Control #: 2201

Clinical Outcomes of Real-World Treatment for Metastatic EGFRm NSCLC after Osimertinib and Platinum-Based Chemotherapy

Jyoti Patel[1], Jie Meng[2], Hoa Le[3], Yoko Tanaka[3], Sudarshan Phani[3], Chuntao Wu[3], Maribel Salas[3,4], David Sternberg[3], Stephen Esker[3], Haiyan Sun[5], Camryn Lieb[5], Karen Reckamp[6]

[1]Northwestern University, Chicago, IL, USA; [2]Daiichi Sankyo, Munich, Germany; [3]Daiichi Sankyo, Basking Ridge, NJ, USA; [4]University of Pennsylvania, Philadelphia, PA, USA ; [5]Genesis Research, Hoboken, NJ, USA; [6]Cedars-Sinai Medical Center, Los Angeles, CA, USA

PURPOSE

- The objective of this study was to characterize clinical outcomes of real-world treatment regimens initiated after osimertinib and PBC in patients from the Flatiron Health electronic health record database who fulfilled the selection criteria adapted from the HERTHENA-Lung01 (HL-01 trial).[4]

DISCUSSION

- Progression-free survival and overall survival for standard treatment were poor in this study of patients with EGFRm mNSCLC after failure of osimertinib and PBC. In the PS-weighted cohort median rwPFS was 4.2 (95% CI: 2.8, 5.2) months and median rwOS was 9.1 (95% CI: 7.4, 11.4) months
- Response to index LOTs was poor in the PS-weighted exploratory matched cohort: confirmed rwORR 14.1% (95% CI: 3.7%, 33.1%). However, it should be noted that the analyses of confirmed rwORR had a small sample size (N=26), and more data is needed to validate this finding.
- A limitation of this study is that only a subset of eligible patients (45%) had the requisite assessments to evaluate confirmed rwORR. As a result, the response subset may represent a specific population with favorable clinical outcomes compared with the overall population.
- This study provides a comprehensive real-world assessment to contextualize investigational treatments in this setting such as HER3-DXd in HL-01.[4]

CONCLUSION

- These observations in real-world patients with EGFRm mNSCLC after osimertinib and PBC indicate that currently available therapies provide only limited benefit, highlighting a significant clinical unmet need.

BACKGROUND

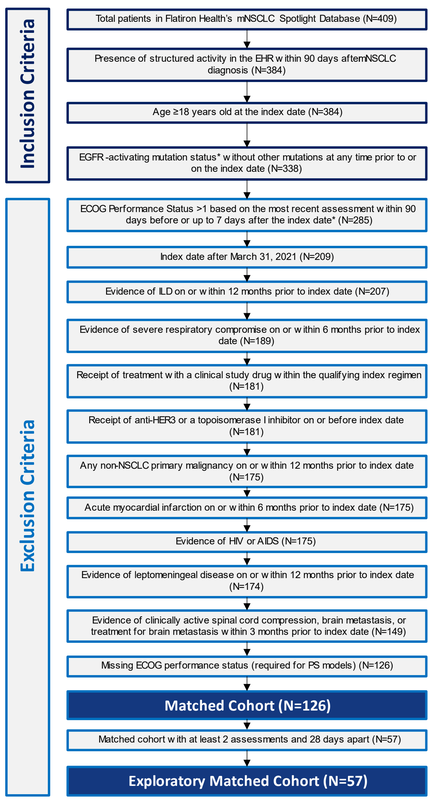
- Osimertinib, a third generation EGFR tyrosine kinase inhibitor (TKI), has emerged as a standard of care for the treatment of EGFR-mutated (EGFRm) metastatic non-small-cell lung cancer (mNSCLC). However, disease progression is a typical outcome.[1] When EGFRm mNSCLC disease progresses after osimertinib and platinum-based chemotherapy (PBC), there is currently no predominant standard of care.[2]
- Ongoing clinical trials are assessing novel treatment options in this setting, including the HERTHENA-Lung01 (HL-01) trial of patritumab deruxtecan (HER3-DXd).[3,4]
- Available prospective data on clinical outcomes are limited for patients with EGFRm mNSCLC after failure of osimertinib and PBC. Results from part 1 of this study have shown that treatment strategies after osimertinib and PBC are fragmented, with no single treatment dominating this setting, and outcomes are poor (median rwOS: 8.6 months; median rwPFS: 3.3 months).[5] [Access via QR Code]
- This study builds on previous results[5] by characterizing clinical outcomes in **real-world** patients who fulfilled the selection criteria adapted from the HL-01 trial.

