLC

4.1.1. Incidence

EGFR mutations are present in approximately 10 % of NSCLC and more prevalent in adenocarcinomas, women, Asian populations and never smokers [10,11,12]. The correlation between age and the prevalence of EGFR mutations remains unclear. In a *meta*-analysis, age as a continuous variable was not significantly associated with EGFR mutations [13]. This was confirmed in a multivariate analysis of a retrospective study of the Dana-Farber Cancer Institute ($p = 0.28$) [14]. In two Asian studies, the presence of EGFR mutations peaked between 40–60 years, with a decreasing rate in patients $\geq$ 60 years [15,16]. In other Asian studies, patients $\geq$ 60 years demonstrated a lower frequency of exon 19 deletions and a higher frequency of L858R mutations [17,18,19]. In addition, one study from Taiwan reported a lower frequency of uncommon EGFR mutations in patients $\leq$ 50 years versus $>$ 50 years [20].

4.1.2. Efficacy

EGFR tyrosine kinase inhibitors (TKIs) are the first line treatment for EGFR mutant NSCLC. First and second-generation EGFR TKIs (gefitinib, erlotinib and afatinib) resulted in higher objective response rate (ORR) and prolonged progression free survival (PFS) compared to platinum-doublet chemotherapy [21–27]. Median age in these trials was approximately 60 years. A subgroup analysis of trials with afatinib and a *meta*-analysis of trials with gefitinib, erlotinib and afatinib demonstrated that age did not influence PFS improvement [28,29]. In addition, different prospective and retrospective trials in older patients ($\geq$70 years) demonstrated comparable results (Table 1) [30–47]. In three trials the PFS benefit was less pronounced in patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) $\geq$ 2 and in patients with comorbidities [40,43,45]. In a multivariate analysis of a retrospective trial, PFS was not significantly correlated with polypharmacy, defined as $\geq$ 5, but overall survival (OS) was [48].

In comparison with gefitinib, the second-generation EGFR TKI dacomitinib resulted in an improved PFS, including in patients $\geq$ 65 years. However, no patients $\geq$ 70 years were included in this trial (age range 53–68) [49].

A PFS benefit was also observed with the addition of the angiogenesis inhibitor ramucirumab to erlotinib, although this benefit seemed less pronounced in the older population (HR 0.77 95 %CI 0.55–1.09 in patients $\geq$ 65 years versus HR 0.53 95 %CI 0.38–0.75 in patients $<$ 65 years) [50]. In a single arm, phase II trial in patients $\geq$ 75 years, the combination of erlotinib and bevacizumab resulted in an ORR of 88 % and a median PFS of 12.6 months [51].

The third generation EGFR TKI osimertinib prolonged both PFS and OS compared to gefitinib or erlotinib [52,53]. Subgroup analysis reported a similar PFS and OS benefit for patients younger and older than 65 years. One open label phase II trial and two retrospective trials confirmed the efficacy of osimertinib as first line treatment in patients $\geq$ 75 years (ORR 73–79 % and median PFS 15.9–19.4 months) [54,55,56]. In a prospective, observational trial in patients with poor performance status (ECOG 2–3) and a median age of 78 years, ORR with osimertinib was 56 % with a median PFS of 10.5 months and 50 % of patients demonstrated an ECOG improvement [57].

Recently, new treatment strategies have emerged. The addition of platinum doublet chemotherapy to osimertinib in first line significantly improved PFS compared to osimertinib alone (HR 0.62) [58]. So far, no subgroup analysis according to age has been reported. Similarly, the combination of amivantamab, a bi-specific antibody against EGFR and MET, and lazertinib, a third generation EGFR TKI, improved PFS compared to osimertinib (HR 0.70) [59]. In this study, 12 % of patients were $\geq$ 75 years and the PFS benefit seemed less pronounced in this subpopulation (HR 0.77 with 95 % CI 0.46–1.30).

Patients with EGFR exon 20 insertions do not respond to treatment with currently available EGFR TKIs and therefore first line treatment remained platinum-doublet chemotherapy. The combination of chemotherapy with amivantamab improved PFS compared to chemotherapy alone in this subpopulation [60]. This benefit was also observed in patients $\geq$ 65 years but only 9 % of patients in this trial was $\geq$ 75 years. There are until now no specific data with amivantamab in older patients.

