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Pre-diagnosis netrophil-to-lymphocyte ratio and lung cancer mortality

Real-world outcomes of first-line Pembrolizumab MONOTHERAPY for PD-L1-positive (TPS≥50%) metastatic NSCLC

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Pre-diagnosis netrophil-to-lymphocyte ratio and lung cancer mortality

#3300

Pre-diagnosis neutrophil-to-lymphocyte ratio and lung cancer mortality

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CARET Carotene and Retinol Efficacy Trial

BACKGROUND

- Inflammation is an established hallmark of cancer development and progression.
- The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation.
  - NLR is associated with smoking status.
  - Increasing NLR is associated with increased mortality from many chronic diseases, including lung cancer.
  - Most studies examine blood at diagnosis, which may reflect disease-related inflammation.
- Hematopoiesis is programmed through epigenetic changes, which enables blood cell proportion estimation from methylation data.
- We examined whether the inflammatory profile reflected by pre-diagnosis DNA methylation-derived NLR (mdNLR) was associated with lung cancer mortality in a prospective study of heavy smokers.

METHODS

- 293 lung cancer cases from the CARET trial with:
  - ≥20 pack years
  - ≤6 years since quit
  - And/or occupational asbestos history
- Blood collected on average 4.1 years pre-diagnosis
- Cases were identified through 2005 and followed for mortality events through 2013
- DNA methylation assayed on the 850K CpG Illumina EPIC array
- Pre-diagnosis mdNLR was computed as the ratio of predicted granulocyte and lymphocyte proportions derived from DNA methylation signatures in whole blood
  - White blood cell mixture deconvolution (Koestler et al. 2017, *CEBP*)
  - mdNLR is defined by quartiles indicating low (Q1) to high (Q4) systemic inflammation
- Assessed associations with pre-diagnosis mdNLR and lung cancer-specific mortality using adjusted Cox proportional hazards models
  - Age, sex, race, smoking status, intervention arm, asbestos exposure, pack years smoked, time between blood draw and diagnosis
  - Stage strata (non-proportional baseline hazards)

RESULTS

Table 1. Characteristics of CARET lung cancer cases at blood draw.

	All cases*	Adenocarcinoma	Squamous cell	Small cell
Mean (SD) or N (%)	(N=293)	(N=122)	(N=100)	(N=62)
Age, years	64.1 (5.6)	64.2 (5.5)	64.3 (5.5)	63.6 (6.1)
Race (White)	282 (96)	120 (98)	93 (93)	60 (97)
Female	99 (34)	51 (42)	23 (23)	23 (37)
Current smoker	188 (64)	68 (56)	76 (76)	39 (63)
Pack-years	59.0 (22.6)	58.1 (20.9)	61.2 (24.4)	58.3 (23.4)
Years since quit smoking	2.3 (4.2)	2.7 (4.5)	1.6 (3.4)	2.4 (4.5)
Active intervention arm	157 (54)	66 (54)	53 (53)	33 (53)
Asbestos exposed	51 (17)	19 (16)	21 (21)	10 (16)
Late stage (III/IV)	215 (73)	85 (70)	62 (62)	59 (95)
Years from diagnosis to death or end of study period (2013)	2.3 (3.6)	3.0 (4.1)	2.4 (3.7)	1.1 (1.9)
Years between blood draw and diagnosis	4.1 (2.4)	4.1 (2.5)	4.3 (2.2)	3.8 (2.4)
Any death (through 2013)	284 (97)	115 (94)	98 (98)	62 (100)
Lung cancer-specific death (through 2013)	247 (84)	96 (79)	82 (82)	60 (97)
mdNLR	2.0 (1.3)	2.0 (1.1)	2.2 (1.6)	1.9 (1.3)

Abbreviation: SD = Standard Deviation

*"All cases" includes adenocarcinoma, squamous cell carcinoma, and small cell cases as well as not otherwise specified non-small cell lung cancer (NSCLC; NOS; n=9).

Figure 1. Hazard ratios for pre-diagnosis mdNLR and mortality in lung cancer cases, overall and by histotype.

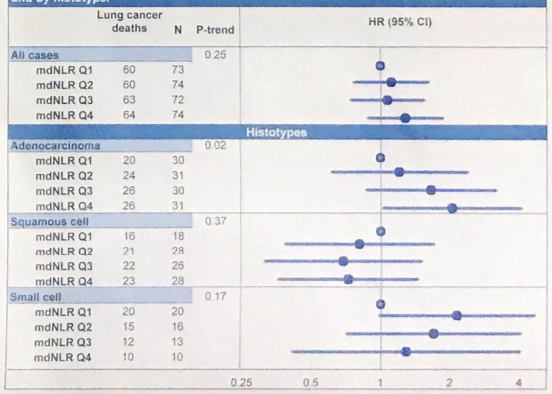

Table 2. Hazard ratios for pre-diagnosis mdNLR and mortality in selected adenocarcinoma case subgroups