METHODS

- This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database, comprising longitudinal patient-level structured and unstructured data, curated via technology-enabled abstraction from approximately 280 US cancer clinics (~800 sites of care). [6,7]
- The index date was defined as the date of initiation of a new line of therapy (LOT) after osimertinib and PBC.
- Selection criteria were adapted from the HL-01 study[3,4] and included: 1) age ≥18; 2) diagnosis of mNSCLC on or after 1 January 2011; 3) evidence of an activating EGFR mutation (exon 19 or L858R); 4) initiation of a new LOT (without a clinical study drug) between 13 November 2015 and 31 March 2021, after treatment with osimertinib and PBC; 5) non-missing ECOG performance status ≤1; 6) no evidence of interstitial lung disease, non-NSCLC primary malignancy, or leptomeningeal disease for 12 months pre-index; and 7) no prior treatment with anti-HER3 therapies or topoisomerase I inhibitors.
- Two cohorts of interest were defined: 1) the matched cohort and 2) the exploratory matched cohort. The matched cohort was designed to mimic the eligibility criteria of patients in the HL-01 trial. The exploratory matched cohort was a subset of the matched cohort consisting of patients with ≥2 response assessments ≥28 days apart, designed to mimic the confirmed rwORR requirements used per RECIST v1.1 in HL-01.
- Propensity score (PS) weighting was used to ensure a similar distribution of baseline characteristics for both cohorts, as compared to HL-01 patients. Nine prespecified covariates (age, sex, race, smoking, ECOG score, prior LOTs, prior immunotherapy, liver metastases, and brain metastases) were used for PS weighting. Effective sample size (ESS) was estimated and reported for PS-weighted models.
- Outcomes included: 1) real-world overall survival (rwOS; the time from index date to death); 2) real-world progression-free survival (rwPFS; defined as the time from index date to disease progression or death); and 3) confirmed real-world objective response rate (confirmed rwORR, defined as the proportion with confirmed partial or complete response among those with ≥2 response assessments ≥28 days apart). rwOS and rwPFS were assessed in the matched cohort; confirmed rwORR was assessed in the exploratory matched cohort.
- Descriptive statistics were used to summarize study variables, including distributions of treatment categories and patient characteristics. Kaplan-Meier methods were used to evaluate time-to-event outcomes (rwPFS, rwOS). Response outcomes (confirmed rwORR) were estimated as proportions with Clopper-Pearson exact 95% confidence intervals (CIs).

RESULTS

Figure 1. Inclusion and Exclusion Criteria



- From 409 total patients with EGFRm mNSCLC previously treated with osimertinib and PBC in the real-world database, 126 patients met the inclusion criteria for the matched cohort. (**Figure 1**)
- Of these 126 patients, 57 patients had evidence of at least 2 response assessments spaced at least 28 days apart required to calculate the confirmed rwORR. These 57 patients comprise the exploratory matched cohort.

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Matched Cohort		Exploratory Matched Cohort	
	Before PS Weighting (N=126)	After PS Weighting (ESS=78)	Before PS Weighting (N=57)	After PS Weighting (ESS=26)
Demographic Characteristics				
Median age at start of index LOT, years (IQR)	67 (59, 73)	63 (56, 72)	69 (59, 74)	62 (54, 72)
Gender, %				
Female	65.9	59.2	68.4	61.4
Male	34.1	40.8	31.6	38.6
Race, %				
Asian	21.4	28.3	28.1	52.2
Black or African American	8.7	14.3	<5.0	<5.0
White	55.6	37.2	59.6	35.3
Other	8.7	11.5	8.8	8.4
Unknown	5.6	8.6	<5.0	<5.0
Ethnicity, %				
Hispanic or Latino	6.3	8.3	<5.0	<5.0
Not Hispanic or Latino	76.2	69.3	86.0	77.1
Unknown	17.5	22.4	10.5	19.6
Practice Type, %				
Academic	8.7	12.1	8.8	19.2
Community	90.5	87.6	89.5	80.1
Academic, Community	0.8	0.3	1.8	0.7
Clinical Characteristics				
Median BMI, kg/m^2 (IQR)	24.9 (21.5, 28.5)	25.2 (21.1, 28.4)	25.6 (22.1, 28.6)	25.9 (22.1, 28.4)
Mean Charlson Comorbidity Index, mean (SD)	0.9 (1.3)	0.7 (1.5)	0.8 (1.2)	0.5 (1.8)
Charlson Comorbidity Index Group, %				
0	54.0	57.7	56.1	65.1
1-2	32.5	32.8	31.6	29.4
3+	13.5	9.5	12.3	5.5
ECOG at index, %				
0	39.7	32.1	47.4	33.7
1	60.3	67.9	52.6	66.3
Median number of prior lines of therapy, n (IQR)	3 (2,4)	3 (3, 4)	3 (2, 4)	3 (3, 4)
Number of prior lines of therapy, %				
≤2	34.9	22.8	40.4	24.8
3	34.1	37.8	28.1	36.6
4+	31.0	39.4	31.6	38.7
Median time between index and last confirmed activity, months (IQR)	8.0 (3.5, 13.9)	9.2 (3.8, 16.0)	13.9 (10.2, 19.6)	15.2 (10.3, 19.6)

