Poster #RWD120

Understanding Treatment Patterns, Disruptions, and Potential Limitations of Tyrosine Kinase Inhibitors in ROS1+ Non-Small Cell Lung Cancer Patients in a Retrospective Review of United States Electronic Medical Transcription Records

Shim A[1], Singhania A[1], Iwanyckyj D[2], Otalora F2, Morrison B[1], Wade SW[3]

[1]Turning Point Therapeutics, San Diego, CA, USA, [2]Amplity Insights, Bucks, UK, [3]Wade Outcomes Research and Consulting, Salt Lake City, UT, USA

Background

- Lung (including bronchus) cancer is the second most common cancer and the leading cause of death, making up almost 25% of all cancer deaths.[1] The American Cancer Society estimates that over 236,000 new cases of lung cancer will be diagnosed in the US in 2022, and over 130,000 lung cancer-related deaths will occur.[2]
- Mortality rates are high in non-small cell lung cancer (NSCLC) which accounts for 84% of lung cancer with an overall 5-year survival at 25% in all patients and 7% in those with metastatic disease.[3]
- *ROS1*+ rearrangement in NSCLC is rare, occurring in up to 2% of patients.[4]
- Tyrosine kinase inhibitors (TKI) are standard front-line treatment, however, there may still be unmet need with these agents as some patients do not experience durable response, and patients treated with TKI may experience disease progression and/or develop treatment resistant mutations.
- Crizotinib and entrectinib are the two TKI approved for treatment of *ROS1*+ NSCLC in the United States.[6,7]
  - Crizotinib, approved in March 2016 for *ROS1*+ rearrangements in NSCLC, is also approved for anaplastic lymphoma kinase (ALK) alterations.[6]
    - After initial response, many *ROS1*+ NSCLC patients develop treatment resistance which inevitably leads to disease progression including brain metastases in some patients.[5,6]
  - In contrast to crizotinib, entrectinib (FDA approval August 2019) has demonstrated intracranial efficacy in patients with brain metastases.[7,8]
- Ceritinib, an ALK-TKI, received FDA approval in 2017 for ALK-positive metastatic NSCLC and is used off-label in *ROS1*+ NSCLC while clinical trials are underway.[5,8]
- Lorlatinib, approved in 2018 for second/third line treatment of ALK+ metastatic NSCLC, is used off-label as a 2nd line therapy for *ROS1*+ NSCLC patients who have not responded to or have resistance to first-line TKI.[9]

Study Objectives

- This exploratory analysis examined real-world, routine care treatment patterns and potential limitations using US physician narratives of patient encounters. Specific objectives were to describe:
  - treatment patterns in patients with *ROS1*+ NSCLC who received a TKI
  - potential limitations of TKI including:
    - reasons for treatment disruption
    - development of treatment resistance
    - treatment response

Methods

- Two-phase retrospective, descriptive analysis included:
  - manual record review/abstraction by 1 abstractor, followed by
  - meta-data summarization and Natural Language Processing (NLP) text mining

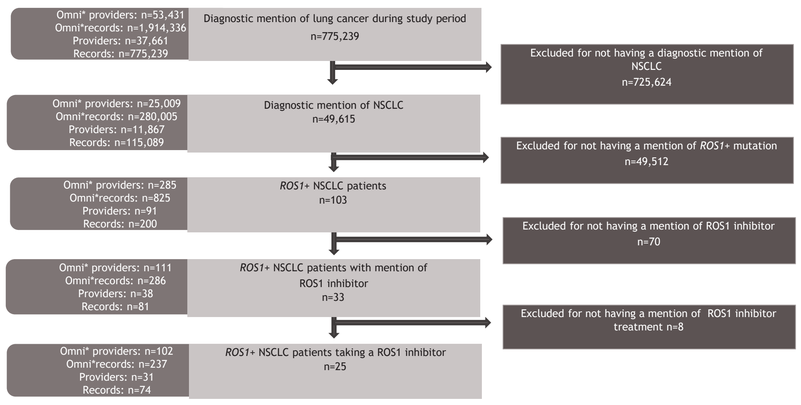
Data Source

- Amplity Insights Real-World Database (at time of study):
  - >50 million electronic medical transcription records of 29 million unique patients from >150,000 multi-specialty providers at approximately 40,000 inpatient/outpatient care sites across 50 states and 2 US territories
- Study evaluated data from January 2015 through November 2021