	Adenocarcinoma deaths	N	HR (95% CI)	P-trend
≤65 years at blood draw				
mdNLR Q1	12	20	Ref	0.002
mdNLR Q2	16	19	2.10 (0.86, 5.23)	
mdNLR Q3	16	18	2.66 (1.06, 6.70)	
mdNLR Q4	14	16	4.70 (1.73, 12.8)	
≤68.2 years at diagnosis (median)				
mdNLR Q1	10	14	Ref	0.001
mdNLR Q2	16	19	2.32 (0.83, 6.50)	
mdNLR Q3	11	13	2.72 (0.94, 7.85)	
mdNLR Q4	15	16	6.09 (1.98, 18.7)	
<53 pack years smoked (median)				
mdNLR Q1	10	15	Ref	0.02
mdNLR Q2	11	14	2.09 (0.74, 5.94)	
mdNLR Q3	20	21	3.17 (1.19, 8.44)	
mdNLR Q4	9	11	2.91 (1.03, 8.22)	
Active intervention				
mdNLR Q1	12	18	Ref	0.03
mdNLR Q2	17	19	1.83 (0.73, 4.61)	
mdNLR Q3	14	16	2.21 (0.86, 5.68)	
mdNLR Q4	12	13	3.32 (1.11, 9.93)	

CONCLUSIONS

- An inflammatory response prior to diagnosis as indicated by higher mdNLR levels may be associated with mortality in heavy smokers who go on to develop lung adenocarcinoma.
  - HR=2.03, 95% CI: 1.03-4.03 comparing mdNLR Q4 to mdNLR Q1.
  - We observed a statistically significant linear trend for increased risk of mortality with increasing mdNLR quartiles (P=0.02).
  - Associations among adenocarcinoma cases were largest in magnitude for those who were younger at blood draw, younger at diagnosis, who had fewer than the median of pack year smoking history, and who were in the active intervention arm.
- We did not observe evidence for associations between mdNLR and mortality for squamous cell or small cell lung cancer.
- Since indicators of survival may be used to guide treatment decisions and gauge response to treatment, further studies are needed to understand the potential clinical utility of pre-diagnosis mdNLR.

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Real-world outcomes of first-line Pembrolizumab MONOTHERAPY for PD-L1-positive (TPS≥50%) metastatic NSCLC

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Real-World Outcomes of First-Line Pembrolizumab Monotherapy for PD-L1-positive (TPS ≥50%) Metastatic Non–Small-Cell Lung Cancer (NSCLC)

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INTRODUCTION

- Pembrolizumab monotherapy was approved in October 2016 for first-line treatment of metastatic non–small-cell lung cancer (NSCLC) with PD-L1 tumor proportion score (TPS) ≥50% based on KEYNOTE-024 (KN024) trial results[1]
- A subsequent trial, KN042, confirmed overall survival (OS) benefit with pembrolizumab monotherapy over platinum doublet chemotherapy in the same population[2]
- In a recently published updated analysis of KN024,[3] median OS was 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab therapy
- In KN042, median OS was 20.0 months (95% CI, 15.4 to 24.9 months)[2]
- Real-world data can provide unique insights into patient characteristics, treatments, and outcomes for patients with lung cancer treated in routine oncology practice settings, where the majority are treated
- Real-world outcomes of pembrolizumab therapy for metastatic NSCLC require study and characterization

OBJECTIVE

- To investigate effectiveness of first-line pembrolizumab monotherapy in the real-world setting of routine clinical practice in the United States (US) for patients clinically similar to those in KN024 and KN042 with stage IV NSCLC, PD-L1 TPS ≥50%, and whose tumors do not harbor targetable mutations

METHODS

Study Design

- Retrospective database analysis
- **Data source:** Flatiron Health[a] database[4]
  - Longitudinal, demographically and geographically diverse database derived from electronic health record (EHR) data covering over 265 US cancer clinics across ~800 sites of care, representing more than 2 million patients with cancer and active medical records available for analysis
  - De-identified patient-level data include structured and unstructured data curated via technology-enabled abstraction
  - The recently validated Flatiron Health mortality 2.0 composite endpoint was used to identify date of death[5]
  - Ethical approval: Institutional Review Board approval obtained before study initiation
- **Index date:** First-line pembrolizumab monotherapy initiation

Patients

- **Inclusion criteria:**
  - Stage IV or recurrent metastatic NSCLC with PD-L1 TPS ≥50% and no documented sensitizing epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) translocation
  - Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1
- **Exclusion criterion:**
  - Clinical trial participation
- **Two patient cohorts:**
  - **EHR cohort:**
    - Initiated first-line pembrolizumab monotherapy Oct. 24, 2016 – May 31, 2018
    - Data cutoff Nov. 30, 2018
  - **Spotlight cohort:** randomly selected from EHR cohort for enhanced manual chart review
    - Initiated first-line pembrolizumab monotherapy Dec. 1, 2016 – Nov. 30, 2017
    - Data cutoff May 31, 2018

[a]Flatiron Health, Inc., did not participate in the analysis of this data.

