RESEARCH ARTICLE

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Exclusion of Patients with Autoimmune Disease in Lung Cancer Clinical Trials

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Abstract

Background: The exclusion of patients with autoimmune disease has been a topic of cancer immunotherapy trial. This study aims to find recent trends in exclusion of autoimmune disease. **Methods:** Using the website clinicaltrials.gov, we searched for clinical trials that were initiated in 2012 or later and enrolled patients with lung cancer who were treated with PD-1/PD-L1 therapy. Only trials including US locations were analyzed. **Results:** A total of 198 trials met screening criteria in this study. There were 68 trials which had complete exclusion of any autoimmune disease in patients. In addition, 13 trials excluded active autoimmune disease and 87 trials excluded active autoimmune disease requiring treatment. The remaining 37 trials had undefined exclusion. Studies that had larger enrollment of patients with autoimmune diseases were largely in industry. The complete exclusion of patients with autoimmune diseases has decreased recently. **Conclusion**: Exclusion of patients with active autoimmune disease requiring treatment was one of the common exclusion criteria found. Strict exclusion of patients with autoimmune diseases has been decreasing over the years.

Keywords: Clinical trials- lung cancer- autoimmune disease- eligibility

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Introduction

Lung Cancer is the third most common cancer in the United States (Centers for Disease Control and Prevention 2022). In 2022, there were approximately 236,000 cases of lung cancer in the United States (The American Cancer Society medical and editorial content team, 2022). In addition, more than 50% of lung cancer cases are diagnosed as stage IV (National Cancer Institute, 2022). Although there is a gradual increase in the 5-year survival rate for overall lung cancer cases, development of new systemic therapy is warranted to further improve the outcome (National Cancer Institute, 2022). Recently, installation of immunotherapy in lung cancer has dramatically changed the landscape in the management of advanced lung cancer (Fountzilas et al., 2022). The Food and Drug Administration (FDA) has approved anti-PD1/PD-L1 agents for several disease settings in thoracic malignancy. Immunotherapy became an important part of systemic therapy; however, many trials do not enroll patients with autoimmune disease due to fear of flare-up secondary to immunotherapy.

By not including patients with autoimmune disease in cancer trials, it will negatively impact our understanding of how to treat those patients with cancer. Including more patients with autoimmune disease will help us to understand more about how to properly care for these patients as well as the relation between autoimmune disease and cancer. In a study done with 210,509 patients with lung cancer, 13.5% of those patients also had autoimmune disease (Khan et al., 2016). Increasing studies to help those in need of care with autoimmune disease and lung cancer will help make results easier to use across a larger variety of patients. If we always exclude them from pivotal clinical trials, the findings cannot be generalized in broad patient population.

To treat lung cancer more effectively, this study aims to find out the parameters of clinical trials regarding exclusion of patients with autoimmune disease. This study is also being conducted to see how this has been changing over the recent years.

Materials and Methods

To select trials which are relevant to the study, the website clinicaltrials.gov was used (NIH, 2022). Search criteria for clinical trials included study initiation year (2012 and later), diagnosis of lung cancer, use of a PD-1/PDL1 inhibitor, and study locations that included US institutions.

The data was analyzed based on several parameters. We obtained eligibility information regarding Eastern cooperative oncology group (ECOG) status , the sponsor type (industry, academic institution, or corporate group),

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type of PD-1/PDL1 treatment, drug of PD-1/PDL1 (Pembrolizumab vs other drugs/cancer treatments), number of participants, stage (stage IV vs other stages), year of trial. Table 1 shows characteristics of selected trials.

The tables were made with categories pertaining to trial status, design, sponsor, location, treatments used, the year the study was initiated, as well as any specific anti-cancer drugs which were used. The tables made were also organized so that the degree of exclusion of patients with autoimmune diseases could be assessed. There was partial exclusion which was divided into two categories "A" and "B". "A" was excluding active autoimmune disease and "B" was excluding active autoimmune disease only if it required treatment. Complete exclusion was strict exclusion of any history of autoimmune disease. The proportion of patients which fit into any of these selections was analyzed. This is not a human-subject study but a study which reviews the publicly available existing clinical trials.

Statistical analyses were conducted according to chi-square tests. A two-sided p-value below 0.05 was considered as statistically significant.

