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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

Link to publication in University of Groningen/UMCG research database

Effects of checkpoint inhibitors in advanced non-small cell lung cancer at population level from the National Immunotherapy Registry

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ARTICLE INFO

ABSTRACT

Objective: Phase III studies of checkpoint inhibitors changed the therapeutic landscape for lung cancer. In 2015 the Dutch Society of Chest Physicians (NVALT) introduced a national immunotherapy registry for patients with lung cancer; quality standards for hospitals were implemented. At population level we studied clinical benefit in daily practice and in patients who are underrepresented in phase III trials.

Materials and Methods: From the initial introduction of checkpoint inhibitors in the Netherlands patients were centrally registered. Educational programs and quality control were provided under supervision of NVALT. The largest immunotherapy providing hospitals were compared to hospitals who provided less checkpoint inhibitors as marker of experience. Patients characteristics, treatment and side effects, response rate and survival were studied.

Results: A total of 2676 patients were registered, 2302 with follow up data were evaluated. Between October 2015 and December 2017 a gradual increase from 12 to 30 qualified hospitals showed no major toxicity differences. Toxicity led to a hospital admission rate of 9.1 with an average duration of 10.4 days.

Overall tumor response was 21.8 % and median overall survival 12.6 months. Overall survival was not significantly different for patients aged ≥ 75 years, those having brain metastases or selected auto-immune diseases before start checkpoint inhibitors compared to younger patients or those without, respectively. Survival outcomes were worse in patients with PS 2 +, non-smokers, and patients who received any palliative radiotherapy (HR 2.1, 95 % CI 1.7–2.7; 1.3, 95 % CI 1.0–1.6 and 1.2, 95 % CI 1.1–1.4, respectively).

Conclusions: Changes in the therapeutic landscape did not lead to major differences in quality of care between hospitals. Elderly patients, those with brain metastases or selected auto-immune disease underrepresented in clinical trials did not do worse on checkpoint inhibitors, except for those with PS 2 +.

1. Introduction

Insight into the therapeutic results of checkpoint inhibitors are obtained from randomized trials and careful observations in population studies [1–4] Phase III studies answer specific questions in selected patient groups with strict inclusion criteria. Patients participating in trials may show favorable outcome compared to patients not participating because of selection bias. When medical practice evolves, physicians will have a broader selection scope of patients and new questions will emerge e.g. whether patients with worse performance status,

non-smokers or elderly who are underrepresented in clinical trials may benefit from a PD-1/PD-L1 inhibitor. The implementation of new PD-1/PD-L1 inhibitors necessitates information on clinical benefit and toxicity in daily clinical practice.

Registries are designed to collect data from real-world practices over longer observation periods. They may transform medical practice by evaluating side effects and efficacy in an unbiased population. Moreover, registries can provide data for questions never asked in phase III studies. Are results from randomized trials extendable to populations where physicians do not always follow the strict inclusion criteria of published phase III studies?

Here, we describe the characteristics and outcome of patients who were registered in the national Dutch NVALT Registry at the introduction of immunotherapy in 2015 until December 31st 2017.

2. Methods

2.1. Registry study population

In October 2015 a national registry for lung cancer patients treated with immunotherapy was established. The registry was scientifically guided by a Registry Steering Committee. The introduction of nivolumab with an early access program started in 12 Dutch hospitals who had previous experience with immune modulating drugs. From May 2016 advanced NSCLC patients progressing on standard platinum therapies were treated with nivolumab as second or further line treatment. By the end of 2016 and 2017 the number of hospitals gradually increased to 21 and 30, respectively and other immune modulating drugs were introduced. Clinical characteristics, duration of treatment, toxicities and post-checkpoint inhibitor treatments were registered.

2.2. Hospital inclusion criteria

With the introduction of nivolumab as first PD-1 inhibitor in the Netherlands a quality assurance program was issued by NVALT, the Dutch Society of Chest Physicians. Quality criteria for potentially participating hospitals were treating > 20 patients yearly with advanced NSCLC with systemic therapy, have regular multidisciplinary meetings, participate in central registration of immunotherapy patients and adhere to the national multidisciplinary oncology quality criteria (SONCOS, www.soncos.org). During the introduction of first PD-1 inhibitors in the Netherlands medical specialists from different hospitals were trained in recognizing and treating side effects of immunotherapy. When the training was successful they could apply at the NVALT Quality Committee to allow providing immunotherapy. This approach of well-thought gradual introduction of ICI may have skewed the results in the beginning towards hospitals with more experienced doctors. We report on all patients who were registered at the central registry by an electronic clinical record form and who were treated with immunotherapy.

