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Ramucirumab+Docetaxel Post Immune Checkpoint Inhibitors (ICIs) and Platinum-based Chemotherapy (chemo) in Advanced or Metastatic Non-Small Cell Lung Cancer (aNSCLC): Learnings from the TREAT-LUNG Observational Study

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BACKGROUND

- Non-small cell lung cancer accounts for more than 80% of lung cancers and is often diagnosed at locally advanced or metastatic stage (IIIB, IIIC, IV).[1]
- For 1L treatment of aNSCLC lacking targetable oncogene driver mutations, which represents ≥ 80% of all aNSCLC cases, treatment guidelines recommend ICIs as single agents or in combination with platinum-based chemotherapy or other ICIs.[2]
- The phase III REVEL trial demonstrated that adding ramucirumab to docetaxel (R+D) after progression on platinum-based chemotherapy improves response rates and survival in aNSCLC compared to single-agent docetaxel.[3]
- However, there are limited RWE studies comparing 2L or 3L treatment with R+D vs single-agent docetaxel after prior treatment with ICIs and platinum-based chemotherapy[4]

OBJECTIVE

- The TREAT-LUNG (TREATment Sequencing Post Frontline Immunochemotherapy For Advanced Non-Small Cell LUNG Cancer) study aimed to characterize real-world outcomes associated with the use of R+D or docetaxel, following ICIs and platinum-based chemotherapy for aNSCLC.

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STUDY DESIGN & DATA SOURCE

Figure 1: Study Design

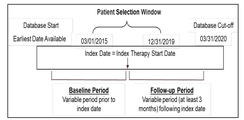
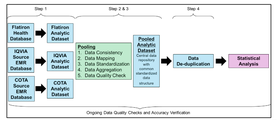


Figure 2: Data Pooling Process Overview



- Retrospective cohort study using pooled (Figure 2) real-world data drawn from 3 large oncology EHR databases in the U.S.:
  - The **Flatiron Health EHR-derived De-identified Database** comprises longitudinal patient-level structured and unstructured data originating from approximately 280 US cancer clinics (~800 care sites), curated via technology-enabled abstraction, and supplemented to resolve data gaps (e.g., Social Security Death Index and commercial death data).[5,6,7]
  - The **COTA RWE Database** comprises longitudinal patient-level structured and unstructured data curated and transformed into a standard data format via both human data abstraction and technologic methods, and survival data is supplemented using public and commercial data sources.
  - The **IQVIA Oncology EHR Database** comprises longitudinal patient-level data from IQVIA's U.S. data partner, Guardian Research Network (GRN), an oncology-focused, nationwide consortium of large multistate hospital systems, employing direct EHR integration of longitudinal inpatient and outpatient structured and unstructured EHR data.

KEY RESULT: RESPONSE RATES

- After adjustment, real-world tumor response assessment was unknown/missing for 122 of 243 patients (50%) in the primary-2L-cohort, 206 of 361 patients (57%) in the 3L-cohort, and 311 of 557 patients (56%) in the combined-(2L/3L)-cohort (Figure 4). As a result, the study failed to achieve adequate power, which impacted the statistical validity and interpretability of the results.
- Among the subset of the 2L-cohort with evaluable real-world tumor response data (n=121), rwORR was 43% in R+D group and 39% in docetaxel group, odds ratio, 1.20; 95% CI, 0.54-2.65. This lack of significant difference between groups was consistent for DCR and across 3L (n=155) and combined (n=246) cohorts.

Table 2: Propensity Score Stratification Adjusted Response Rates

	Primary 2L Cohort		Secondary 3L Cohort		Combined 2L/3L Cohort	
	R+D (N=78*)	Docetaxel (N=43*)	R+D (N=80*)	Docetaxel (N=75*)	R+D (N=142*)	Docetaxel (N=104*)
Best Response**, %						
CR	3	0	0	1	0	1
PR	40	39	61	53	60	52
SD	34	31	32	33	32	33
PD	23	30	7	13	8	14
rwORR & rwDCR, %						
rwORR	43	39	61	54	60	53
rwDCR	77	70	93	87	92	86

R+D vs Docetaxel comparisons after adjustment, via multivariate logistic regression, were not statistically significant (P > 0.05); *Denominator = subset (<50%) of overall study cohort with evidence of tumor response assessment; **Defined as the best tumor response (from PD [worst], SD, PR, to CR [best]) that a patient experienced during index therapy.

CONCLUSIONS

- Patients in TREAT-LUNG were reflective of routine clinical practice, with over 20% of patients with an ECOG performance status ≥2.
- No statistically significant differences were seen in primary or secondary efficacy endpoints. This finding must be interpreted in context of study limitations including
  - Insufficient sample size and power for primary and secondary analyses, potential selection bias inherent in passively collected EHR datasets, and residual confounding despite PS stratification adjustment.
  - More importantly, the high rate of missing tumor response data (>50% overall) may have implications for the design of future real-world data studies.
  - Direct comparison between results of REVEL and TREAT-LUNG is challenging owing to irreconcilable differences in study designs and patient populations.[3]
- Patterns of adverse events were consistent with established safety profiles for ramucirumab and docetaxel, with some (≤5%) occurrence of immune-related toxicities in both groups.

