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Efficacy and Side Effects of Single Agent Immunotherapy for Non-Small Cell Lung Cancer in Older and Younger Patients: A Systematic Review and Meta-Analysis

Research Article

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Abstract: Lung cancer is a leading cause of cancer related death and more common in older people. Immunotherapy has improved efficacy compared to chemotherapy in non-small cell lung cancer (NSCLC). We aimed to review existing data on efficacy and adverse events (AEs) of single agent immunotherapy for NSCLC by age. We reported OS, progression-free survival (PFS) and AEs by age. Suitable results were meta-analysed using the random effects model. 1803 papers were screened, ten eligible papers identified, seven included in meta-analyses. Included individual papers did not demonstrate a difference in OS, PFS or AEs. Meta-analyses showed no significant difference in OS (HR: 1.03, 95% CI 0.92-1.15; p=0.58), PFS (HR 0.96, 95% CI: 0.92-1.01; p=0.15) or AEs (HR:1.01 95% CI:0.83-1.23; p=0.91) in older vs younger patients. Existing data on differences in efficacy and AEs of immunotherapy by age is largely observational and points to similar efficacy and adverse events by age.

Keywords: Lung cancer; Immunotherapy; Elderly; Programmed death-1

Background

Lung cancer and older people

Lung cancer is the most common cause of cancer related deaths in the UK accounting for around 35,100 of deaths in 2017 [1]. Five-year survival outcomes are less than 10% having improved from 4.5% in 1971 to 9.6% in 2011[2] meanwhile over the same duration five-year survival in bowel cancer has increased from 24.4% to 58.7% [3]. Age is a significant risk factor for developing lung cancer. This is related to increased time for oncogenic genetic mutations to occur and for increased exposure to carcinogenic substances such as tobacco smoking [4]. Between 2015-2017 in the UK 44% of new cases occurred in people aged 75 years or above [5].

Survival outcomes for older patients with lung cancer are poorer than younger patients. Five year survival rates in the UK for women aged 50-59 are 18.7% and for those aged 60-69 are 17.2% compared to 13.2% for women aged 70-79 and for women aged 80-99 years are 7.4% [2]. Mortality rates from lung cancer for men aged 80 and above have remained stable [6] with mortality rates decreasing for younger age groups since the 1970s.

Programmed death-1 pathway and immunotherapy

The programmed death membrane receptor was identified by Ishida et al. [7]. Its role in immune activity was investigated and mice genetically modified to not express this receptor demonstrated higher immune activity and higher rates of auto-immune disease [8,9]. The programmed death receptor was shown to have a role in immune tolerance. Expression of the programmed death receptor on non-small cell lung cancer cells and its role in down-regulation of immune response was demonstrated [10].

The programmed death pathway was developed as a treatment target in non-small cell lung cancer. Three agents targeted at this pathway are currently used in the UK. Pembrolizumab has been demonstrated to be more effective than chemotherapy as first line treatment for patients with programmed death ligand-1 expression on ≥50% of tumour cells [11,12]. Nivolumab and Atezolizumab were demonstrated to improve

outcomes compared to second-line chemotherapy for patients with pre-treated advanced or metastatic non-small lung cancer [12,13]. These agents are immune checkpoint inhibitors. Their anti-cancer effect is brought about through increased anti-tumour immune activity due blocking of the programmed death pathway.

Due to the increased immune activity these agents induce their side-effect profile is different from conventional chemotherapies. By upregulating immune activity, they can lead to auto-immune events against healthy tissues in the body [14], common side effects include, pneumonitis, colitis, thyroid dysfunction, fatigue and hypophysitis.

Immunotherapy in older patients

Doubt exists over the efficacy of these agents in older people due to their mechanisms of action. As part of ageing changes occur in the immune system that result in reduced in immune activity, a process known as immunosenescence [15].

Older people are more likely to have a higher burden of co-morbidities and reduced level of physiological reserve. This could give a different tolerability of these agents in this group and different side effect profile. In addition, there is a lack of understanding surrounding how immunosenescence may impact on immune related side effects.

The rates of older people included in key trials for these agents are lower than the rates treated with these agents in clinical practise [16]. This under-representation in trials means the evidence base for these agents in older people is less robust. A review into efficacy of anti-programmed death 1 and anti-programmed death ligand-1 inhibitors in solid tumours found these agents to have similar efficacy in older and younger patients [17], however they did not evaluate differences in side effect rates.

Zhang et al. [18] carried out a systematic review of the differences in overall survival by age in people with lung cancer treated with immunotherapy. They included data from randomised control trials only and did not evaluate progression-free survival or differences in adverse events. Also, patients treated with combinations of immunotherapy with other immunotherapies or chemotherapy regimens were included. This review found no significant difference in the overall survival for older people compared to younger people.

Rationale and aims for review

Older patients make up a large proportion of patients diagnosed with non-small cell lung cancer each year and disease specific survival outcomes in this group of patients are poorer than in younger people.

Novel treatments including immunotherapies targeted at programmed death pathways have been demonstrated to be more effective than conventional treatments. These treatments have different side-effect profiles and mechanisms of action compared to standard chemotherapy. The number of older people represented in trials is less than the number of older people that have been treated in clinical practice. The underrepresentation of older people in key trials means the evidence base for survival and adverse event rates of these agents in older people is weaker.

The systematic review by Zhang et al. [18] identified similar outcomes in overall survival in older and younger patients, however this review included patients with small cell lung cancer and did not evaluate adverse events. We therefore aimed to undertake an updated review with more specific investigation into the non-small cell lung cancer population who received single agent immunotherapy. We also included a review of the side-effect profile of these agents by age.

