Examining Longitudinal Practice Patterns in the use of Anti-PD-1 and Anti-PD-L1 Inhibitors as First-Line Therapy in Non-Small Cell Lung Cancer Patients in the US

Rajwanth Veluswamy[1], Gisoo Barnes[2] , Ross Strauss[2], Douglas Harrough[2], and Boxiong Tang[2]

[1]Tisch Cancer Institute, The Mount Sinai Hospital, [2]BeiGene, Ltd., Emeryville, CA, US

Virtual ISPOR 2021
17-20 May 2021, Virtual Conference

BACKGROUND

- Lung cancer is the leading cause of cancer-related deaths worldwide with 1,796,144 deaths and 2,206,771 new cases reported in 2020 (1).
- Immune checkpoint inhibitors targeting the programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) axis (collectively referred to as PD(L)1i) have demonstrated unprecedented clinical activity in patients with non-small cell lung cancer (NSCLC) (2,3).
- High tumor expression of PD-L1 (≥50%) is the primary determinant of PD(L)1i monotherapy. For majority of patients with PD-L1 expression <50%, combination PD(L)1i with chemotherapy is recommended.
- The objective of this US-based real-world study was to examine changes in the practice patterns in first-line therapies for NSCLC since the introduction of PD(L)1i.

METHODS

Data Source and Cohort Creation

- NSCLC patients were identified in the IBM MarketScan Commercial and Medicare Supplemental databases May 1, 2017 (when PD(L)1i first received approval) through July 31, 2020.
- Eligible patients met the following criteria:
  - At least two claims for NSCLC (ICD9: 162.x; ICD10 34.x) during the study period (second claim within 365 days of the first claim).
  - No previous NSCLC claim in the database prior to the study period.
  - Continuous enrollment at least 90 days prior to and 60 days after first NSCLC claim.
  - ≥ 18 years old.
  - First-time diagnosis and first time a claim for NSCLC therapy was filed, indicating the first-line therapy (see below).
- Newly diagnosed patients were assigned to one of four patient-cohorts based on the drug therapy they received:
  - **PD(L)1i Monotherapy** = Patients whose first claim was a PD(L)1i only and had no other claim for chemotherapy within 45 days.
  - **Chemotherapy without PD(L)1i** = Patients whose first claim was for a chemotherapy regimen and did not have a PD(L)1i claim within 45 days. Patients could have also received radiation or undergone surgery along with chemotherapy.
  - **PD(L)1i with Chemotherapy** = Patients who had a claim for a PD(L)1i and a chemotherapy within 45 days.
  - **Targeted Therapy** = Patients who had a claim for an EGFR, ALK, ROS1, BRAF V600E, or NTRK targeting agent and who did not have a claim for chemotherapy or PD(L)1i within 45 days.

Key Variables and Analytic Approach

- A descriptive analysis was used for analysis of demographics and clinical characteristics of the four cohorts.
- Comorbidity index (4) and specific comorbid conditions were calculated over the 180 days prior to NSCLC diagnosis.
- Baseline differences between cohorts were tested using chi-square for categorical variables and for continuous variables, parametric tests (e.g., ANOVA) were used for normally distributed variables and non-parametric tests (e.g., Kruskal-Wallis test) for non-normally distributed variables.
- Logistic regression was used to examine predictors of the dichotomous variable: PD(L)1i with Chemotherapy vs. Chemotherapy alone in NSCLC patients. Specific predictors for evaluation included age, gender, insurance type, as well as comorbidities.

RESULTS

- A total of 5,150 newly diagnosed NSCLC patients starting first-line therapy were identified.
- The majority of patients received chemotherapy without PD(L)1i (n = 2,459) followed by PD(L)1i with chemotherapy (n = 1,286) and PD(L)1i monotherapy (n = 743).

Therapy Cohorts by Year

Table 1. Therapy Cohorts by Year

	PD(L)1i Monotherapy	Chemotherapy without PD(L)1i	PD(L)1i with Chemotherapy	Targeted Therapy
2017 (n = 1,215)	185 (15.2%)	742 (61.1%)	158 (13.0%)	130 (10.7%)
2018 (n = 1,711)	254 (14.8%)	843 (49.3%)	390 (22.8%)	224 (13.1%)
2019 (n = 1,593)	231 (14.5%)	623 (39.1%)	518 (32.5%)	221(13.9%)
2020 (n = 631)	73 (11.6%)	251 (39.8%)	220 (34.9%)	87 (13.8%)

- The proportion of patients that received PD(L)1i monotherapy has remained relatively stable over the past 4 years.
- The proportion of patients that received chemotherapy without PD(L)1i has decreased by a third over 4 years.
- The proportion of patients receiving PD(L)1i with chemotherapy has more than doubled from 2017 to 2020.