2.3. Statistics

Descriptive statistics were used for patient characteristics such as age, performance status, presence of brain metastasis, prior and subsequent treatments, duration of treatment, tumor response (investigator assessed), and side effects of immunotherapy. Logistic regression analysis was performed to detect differences between groups with and without follow up. Survival was defined from start date of checkpoint inhibitor until death. Patients who were still alive at the last date of follow-up were censored. For this registry the median observation period for survival is one year and for inclusion of patients 2 years. Central data monitoring was performed to check for inconsistencies in the data and to resolve missing data. Missing values were imputed for factors with less than 2 % missing values. Categorical values were imputed with the most frequent value and continuous variables with the

Table 1
Characteristics of advanced non-small cell lung cancer population who received immune modulating therapy and were registered in National NVALT Registry.

Variable	Total cases N = 2676 (%)	With follow up N = 2302 (%)	Without follow up N = 374 (%)	p-value*
Age, mean + SD; range; yrs	63 + 9.1; 28-88	63 + 9.2; 28-88	63 + 8.7; 40-86	0.18
Age 75 + yrs	242 (9.0)	207 (9.0)	35 (9.4)	0.82
Gender M/F	1523 (56.9)/ 1153 (43.1)	1318 (57.3)/ 984 (42.7)	205 (54.8)/ 169 (45.2)	0.38
Performance score:				0.48
0-1	2471 (92.3)	2129 (92.5)	342 (91.4)	
2 +	205 (7.7)	173 (7.5)	32 (8.6)	
Pathology:				0.54
Adenocarcinoma	1767 (66.1)	1502 (65.3)	265 (70.8)	
Squamous cell carc	713 (26.6)	629 (27.3)	84 (22.5)	
NSCLC-NOS	124 (4.6)	107 (4.6)	17 (4.5)	
Adenosquamous	11 (0.4)	10 (0.4)	1 (0.3)	
Small cell lung carc	1 (0.0)	1 (0.4)	0 (0.0)	
Large cell neuro endocrine carc	30 (1.1)	25 (1.1)	5 (1.3)	
Mesothelioma	7 (0.3)	7 (0.3)	0 (0.0)	
Others	23 (0.8)	21 (0.8)	2 (0.5)	
Smoking:				0.10
Never smoker	194 (8.5)	178 (9.0)	16 (5.3)	
Ex-smoker**	1448 (63.2)	1251 (62.9)	197 (65.0)	
Smoker	649 (28.3)	559 (28.1)	90 (29.7)	
Unknown	385	314	71	
Pack years:				0.39
Mean + SD	32.9 + 15.6	32.7 + 15.8	33.7 + 14.7	
Brain metastasis:				0.35
Present	445 (16.6)	389 (16.9)	56 (15.0)	
Absent	2231 (83.4)	1913 (83.1)	318 (85.0)	

* p-value for differences between groups.

** Quit > 3 months ago.

median value. Calculations were performed with R version 3.4.3.

3. Results

3.1. Study population

From October 2015 to December 2017 a total of 2675 patients were registered from 30 hospitals. Among those, 373 patients (14 %) had no follow up or incomplete data and were not included in this report. Five hospitals registered together half of the total number of patients. Ten hospitals treated each 1 % or less of all patients partly due to their later introduction into the program.

A total of 2302 patients with advanced NSCLC who were treated with checkpoint inhibitors were further analyzed. Patient characteristics are given in Table 1. All patients had stage IV NSCLC, M1c. Most common metastatic sites were mediastinal lymph nodes, lung, bone, liver and brain. In their medical history 108 (4.7 %) had an autoimmune disease at baseline, mostly rheumatoid arthritis. In less than 20 % of patients PD-L1 expression on tumor tissue was reported, ≥ 1 % expression occurred in 63 % of patients. Median follow up was almost 9 months.