Our aim was to systematically review data on differences in efficacy and side-effects by age in patients receiving programmed death pathway targeted immunotherapy for advanced or metastatic non-small cell lung cancer.

Methods

Search strategy

We devised a review protocol which was prospectively registered with Prospero and given a unique reference number (CRD42020181990) [19]. No external funding was received. We performed a search of Medline, EMBASE and Web of Science databases from inception to 10th April 2021. The population, intervention, control, outcome, setting, and study design criteria were used to find papers relevant to answer our review aims. Eligible papers included patients with advanced or metastatic non-small cell lung cancer who had been treated with pembrolizumab, atezolizumab or nivolumab as a single agent. These agents could have been received by patients in control or experimental groups. Control group treatment was not relevant as outcomes of interest were the differences in overall survival, progression free survival and adverse events between older and younger participants. The final search terms were selected as displayed in Supplementary Appendix A, to cover the areas above with relevant map to subject heading terms included.

Eligibility

The results from the database searches were pooled and duplications identified using the reference management software Mendeley. After removal of duplications, a final list of titles was produced. This list was independently reviewed by two reviewers (M.B. and P.G.) based on title and abstract initially, suitable papers were then included for full text review. Papers needed to meet the following criteria, (i) included results of patients with non-small cell lung cancer (ii) participants with non-small cell lung cancer received atezolizumab, or pembrolizumab or nivolumab as single agent and not in combinations (iii) outcomes for overall survival and adverse events/side effects were reported for an older and a younger age group (iv) studies were a randomized control trial or cohort design, either prospective or retrospective (v) studies were published in English. We did not place any restriction on location of study. References of included studies at full text review were reviewed for identification of other papers relevant to our aim.

Assessment for methodological bias

We performed an assessment of quality and bias for each included study. We assessed for risk of bias regarding our outcomes. The context of our assessment was for how rigorous each papers method was for detecting a difference in overall survival, progression free survival and rates of adverse events between the younger and older populations reported. We used the Cochrane risk of bias 2.0 tool [20] to assess randomized control trials and the Newcastle-Ottawa scale [21] to assess cohort studies. When assessing comparability in the Newcastle-Ottawa scale this was with regards to comparability of the older and younger groups. Assessment of methodological bias was discussed jointly by M.B. and P.G. and decision made on consensus.

Data extraction

A pre-designed data collection sheet was produced; this was piloted by M.B. on the first eligible study by unique study number from the list generated after duplications removed. A pre-designed data extraction sheet was used to collect data from each study displayed in Supplementary Appendix B. Data was extracted on the study characteristics including lead author, year of publication, number of participants, study design, immunotherapy delivered, and the age ranges included for subgroup analysis of outcomes. Data on the populations including median ages when present were collected. For overall and progression free survival outcomes we collected the median and the corresponding 95% confidence intervals. Alternatively, the hazard ratio for the older group compared to the younger group with its 95% confidence interval was recorded. Where present p-values were collected. Where median survival data was collected this was used to calculate a hazard ratio and confidence interval for older

versus younger groups. The natural logarithm of the median survival and the number of events observed was used to calculate this [22].

For adverse event/side effects, data was collected for the total number of events for the younger and older populations. Where possible data was collected for the total number of all grade events, grade one and two events and grade three or above events.

Data Analysis

Descriptive statistics from each included study are reported as well as a narrative description of their finding. Results from the methodological bias assessments were analysed and presented.

A meta-analysis of overall survival, progression-free survival and adverse event rates was performed using the software Review Manager (RevMan) 5.3. The random effects model was used due to the variety of study populations and interventions. Hazard ratios between older and younger populations were displayed with their 95% confidence intervals in a forest plot. Heterogeneity was assessed using the forest plot and an I^2 value of >50% was used as a cut off of as this infers moderate heterogeneity [23]. Successive removal of included studies and repeat analysis was performed as a sensitivity analysis. A funnel plot was produced from this analysis to assess for publication bias.

Where efficacy data was present for multiple age subgroups a pooled hazard ratio was produced using a fixed effect model meta-analysis for an older population compared to younger population. A subgroup analysis was performed for the hazard ratios of, all grade, grade one and two and grade three or above events where subgroup data was available.

Results

Studies included

Searches of the three databases produced 2209 results in total. After removal of duplications using Mendeley software, 1803 papers remained. Screening of titles and abstracts identified 124 papers full for text review. Reasons for exclusion included being case reports/series, not reporting outcomes for non-small cell lung cancer, immunotherapies not given or given in combination with other agents, study focus for a site-specific side effect, laboratory studies and abstracts only. This review was completed in line with the preferred reporting in systematic reviews and meta-analysis (PRISMA) statement [24], a flowchart of the assessment of papers for eligibility was produced see Figure 1.

