Programmed Cell Death Ligand-1 Testing Among Patients With Metastatic Non-Small Cell Lung Cancer: A Multinational Medical Record Review Study

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BACKGROUND

- Lung cancer is the most common cancer in the world, with 1.82 million new cases diagnosed in 2012 (12.9% of all new cancers) and 1.59 million deaths in 2012.[1]
- The majority of patients with non-small cell lung cancer (NSCLC) are diagnosed at an advanced stage of the disease.[2] Among those with stage IV disease at diagnosis, 5-year relative survival is 5.2%.[3]
- Treatment options for patients with metastatic NSCLC depend on tumor histology, patient age, performance status, comorbid conditions, and patient preferences.[4]
- The availability of immunotherapy agents since 2015 — i.e., anti-programmed cell death protein 1 (PD-1) and anti-programmed cell death ligand 1 (PD-L1) therapies — has increased the number of effective treatments available for patients with metastatic NSCLC who are not eligible for epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) targeted therapies.[5] Compared with cytotoxic chemotherapy, these agents are associated with improved survival, longer duration of response, and fewer adverse events.[6-9]
- Identification of tumor PD-L1 expression at initial diagnosis may identify patients who are more likely to benefit from PD-L1 inhibitors.[10]

OBJECTIVE

- To describe PD-L1 testing and results among patients with metastatic NSCLC in the United States (US), United Kingdom (UK), Germany, Spain, and Canada.

METHODS

- We conducted a retrospective review of medical records of patients diagnosed with metastatic NSCLC who were eligible for first-line treatment between January 1, 2011, and March 31, 2016 in the US, UK, Germany, Spain, and Canada.
- A convenience sample of oncologists selected a quasi-random sample of patients from their practice and abstracted anonymized, retrospective data from the patients' medical records.
- The sample consisted of 61, 42, 89, 50, and 13 physicians in the US, UK, Germany, Spain, and Canada, respectively. Participating physicians were geographically dispersed in their respective countries.
- Patient selection criteria are listed in Table 1.
- PD-L1 biomarker testing at initial diagnosis of NSCLC was collected.
  - Among patients who received PD-L1 testing, we recorded the type of assay used for PD-L1 testing (free-text), PD-L1 test result values, recorded result of the test (i.e., positive; negative; test performed, but result inconclusive; or test performed, but result unavailable), and threshold used to classify PD-L1 test as positive.

Table 1. Patient Selection Criteria

Inclusion Criteria	Exclusion Criteria
• Confirmed diagnosis of metastatic NSCLC between January 1, 2011, and March 31, 2016. – Patients may have been initially diagnosed with metastatic disease or initially diagnosed with more limited disease and progressed to having disease at distant sites (i.e., metastatic disease).	• Evidence of other malignant neoplasms (except nonmelanoma skin cancer or carcinoma in situ).
• Did not receive chemotherapy or any other systemic therapy for locally advanced NSCLC. – Patients who received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for locally advanced disease prior metastatic diagnosis were eligible if progression occurred more than 6 months from last therapy. – Aged 18 years or older at metastatic NSCLC diagnosis.	• Mixed small cell and non-small cell histology or not otherwise specified histology. • Participation in a clinical trial related to treatment of metastatic NSCLC . • Patients with evidence of certain other treatments/conditions were excluded.[a]

[a]The treatments/conditions that were excluded are epidermal growth factor receptor (EGFR) mutations; anaplastic lymphoma kinase (ALK) rearrangement; brain metastases or spinal cord compression unless asymptomatic or treated and stable (not requiring steroids); exposure to immunomodulatory therapy prior to metastatic diagnosis; active or prior documented autoimmune or inflammatory disorder; prior exposure to any anti-PD-L or PD-L1 antibody; severe or uncontrolled systemic diseases, including active bleeding diatheses or active infections including hepatitis B and C and HIV; uncontrolled illness such as symptomatic congestive heart failure, uncontrolled hypertension, or unstable angina pectoris; any unresolved toxicity Common Terminology Criteria for Adverse Events > grade 2 from the prior chemoradiation therapy; active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