3.2. Treatment

At first, only nivolumab was administered as second line treatment, later pembrolizumab was introduced. Atezolizumab, durvalumab and others were administered in different programs. Immunotherapy was administered as an intravenous infusion on an outpatient basis. Most patients (74.4 %) received immunotherapy as second line treatment, 19.9 % as third or further line treatment and 5.7 % as first-line treatment (Table 2). Previous treatments prior to immunotherapy were chemotherapy (94.7 %), high-dose thoracic (34.9 %) and palliative

Table 2
Treatment lines, number of cycles and reasons to stop immune modulating treatment in advanced non-small cell lung cancer population who were registered in National NVALT Registry.

Variable	Number of cases (n = 2302) (%)
Treatment line:	
First	131 (5.7)
Second	1713 (74.4)
Third or more	458 (19.9)
Number of cycles:	
Mean + SD	7.6 (7.4)
Range	1-42
Reason for stopping nivolumab:	
Progression of disease	1282 (71.1)
Toxicity	176 (9.8)
Choice patient	86 (2.4)
Others	278 (15.4)
Still on treatment	498 (21.6)

Table 3
Toxicity and hospital admissions during immune modulating treatment in advanced non-small cell lung cancer population who were registered in National NVALT Registry.

Variable	Overall cases (n = 2302) (%)
Type of toxicity grade 2-4:	
Pneumonitis	60 (22.4)
Colitis	46 (17.2)
Hepatitis	39 (14.6)
Hypo/hyperthyreoiditis	24 (8.9)
Skin rash	14 (5.2)
Hypophysitis	4 (0.4)
Vasculitis	1 (0.4)
Infusion related toxicity	9 (3.4)
Others	65 (24.4)
Unknown	5 (1.9)
(Auto) immune related toxicity grade 2-4:	
Yes	267 (11.6)
No	2035 (88.4)
Non-immune related toxicity reported*:	
Yes	285 (12.4)
No	2017 (87.6)
Number of hospital admissions:	
1	126 (78.8)
2	24 (15.0)
3+	10 (6.3)
Number of hospital admissions in days:	
Mean + SD	10.4 (8.8)
Range	1-52

* Treating physician reported toxicity.

radiotherapy (37.8 %) Mean number of immunotherapy administrations was 7.5 (SD 7.4; range 1–42). Mean duration of treatment was 17.1 weeks (SD 7.4; range 4–86).

3.3. Tumor response

Investigator assessed tumor responses were available in 1878 out of 2302 patients, 21.8 % had an objective tumor response, CR 2.1 %, PR 19.7 %, SD 32,0 %, PD 36,9 %. In 9.3 % of patients tumor response according RECIST was not evaluable. Tumor responses in patients with PS 0–1 versus PS > 1 were not significantly different, 24.3 % and 19.6 %, respectively (p = 0.32). Tumor responses observed in patients previously treated with radiotherapy versus those who had no prior radiation were 25.0 % versus 22.5 % (p = 0.26), while high-dose thoracic radiotherapy showed a trend to a higher tumor response (25.4 % versus 21.6 %, p = 0.08). Tumor responses in respectively smokers, ex-smokers and non-smokers were 24.8, 23.7 and 19.6 % (p = 0.43). Tumor response in those with and without brain metastases treated with immunotherapy was 27.3 and 23.4 % (p = 0.14).

3.4. Side effects

Two hundred sixty seven (11.6 %) patients had severe (CTC grade 3 or 4) immune related toxicity. Eight immunotherapy related deaths were reported. Most common immune reactions due to immunotherapy were pneumonitis (n = 60), colitis, (n = 46), and hepatitis (n = 39). Others were autoimmune thyreoiditis and SLE. Infusion related toxicity occurred in 9 patients. The number of immune flairs were not recorded. Immunotherapy was stopped due to progression of disease (71.1 %), side effects (9.8 %), patient's choice (3.8 %) and for other reasons (15.4 %). An overview of toxicity is provided in Table 3.