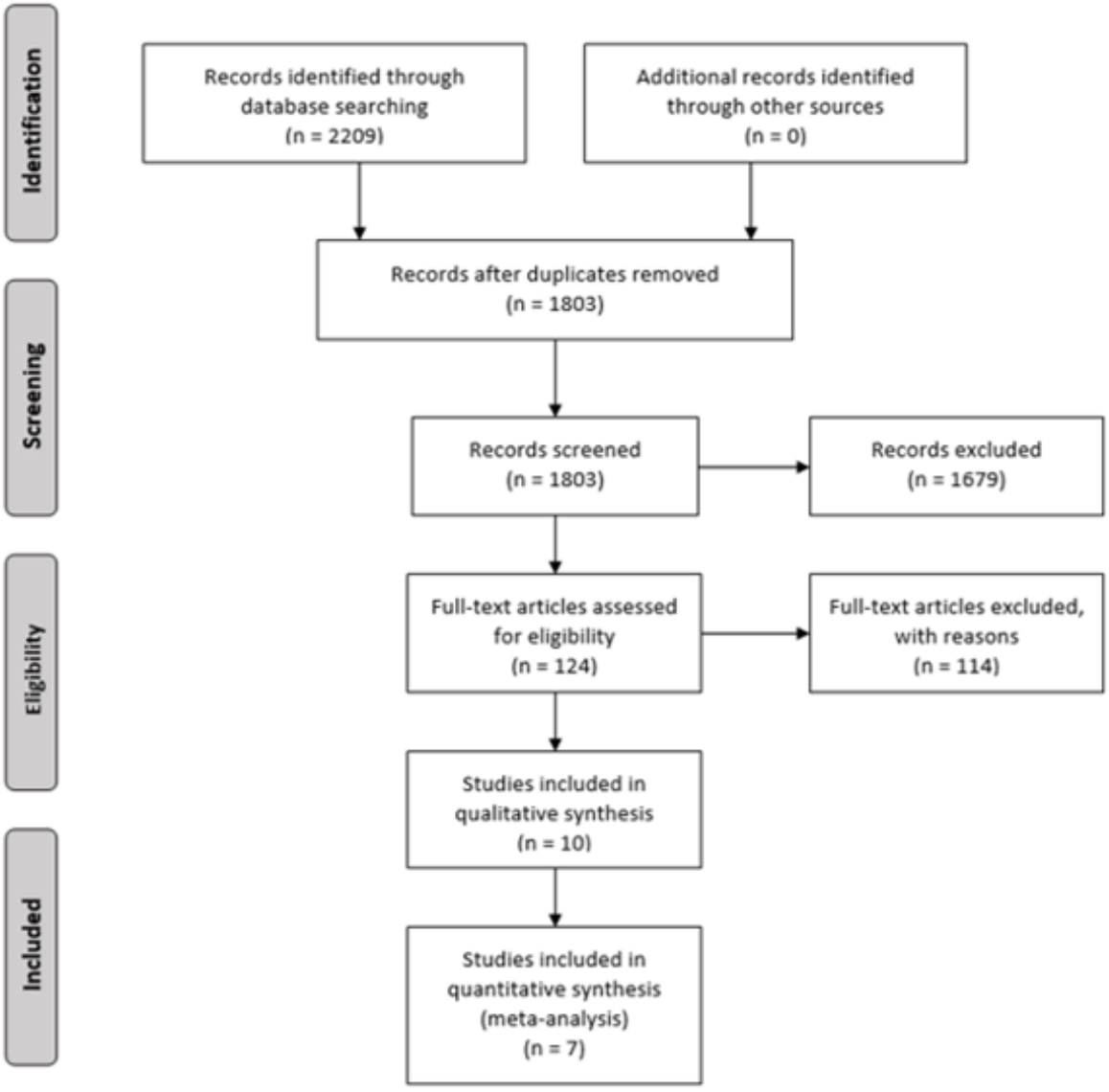

Figure 1: Flowchart of paper retrieved and assessed for eligibility.

Full text review of remaining papers produced 33 papers that reported overall survival data for a younger and an older subpopulation. Of these 10 were identified that reported overall survival and adverse event data for a younger and older subpopulation. The following studies were included, Grossi et al. [25], Dumenil et al. [26], Lichtenstein et al. [27], Nosaki et al. [28], Muchnik et al. [29], Cortellini et al. [30], Baldini et al. [31], Bjørnhart et al. [32], Joris et al. [33]. Of these included papers, one was a pooled randomized control trial analysis, three were prospective cohort studies, and six were retrospective cohort studies. One study, Muchnik et al. [29] was identified that had a minimum age threshold of 70 years and age subgrouping was at age 80 years.

Included study characteristics

The total number of patients from all included studies was 6785. Comparison for older and younger outcomes was divided at different ages, five studies divided outcomes at age 70 years, one study divided outcomes at age 65 years, one study divided outcomes at age 75 years and one study divided outcomes at age 80 years. Two studies divided outcomes at multiple age points. Study characteristics are demonstrated in Table 1.

Quality assessment

Cohort studies: Nine cohort studies were identified; these were assessed using the Newcastle-Ottawa Scale for cohort studies [21]. Studies were assessed to establish the quality of the evidence for differences in overall and progression-free survival and adverse event differences in older and younger populations. Of the nine cohort studies seven were assessed to be poor and two were assessed to be good quality, full results of the assessment are presented in Supplementary Appendix C. Assessment of comparability was performed with reference to whether risk in older and younger groups could be compared. Seven studies did not make an adjustment for other baseline characteristic in their comparison of outcomes between older and younger patients and so received no stars for this section. Two studies included a multi-variate analysis of outcomes between older and younger patients.

Randomised control trial: One paper that reported results from three pooled randomised control trials was assessed using the Cochrane risk of bias assessment tool [20]. The paper was overall assessed to be low risk of bias. The full results of this assessment are displayed in Supplementary Appendix D.

Table 1: Included study characteristics – Study characteristics of included studies as extracted from published materials for each paper.