Study Population

- Adult (age >18 years) patients with *ROS1*+ NSCLC treated with crizotinib, entrectinib, ceritinib, lorlatinib
- Total of 389,973 patients with lung cancer and corresponding 775,239 records were identified (Figure 1)
  - 49,615 patients had NSCLC
  - 33 patients were confirmed to be NSCLC and *ROS1*+ adults with a mention of ROS1 inhibitor
- Final patient population for this analysis was narrowed down to 25 representing <0.006% of the total lung cancer population in the Amplity Health transcription records

Figure 1. Study Population and Amplity Insights Real-World Database

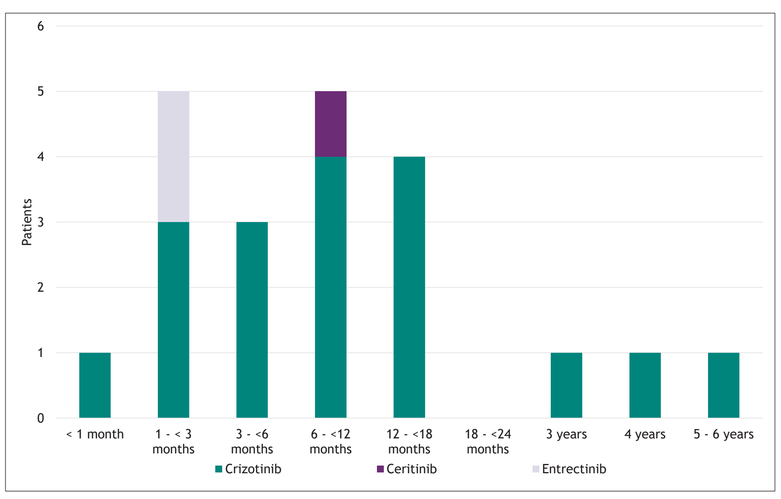


*Omni represents longitudinal records for a patient that may not mention the disease or medication directly
1 at least one record per patient has a mention of any ROS1 inhibitor. The patient has not necessarily ever taken a ROS1 inhibitor
2 at least one record per patient stipulates that the patient has at any time taken at least one ROS1 inhibitor

Results

- 103 *ROS1*+ NSCLC patients were identified; 25 used TKI in any line. The low number of patients identified is consistent with rare nature of ROS1 driver mutation in NSCLC.
  - 23 patients used crizotinib, 4 used lorlatinib, 4 used ceritinib, and 2 used entrectinib.
- The mean and median age of this treatment cohort was 62 years; 52% of patients were female, 8% were current smokers and 80% had no mentioned history of cancer; race/ethnicity was unknown for 40% of patients but 44% of patients were Caucasian.
- Total time on first-line primarily TKI ranged from <1 to <18 months (Figure 2).
  - Crizotinib was the most commonly used 1L TKI (i.e., first observed TKI in patient record) with 44% of 1L crizotinib users treated for 6 to <18 months (n=8); 39% for<6 months (n=7).
- Only 7 patients had second-line (2L) TKI, most were treated for <6 months.