METHODS

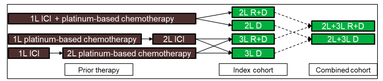
Study Population

- Patients were included if they
  - were at least 18 years of age at the time of diagnosis with aNSCLC
  - received second-line or third-line R+D or single-agent docetaxel between 03/2015-12/2019
  - were previously treated with an ICI and platinum-based chemotherapy (in combination or sequential)
- Patients with insufficient data or multiple primary tumor diagnoses were excluded.

Study Cohorts

- Based on the index therapy received (R+D or D) and line of index therapy (2L or 3L), patients were assigned to a treatment group in the Primary-2L, Secondary-3L, and Combined 2L+3L cohorts (Figure 3).

Figure 3: Treatment Groups



Study Endpoints

- Primary endpoint was real-world objective response rate (rwORR) among the primary-2L-cohort with evaluable tumor response assessment data.
- Secondary endpoints included real-world disease control rate (rwDCR), real-world progression free survival (rwPFS), and overall survival (OS).*

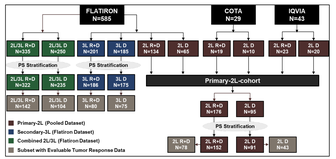
Statistical Analysis

- Minimum required sample size for primary analysis of rwORR among the primary-2L-cohort was 286 patients (power=0.80), powered a priori to detect the ORR effect size observed in REVEL.[3]
- Treatment-group comparisons were adjusted for selection bias using propensity score (PS) stratification.
  - Eligible patients were ranked and stratified into relatively homogenous, mutually exclusive, and approximately equal-sized subsets/strata based on their estimated PS i.e., probability of R+D cohort assignment conditional on observed baseline/prognostic characteristics, estimated using multivariable logistic regression model.
- Descriptive statistics were reported for all baseline variables before and after PS stratification adjustment.
- Response rates were assessed using unadjusted logistic regression and multivariable logistic regression analyses after PS stratification.
- OS and rwPFS were assessed using Kaplan-Meier method and Cox proportional hazards regression adjusted for PS stratification.
- AEs were selected based on 1) common (>5%) grade ≥3 AEs of ramucirumab or docetaxel observed in the REVEL trial, 2) early reports suggesting increased risk of immune-related AEs following ICI therapy, and 3) expert opinion on clinically relevant AEs.[3] Of the selected AEs, dyspnea and fatigue were not assessed as these AEs could not be reliably captured in the EHR.

rwORR = Percentage of patients who achieved complete or partial response from the date a patient initiates index therapy.PFS = time from index therapy start date to date of disease progression or death; OS = time from index therapy start date to date of death; DCR = percentage of patients with complete response, partial response, or stable disease during index therapy. Abbreviations: ORR, Objective Response Rate;

RESULTS

Figure 4: Patient Attrition



- The pooled analytic study data set was used for analysis of the primary-2L cohort (Figure 4).
- To minimize variability, the Flatiron Health data set was used for analysis of secondary study cohorts (3L and 2L/3L).

Table 1: Baseline Demographics- Before PS Stratification

Patient Characteristics	Primary 2L Cohort		Secondary 3L Cohort		Combined 2L/3L Cohort	
	R+D (N=178)	Docetaxel (N=93)	R+D (N=386)	Docetaxel (N=201)	R+D (N=335)	Docetaxel (N=250)
Age in years, median (IQR)	64.0 (55.0-71.0)	67.0 (58.0-75.0)	68.0 (61.0-73.0)	70.0 (61.0-76.0)	66.0 (59.0-73.0)	69.0 (61.0-76.0)
Female, %	39	43	40	43	40	42
White, %	68	71	69	66	69	67
BMI at index kg/m2, mean (SD)	26.1 (5.4)	24.8 (4.9)*	25.0 (5.3)	25.7 (5.5)	25.4 (5.5)	25.5 (5.5)
ECI, mean (SD)	0.9 (0.9)	0.8 (0.9)	0.9 (1.0)	1.1 (1.1)*	0.9 (1.0)	0.9 (1.1)
Stage at Index Date, %						
Stage IIIB	7	8	16	12	13	12
Stage IV	93	94	84	88	87	88
Tumor Histology*, %						
Squamous	9	7	33	31	23	25
Nonsquamous	85	86	66	65	74	71
Site(s) of metastatic disease at Index**, %						
Brain	16	19	11	14	13	13
Bone	53	46	30	29	37	30
Duration of aNSCLC at Index in Months, mean (SD)	11.8 (19.5)	10.5 (16.8)	22.3 (21.6)	21.7 (19.6)	18.7 (22.2)	19.1 (20.1)
ECOG PS at Index, %						
0-1	66	64	66	60	65	61
≥2	23	23	23	28	24	26
Missing	11	13	11	12	11	13
ALK Mutation Status, %						
Positive	1	1	0	0	0	0
Negative	86	79	84	74*	86	76*
Missing	13	20	16	26*	14	24*
EGFR Mutation Status, %						
Positive	6	1*	2	2	4	1
Negative	82	75	83	77	82	78
Missing	12	24*	15	21	13	21
PD-L1 Expression, %						
Positive	14	15	8	4	7	4
Negative	38	40	24	20	27	24
Missing	48	45	68	76	65	73

* Percentages may not add up to 100, since missing values are not reported; [a]Patient may have more than one metastatic site; *p≤0.05;

- After propensity score stratification adjustment, baseline characteristics were balanced between treatment groups in all 3 cohorts (data not shown).