Study	Study Design	Age groups (n)	Immunotherapy given	Median age	Median follow up
Grossi et al. [25]	Prospective cohort-Non-squamous only	Overall (1588)	Nivolumab	66yrs	8.1 months
		≥70yrs (522)		74yrs	
		≥75yrs (232)		77yrs	
Dumenil et al. [26]	Prospective cohort	<70yrs vs ≥ 70yrs: (n= 39 vs 28)	Nivolumab	-	-
Grossi et al. [34]	Prospective cohort – squamous only	<65yrs (n= 126)	Nivolumab	68yrs	7.5 months
		65-<75yrs (n=175)		70yrs	
		≥75yrs (77)		77yrs	
Nosaki et al. [28]	Pooled RCTs	<75yrs (1323)	Pembrolizumab	62yrs	12.9 months
		≥75yrs (149)		77yrs	11.7 months
Lichtenstein et al. [27]	Retrospective cohort	<60yrs (n=64)	Anti-PD-1 or anti-PD-L_1 agents	-	-
		60-69yrs (n=77)		-	-
		70-79yrs (n=76)		-	-
		≥ 80yrs (n=28)		-	-
Muchnik et al. [29]	Retrospective cohort	>/70-<80yrs vs ≥80yrs: (n=58 vs 17)	Anti-PD-1 or anti-PD-L1 agents	-	-
Cortellini et al. [30]	Retrospective cohort	≥70 vs <70: (n=259 vs 300)	Pembrolizumab or Nivolumab	69yrs	11.2months
Baldini et al. [31]	Prospective cohort	≥70 vs <70: (1278 vs 681)	Nivolumab	66yrs	16.4 months
Bjørnhart et al. [32]	Prospective cohort	>/65 vs <65: (n= 59 vs 59)*	Nivolumab or pembrolizumab	66yrs	15.7 months
Joris et al. [33] 2019	Retrospective cohort	≥70: (n=216)	Nivolumab	60yrs	-
		≥70: (n=108)		74yrs	

*Subgroup populations for Bjørnhart et al 2019 were not given so were estimated from calculations of percentages in graphs.

Papers excluded from meta-analyses

Of the 10 papers included three were excluded from meta-analyses. Their results are discussed and presented in Table 2. Grossi et al. [34] and Grossi et al. [25] were not included as their results were for squamous and non-squamous populations only and updated results for these participants are included in Baldini et al. [31]. Their results have been displayed in the table for reference to sub population information. Muchnik et al. [29] was excluded from meta-analyses as the participants were all aged ≥70 years and the age division of outcomes was at 80 years. Most papers used an age divide at 70 years, Muchnik et al. [29] was assessed to be inappropriate for meta-analysis as the participants in the younger arm of this study would have been in the older group of most other included studies.

Table 2: Outcome data as extracted from papers – data for overall survival, progression-free survival and side effects as presented in published materials for each included paper. Figures are presented for each age group as reported or with the hazard ratio for comparison where age difference was reported by this method. HR – hazard ratio, irAE – immune-related adverse event, trAE – treatment related adverse events, AE – adverse events non-specified.

Study	Age groups	Overall survival (95% confidence interval)	Progression-free survival (95% Confidence Interval)	Side effects younger	Side effects older
Grossi et al. [25] (Non-squamous)	Overall:	11.3 months (10.2-12.4 months)	3.0 months (2.9-3.1 months)	trAE: All grades: 351/1066 Grade 3-4: 68/1066	
	≥70:	11.5months (10.0-13.0 months)	4.0 months (3.6–4.4 months)	All grades: 172/522 Grade 3-4: 34/522	
	≥75:	12.0 months (9.2-14.8 months)	4.2 months (3.0-5.4 months)	All grades: 79/232 Grade 3-4: 16/232	
Dumenil et al. [26]	<70 vs ≥ 70:	HR: 0.22 (0.81-2.59)* p=0.215	HR: 1.01 (0.98-1.05) p=0.539	trAE: Grade 3+: 16/39	Grade 3+: 12/28 P=0.881
Grossi et al. [34] (Squamous)	<65	8.6 months (5.2-11.9 months)	4.0 months (2.3-5.7 months)	trAE: All grades: 40/126 Grades 1-2: 36/126 Grades 3+: 4/126	
	65-<75	8.0 months (5.6-10.4 months)	4.5 months (3.5-5.5 months)	trAE: All grades: 49/175 Grades 1-2: 34/175 Grades 3+: 15/175	
	≥75	5.8 months (3.5-8.1 months)	3.2 months (1.1-5.3 months)	trAE: All grades: 20/70 Grades 1-2: 18/70 Grade 3+: 2/70	
Nosaki et al. [28]	<75	TPS ≥ 1%: 14.6 months (13.1-16.6 months) Hazard rate: 0.047 TPS ≥ 50%: 19.2 months (16.4-22.4 months) Hazard rate: 0.036		trAE: All grades: 862/1323 grade 1-2: 638/1323 grade 3+: 224/1323 irAE: all grades: 331/1323 grade 1-2: 237/1323 grade 3+: 94/1323	
	>/=75	TPS ≥1%: 15.7 months (10.7-20.2 months) Hazard rate: 0.044 TPS ≥ 50%: 23.1 (11.9-NR months) Hazard rate: 0.030	-	trAE: all grades: 102/149 grade 1-2: 66/149 grade 3+: 36/149 irAE: all grades: 37/149 grade 1-2: 23/149 grade 3: 14/149	
Lichtenstein et al. [27]	<60	reference	Reference	irAE: All grades: 28/64	
	60-69	0.758 (0.461-1.246)	0.768 (0.520-1.133)	irAE: All grades: 29/77	
	70-79	0.927 (0.568-1.513)	0.599 (0.397-0.905)	irAE: All grades: 35/76	
	>/= 80	2.741 (1.429-5.254)	1.618 (0.915-2.862)	irAE: All grades: 10/28	
Muchnik et al. [29]	≥70-<80 vs ≥80:	Unadjusted: 0.92 (0.48-1.74) p=0.79 Adjusted: 0.83 (0.43-1.63) p=0.59	-	irAE: All grades: 29/58	All grades: 8/17