RESULTS

Table 2. Clinical Characteristics of Patients at Initial and Metastatic Diagnosis

Characteristic	US		UK		Germany		Spain		Canada	
Total patient sample (N)	204	100.0%	206	100.0%	212	100.0%	205	100.0%	55	100.0%
Clinical stage at initial diagnosis (n, %)										
Stage 0 to IIB	17	8.3%	5	2.4%	1	0.5%	4	2.0%	11	20.0%
Stage IIIA	11	5.4%	13	6.3%	3	1.4%	2	1.0%	7	12.7%
Stage IIIB	24	11.8%	13	6.3%	19	9.0%	12	5.9%	13	23.6%
Stage IV	152	74.5%	169	82.0%	188	88.7%	171	83.4%	24	43.6%
Don't know	0	0.0%	6	2.9%	1	0.5%	16	7.8%	0	0.0%
Tumor histology at initial diagnosis (n, %)										
Squamous cell carcinoma	59	28.9%	85	41.3%	60	28.3%	80	39.0%	21	38.2%
Large cell carcinoma	7	3.4%	5	2.4%	5	2.4%	24	11.7%	8	14.6%
Adenocarcinoma	137	67.2%	112	54.4%	144	67.9%	99	48.3%	24	43.6%
Other NSCLC	1	0.5%	1	0.5%	1	0.5%	2	1.0%	2	3.6%
Don't know	0	0.0%	3	1.5%	2	0.9%	0	0.0%	0	0.0%
Tumor grade at initial diagnosis[a] (n, %)										
Grade 1/2	124	60.8%	68	33.0%	76	35.9%	93	45.4%	30	54.6%
Grade 3/4	61	29.9%	87	42.2%	111	52.4%	96	46.8%	24	43.6%
Could not be assessed	4	2.0%	13	6.3%	4	1.9%	6	2.9%	0	0.0%
Don't know	15	7.4%	38	18.5%	21	9.9%	10	4.9%	1	1.8%
Site(s) of metastases at initial diagnosis, among stage III and IV patients (n, %)										
Adrenal gland	49	26.20%	60	30.77%	38	18.10%	50	27.03%	4	9.09%
Bone	86	45.99%	79	40.51%	75	35.71%	83	44.86%	25	56.82%
Brain	7	3.74%	17	8.72%	27	12.86%	23	12.43%	3	6.82%
Liver	73	39.04%	61	31.28%	57	27.14%	75	40.54%	14	31.82%
Other lung	75	40.11%	67	34.36%	56	26.67%	105	56.76%	16	36.36%
Regional lymph nodes	94	50.27%	75	38.46%	46	21.90%	54	29.19%	35	79.55%
Distant lymph nodes	61	32.62%	65	33.33%	46	21.90%	56	30.27%	16	36.36%
Renal/kidney	3	1.60%	4	2.05%	6	2.86%	7	3.78%	0	0.00%
Skin/soft tissue	6	3.21%	11	5.64%	5	2.38%	13	7.03%	1	2.27%
Other	7	3.74%	2	1.03%	0	0.00%	8	4.32%	1	2.27%
None	2	1.07%	5	2.56%	1	0.48%	3	1.62%	0	0.00%
Don't know	2	1.07%	8	4.10%	8	3.81%	1	0.54%	0	0.00%
Performance status at metastatic diagnosis[b] (n, %)										
0	40	19.6%	29	14.1%	40	18.9%	23	11.2%	10	18.2%
1	116	56.9%	143	69.4%	156	73.6%	132	64.4%	21	38.2%
≥ 2	47	23.0%	27	13.1%	16	7.5%	46	22.5%	23	41.8%
Don't know	1	0.5%	7	3.4%	0	0.0%	4	2.0%	1	1.8%
Length of follow-up, months[c] (mean [SD])	18.3	11.2	14.8	8.0	16.5	5.9	15.6	8.6	15.2	7.8
Charlson Comorbidity Index[d] (mean [SD])	1.6	1.6	1.2	1.3	1.0	0.9	1.4	1.4	1.5	1.5