Results

More than 50% of the trials are recruiting trials (Table 1). The phase I trials are the most prevalent (33%) compared to phase II and phase III trials (28% vs 11%). About 1% of the trials had an undefined phase. The location of the trials was also closely split with there being about 48% in the United States only and 52% of the trials in the United States and other countries. There were far more trials being conducted in industry making up 75% of the trials. The remaining sponsors were corporate groups and academic institutions (10% vs 15%). Most of the trials used a combination of PD-1/PD-L1 inhibitors with other agents (88%). There was about 7% of trials which used a PD-1/PD-L1 inhibitor with radiation and 4% used only PD-1/PD-L1 inhibitor. The remaining trial had an undefined treatment. The PD-1/PD-L1 inhibitor used was slightly more with Pembrolizumab at 55% and 45% for other drugs/cancer treatments. Most trials were conducted with 101-1000 participants at 59%. Non-small cell lung cancer was the most prevalent disease being studied in clinical trials making up 51% of all clinical trials in the study. Lung cancer and any other cancer was the next largest at 43%. The stage IV lung cancer made up most trials at 94%. The ECOG score for most trials was 0-1 since they made up 74% of all trials.

In Table 1, the type of exclusion for each category is also shown along with its percentage of the total. Exclusion of autoimmune diseases which requires systemic treatment as well as strict exclusion are the most common in all the categories. Exclusion of only active autoimmune diseases is the least common among each category.

In Table 2, there are 11 categories from which chi square calculations were performed. Strict exclusion is less frequent in phase II/III and III trials and pembrolizumab trials than other trials (both $p<0.001$). Partially allowing patients with autoimmune disease is less frequent in trials with stage IV (45%) than those with others (82%) ($p=0.033$). There is no significant association between the exclusion type and other study characteristics.

The Table 3 and Figure 1 show a trend of different exclusion types over a period of years from 2012 to 2022. Trials in more recent years have allowed more patients with autoimmune diseases than previously.

Discussion

Historically, many of the trials in cancer immunotherapy excluded patients with active or history of autoimmune diseases. In our study, more than 60% of the trials at least conditionally allowed patients with autoimmune disease. Over the years from 2012 to 2022 the number of trials with strict exclusion of autoimmune disease has been decreasing. This may suggest that the treating oncologists are now used to and more capable of managing patients with autoimmune disease.

Recent studies reported that cancer patients with autoimmune disease can be safely treated with modern immunotherapy. Immune checkpoint inhibitors were found to be suitable for active or inactive autoimmune