4.1.3. Toxicity

The most frequently observed adverse events (AEs) with EGFR TKIs are rash, diarrhea, paronychia and increased liver transaminases. In addition, pneumonitis, although less frequent, is a very important AE. In patients $\geq$ 70 years similar AEs were observed [30–47,54–56]). In a small monocentric prospective study, patients $\geq$ 75 years treated with erlotinib experienced significantly more all grade AEs ($p = 0.003$) and a trend for more grade $\geq$ 2 AEs ($p = 0.06$) than younger patients [61]. In a retrospective study, no statistically significant differences in AEs were observed between the older and the younger population ($\geq$75 years versus $<$ 75 years) but there was more appetite loss (60 % vs 35.9 %; $p = 0.075$) [62]. Although the type of toxicity is comparable for all EGFR TKIs, the second generation TKIs afatinib and dacomitinib are associated with a higher incidence, especially for diarrhea [21–27]). In the subgroup analysis of Lux-Lung 3,6 and 7 the safety profile of afatinib was similar in the older ($\geq$65 years) and the younger subgroups but with slightly greater incidence of grade 3/4 diarrhea in the older population [28]. Osimertinib on the other hand has a more favorable side-effect profile than both 1st and 2nd generation TKIs [52,53]. However, in a retrospective observational study, osimertinib was associated with a higher risk of long QT syndrome than first/second generation EGFR TKI (HR 1.94) [63]. This increased risk was even higher in females, whites and patients $\geq$ 75 years.

Novel combination strategies with chemotherapy or amivantamab are associated with an increased risk of toxicity compared to osimertinib alone [58,59,60]. Such combinations should therefore only be considered for fit older patients after discussion of benefits and risks.

4.1.4. Other relevant outcomes

Gefitinib, erlotinib and afatinib demonstrated a QoL improvement compared to chemotherapy [21,26,27,64]. In patients $\geq$ 70 years, the functional assessment of cancer therapy (FACT) – Lung cancer subscale (LCS) showed also a significant improvement during treatment with gefitinib [30]. Osimertinib further improved QoL compared to gefitinib and erlotinib [65]. QoL improvements in the osimertinib arm were statistically greater than the gefitinib/erlotinib arm for emotional functioning and social functioning. Cognitive functioning remained stable in the osimertinib arm but deteriorated in the gefitinib/erlotinib

arm. However, none of the mean changes reached the clinical relevance of 10 points.

Data on the effect of EGFR TKIs on QoL, daily functioning and maintenance of independency in older patients are lacking.

4.2. ALK rearranged NSCLC

4.2.1. Incidence

ALK rearrangements are present in 1–7 % of all NSCLC with a higher frequency in adenocarcinoma and never/light smokers [10,11]. These rearrangements are reported to be more frequent in patients in their fourth or fifth decade [11]. In a series of 141 patients, mainly from the USA, Shaw et al reported that ALK rearranged lung cancers were significantly younger than EGFR mutant NSCLC and wild type/wild type NSCLC patients: median age 52 years (range 29–76) versus 66 years (range 36–90) versus 64 years (range 29–87) respectively [66]. This was confirmed in the cohort of the Dana Farber Institute where ALK rearrangements were associated with an increased likelihood in younger patients ($p < 0.01$) in multivariate analysis [14]. Similar findings with regards to age of ALK positive NSCLC were reported in Asian studies [67,68,69].

4.2.2. Efficacy

ALK TKIs are currently the first line treatment for ALK rearranged NSCLC. Crizotinib and ceritinib, a first and second generation respectively, significantly improved PFS compared to chemotherapy [70,71]. In both studies median age was below 60 years (52 and 55 years respectively, range 19–78 and 22–81 respectively). Patients ≥ 65 years represented a total of 16–22 % in these two studies and equally demonstrated a PFS benefit. There are no studies with crizotinib or ceritinib dedicated to the older population. Two case reports described drastic responses in two octogenarians treated with crizotinib for ALK rearranged NSCLC [72,73].