Demographic and Clinical Characteristics

- The PD(L)1i monotherapy and chemotherapy without PD(L)1i cohorts were, on average, older than the other two cohorts. As expected, patients who received targeted therapies were generally younger than those that received other systemic treatments.
- The distribution of gender was similar in all of the cohorts with the exception of the Targeted Therapy cohort, which consisted of a greater proportion of females (62.8%).
- Most of the patients resided in an urban setting.
  - The distributions were similar across cohorts with the exception of the Targeted Therapy Cohort, which had significantly more urban patients.
  - The majority of the patients were covered by a traditional health plan. We observed no statistical difference of insurance type across treatment groups.

Table 2. Demographic Characteristics

	PD(L)1i Monotherapy (n = 743)	Chemotherapy without PD(L)1i (n = 2,459)	PD(L)1i with Chemotherapy (n = 1,286)	Targeted Therapy (n = 662)	*P*
Age at first-line, years, mean (SD), median	63.75 ᵃ (11.58) 62.00	61.81ᵃ (9.58) 61.00	60.33 ᵃ (9.09) 60.00	59.43 ᵃ (11.48) 59.0	< .001
Age category, n (%)					< .001
≤ 64 years (n = 3,811)	499 (13.1%)	1,785 (46.8%)	1,015 (26.6%)	512 (13.4%)	
≥ 65 years (n = 1,339)	244 (18.2%)	674 (50.3%)	271 (20.2%)	150 (11.2%)	
Gender					< .001
Males, n (%)	412 ᵃ (55.5%)	1,225 ᵇ (50.2%)	661 ᵃᵇ (51.4%)	245 ᵃ (37.2%)	
Females, n (%)	331 ᵃ (44.5%)	1,224 ᵇ (49.8%)	625 ᵃᵇ (48.6%)	416 ᵇ (62.8%)	
Rural/Urban, n (%)					= .002
Rural	108 ᵃ (14.5%)	376 ᵃ (15.3%)	189 ᵃ (14.7%)	62 ᵃ (9.4%)	
Urban	685 ᵃ (85.5%)	2,083 ᵃ (84.7%)	1,097 ᵃ (85.3%)	600 ᵃ (90.6%)	
Insurance Type, n (%)					= .39
Traditional Health Plan*	608 (81.8%)	2,041 (83.0%)	1,045 (81.3%)	536 (81.0%)	
Consumer Driven Plan**	120 (16.2%)	369 (15.0%)	215 (16.7%)	114 (17.0%)	
Missing	15 (2.0%)	49 (2.0%)	26 (2.0%)	12 (2.0%)	

Note: ᵃ,ᵇ Each superscript denotes a subset of cohort categories whose column proportions do not differ significantly from each other at the .05 level.* Traditional Health Plan = preferred provider organization, health maintenance organization, comprehensive, point of service plan w/wo cap, exclusive provider organization; ** Consumer Driven Plans= consumer-driven health plan, high-deductible health plan.

Clinical Characteristics

- The PD(L)1i Monotherapy and Targeted Therapy cohorts initiated first-line therapy earlier than cohorts using chemotherapy.
- The PD(L)1i Monotherapy cohort had the highest comorbidity index (mean=7.30) and Chemotherapy without PD(L)1i cohort had the lowest (mean=5.94). The PD(L)1i Monotherapy cohort also had the largest proportion of patients that had experienced congestive heart failure.
- Diabetes and COPD/Emphysema were the most prevalent co-morbidities among the Chemotherapy without PD(L)1i cohort.
- The Targeted Therapy cohort had the lowest proportions across all of the comorbidities with the exception of liver disease.