Cortellini et al. [30]	≥70 vs <70:	HR: 1.18 (0.92-1.51) p=0.1823	HR 0.88 (0.71-1.09) p=0.2709	irAE: All grades: 137/300 (95% Confidence interval) 38.3%-53.9%	All grades: 94/259 (95% Confidence interval 29.3%-44.4%)
Baldini et al. [31]	≥70 vs <70:	HR: 0.99 (0.87-1.12) p=0.84	HR: 0.93 (0.84-1.04) p=0.19	irAE: All grades: 116/681	All grades: 226/1278
Bjørnhart et al. [32]	≥65 vs <65:	HR: 1.60 (0.94-2.71) p=0.08	HR: 0.93 (0.60-1.46) p=0.76	irAE: Grade 3+: 19/59	Grade 3+: 13/59**
Joris et al. [33]	<70:	8.4 months (6.3-10.5 months) P=0.638	3.7 months (2.6-4.8 months) P=0.483	AE: All grades: 120/216 Grade 1-2: 81/216 Grade 3+: 39/216 p=0.526	
	≥70:	9.3 months (5.5-13.1 months)	4.0 months (1.0-7.0 months)	AE: All grades: 64/108 Grade 1-2: 47/108 Grade 3+: 17/108 p=0.603	

Study	Age groups	Overall survival (95% confidence interval)	Progression-free survival (95% Confidence Interval)	Side effects younger	Side effects older
Grossi et al. [25] (Non-squamous)	Overall	11.3 months (10.2-12.4 months)	3.0 months (2.9-3.1 months)	trAE: All grades: 351/1066 Grade 3-4: 68/1066	
	≥70:	11.5months (10.0-13.0 months)	4.0 months (3.6 – 4.4 months)	All grades: 172/522 Grade 3-4: 34/522	
	≥75:	12.0 months (9.2-14.8 months)	4.2 months (3.0-5.4 months)	All grades: 79/232 Grade 3-4: 16/232	
Dumenil et al 2018	<70 vs ≥ 70:	HR: 0.22 (0.81-2.59)* p=0.215	HR: 1.01 (0.98-1.05) p=0.539	trAE: Grade 3+: 16/39	Grade 3+: 12/28 P=0.881
Grossi et al 2018 (Squamous)	<65	8.6 months (5.2-11.9 months)	4.0 months (2.3-5.7 months)	trAE: All grades: 40/126 Grades 1-2: 36/126 Grades 3+: 4/126	
	65-<75	8.0 months (5.6-10.4 months)	4.5 months (3.5-5.5 months)	trAE: All grades: 49/175 Grades 1-2: 34/175 Grades 3+: 15/175	
	≥75	5.8 months (3.5-8.1 months)	3.2 months (1.1-5.3 months)	trAE: All grades: 20/70 Grades 1-2: 18/70 Grade 3+: 2/70	
Nosaki et al 2019	<75	TPS ≥ 1%: 14.6 months (13.1-16.6 months) Hazard rate: 0.047 TPS ≥ 50%: 19.2 months (16.4-22.4 months) Hazard rate: 0.036	-	trAE: All grades: 862/1323 grade 1-2: 638/1323 grade 3+: 224/1323 irAE: all grades: 331/1323 grade 1-2: 237/1323 grade 3+: 94/1323	
	>/=75	TPS ≥1%: 15.7 months (10.7-20.2 months) Hazard rate: 0.044 TPS ≥ 50%: 23.1 (11.9-NR months) Hazard rate: 0.030	-	trAE: all grades: 102/149 grade 1-2: 66/149 grade 3+: 36/149 irAE: all grades: 37/149 grade 1-2: 23/149 grade 3: 14/149	

Lichtenstein et al 2019:	<60	reference	Reference	irAE: All grades: 28/64	
	60-69	0.758 (0.461-1.246)	0.768 (0.520-1.133)	irAE: All grades: 29/77	
	70-79	0.927 (0.568-1.513)	0.599 (0.397-0.905)	irAE: All grades: 35/76	
	>/= 80	2.741 (1.429-5.254)	1.618 (0.915-2.862)	irAE: All grades: 10/28	
Muchnik et al 2019	≥70-<80 vs ≥80:	Unadjusted: 0.92 (0.48-1.74) p=0.79 Adjusted: 0.83 (0.43-1.63) p=0.59	-	irAE: All grades: 29/58	All grades: 8/17
Cortellini et al 2019	≥70 vs <70:	HR: 1.18 (0.92-1.51) p=0.1823	HR 0.88 (0.71-1.09) p=0.2709	irAE: All grades: 137/300 (95% Confidence interval) 38.3%-53.9%	All grades: 94/259 (95% Confidence interval 29.3%-44.4%)
Baldini et al 2020	≥70 vs <70:	HR: 0.99 (0.87-1.12) p=0.84	HR: 0.93 (0.84-1.04) p=0.19	irAE: All grades: 116/681	All grades: 226/1278
Bjørnhart et al 2019	≥65 vs <65:	HR: 1.60 (0.94-2.71) p=0.08	HR: 0.93 (0.60-1.46) p=0.76	irAE: Grade 3+: 19/59	Grade 3+: 13/59**
Joris et al 2019	<70:	8.4 months (6.3-10.5 months) P=0.638	3.7 months (2.6-4.8 months) P=0.483	AE All grades: 120/216 Grade 1-2: 81/216 Grade 3+: 39/216 p=0.526	
	≥70:	9.3 months (5.5-13.1 months)	4.0 months (1.0-7.0 months)	AE: All grades: 64/108 Grade 1-2: 47/108 Grade 3+: 17/108 p=0.603	