[a] Edge and Compton, 2010.[13] [b] Eastern Cooperative Oncology Group score. [c] Length of follow-up is the duration of time between the date of metastatic diagnosis and death or end of patient record. [d] Calculation does not include cancer as a comorbidity

Table 3. Programmed Cell Death Ligand 1 Testing by Year, Test Results, and Thresholds Used at Initial Diagnosis

Characteristic	US		UK		Germany		Spain		Canada	
Total patient sample (N)	204	100.0%	206	100.0%	212	100.0%	205	100.0%	55	100.0%
Patients with initial diagnosis prior to 2015 (n)	64		48		4		60		24	
PD-L1 test received	10	15.63%	2	4.17%	1	25.00%	3	5.00%	2	8.33%
Patients with initial diagnosis in 2015 (n)	71		77		20		72		19	
PD-L1 test received	24	33.80%	16	20.78%	5	25.00%	0	12.50%	12	63.16%
Patients with initial diagnosis in 2016 (n)	69		81		188		73		12	
PD-L1 test received	36	52.17%	38	46.91%	61	32.45%	23	31.51%	5	41.67%
PD-L1 testing at initial diagnosis (n)	70		56		67		35		19	
Proportion of TC stained positive for PD-L1 among those with test result reported (n, %)	69	98.57%	48	85.71%	60	89.55%	27	77.14%	17	89.47%
Mean (SD)	33.9	34.3	31.1	31.1	16.7	24.0	17.2	23.5	33.1	21.7
Median	30.0		20.0		1.0		10.0		30.0	
Threshold used to classify test result as "positive" among those with threshold reported (n, %)	61	87.14%	49	87.50%	51	76.12%	28	80.00%	17	89.47%
1% TC	19	31.15%	32	65.31%	37	72.55%	15	53.57%	1	5.88%
5% TC	7	11.48%	1	2.04%	0	0.00%	5	17.86%	0	0.00%
10% TC	0	0.00%	1	2.04%	0	0.00%	0	0.00%	1	5.88%
20% TC	1	1.64%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
25% TC	9	14.75%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
50% TC	25	40.98%	15	30.61%	14	27.45%	8	28.57%	15	88.23%

TC = tumor cell.

Figure 1. PD-L1 Testing at Initital Diagnosis

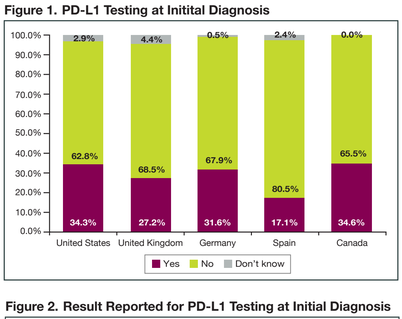
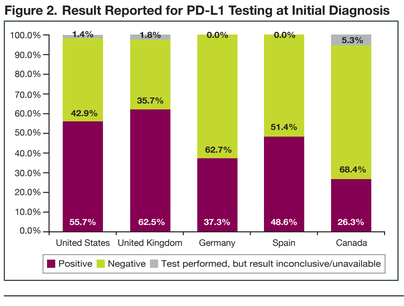