3.5. Survival and biomarker analysis

Overall survival was not significantly different for patients aged > 75 years and those with brain metastases or selected auto-immune disease before start checkpoint inhibitors and line of treatment. However, survival was worse for patients with a performance score of 2 and higher compared to those with 0–1, non-smokers compared to (ex-)smokers and patients who had any palliative radiotherapy before immunotherapy (respectively, HR 2.1, 95 % CI 1.7–2.7; 1.3, 95 % CI 1.0–1.6 and 1.2, 95 % CI 1.1–1.4) (Table 4).

For first-, second- and thirdline (or more) checkpoint inhibitors the median overall survival was 15.6 (95 % CI 2.1–13), 13.8 (95 % CI 0.4–12.3) and 14.6 (95 % CI 0.7–13.3), respectively (Fig. 1). Progression-free survival was 9.8 (95 % CI 1.5–4.8), 8.5 (95 % CI 0.3–3.9) and 9.2 (95 % CI 0.6–4.0), respectively (Supplementary Fig. 1).

3.6. Hospital outcome

The five largest immunotherapy providing hospitals were compared on clinicopathologic and outcome variables with the rest of the hospitals. These five hospitals registered more invasive rather than in situ adenocarcinoma (p < 0.001) and had more patients with a higher performance score (p < 0.001). Tumor responses were higher in the five largest immunotherapy hospitals (26.1 % vs 21.3 %, p = 0.017) (Supplementary Data). Toxicity eg. pneumonitis grade 3/4, the number of administered cycles and survival were not different, even after adjusting for clinicopathologic factors (Tables 4B and 5).

3.7. Hospital utilization

Hospital admissions were recorded for 160 patients, 126 (78.8 %) needed one admission, 24 (15 %) two admissions and 10 patients (6.3 %) more than two. The hospital admission rate was 9.1 (210/2302). Mean duration of hospital admissions was 10.4 days (range 1–52).

4. Discussion

Checkpoint inhibitors against PD-1/PD-L1 receptors have become standard in first-line (PD-L1 > 50 % expression) and further lines of treatment in advanced NSCLC. This was due to an improved efficacy and a different and better tolerated safety profile as compared with chemotherapy in phase III studies. In this population study we report the gradual introduction of checkpoint inhibitors and confirm the magnitude of the tumor response rate of 21.8 % and 1-year progression-free survival of 25.6 % at the expense of 11.6 % immune related toxicities, a hospital admission rate of 9.1 with an average duration of 10.4 days. Most admissions were related to immune mediated toxicity.

Implementing a new class of drugs that has a distinct toxicity profile in routine practice should ideally be initiated in centers that already gained experience. Subsequently, implementation can follow in other hospitals requiring the training of clinicians in the management of immune related toxicities and the immune related tumor response. The introduction of new treatments delivered in hospitals with less

Table 4

(A) Univariable and (B) multivariable survival analysis of all factors including hospital utilization associated with characteristics of 2302 advanced NSCLC patients.

A

Patient characteristics	Events	N	Median OS (95 % CI)	*p*-value	HR	95 % CI	*p*-value
Age:							0.17
28-≤75	892	2095	12.3 (11.3–13.3)		1		
> 75-88	68	207	13.7 (12.3–19.9)	0.17	0.84	0.66-1.08	
Performance score:							< 0.0001
0–1	866	2129	13.3 (12.1–14.5)		1		
>1	94	173	4.6 (3.0–6.6)	< 0.0001	2.15	1.74-2.66	
Previous auto-immune disorder[a]:							0.71
No	920	2194	12.5 (11.5–13.4)		1		
Yes	40	108	13.3 (7.8-NA)	0.71	0.94	0.69-1.29	
Smoking[b]:							0.03
Smoker	234	559	12.2 (10.0–14.6)		1		
Ex-smoker	527	1251	13.3 (12.0–15.2)	0.49	0.94	0.81-1.11	
Non-smoker	92	178	8.6 (5.9–12.2)	0.047	1.28	1.00–1.63	
Brain metastasis:							0.07
No	793	1913	13.2 (11.8–13.9)		1		
Yes	167	389	9.8 (7.2–13.3)	0.069	1.17	0.99-1.38	
Previous palliative radiotherapy:							0.004
No	546	1431	13.3 (11.7–14.6)		1		
Yes	414	871	11.8 (9.5–13.3)	0.004	1.20	1.06-1.37	
Previous thoracic radiotherapy:							0.75
No	625	1499	12.6 (11.5–13.9)		1		
Yes	335	803	12.3 (11.1–13.9)	0.75	0.98	0.86-1.12	