The second generation ALK TKIs alectinib and brigatinib both improved PFS compared to crizotinib [74–76]. Median age in these studies was approximately 60 years with 23–31 % of patients ≥ 65 years. Again, the PFS benefit was also observed in this older subgroup. There are no specific studies with alectinib or brigatinib in the older population, but one case report did demonstrate an important partial response in a 90-year-old with ECOG-PS 3 treated with alectinib [77]. In a real-life cohort, there was no significant efficacy difference between younger and older patients in PFS with either crizotinib, ceritinib or alectinib and in univariate analysis age did not affect OS [78].

Finally, lorlatinib, a third generation ALK TKI, demonstrated improved PFS compared to crizotinib [79]. Median age in this study was 61 years (range 26–90 years with 30.5 % ≥ 65 years). In this older population PFS was also improved with lorlatinib (HR 0.26 vs 0.16 in patients < 65 years).

4.2.3. Toxicity

Toxicity of ALK TKIs varies between the different drugs. Although none of the registration trials reported toxicity specifically for older patients, some of the reported AEs may be of concern in this population.

Crizotinib is frequently associated with vision disorders, which included visual impairment, photopsia, blurred vision, vitreous floaters, diplopia and photophobia [70]. These disturbances may be of relevance in older patients with impaired vision at baseline or with a fall risk. In addition, edema and dizziness may also be of higher importance in the older population, increasing for example the risk of falls. Ceritinib is associated with gastrointestinal events including diarrhea, nausea and vomiting which may increase the risk of dehydration in older patients [71]. Alectinib shows less gastrointestinal AEs and visual impairment but is associated with peripheral edema and myalgia [75,76]. Brigatinib also demonstrated gastrointestinal AEs as well as hypertension, which is frequently present at baseline in older patients [77]. Finally, lorlatinib is associated with some toxicities relevant for the older population such as cognitive effects, peripheral neuropathy, hypercholesterolemia and hypertriglyceridemia as well as edema and fatigue [79]. In an analysis of two NSCLC cohorts (one with 124 and one with 248 patients) treated with lorlatinib, age was not associated with cognitive or mood effects, but it was associated with psychotic effects in one of the two cohorts [80].

In a real-world cohort, patients ≥ 65 years old treated with either crizotinib, ceritinib or alectinib were more likely to develop all grade AEs compared to younger patients. There was a significantly higher rate of fatigue with ceritinib and alectinib; nausea, diarrhea and creatinine elevation with crizotinib and ceritinib; vision disorders with Crizotinib; myalgia with alectinib and transaminase elevation and fluid retention with all agents. In this retrospective analysis, patients ≥ 65 years treated with crizotinib and ceritinib demonstrated a higher percentage of grade 3–5 AEs and a higher treatment discontinuation rate due to AEs compared to the patients treated with alectinib [78].

4.2.4. Other relevant outcomes

Both crizotinib and ceritinib resulted in better QoL and a greater overall reduction in symptoms of dyspnea, pain and coughing compared to chemotherapy [71,72]. When comparing alectinib with crizotinib, both drugs resulted in a clinical meaningful improvement in QoL and lung cancer symptoms but the duration of these improvements was longer in patients treated with alectinib [81]. None of the registration trials reported on QoL or other relevant outcomes such as autonomy or cognition in the older population.

4.3. ROS1 rearranged NSCLC

4.3.1. Incidence

ROS1 rearrangements are present in 0.9–2.6 % of all NSCLC with a higher frequency in adenocarcinoma, females and never smokers [10,11]. In the Dana Farber cohort, a non-significant trend towards younger age for the ROS1 genotype was seen ($p = 0.10$) [14].

4.3.2. Efficacy

In a phase I, ROS1 expansion cohort, crizotinib demonstrated significant activity: ORR 72 % and median PFS 19.2 months [82]. Median age in this cohort was 53 years (range 25–77). No efficacy data in older patients were reported. Two real world cohorts supported the benefit of crizotinib in ROS1 rearranged NSCLC, but none reported results in the older population [83,84].

Entrectinib demonstrated significant activity with ORR 77 % based on an integrated analysis of three phase 1–2 trials [85]. Median age in this analysis was 54 years (range 20–86). Lorlatinib also demonstrated activity in ROS1 positive NSCLC with an ORR of 62 % in first line but no patients > 61 years old were included (median age 54 years, range 44–61) [86].