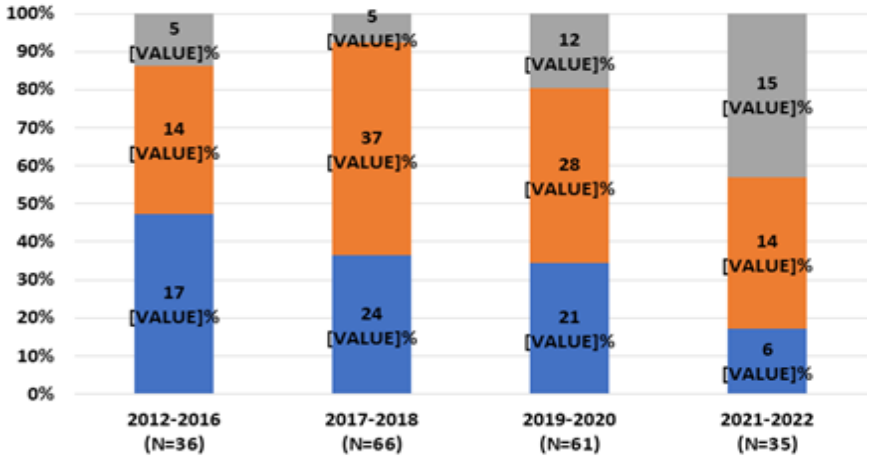

Figure 1. Trend in Exclusion

Table 1. The Study Characteristics and Exclusion Status

Characteristics	Strict Exclusion, N (%)	Partial A	Partial B	Other, N (%)	Total, N (%)
		Excluding Active Autoimmune Disease, N (%)	Excluding Autoimmune Disease which requires systemic treatment, N (%)		
Total	68 (34)	13 (7)	80 (40)	37 (19)	198 (100)
Trial Type					
Recruiting	28 (28)	6 (6)	41 (41)	26 (26)	101 (100)
Active, not recruiting	19 (33)	4 (7)	28 (49)	6 (11)	57 (100)
Completed	21 (53)	3 (8)	11 (28)	5 (13)	40 (100)
Trial Phase					
Phase 1/2/1 and 2	66 (38)	13 (8)	62 (36)	31 (18)	172 (100)
Phase 2 and 3/3	2 (8)	0 (0)	18 (75)	4 (17)	24 (100)
Phase NA	0 (0)	0 (0)	0 (0)	2 (100)	2 (100)
Location					
United States only	38 (40)	6 (6)	33 (35)	18 (19)	95 (100)
United States and other countries	30 (29)	7 (7)	47 (46)	19 (18)	103 (100)
Sponsor Type					
Industry	46 (31)	9 (6)	62 (42)	32 (22)	149 (100)
Corporate Group	7 (37)	4 (21)	4 (21)	4 (21)	19 (100)
Academic Institution	15 (50)	0 (0)	14 (47)	1 (3)	30 (100)
Treatment Type					
Combination of PD-1/PD-L1 with other agents	58 (33)	12 (7)	69 (39)	36 (21)	175 (100)
PD-1/PD-L1 with Radiation	6 (43)	0 (0)	7 (50)	1 (7)	14 (100)
PD-1/PD-L1 only	4 (50)	0 (0)	4 (50)	0 (0)	8 (100)
Treatment Type Not Available (Undefined)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)
PD-1/PD-L1 Agent Used					
Including Pembrolizumab	24 (22)	4 (4)	57 (53)	23 (21)	108 (100)
Other drugs/cancer treatments	44 (49)	9 (10)	23 (26)	14 (16)	90 (100)
Participants Involved (Sample Size)					
0-20 Participants	8 (47)	1 (6)	6 (35)	2 (12)	17 (100)
21-100 Participants	28 (48)	6 (10)	22 (37)	3 (5)	59 (100)
101-1000 Participants	31 (27)	6 (5)	49 (42)	31 (27)	117 (100)
1001-2000 Participants	1 (20)	0 (0)	3 (60)	1 (20)	5 (100)
Type of Lung Cancer					
Non-small cell lung Cancer	32 (32)	5 (5)	49 (49)	15 (15)	101 (100)
Small Cell lung Cancer	2 (20)	1 (10)	7 (70)	0 (0)	10 (100)
Both Non-small cell lung cancer and Small Cell lung Cancer	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)
Lung Cancer and any other type of Cancer	33 (38)	7 (8)	24 (28)	22 (26)	86 (100)
Stage of Lung Cancer					
Including Stage 4	67 (36)	13 (7)	71 (38)	36 (19)	187 (100)
Other Stages	1 (9)	0 (0)	9 (82)	1 (9)	11 (100)
ECOG					
0-1	52 (36)	10 (7)	62 (43)	22 (15)	146 (100)
Including 2	12 (35)	2 (6)	12 (35)	8 (24)	34 (100)
Not Available	4 (22)	1 (6)	6 (33)	7 (39)	18 (100)

Table 2. Association between the Characteristics and Exclusion Criteria: Consolidated Analysis