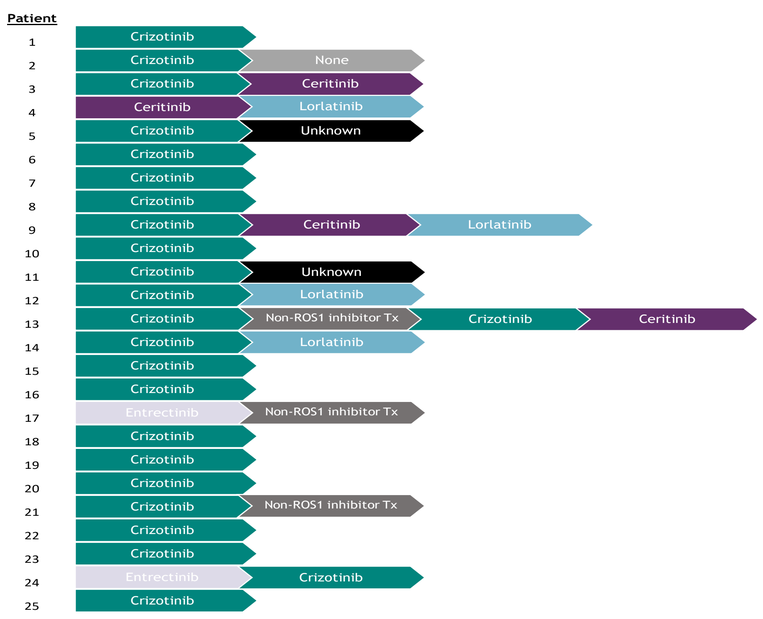
Figure 2. Duration of First-line TKI Treatment



Results (continued)

- Treatment sequencing is shown in Figure 3.
  - In almost all cases, crizotinib was selected as the 1L TKI (88%),
  - Choice of 2L therapy post TKI was more diverse,
    - 55% of patients were prescribed either crizotinib, ceritinib, or lorlatinib while other patients used check point inhibitors, chemotherapy, or had an unspecified 2L treatment.

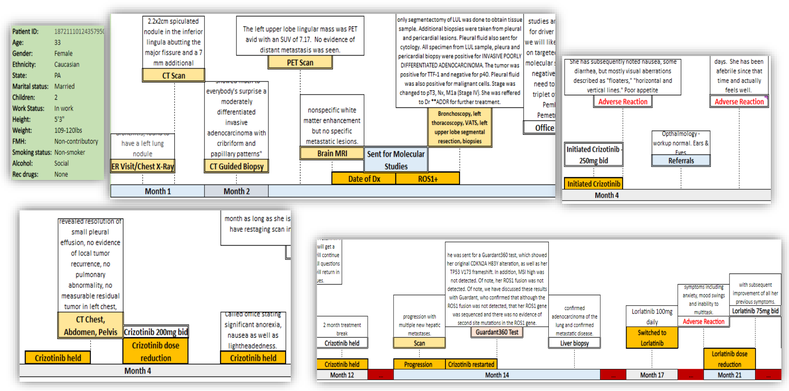
Figure 3. TKI Treatment Sequencing



Unknown is due to the last known patient record being at the time of the therapy line change
Non-ROS1 inhibitor treatment included IV chemotherapy, Nivolumab, or Carboplatin/Pemetrexed/Bevacizumab

- Patient journeys were also mapped for 14 patient records, including the start of their TKI therapy and events of notable interest such as adverse events, treatment disruption and disposition, HCRU event, and progression (Figure 4).

Figure 4. Example Patient Journey



CT: computerized tomography; DX: diagnosis; HCRU: healthcare resource utililizaton; PET: positron emission tomography

- Over 2/3 of patients (17/25) experienced a TKI treatment disruption, defined as hold, dose reduction, switch, and/or stop. Disruptions occurred for all TKI agents (Figure 5, Figure 6).
  - Holding or switching the patient's drug were the most commonly noted disruption types, followed by dose reduction.
  - Most patients experienced 1 treatment disruption (12) followed by 3 disruptions (4)
- 50% of patients who experienced a TKI disruption had their first disruption within 3 months:
  - 44% were holds, 33% dose reduction, 22% switch, and 11% discontinuation.
  - The remainder of patients with a TKI disruption experienced their first disruptions after 3 months: 11%, 17%, and 22% of patients experienced a TKI disruption within 3-6 months, 6-12 months, and ≥12 months of being on therapy, respectively.
- 65% (15/23) of crizotinib patients experienced at least one disruption. Over ¼ of patients experienced more than one disruption (4).
  - Of the 24 total crizotinib disruptions (Figure 6), 42% were holds (10), 38% discontinuation or switch (9), 21% dose reduction (5).