There have been no trials of ROS inhibitors specifically in older adults with ROS1 positive advanced NSCLC, but one case report demonstrated efficacy of crizotinib in a 90-year-old female patient [87].

4.3.3. Toxicity

There are no data concerning toxicity of ROS TKIs in older patients. Nevertheless, these TKIs may demonstrate relevant AEs for the older population. The concerns of crizotinib were extensively discussed above. For entrectinib the most frequently reported AEs are dysgeusia, dizziness and gastrointestinal AEs including diarrhea [85]. Importantly for older adults AEs such as cognitive disorders, congestive heart failure, QTc interval prolongation and skeletal fractures were reported in different clinical trials with entrectinib, which may highly impact daily functioning and QoL [88,89]. Cognitive disorders included confusion, mental status changes, memory impairment and hallucinations were more frequently observed in patients ≥ 65 years [88].

4.3.4. Other relevant outcomes

To our knowledge, there are no data on the effect of ROS1 inhibitors on other outcomes including QoL.

4.4. BRAF mutated NSCLC

4.4.1. Incidence

BRAF mutations are present in 2–4 % of NSCLC and comprise 50 % BRAF V600E point mutations and 50 % non V600E mutations [10,11,90]. In NSCLC, BRAF mutations are more frequently observed in adenocarcinoma, males and current or former smokers [90,91,92]. In female patients and in never smokers, BRAF V600E are more frequent [11,92]. No correlation with BRAF mutations and age has been reported although in multivariate analysis of the Dana Farber cohort BRAF V600E mutations were associated with older age ($p < 0.01$; highest incidence in patients > 70 years) [11,14].

4.4.2. Efficacy

The combination of dabrafenib and trametinib as first line treatment for BRAF V600E NSCLC, resulted in an ORR of 64 % and a median PFS of 14.6 months in a phase 2 trial [93]. In this study median age was 67 years (range 62–74). In another phase 2 trial, the combination of encorafenib and binimetinib resulted in an ORR of 75 % in treatment naïve, BRAF V600E NSCLC [94]. Median age in this study was 68 years (range 47–83) in the treatment naïve subgroup. In the subgroup of patients ≥ 65 years, ORR was 75 %.

There are no studies specific for older patients with BRAF V600E NSCLC. One case report in an 86-year-old patient reported a good efficacy of dabrafenib/trametinib combination resulting in tumor shrinkage and improvement of performance status [95].

4.4.3. Toxicity

There are no data on the toxicity of dabrafenib/trametinib or encorafenib/binimetinib combinations in older patients. The most frequently observed AEs are pyrexia, gastrointestinal symptoms, fatigue and peripheral edema [93,94]. AEs of interest to older patients are arthralgia (+/- 15 %) and myalgia (14 %) as well as decrease in ejection fraction (9 %) and blurred vision (11 %) [93,94]. In the case report mentioned above, treatment with dabrafenib/trametinib, was discontinued because of peripheral edema grade 3 [95].

In patients ≥ 75 years with melanoma, the combination of dabrafenib/trametinib did not result in significant differences in AE rate or grade compared to younger patients, although pyrexia was less frequent [96].

4.5. Other relevant outcomes

There are no data on other relevant outcomes for older patients.

4.6. RET rearranged NSCLC

4.6.1. Incidence

RET rearrangements occur in 1–2 % of NSCLC and are more frequent in adenocarcinoma and in never smokers [10,97–100]. In three studies, patients with RET rearranged NSCLC were younger than RET negative patients [97–99]. In two studies (one from the USA and one from Asia) RET positive NSCLC patients tended to be younger than RET negative NSCLC patients (median age 62.9 (range 54.8–70.1) and 57.5 (range 28–78) respectively versus 67.2 (range 60.3–74.9) and 63.2 (range 23–89) respectively with $p = 0.0004$ and $p = 0.038$ respectively) [97,98]. Similarly, in a Chinese study, patients with RET rearranged NSCLC tended to be younger (72.7 % aged ≤ 60 years) [99]. A *meta*-analysis concluded that patients with RET positive NSCLC were younger (2 % positive in patients < 60 versus 1 % in patients ≥ 60 years; OR 0.43, $p = 0.046$) [100].