Study Endpoints

- **Overall survival (OS):** for both Spotlight and EHR cohorts
  - OS (months) = (date of death – start date of pembrolizumab) + 1 day
  - Patients with no recorded date of death were censored at the last contact date or the end of the dataset, whichever occurred first
- **Real-world progression (rwP):** for Spotlight only
  - rwP = a distinct episode in which the treating clinician concluded that there had been growth or worsening of NSCLC (episodes ≤14 days after index date were excluded)
  - Used to estimate real-world progression-free survival (rwPFS) = time from pembrolizumab initiation to first documented rwP event or death, whichever occurred first
  - rwPFS: Patients with no rwP were censored at their last clinic date, or last clinic date before initiating new treatment
- **Real-world tumor response (rwTR):** for Spotlight only
  - rwTR = assessment of changes in NSCLC tumor burden as indicated by radiology reports (changes ≤30 days after index date were excluded)
  - Mapped as complete response, partial response, stable disease, progressive disease, pseudoprogression, indeterminate response, not documented
- **Reasons for pembrolizumab discontinuation:** for Spotlight only
  - One or more reasons for discontinuation identified via enhanced manual chart review
- **Subsequent systemic anticancer therapy:** for both Spotlight and EHR cohorts

Statistical Analyses

- Baseline patient characteristics, rwTR, reasons for pembrolizumab discontinuation, and subsequent therapy were summarized descriptively
- Time to event endpoints were estimated using the Kaplan Meier method
- Analyses were conducted using R version 3.5.0 (https://www.R-project.org/)

RESULTS

Patients

- 362 patients were eligible for the EHR cohort and 186 patients were eligible for the Spotlight cohort (**Figure 1**)
- Patient characteristics in the two real-world cohorts were similar, with the exception of proportionately fewer men, and fewer patients with ECOG PS of 1, in the Spotlight cohort as compared with the EHR cohort (**Table 1**)

Figure 1. Patient Selection for the EHR and Spotlight Cohorts From the Flatiron Health (FH) Database

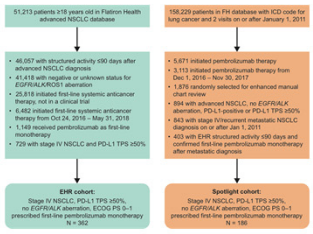

Table 1. Baseline Demographic and Clinical Characteristics of Patients With Stage IV NSCLC, PD-L1 TPS ≥50%, Without Targetable Mutations, and ECOG PS 0–1

Variable	Real-World Cohorts: EHR (n = 362)	Spotlight (n = 186)
Men	194 (54)	90 (48)
Age, median (range), years	72 (45–85)	72 (46–84)
≥65 years	256 (71)	140 (75)
Race, white[a]	254 (77)	128 (79)
Black[a]	28 (9)	17 (10)
Asian[a]	11 (3)	3 (2)
Other race[a]	35 (11)	15 (9)
Current/former smoker	332 (92)	169 (91)
Squamous histology	88 (24)	46 (25)
Stage IV at diagnosis	362 (100)	156 (84)
ECOG performance status of 1	231 (64)	111 (60)
Brain metastasis	43 (12)	22 (12)

Data are n (%) unless otherwise indicated.
[a]Race data represent percentages of patients with available data (approximately 90%).

Table 2. Outcomes With First-Line Pembrolizumab Monotherapy in Real-World Settings Calculated Using the Kaplan-Meier Method for Patients With Stage IV NSCLC, PD-L1 TPS ≥50%, Without Targetable Mutations, and ECOG PS 0–1

Variable	Real-World Cohorts: EHR (n = 362)	Spotlight (n = 186)
Observed follow-up, median (range), mo[a]	15.9 (6.0–24.8)	11.7 (6.0–18.0)
Patient follow-up, median (range), mo[a]	9.7 (0.1–24.7)	7.7 (0.1–17.5)
Overall survival (OS)		
Events, n (%)	149 (41)	62 (33)
OS, median (95% CI), mo	21.1 (15.3–NR)	NR (15.1–NR)
6-month survival, % (95% CI)	74 (69–78)	74 (67–80)
12-month survival, % (95% CI)	61 (56–66)	64 (55–71)
rwTR: complete or partial response, n	–	86
Complete or partial response, % (95% CI)	–	46 (39–54)
Real-world progression-free survival (rwPFS)		
Events, n (%)	–	110 (59)
rwPFS, median (95% CI), mo	–	7.0 (5.6–8.4)
6-month rwPFS, % (95% CI)	–	54 (47–61)
12-month rwPFS, % (95% CI)	–	35 (27–43)

EHR data cutoff: Nov. 30, 2018; Spotlight data cutoff May 31, 2018.
[a]Observed follow-up was defined as the duration of EHR database follow-up from pembrolizumab initiation to database cutoff. Patient follow-up was defined as time from pembrolizumab initiation in EHR data to the date of death or data cutoff, whichever occurred first.
EHR, electronic health record; mo, months; NR, not reached; rwTR, real-world tumor response.