B

Patient characteristic	HR	95 % CI	*p*-value
Performance score:			< 0.0001
0–1	1		
>1	2.16	1.74-2.68	
Hospital utilization[c]:			0.63
Top 5 hospitals	1		
Smaller hospitals	1.02	0.89-1.17	

HR > 1 performs worse and < 1 performs better.

[a] Mainly mild rheumatoid arthritis and psoriasis.

[b] 314 missing data excluded.

[c] Hospital utilization is measured as survival adjusted for age and PS but not for comorbidity.

median OS – first line : 15.6 (95% CI: 2.1 – 13.0)
median OS – second line : 13.9 (95% CI: 0.4 – 12.3)
median OS – third line : 14.6 (95% CI: 0.7 – 13.3)
Log–rank p = 0.73

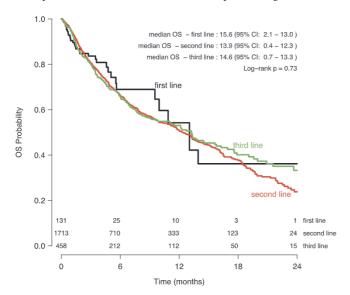|					
131	25	10	3	1	first line
1713	710	333	123	24	second line
458	212	112	50	15	third line

Fig. 1. Overall survival of 2302 patients with advanced NSCLC who were registered for first, second or thirdline (or more) checkpoint inhibitors. Subscription under Fig. 1
Median overall survival is 12.6 months (95 % CI 11.7–13.4).

Table 5

Outcome of largest 5 immunotherapy providing hospitals versus the smaller 25 hospitals as marker for experience.

Outcome	5 largest hospitals (n = 1181)	Other hospitals (n = 1121)	*p*-value
Tumor response rate (%)	26.1	21.3	0.017
Median overall survival (months)	12.5	12.9	0.713
Toxicity (%):			0.23
Grade 2	84.2	82.1	
Grade 3	10.8	16.1	
Grade 4	5.0	1.8	
Auto-immune toxicity (%)	11.7	11.4	0.839
Mean number of cycles (SD)	7.7 (7.8)	7.4 (6.9)	0.076

experience can be guided by quality rules and monitored through national registries. The NVALT have set protocols and standard operating procedures for all hospitals that were included into this Registry project. As a result, the outcome in 25 hospitals was similar on toxicity and number of administered cycles as the largest top-5 immunotherapy providing hospitals. Tumor responses were better in the largest centers. A lower adjusted survival outcome in the top-5 hospitals was observed probably due to worse co-morbidities in these referred patients. Especially in the beginning of the program many ineligible patients were referred to the largest centers as last resort. Overall survival in the first half year of implementation was worse compared to the last half year in 2017.

Although at that time autoimmune diseases were a contra-indication for immune modulating treatments, 4.7 % of patients were reported to have an immune related disease, mostly rheumatoid arthritis.

Their tumor response was numerically better ($p = 0.084$) but overall survival was not different from those without pretreatment autoimmune disorders. They appeared to develop more often swollen joints and arthralgia.

Clinical trials in advanced solid tumours are tentatively expanding to include patients with pre-existing autoimmune disease [5]. Patients with a pre-existing autoimmunity showed a flare during PD-1 inhibition that is manageable in clinical practice [6,7]

It is known that about 13 % of lung cancer patients have autoimmune disease such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, polymyalgia rheumatic and Addison's disease as most prevalent [8]. Patients with autoimmune diagnoses are more likely to be older, female, have earlier-stage disease, and have improved clinical outcomes compared to those without autoimmune diseases. The main immune related toxicity observed was pulmonary toxicity. Although the frequency of pulmonary inflammatory conditions in whole populations is reported to be low (1.8 %), 2.6 % (60/2302) of patients in this population study had pulmonary toxicities. We could not confirm higher serious events that have been reported in non-academic hospitals or even 19 % at a retrospective study at John Hopkins Hospital[4,] [9]. In literature pneumonitis has been described in less than 10 % of patients treated with PD-1 inhibitors [10–13]. Pulmonary inflammatory conditions included in our study were mostly pneumonitis, but some were probably pneumonia or radiation related toxicity.