*unsuitable for meta-analysis as HR is outside the CI, therefore not included in meta-analysis of overall survival. ** Based on calculations from graphs.

Efficacy

Overall survival: All included papers reported measuring overall survival as time from starting immunotherapy until death and included statistics allowing for comparison of older and younger subgroup/s. Four studies reported greater overall survival in the older population however none reported a statistically significant difference. Five studies reported greater overall survival in younger subgroup/s only one of these showed a significant statistical difference. This statistical difference was reported in Lichtenstein et al. [27] and demonstrated that patients aged ≥80 years had a hazard ratio for overall survival of 2.741, 95% confidence interval 1.429-5.254 compared to patients aged <60 years. Data as extracted from papers is demonstrated in Table 2.

Results from five papers are demonstrated in a forest plot (Figure 2) with a meta-analysis. Comparison of overall survival by age in Dumenil et al. [26] was not included as the reported hazard ratio and confidence interval were not suitable for meta-analysis as the reported hazard ratio was lower than the lower limit of the confidence interval. This was not resolved after contacting the authors. For Nosaki et al. [28] a hazard ratio and confidence interval were calculated from the median overall survival data and number of events that occurred in the older and younger groups using natural logarithm equations [22]. For Lichtenstein et al. [27] hazard ratios for the three older subgroups compared to the under 60s were pooled using the fixed effect meta-analysis function of RevMan 5.3, this produced a pooled HR for ≥60yrs vs <60yrs of 1.09 with 95% confidence interval of 0.80-1.49.

This forest plot (Figure 2) showed three studies demonstrated a better outcome in younger patients. This improved overall survival in younger patients was not statistically significant in any included studies. Improved overall survival in older patients was demonstrated in two studies but neither was statistically significant.

The pooled hazard ratio favoured younger patients with a hazard ratio of 1.03 and a 95% confidence interval of 0.92-1.15 (p=0.58). Heterogeneity was assessed using the I^2 statistic. For the overall assessment this was 31%. This indicates mild to moderate heterogeneity.

Progression-free survival: Of the included papers eight reported progression-free survival with a statistic allowing a comparison between an older and younger subgroup. Progression-free survival in all these papers was measured from start of immunotherapy until radiological or clinical progression of disease or death. Six papers reported a greater progression-free survival in older patients. One paper, Grossi et al. [25] reported a significant statistical difference between older and younger patients. Intermediate range subgroups in Grossi et al. [25] and Lichtenstein et al. [27] reported improved progression-free survival in older patients than the younger comparator groups. Only the Lichtenstein et al. [27] 70-79yrs subgroup demonstrated a statistically significant results, demonstrating improved progress-free survival in the older group than the younger reference group. Three papers reported greater progression-free survival in younger patients

The progression-free survival comparisons from five of these studies were plotted in a forest plot (Figure 3) of hazard ratios and confidence

intervals and a meta-analysis performed. This demonstrated greater but not statistically significant greater progression-free survival in older subgroups in all included studies.

The pooled hazard ratio and confidence interval was 0.96 with a 95% confidence interval of 0.92-1.01 (p=0.15) showing no statistically significant difference between older and younger patients. Heterogeneity was assessed using the I^2 statistic which gave an overall value of 10%, indicating a mild level of heterogeneity.

Adverse events

Adverse event data was present in all included studies. Inter study variability was present with six studies reporting immune-related adverse event rates, four reporting treatment related events and one reporting adverse events. In the meta-analysis we have used the most encompassing reported adverse events rate from each study, where present we have recorded and used the sub-grouped event rates based on grading.

Adverse events as reported in each study are demonstrated in Table 2. Adverse event rates by age were demonstrated in a graph without counts in Bjørnhart et al. [32] and therefore were deduced based on calculations for Table 2, we did not deem this reliable enough to include these values in the meta-analysis.

These data were used to produce a meta-analysis and forest plot (see Figure 4) with subgroup analysis based on all grades, grades one and two, grades three or more. For Lichtenstein et al. [27] the two older subgroups were combined, and the two younger subgroups combined. This gave an age comparison between those ≥70 and those <70 years, this is in keeping with most included papers.