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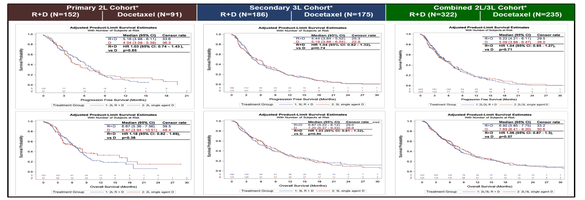
Table 3: Selected AEs for Flatiron Health 2L Cohort before PS Stratification

Type of Adverse Event	90-day Baseline Period Grade, % Any		3		During Index 2L Therapy Grade, % Any		3	
	Ram+D (N=134)	Docetaxel (N=65)	Ram+D (N=134)	Docetaxel (N=65)	Ram+D (N=134)	Docetaxel (N=65)	Ram+D (N=134)	Docetaxel (N=65)
Abstracted AE								
Hypertension	0	0	*	*	2	0	*	*
Immune-related (IR) AE								
IR colitis	0	0	*	*	1	0	*	*
IR pneumonitis	0	0	*	*	0	2	*	*
IR rash	0	0	*	*	4	3	*	*
IR disorder, other	0	0	*	*	0	3	*	*
Lab-Derived AE								
Neutropenia	17	9	10	5	31	18	22	12
Anemia	88	88	18	9	90	91	7	20
Leucopenia	61	69	18	31	62	68	20	29
Proteinuria	0	0	0	0	3	0	3	0
Thrombocytopenia	24	23	7	5	33	18	2	8

- The distribution of selected AEs in the Flatiron Health 2L cohort was consistent with the safety profile reported in REVEL.[3] Both treatment groups experienced immune-related AEs after discontinuation of ICI treatment, albeit at relatively low rates.
- Similar results were observed among the Secondary 3L cohort as well (data not shown).

AEs were not statistically compared between groups; As selected AEs were not consistently captured across all source EHR data sets, only the Flatiron Health data set was used for safety analysis.*Grade not available.

Figure 5: PS stratification adjusted PFS & OS



*Secondary endpoints (progression-free survival, overall survival) were not alpha controlled for testing statistical significance.

LEARNINGS & LIMITATIONS

- This study demonstrated feasibility of combining multiple complementary sources of EHR data, mitigating sample size constraints with existing single real-world data sources, to enable more timely generation of comparative effectiveness evidence.
- We learned that 1) developing source databases based on a similar pre-specified set of patient selection criteria, variables, and variable definitions, 2) integrating source data into a common data model with common variable definitions, 3) investigating and resolving duplicates, and 4) including source database ID as a covariate in PS adjustment are key to successfully implementing this approach.
  - Accordingly, baseline characteristics were largely similar across the source data sets before propensity adjustment, despite varying sample sizes and data sources.
- While pooling provided additional information, necessary sample size was still not achievable as the approach does not overcome common limitations of real-world data, particularly 1) missing data on key baseline (ECOG PS status, PD-L1 expression, molecular markers, sites of metastases) and outcomes (tumor response or progression events) variables, and 2) potential for unknown, unmeasured, or residual confounding bias despite propensity adjustment.
  - In this study, tumor response assessment was missing or unknown for most of the eligible pooled cohort, limiting interpretability of our primary analysis among patients with evaluable response assessment data.
  - While rwORR may be an attractive endpoint for comparative effectiveness research when survival endpoints are immature, thoughtful consideration and investment must be given to ensure quality and completeness of response data prior to outcomes analysis.
- Despite best efforts to increase representation of patients treated in academic settings, the pooled data set included EHR data generated predominantly in community oncology setting, highlighting the need for improved coordination/shared data amongst academic practices.

Abbreviations: 1L, first-line therapy; 2L, second-line therapy; 3L, third-line therapy; AE, Adverse Events; aNSCLC, advanced/metastatic non-small cell lung carcinoma; ALK, Anaplastic lymphoma kinase; BMI, Body Mass Index; CI, Confidence Interval; CCI, Charlson Comorbidity Index; D, single-agent docetaxel; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, Epidermal Growth Factor Receptor; EHR, electronic health record; HR, Hazard Ratio; ICI, immune-checkpoint inhibitors; kg/m^2, kilograms per squared meter; N, total number of patients; n, number of patients in the group; PDL1, programmed cell death receptor ligand 1; R+D, Ramucirumab+Docetaxel; RWE, Real-World Evidence. SD, Standard Deviation;

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