4.6.2. Efficacy

Two specific RET inhibitors, selpercatinib and pralsetinib, have demonstrated significant activity in RET rearranged NSCLC [101,102]. Median age in both trials was 61 and 60 years respectively (range 23–86 and 26–87 respectively). In a randomized, first line, phase 3 study, selpercatinib demonstrated higher ORR (84 % vs 65 %) and prolonged median PFS (24.8 vs 11.2 months, HR 0.46) compared to chemotherapy and pembrolizumab [103]. Median age in this study was 61 for the patients treated with selpercatinib (range 31–87). In a subgroup analysis, the PFS benefit was also observed in patients ≥ 65 years (HR 0.52).

There are no trials specifically in older patients. One case report described a tumor shrinkage with selpercatinib in an 83-year-old female patient with RET rearranged NSCLC [104].

4.6.3. Toxicity

Although there are no data of toxicity specific for older patients, some of the reported toxicities may present a concern to the older population with a major impact on QoL. The most frequently reported AEs in the phase 3 trial with selpercatinib were an increase in transaminases (60 %), hypertension (48 %), diarrhea (44 %), edema (41 %) and dry mouth (39 %) [103]. Other AEs may also be important in older adults including fatigue, blood creatinine increase and QT prolongation on ECG. The case report mentioned above, described severe transaminitis in the 83-year-old patient needing dose interruption and corticosteroids with complete resolution [104].

4.6.4. Other relevant outcomes

There are no data with regards to RET inhibitors and other outcomes.

4.7. MET exon 14 mutated NSCLC

4.7.1. Incidence

MET exon 14 skipping mutations are present in 3–5 % of NSCLC and more frequent in the older population [10,11]. In a *meta*-analysis on clinical characteristics of MET exon 14 skipping in NSCLC, median age was 73 years (range 64–80.5) [105]. In a study by Awad et al, patients with MET exon 14 mutant NSCLC were significantly older than patients with EGFR or KRAS mutant NSCLC (median age 72.5 versus 61 versus 65 years respectively, $p < 0.01$ for both) [106].

4.7.2. Efficacy

Two MET inhibitors, tepotinib and capmatinib, have demonstrated significant activity in MET exon 14 mutated NSCLC [107,108]. In both phase 2 trials median age was relatively high (71 and 74 years respectively, range 49–90 and 41–94 respectively). In a subgroup analysis of tepotinib, a clinical meaningful activity was observed across all age groups, including in patients ≥ 80 years (ORR 35.1 % and median PFS 8.6 months) [109]. In two case reports, treatment with tepotinib in octogenarians resulted in a partial response which was maintained for > 12 months [110,111].

4.7.3. Toxicity

Since the population in both trials was relatively older, described toxicities may also be a good representation of expected toxicity in the (fit) older patients. AEs of interest for this population are peripheral edema, gastrointestinal events and blood creatinine increase. In patients younger or older than 75 years, treatment related AEs were observed in 87.7 % versus 84.4 % and grade 3 AEs in 18.5 % versus 33.9 % respectively [109]. AEs led to dose reduction in 23.3 % of the younger population and 33.9 % of the older population and to permanent discontinuation in 7.5 % and 14.7 % respectively.

4.7.4. Other relevant outcomes

There are no data on alternative outcomes.

4.8. NTRK rearranged NSCLC

4.8.1. Incidence

The frequency of NTRK rearrangements in NSCLC is approximately 0.2 % [10]. There are limited data with regards to the frequency in older versus younger patients. In a cohort of 11 patients from the USA, median age was 48 years with range 25–86 [112].

4.8.2. Efficacy

Two NTRK inhibitors have demonstrated activity in a small number of NTRK rearranged NSCLC [113,114]. Patients in the analysis of Larotrectinib had a median age of 48.5 years (range 25–76) while in the entrectinib trial no patients ≥ 70 years were included [113,114].

4.8.3. Toxicity

NTRK inhibitors may demonstrate relevant AEs for older patients including dizziness, myalgia, increased transaminases and peripheral edema. For larotrectinib, dizziness (32 % vs 28 %), anemia (32 vs 25 %), muscular weakness (14 % vs 11 %) and gait disturbance (8 % vs 5 %) were more frequent in patients ≥ 65 years (n = 65) compared to all adults in the overall safety population [115]. AEs with entrectinib with potential impact in older patients were discussed previously.