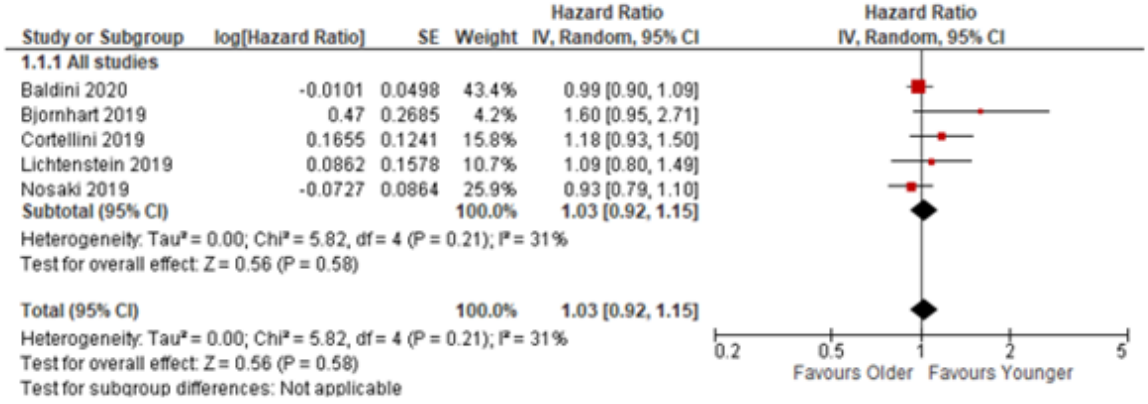

Figure 2: Forest plot of Overall Survival by age: Forest plot of hazard ratios for overall survival of older people compared to younger people from eligible included studies.

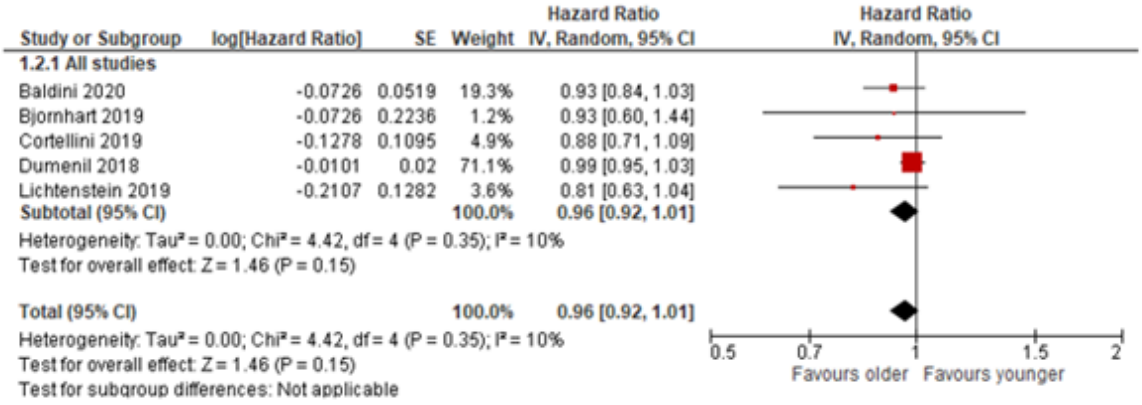

Figure 3: Forest plot of Progression free survival by age - Forest plot of hazard ratios for progression-free survival of older people compared to younger people from eligible included studies.

For papers that reported all grade events, two papers showed increased risk of adverse event in the younger population, these were not statistically significant. One study demonstrated as statistically significant increased rate of adverse events in older people. For grade one and two events, one paper reported increased risk in the younger population and one reported increased adverse event rates in the older population. Neither of these was as statistically significant difference. For grade three and above events, two papers demonstrated an increased risk of adverse events in the younger population and one paper reported an increased rate in the older population. One of these results demonstrating increased risk of adverse events in younger patients was statistically significant.

The meta-analysis produced a pooled odds ratio of adverse event of 1.01 with 95% confidence interval 0.83-1.23 showing no statistical difference between the older and younger groups. Heterogeneity was assessed giving an overall I^2 value of 43%, a mild-moderate level of heterogeneity. A sensitivity analysis was performed with each included study being removed from the analysis individually. In each case the result demonstrated no statistical difference between older and younger patients.

Assessment of publication bias

Publication bias was assessed using the funnel plot method see Figure 5, this was deduced from the adverse events rates meta-analysis and generated in RevMan. There is no clear asymmetry, which indicates low possibility of publication bias across studies. This assessment is limited due to the limited number of included articles.