	Strict Exclusion, N (%)	Allowed Partially, N (%)	Other N (%)	Total N (%)	p Value
Total	68 (34)	93 (47)	37 (19)	198 (100)	
Trial Type					0.055
Recruiting	28 (28)	47 (47)	26 (26)	101 (100)	
Active, not recruiting	19 (33)	32 (56)	6 (11)	57 (100)	
Completed	21 (53)	14 (35)	5 (13)	40 (100)	
Trial Phase					p<0.001
Phase I, II, I/II	66 (38)	75 (44)	31 (18)	172 (100)	
Phase II/III, III	2 (8)	18 (75)	4 (17)	24 (100)	
Phase NA	0 (0)	0 (0)	2 (100)	2 (100)	
Location					0.08
United States only	38 (40)	39 (41)	18 (19)	95 (100)	
United States and other countries	30 (29)	54 (52)	19 (18)	103 (100)	
Sponsor Type					0.449
Industry	46 (31)	71 (48)	32 (22)	149 (100)	
Corporate Group	7 (37)	8 (42)	4 (21)	19 (100)	
Academic Institution	15 (50)	14 (47)	1 (3)	30 (100)	
Treatment Type					0.795
Combination of PD-1/PD-L1 with other agents	58 (33)	81 (46)	36 (21)	175 (100)	
PD-1/PD-L1 with Radiation	6 (43)	7 (50)	1 (7)	14 (100)	
PD-1/PD-L1 only	4 (50)	4 (50)	0 (0)	8 (100)	
Treatment Type Not Available (Undefined)	0 (0)	1 (100)	0 (0)	1 (100)	
PD-1/PD-L1 Agent Used					p<0.001
Including Pembrolizumab	24 (22)	61 (57)	23 (21)	108 (100)	
Other drugs/cancer treatments	44 (49)	32 (36)	14 (16)	90 (100)	
Participants Involved (Sample Size)					0.264
0-20	8 (47)	7 (41)	2 (12)	17 (100)	
21-100	28 (48)	28 (48)	3 (5)	59 (100)	
101-1000	31 (27)	55 (47)	31 (27)	117 (100)	
1001-2000	1 (20)	3 (60)	1 (20)	5 (100)	
Type of Lung Cancer					0.087
Non-small cell lung Cancer	32 (32)	54 (54)	15 (15)	101 (100)	
Small Cell lung Cancer	2 (20)	8 (80)	0 (0)	10 (100)	
Lung Cancer and any other type of Cancer	33 (38)	31 (36)	22 (26)	86 (100)	
Both Non-small cell lung cancer and Small Cell lung Cancer	1 (100)	0 (0)	0 (0)	1 (100)	
Stage of Lung Cancer					0.033
Including Stage IV	67 (36)	84 (45)	36 (19)	187 (100)	
Other Stages	1 (9)	9 (82)	1 (9)	11 (100)	
ECOG					0.851
0-1	52 (36)	72 (49)	22 (15)	146 (100)	
Including 2	12 (35)	14 (41)	8 (24)	34 (100)	
Not Available	4 (22)	7 (39)	7 (39)	18 (100)	

Table 3. Trends in Exclusion Status Since 2012

Year	Strict Exclusion (%)	Allowed Partially (%)	Other (%)	Total (%)	p Value*
Total	68 (34)	93 (50)	37 (19)	198 (100)	p<0.001
2012-2016	17 (47)	14 (38)	5 (14)	36 (100)	
2017-2018	24 (36)	37 (56)	5 (8)	66 (100)	
2019-2020	21 (34)	28 (46)	12 (20)	61 (100)	
2021-2022	6 (17)	14 (40)	15 (43)	35 (100)	

*, the trend among study periods.

disease (Antonuzzo et al., 2020). Another study also found that involving patients with autoimmune disease with immune checkpoint inhibitors would not only be safe but also increase the efficacy of these treatments in both active and inactive autoimmune disease while having similar results and tolerability. (Boland et al., 2020; Florou et al., 2021; Rakshit et al., 2020; Zakharian et al., 2021). Other studies also suggest excluding treatment for patients with autoimmune diseases may affect their health from which no alternative treatment is available (Duma et al., 2019; Pantuck et al., 2019). It has been suggested that patients with autoimmune diseases can participate in clinical trials with immune checkpoint inhibitors if the managing physicians monitor the effects that the treatment has on the patient (Pantuck et al., 2019). These observations and considerations are in line with the recent decrease in strict exclusion of autoimmune disease from lung cancer clinical trials.

There are some limitations to this study. Study locations and primary cancer site must have included US and lung, respectively. The use of clinicaltrials.gov to screen trials may have limited information and lead to some biases. Trials that have discontinued were not included. Nevertheless, our findings suggest that researchers became more permissive to enrolling patients with autoimmune disease.

In conclusion, our retrospective study using clinical trial registry suggests that patients with lung cancer and autoimmune disease are increasing allowed to participate in immunotherapy trials. This observation is supported by several studies that immunotherapy seems well-tolerated in those individuals. Further investigations to validate the findings are warranted.

Author Contribution Statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Shamsher S. Khan. The first draft of the manuscript was written by Shamsher S. Khan and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethical Approval

This is not a human-subject study but is a study which reviews publicly available clinical trials. The article does not contain any studies performed by the authors that were with human participants or animals.

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