Figure 5. Number of Patients With Treatment Disruptions by Agent

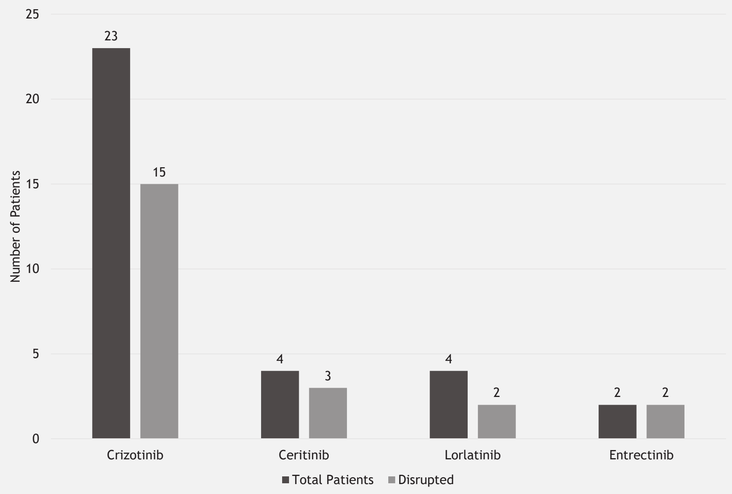
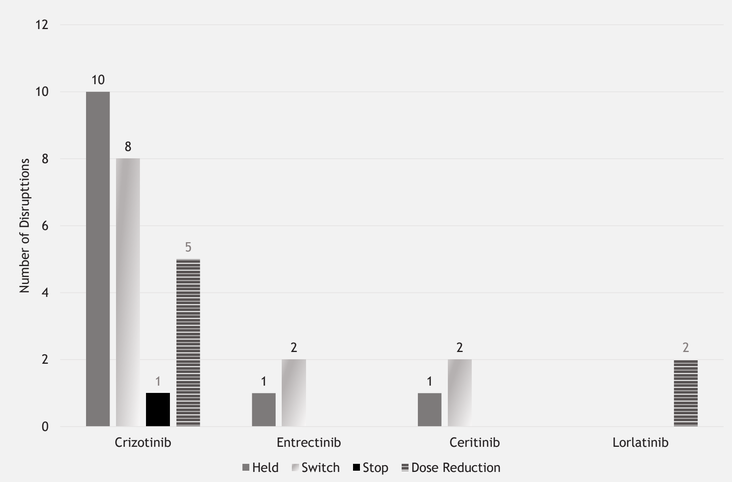


Figure 6. Disruption Type by Agent*

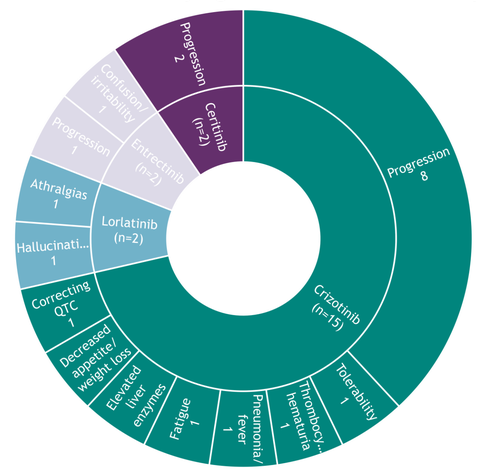


*Any disruption, not restricted to the first

Results (continued)