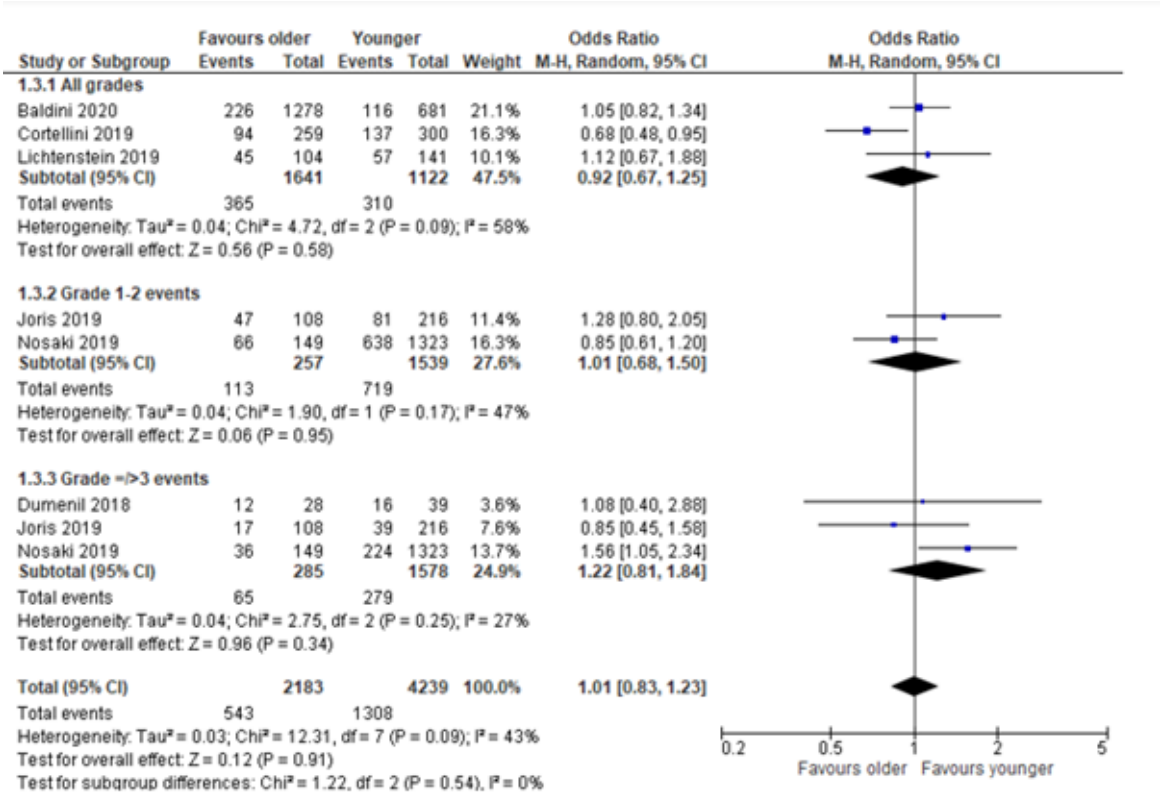

Figure 4: Forest plot of reported adverse event rates - Forest plot of odds ratios of adverse events in older people compared to younger people from eligible included studies with subgroup analysis based on graded severity of event.

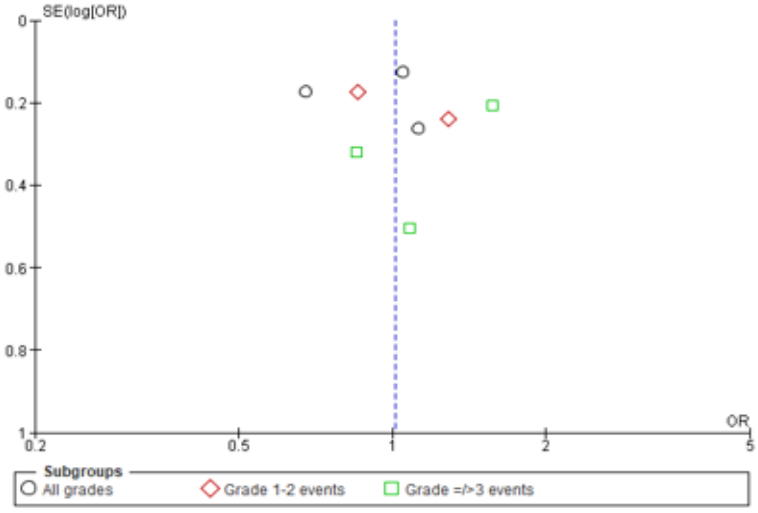

Figure 5: Funnel plot of adverse events data.

Discussion

Based on existing literature it is clear there are doubts over the efficacy and tolerability of targeted immune checkpoint inhibitors in older patients. Doubts around efficacy are present due to the understanding we have around immunosenescence that occurs as part of ageing. Increased rates of co-morbidity and reduced physical reserve in older patients with lung cancer are thought to increase the risk of immune checkpoint inhibitor induced adverse events.

We set out to review what data existed in current literature comparing efficacy and side effects of these agents in older patients compared to younger patients. We used a systematic review methodology with narrative synthesis and meta-analyses of suitable results to investigate our aims.

Our systematic search results demonstrate that only a few studies have reported the overall and progression-free survival as well as overall adverse event rates for older patients separately from younger patients. In addition, most of the knowledge in this field comes from non-randomised observational data and research where impact of age was not a primary aim of investigation.

The results we have extracted demonstrate no pattern of difference in overall survival, progression-free survival or adverse event rates in older patients compared to younger patients. A number of these studies did not have age comparison as their main aim and aimed to investigate multiple factors affecting outcomes with age being one of them. Most of these nine cohort studies did not perform a multivariate analysis for age as a risk factor for survival outcomes or adverse events. This is reflected in the results of our bias assessment. The results of

the Newcastle-Ottawa scale for these studies highlighted that the comparability of results for the older and younger groups was weak in most studies. One study Lichtenstein et al. [27] achieved a star for comparability on this score, this study had the main aim of comparing outcomes in older and younger patients and performed multivariate analysis for the efficacy data.

The results of our review of overall survival and progression-free survival support the findings of two similar reviews [17, 18] described in section 1.3. Our review adds further evidence to their findings and adds evidence in the specific non-small cell lung cancer population who are treated with single agent immunotherapy. In addition, we have provided a review of side effects of these agents by age.

The limitation in the number and quality of published studies comparing both efficacy and adverse event rates by age demonstrates this as an area where further focused research is needed.

This is the first review and meta-analysis to compare the efficacy and the adverse event rates in older and younger patients receiving programmed death pathway immunotherapy for patients with non-small cell lung cancer. We have found that existing data suggest there is no overall difference in efficacy and side-effects rates between older and younger patients treated with single agent immunotherapy for non-small cell lung cancer. Therefore, this review supports the use of single agent immunotherapy for older patients just as for younger patients with non-small cell lung cancer. This is based on a limited number of studies, many observational, and emphasises the lack of evidence that effects of these agents are the same as age increases. Further studies that focus on this this difference as a primary aim are needed to increase the body and strength of evidence.

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