Figure 2. Overall Survival in the EHR Cohort: Patients With Stage IV NSCLC, PD-L1 TPS ≥50%, Without Targetable Mutations, and ECOG PS 0–1 Prescribed First-Line Pembrolizumab Monotherapy

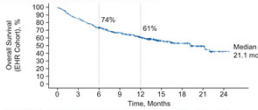

Figure 3. Overall Survival in the Spotlight Cohort: Patients With Stage IV NSCLC, PD-L1 TPS ≥50%, Without Targetable Mutations, and ECOG PS 0–1 Prescribed First-Line Pembrolizumab Monotherapy

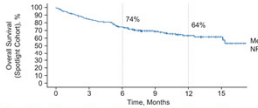

Figure 4. Real-World Progression-Free Survival in the Spotlight Cohort: Patients With Stage IV NSCLC, PD-L1 TPS ≥50%, Without Targetable Mutations, and ECOG PS 0–1 Prescribed First-Line Pembrolizumab Monotherapy

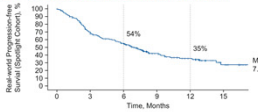

Table 3. Reasons for Pembrolizumab Discontinuation in the Spotlight Cohort

	Spotlight (n = 186)
Discontinued, n (%)	93 (50)
Reasons for discontinuation (n = 93), n (%)[a]	
Progression	42 (45)
Toxic effect of therapy	22 (24)
Disease-related symptoms not due to therapy	17 (18)
Patient request	4 (4)
Financial	1 (1)
Other[b]	13 (14)
Unknown	0

[a]Patients could have >1 reason for discontinuation.
[b]The "Other" category could include patients who remained on pembrolizumab until death (to maintain data de-identification).

Table 4. Subsequent Systemic Therapy

Variable	EHR (n = 362)	Spotlight (n = 186)
Second-line systemic therapy, n (%)	100 (28)	44 (24)
Platinum-based chemotherapy combination (without anti-VEGF)	39 (11)	22 (12)
Anti-PD-1/PD-L1-based combination therapy	16 (4)	6 (3)
Anti-PD-1/PD-L1 monotherapy	14 (4)	6 (3)
Single agent chemotherapy	10 (3)	7 (4)
Anti-VEGF-based combination therapy	17 (5)	2 (1)
Non-platinum-based chemo combination	2 (<1)	1 (<1)
Tyrosine kinase inhibitor	2 (<1)	0
Third-line systemic therapy, n (%)[a]	18 (5)	5 (3)
Platinum-based chemotherapy combination (without anti-VEGF)	3 (<1)	1 (<1)
Anti-PD-1/PD-L1-based combination therapy	1 (<1)	1 (<1)
Anti-PD-1/PD-L1 monotherapy	4 (1)	0
Single agent chemotherapy	7 (2)	1 (<1)
Anti-VEGF-based combination therapy	1 (<1)	0
Non-platinum-based chemo combination	1 (<1)	0
Tyrosine kinase inhibitor	1 (<1)	2 (1)

[a]4 patients in EHR cohort and 1 patient in Spotlight cohort also received fourth-line therapy.
Chemo, chemotherapy; PD-1/PD-L1, programmed death 1/programmed death ligand-1; VEGF, vascular endothelial growth factor.

CONCLUSIONS

- In real-world US oncology practice, patients prescribed first-line pembrolizumab monotherapy for PD-L1-positive (TPS ≥50%) metastatic NSCLC tended to be older and included fewer men than in clinical trials, even after limiting to key trial eligibility criteria
- Enhanced manual chart review enabled us to capture episodes of progression and assessments of radiologic change in NSCLC, thereby to more closely evaluate the outcomes of first-line pembrolizumab monotherapy in the Spotlight cohort
- The benefits observed, including OS, real-world PFS, and real-world tumor response, were consistent with phase 3 trial findings, supporting the effectiveness of pembrolizumab in real-world settings
- Disease progression was the most common reason for pembrolizumab discontinuation
- At the time of data cutoff, 24% of patients in the Spotlight cohort had received second-line systemic therapy, most commonly a platinum-based chemotherapy combination

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Disclosures

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