Non-smoking patients performed significantly worse with checkpoint inhibitors than ex-smokers or current smokers. Many studies reported similar effects and therefore one should question the use of checkpoint inhibitors in non-smokers. They may fare better with chemotherapy.

It is unknown how patient selection, specific dosing and toxicity management practices influences outcome. In this study the hazards for death at first, second and third line treatment were similar. An important selection marker - PD-L1 immunohistochemistry - was collected during the time that many laboratories introduced PD-L1 IHC. We observed a large diversity in IHC methods and a wide variation in pathological experience to assess the expression. Therefore, we did not perform additional analyses on PD-L1 expression and patient characteristics. Another issue is the outcome of underrepresented patients in clinical trials such as those with PS 2+, brain metastases and pre-existing auto-immune disorders. This Registry shows that PS 2+ remains a poor prognostic factor in patients treated with checkpoint inhibitors and that brain metastases and (selected) auto-immune disorders have a similar outcome compared to patients without these conditions and therefore are not a contra-indication for these inhibitors.

Registry studies have limitations as compared with phase III studies. Only a limited number of essential variables are registered and with larger time intervals checked by a datamanager to complete the data.

In conclusion, the gradual introduction of nivolumab followed by other checkpoint inhibitors for advanced NSCLC in the Netherlands showed similar outcome as those of phase III studies in terms of tumor response and survival at the expense of less than one hospital admission for 10 treated patients for 10 days with manageable moderate toxicity.

Funding

Author's contribution

H.J.M. Groen wrote the manuscript, H. van Tinteren analysed the data set. All authors had insight into the data and contributed to the manuscript. All authors agreed on the submitted version.

Addendum

Participating hospitals

Antoni Van Leeuwenhoek hospital, Amsterdam
Amphia hospital, Breda
University Medical Center Groningen, Groningen
Amsterdam Medical University Hospital, Amsterdam
Erasmus Medical Center, Rotterdam
Rijnstate hospital, Arnhem
Catharina hospital, Eindhoven
University Medical Center Maastricht, Maastricht
Jeroen Bosch hospital, s'-Hertogenbosch
Isala hospital, Zwolle
Atrium Medical Center, Heerlen
St. Antonius hospital, Nieuwegein
Deventer hospital, Deventer
Martini hospital, Groningen
Meander Medical Center, Amersfoort
Zorggroep Twente, Almelo
Maasstad hospital, Rotterdam
Maxima Medical Center, Veldhoven
Gelderse Vallei hospital, Ede
St. Jansdal hospital, Harderwijk
Noordwest hospitalgroup, Alkmaar
University Medical Center Radboud, Nijmegen
Medical Spectrum Twente, Enschede
Sint Elisabeth hospital, Tilburg
Haga hospitals, the Hague
Tergooi hospital, Hilversum
Medical Center Haaglanden, The Hague
University Medical Center Leiden, Leiden
Onze Lieve Vrouwe Gasthuis, Amsterdam
Medical Center Leeuwarden, Leeuwarden

Declaration of Competing Interest

H.J.M. Groen reports other from Pfizer, other from Novartis, other from Bristol Meyer Squibb, other from MSD Oncology, other from Eli Lilly, other from Abbvie, other from Roche/Genentech, outside the submitted work.

E.F. Smit reports other from Lilly, other from Boehringer Ingelheim, other from Bayer, other from Roche/Genentech, other from AstraZeneca, outside the submitted work.

J. Aerts reports other from MSD, other from Boehringer, other from BMS, other from Eli-Lilly, other from Astra-Zeneca, outside the submitted work.

A-M.C. Dingemans reports other from Roche/ Genentech, other from MSD Oncology, other from AstraZeneca, other from Pfizer, other from Lilly, other from Boehringer Ingelheim, other from Bristol-Myers Squibb, other from Clovis Oncology, outside the submitted work.

The remaining authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.12.011.

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