4.8.4. Other relevant outcomes

There are no data on alternative outcomes.

4.9. KRAS G12C mutated NSCLC

4.9.1. Incidence

KRAS mutations are found in up to 30 % of NSCLC with the KRAS G12C as the most frequent variant (approximately 13 %) [10]. KRAS mutations are more common in Western than in Asian populations (23–33 % vs 2–15 % respectively) and in smokers than in never smokers (20–44 % vs 6–10 % respectively) [10,11]. In a retrospective study of the Dana Farber Cancer Institute, KRAS mutations were associated with older age in multivariate analysis ($p = 0.04$) [14]. Similarly, in a Korean retrospective study, KRAS mutations were more frequent in older patients in multivariate analysis, (OR for 1-year increase: 1.03, $p < 0.001$) [16]. In a retrospective analysis of KRAS mutant NSCLC, there was no significant difference in age between patients with KRAS G12C and KRAS non-G12C mutations [116].

4.9.2. Efficacy

The KRAS G12C TKIs, sotorasib and adagrasib, were compared to docetaxel in previously treated KRAS G12C mutant NSCLC [117,118]). Both drugs resulted in a significant PFS improvement (median 5.6 vs 4.5 months, HR 0.66 for sotorasib and 5.5 vs 3.8 months, HR 0.58 for adagrasib) [117,118]. Median age in both trials was 64 years (range 32–88 for sotorasib and 34–83 for adagrasib). In both trials, PFS benefit was also observed in patients ≥ 65 years (HR 0.64 for sotorasib and 0.60 for adagrasib).

4.9.3. Toxicity

There are no specific data regarding toxicity for the older population. The most frequently observed AEs were gastrointestinal with diarrhea, nausea and vomiting as well as fatigue [117,118]. Increase in transaminases or blood creatinine may be relevant for older patients with baseline decreased organ function. For sotorasib, no difference in AEs between patients < 65 and ≥ 65 years has been observed while for adagrasib fatigue (62.4 vs 51.7 %), decreased appetite (37.6 vs 23.8 %) and dizziness (27.4 vs 15.4 %) were more frequent [119,120].

4.9.4. Other relevant outcomes

Sotorasib showed clinically meaningful improvements in patient-reported outcomes compared with docetaxel [117] but no specific data in older patients are reported.

4.10. HER2 mutated NSCLC

4.10.1. Incidence

HER2 mutations account for 2–3 % of NSCLC and are more prevalent in Asian patients, never smokers and females [10,11]. In retrospective studies from the USA, Europe and Asia, median age ranged between 57 and 63 years (respectively median 63 years with 45 % ≥65, median 60.4 years with range 31–86 and median 57 years with range 33–84) [121,122,123]. In a retrospective analysis of the Dana-Farber Cancer Institute, a non-significant trend towards younger age was seen for HER2 mutated NSCLC ($p = 0.15$) [14].

4.10.2. Efficacy

A phase II study with trastuzumab-deruxtecan at 6.4 mg/kg in Her2 mutant NSCLC demonstrated an ORR of 55 % with median PFS 8.2 months [124]. Median age in this study was 60 years (range 29–88). Efficacy was not reported for age subgroups. In a subsequent, randomized phase II study with two doses of trastuzumab-deruxtecan (5.4 mg/kg versus 6.4 mg/kg every 3 weeks), ORR was similar between the two arms (respectively 49 % and 56 %) [125]. Median age was 59.4 years (range 31–84) and 61.3 years (range 28–86) for both arms respectively. No subgroup analysis according to age was reported.

4.10.3. Toxicity

Most frequent AEs with trastuzumab-deruxtecan were gastrointestinal (nausea, vomiting, diarrhea) and hematological (anemia and neutropenia), fatigue, decreased appetite and alopecia [124,125]. Grade 3/4 AEs occurred in 46 % with neutropenia and anemia being the most common. Importantly drug-related interstitial lung disease occurred in a lower frequency with the lower dose (13 % vs 28 %) [125]. There are no data on toxicity in the older population

5. Polypharmacy and potential interactions

Drug-drug interactions (DDI) in cancer patients treated with oral anti-cancer therapies occur in up to 46 %. The risk of DDI and AEs are significantly increased in older adults with cancer when initiating anticancer therapy [126,127].