Table 3. Clinical Characteristics

	PD(L)1i Monotherapy (n = 743)	Chemotherapy without PD(L)1i (n = 2,459)	PD(L)1i with Chemotherapy (n = 1,286)	Targeted Therapy (n = 662)	*P*
Days to Therapy, mean (SD)	30.35 ᵃ (16.19)	32.53 ᵇ (15.19)	32.24 ᵇ (14.44)	29.82 ᵃ (12,27)	< .001
Comorbidity Index, mean (SD)	7.30 ᵃ (3.06)	5.94 ᵇ (3.72)	6.76 ᶜ (2.74)	6.75 ᶜ (2.57)	< .001
Cerebrovascular Disease, n (%)	119 ᵃ (16.0%)	298 ᵇ (12.1%)	179 ᵃ,ᵇ (13.9%)	79 ᵇ (11.9%)	= .03
Congestive Heart Failure, n (%)	65 ᵃ (8.7%)	178 ᵃ (7.2%)	89 ᵃ,ᵇ (6.9%)	27 ᵇ (4.1%)	= .01
Diabetes, n (%)	132 ᵃ,ᵇ (17.8%)	471 ᶜ (19.2%)	202 ᵃ,ᵇ (15.7%)	95 ᵃ (14.4%)	= .01
Liver Disease, n (%)	110 ᵃ,ᵇ (14.8%)	305 ᵇ (12.4%)	178 ᵃ,ᵇ (13.8%)	119 ᵃ (18.0%)	= .002
Kidney Disease, n (%)	76 ᵃ (10.2%)	162 ᵇ (6.6%)	48 ᶜ (3.7%)	22 ᶜ (3.3%)	< .001
COPD, n (%)	223 ᵃ (30.4%)	970 ᵇ (39.4%)	427 ᶜ (33.2%)	52 ᶜ (7.9%)	< .001
Emphysema, n (%)	132 ᵃ (17.8%)	555 ᵇ (22.6%)	231 ᵃ (18.0%)	23 ᶜ (3.5%)	< .001
Rheumatic Disease, n (%)	0	0	0	0	NA

Note: ᵃ,ᵇ Each superscript denotes a subset of cohort categories whose column proportions do not differ significantly from each other at the .05 level. Days to Therapy = # of days between diagnosis and initiation of first-line.

Predictors of treatment selection between Combination PD(L)1i with Chemotherapy vs. Chemotherapy Alone in NSCLC Patients

- Older patients were less likely to have received combination PD(L)1i with chemotherapy.
- Patients with higher comorbidity index score were more likely to have received combination PD(L)1i with chemotherapy.
- However, patients with a specific comorbidity (i.e., diabetes, kidney disease, or emphysema) were less likely to have received combination PD(L)1i with chemotherapy.

Table 4. Logistic Regression Predicting use of Combination PD(L)1i with Chemotherapy vs Chemotherapy without PD(L)1i

Patient Demographic or Clinical Characteristic	OR	95% CI	*P*
Age	.989	.989 - .997	= .006
Gender (1 = female; 0 = male)	.907	.790 – 1.041	= .163
Comorbidity Index	1.074	1.052 – 1.097	< .001
Insurance type (1 = consumer driven; 2 = traditional)	1.037	.858 – 1.253	= .708
Cerebrovascular Disease	1.149	.935 – 1.413	= .187
Congestive Heart Failure	1.017	.772 – 1.338	= .907
Diabetes	.818	.678 - .986	= .035
Liver Disease	.978	.796 – 1.202	= .831
Kidney Disease	.533	.378 - .751	< .001
COPD	.859	.737 – 1.001	= .051
Emphysema	.809	.675 - .969	= .022

Note: Chemotherapy with PD(L)1i = 1; Chemotherapy without PD(L)1i = 0.

DISCUSSION

- Since the approval of PD(L)1i for NSCLC, their use in combination with chemotherapy has significantly increased for first-line treatment.
- However, over a third of patients in 2019 and 2020 received chemotherapy without PD(L)1i despite significant evidence that the addition of PD(L)1i to chemotherapy is associated with prolonged survival compared to chemotherapy alone (2).
- Patients who received PD(L)1i monotherapy were generally older and had higher comorbidities than those who received chemotherapy or target therapies.
- Among patients who received chemotherapy, age and comorbidities significantly predicted the addition of PD(L)1i combination vs. chemotherapy alone.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*.n/a(n/a).
2. Wang C, Qiao W, Jiang Y, Zhu M, Shao J, Wang T, et al. The landscape of immune checkpoint inhibitor plus chemotherapy versus immunotherapy for advanced non-small-cell lung cancer: A systematic review and meta-analysis. *J Cell Physiol*. 2020;235(5):4913-27.
3. Ferrara R, Imbimbo M, Malouf R, Paget-Bailly S, Calais F, Marchal C, et al. Single or combined immune checkpoint inhibitors compared to first-line platinum-based chemotherapy with or without bevacizumab for people with advanced non-small cell lung cancer. *The Cochrane database of systematic reviews*. 2020;12:Cd013257.
4. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson Comorbidity Index: ICD-9 Update and ICD-10 Translation. *American health & drug benefits*. 2019;12(4):188-97.

Acknowledgments
The authors wish to thank Jason Allaire, PhD of Generativity Solutions Group for his assistance in medical writing. This assistance was funded by BeiGene, Ltd.

Declaration of Funding
This study was funded by BeiGene, Ltd.