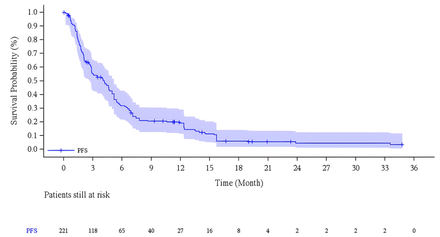
- Following PS weighting the 9 covariates in the matched cohort were balanced (standardized mean differences for each of 9 variables <0.2). (**Table 1**)
- While the same 9 covariates were planned to be used for weighting in the exploratory matched cohort, covariate balance could not be achieved with all 9 variables. Thus, the sex variable was excluded based on the clinical judgment that sex is the least impactful covariate, and balance was achieved in the exploratory matched cohort among the 8 included covariates (standardized mean differences for each of 8 variables <0.2).
- In the matched cohort before weighting, the median (IQR) age was 67 (59, 73) years. The majority of patients were female (65.9%) and White (55.6%), and more than half (65.1%) had at least 3 previous lines of therapy.
- In the exploratory matched cohort before weighting, the median (IQR) age was 69 (59, 74) years. The majority of patients were female (68.4%) and White (59.6%), and more than half (59.7%) had at least 3 previous lines of therapy.

Table 2. Confirmed rwORR of Exploratory Matched Cohort

	N/ESS*	Confirmed rwORR (95% CI)
Before PS weighting	57	17.5% (8.7%, 29.9%)
After PS weighting	26	14.1% (3.7%, 33.1%)

* N refers to the number of patients before PS weighting. ESS refers to the equivalent number of patients after applying PS weightings.

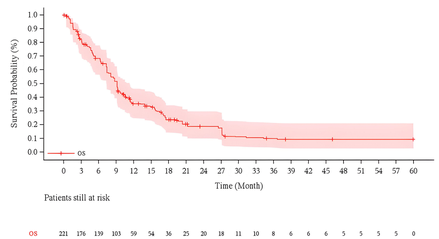
Figure 2. rwPFS of Matched Cohort



	N/ESS*	Median rwPFS in Months (95% CI)
Before PS weighting	126	4.2 (3.1, 5.4)
After PS weighting	78	4.2 (2.8, 5.2)

* N refers to the number of patients before PS weighting. ESS refers to the equivalent number of patients after applying PS weightings.

Figure 3. rwOS of Matched Cohort



	N/ESS*	Median rwOS in Months (95% CI)
Before PS weighting	126	10.7 (8.7, 14.9)
After PS weighting	78	9.1 (7.4, 11.4)

* N refers to the number of patients before PS weighting. ESS refers to the equivalent number of patients after applying PS weightings.

- Among the 57 eligible patients in the exploratory matched cohort, the confirmed rwORR after PS weighting was 14.1% (95% CI, 3.7%, 33.1%). (**Table 2**)
- Among the 126 eligible patients in the matched cohort, the median rwPFS was 4.2 (95% CI, 2.8, 5.2) months after PS weighting. (**Figure 2**)
- Among the 126 eligible patients in the matched cohort, the median rwOS was 9.1 (95% CI, 7.4, 11.4) months after PS weighting. (**Figure 3**)

REFERENCES

1. Wu L, Ke L, Zhang Z, Yu J, Meng X. Development of EGFR TKIs and Options to Manage Resistance of Third-Generation EGFR TKI Osimertinib: Conventional Ways and Immune Checkpoint Inhibitors. Front Oncol. 2020;10:602762. doi:10.3389/fonc.2020.602762

2. NCCN. Non-Small Cell Lung Cancer (Version 3.2023). 2023. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

3. NCT04619004. HERTHENA-Lung01: Patritumab Deruxtecan in Subjects With Metastatic or Locally Advanced EGFR-mutated Non-Small Cell Lung Cancer. 2020. https://clinicaltrials.gov/ct2/show/NCT04619004

4. Yu, HA, Goto Y, Hayashi, H, et al. Patritumab Deruxtecan (HER3-DXd) in EGFR-Mutated NSCLC Following EGFRTKI and Platinum-Based Chemotherapy: HERTHENA-Lung01. In: 2023 World Conference on Lung Cancer; 2023 Sept 9-12; Singapore. Abstract OA05.03.

5. Patel JD, Meng J, Phani S, et al. Abstract 6754: Clinical characteristics, real-world treatment patterns, and clinical outcomes among patients with previously treated metastatic or unresectable EGFR-mutated non-small cell lung cancer in the United States. Cancer Research. 2023;83(7_Supplement):6754-6754. doi:10.1158/1538-7445.Am2023-6754

6. Birnbaum B, Nussbaum N, Seidl-Rathkopf K, et al. Model-assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research. arXiv pre-print server. 2020-01-13 2020;doi:None arxiv:2001.09765

7. Ma X, Long L, Moon S, Adamson BJS, Baxi SS. Comparison of Population Characteristics in Real-World Clinical Oncology Databases in the US: Flatiron Health, SEER, and NPCR. medRxiv. 2023:2020.03.16.20037143. doi:10.1101/2020.03.16.20037143

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