Figure 2. Result Reported for PD-L1 Testing at Initial Diagnosis



Patient Demographics and Clinical Characteristics

- Medical records were abstracted for 204 US patients, 206 UK patients, 212 German patients, 205 patients from Spain, and 55 Canadian patients.
- The majority of patients with metastatic NSCLC were males (US, 63.2%; UK, 60.7%; Germany, 69.3%; Spain, 75.1%; Canada, 65.5%), and white (US, 73.0%; UK, 86.4%; Germany, 94.3%; Spain, 100.0%; Canada, 80.0%). In the US, 89.7% of patients were non-Hispanic.
- Table 2 presents clinical characteristics for patients with metastatic NSCLC at initial diagnosis and at metastatic diagnosis. In the US, UK, Germany, and Spain most (> 74%) patients had stage IV disease at diagnosis; while 43.6% of patients in Canada had stage IV disease at initial diagnosis. Distant lymph node metastases were observed in 32.6% (US), 33.3% (UK), 21.9% (Germany), 30.3% (Spain), and 36.4% (Canada) of patients.
- At metastatic diagnosis, the mean age was 63.1 years in the US, 62.7 years in the UK, 60.4 years in Germany, 60.7 years in Spain, and 65.1 years in Canada.
- At metastatic diagnosis, 56.9% of patients in the US, 69.4% in the UK, 73.6% in Germany, 64.4% in Spain, and 38.2% in Canada had an ECOG performance score of 1 (Table 2).
- The most common comorbidities recorded were hypertension (US, 47.6%; UK, 36.4%; Germany, 33.5%; Spain, 40.0%; Canada, 43.6%), chronic pulmonary disease (US, 25.0%; UK, 26.2%; Germany, 23.1%; Spain, 30.7%; Canada, 25.5%), and diabetes without chronic complication or end organ disease (US, 16.6%; UK, 11.2%; Germany, 8.5%; Spain, 18.1%; Canada, 23.6%).
- The majority of the patients were former smokers (US, 70.1%; UK, 57.8%; Germany, 60.4%; Spain, 56.1%; Canada, 74.5%), and up to one-third of patients (except Canada [11.0%]) were current smokers (US, 23.5%; UK, 28.6%; Germany, 30.7%; Spain, 32.7%).

PD-L1 Testing

- Figure 1 shows the proportion of patients who received PD-L1 testing at initial diagnosis.
  - PD-L1 testing at initial diagnosis occurred in 34.3% (US), 27.2% (UK), 31.6% (Germany), 17.1% (Spain), and 34.6% (Canada) of patients.
- Reported by physicians as free-text answers, the Dako assay was used most often in the UK (44.6%), while "other/not specified" was most frequently reported in the US (57.1%) and Canada (73.4%). Most physicians in Germany (68.7%) and Spain (37.1%) did not know which assay was used to test for PD-L1.
- The mean (SD) percentage of stained cells was 33.9% (34.3) in the US, 31.1% (31.1) in the UK, 16.7% (24.0) in Germany, 17.2% (23.5) in Spain, and 33.1% (21.7) in Canada (Table 3).
- Among patients who received PD-L1 testing at initial diagnosis (US: n = 70; UK: n = 56; Germany: n = 67; Spain: n = 35; Canada: n = 19) the results are shown in Figure 2.
  - Among these patients, 55.7% (US), 62.5% (UK), 37.3% (Germany), 48.6% (Spain), and 26.3% (Canada) were reported to have tested positive.
- Either 1% or 50% of tumor cells stained was the most commonly used threshold for positivity (Table 3).

DISCUSSION

- PD-L1 testing rates from this study present a historical perspective of PD-L1 testing before the adoption of highly effective anti-PD-L1 agents in routine clinical practice for patients with metastatic NSCLC.
  - Although only approximately one-third of patients received testing for PD-L1 at initial diagnosis in our study, the proportion of patients whose tumors tested positive (per cutoffs used by each physician/institution) is similar to the prevalence of PD-L1 positivity reported in a previous study (24%-60%).[10]
  - Although the distribution of risk factors (e.g., smoking history, nodal disease, stage IV disease) was similar across countries, variation was observed in the proportion of patients who tested positive for PD-L1 expression.[11,12]
- As the use of recently approved anti-PD-L1 therapy increases in routine clinical practice, an increase in testing for PD-L1 expression may be observed.
  - Further research is needed to establish standardized methods and define PD-L1 positivity.
- A similar study using more recent data may provide better understanding of PD-L1 testing in the real world after approval and initial uptake period of anti-PD-L1 agents.
- Included patients represented a convenience sample, and the study findings may not be generalizable to the overall metastatic NSCLC population or to physicians treating metastatic NSCLC in the countries studied. To mitigate this, physicians were recruited from a variety of geographic regions and practice types in each country.
- Data were limited to those recorded in medical records to which physicians have access. Data also were entered directly by the treating physicians and may be subject to entry errors and resulting inaccuracies in reporting.

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