Acid-reducing agents are frequently used in the older population and potential interactions with TKIs should be verified since the aqueous solubility of TKIs are often pH dependent and acid-reducing agents could affect TKI absorption. A review found adverse clinical outcomes when oral anticancer therapies were concomitantly used with acid-reducing agents [128].

Almost all TKIs undergo metabolism by cytochrome P450 enzymes and therefore strong inducers should be avoided.

Finally, QT prolongation on ECG should be monitored. Important risk factors for developing prolonged QT interval include history of cardiovascular disease, previous history of drug-induced torsades de pointes, older age (>65 years), female sex, history of congenital long QT syndrome, high baseline QTc, hypothyroidism, reduced kidney or function, and the use of other drugs known to prolong QT interval [129]. The risk of QT prolongation with TKI is reported to be up to 22.7 %, however, severe QTc prolongation (>500 ms) was reported in 0–5.2 %. Reassuringly, the incidence of arrythmia and sudden cardiac death due to QTc prolongation is rarely reported in the literature [130]. The European Society of Cardiology made recommendations for baseline risk assessments and monitoring during EGFR and ALK inhibitors [131].

6. Discussion

The standard of care for oncogene-driven NSCLC is targeted therapy based on the genetic alteration identified [8,9]. These recommendations are primarily derived from registration trials with stringent inclusion and exclusion criteria, typically resulting in a study population that is younger and fitter than the real-world population. Consequently, it

remains unclear whether the current registrational study-derived data are broadly applicable to older (≥70 years) and/or frailer patients.

The present review demonstrates the lack of (randomized) trials specifically addressing the growing group of older NSCLC patients, as well as the lack of data regarding important outcomes in this population such as daily functioning and QoL. The absence of level A evidence in the older population as well as the heterogeneity of this population makes the formulation of recommendations difficult. Important for each patient is a frailty assessment by means of a geriatric assessment, as recommended by ASCO guidelines [132], a discussion on patient expectations and preferences and a medication review to avoid DDI.

For older patients with NSCLC and common EGFR mutations, subgroup analyses as well as prospective and retrospective trials confirm results of registration trials for gefitinib, erlotinib, afatinib and osimertinib. The combination strategies of osimertinib with chemotherapy or Lazertinib with amivantamab have demonstrated longer PFS compared to osimertinib alone, but there are currently no data in the older population. In addition, these combination strategies require regular intravenous administrations and are associated with more toxicity, which may impact QoL. Choice of first line treatment should therefore be based on toxicity profile as well as patient fitness and patient preferences.

For older NSCLC patients with MET exon 14 mutations results with tepotinib and capmatinib may be representative for the fit older population since median age in these trials was relatively high. Nevertheless, data in frail older patients are lacking. Treatment options should be discussed based on potential AEs, potential impact on function and QoL and patient preferences.

For older NSCLC patients with ALK rearrangements, subgroup analysis in patients ≥ 65 years in the registration trials demonstrated similar activity. However no specific trials in patients ≥ 70 years are reported. Once again, the AE profile and patient preferences should determine treatment of choice.

For other genetic alterations in NSCLC there are no data specific for the older population. Therefore, no formal recommendation can be formulated, but treatment discussions with patients should include potential benefits, potential risks as well as patient preferences.

In conclusion, based on currently available data, targeted therapies are active in older adults with oncogene driven NSCLC and should be considered as a treatment option. The choice of targeted therapy should be personalized, based on the toxicity profile, potential impact on daily functioning and QoL as well as patient preferences. In addition, an evaluation of DDI should be performed at baseline and close monitoring is mandatory.

CRediT authorship contribution statement

L. Decoster: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **D.R. Camidge:** Conceptualization, Supervision, Visualization, Writing – review & editing. **J.A. Fletcher:** Supervision, Visualization, Writing – review & editing. **A. Alfredo:A. Greystoke:** Visualization, Writing – review & editing. **K. Kantilal:** Visualization, Writing – original draft, Writing – review & editing. **L.Bigay Game:** Visualization, Writing – review & editing. **R. Kanesvaran:** Supervision, Writing – review & editing. **F. Gomes:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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