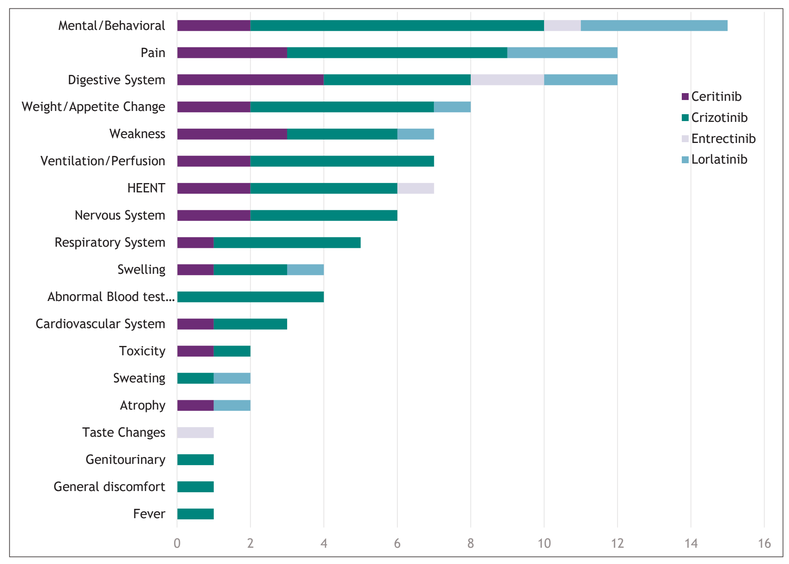
- Reasons for TKI treatment disruption are shown in Figure 7.
  - The most common reasons for treatment disruptions were progression and tolerability/adverse effects (AE).
    - Treatment 'resistance' was not noted in any records although absence of documentation does not confirm absence of resistance.
- Among 15 crizotinib users with treatment disruptions:
  - progression was noted as a reason for disruption in 53% (8) of patients
  - AEs/tolerability were in 47% (7) of patients
- Among other TKI patients, reasons for disruption given as follows; 2 entrectinib patients had confusion / irritability or progression, 2 ceritinib patients had progression, and lorlatinib had arthralgia and hallucination noted as reasons for disruptions.

Figure 7. Number of Patients by Agent and Reason for Disruption



- Various symptoms were mentioned on the same records, in close time proximity, as mentions of TKI disruption, along with specific reasons for treatment disruptions, however, these may not necessarily be contributing factors (Figure 8).
- Top 5 symptom types mentioned:
  - mental /behavioral issues (e.g., fatigue, anxiety, confusion, irritability, hallucinations)
  - pain (e.g., chest/thorax pain)
  - digestive system problems (e.g., nausea/vomiting, diarrhea, constipation, liver dysfunction, hepatotoxicity)
  - weight/appetite change (e.g., weight loss, appetite decrease)
  - weakness

Figure 8. Number of Patients With Concurrent Mention of Symptoms and Treatment Disruption



Limitations and Conclusions

Limitations

- This was an exploratory, descriptive study.
- Generalizability of results may also be limited by small sample sizes.
- The treatment landscape shifted during the study period with the 2019 approval of entrectinib, and future studies will need to include all newly available agents.
- Patients may be lost to follow-up for a variety of reasons, and follow-up may be incomplete for study patients.
- Medical transcriptions are providers' narrative descriptions of patient-provider encounters. As such, only events/terms specifically mentioned by providers (i.e., positive mentions) would be identified in these records.
- Positive mentions have credibility, but absence of keywords should not be interpreted to mean the event/symptom was necessarily absent.

Conclusions

- Consistent with the rare nature of *ROS1*+ NSCLC, a small number of patients were identified in the medical transcription records as having *ROS1*+ cancer and corresponding use of a ROS1 TKI.
- In this study, crizotinib was the most often used 1L TKI therapy (88% of patients) since it was the only FDA approved ROS1+ TKI until late 2019. There was no true consensus for 2L or later line therapies with patients who failed their first TKI moving to either a different TKI, a checkpoint inhibitor, chemotherapy or an unspecified treatment during the study period (Jan 2015 – Nov 2021).
- Time on TKI therapy varied considerably, with the majority of patients continuing their 1L TKI for less than 12 months.
  - Half of patients with a TKI treatment disruption had their first disruption within <3 months of TKI initiation.
  - Approximately 65% of crizotinib users experienced at least one treatment disruption with progression and adverse events/tolerability most often noted as the reason for disruption.
- Results suggest possible unmet need among *ROS1*+ NSCLC patients using contemporary TKIs since treatment disruptions are common and often occur soon after initiation, with disease progression and/or tolerability issues contributing to short, likely sub-optimal, durations of TKI use.
- New therapies that are effective, have lower risk of treatment-resistance, and that offer better tolerability than current TKIs are needed to simplify and improve patient journeys for individuals with *ROS1*+ NSCLC.

References

1. Key Lung Cancer Statistics. Accessed September 21, 2022 at https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html;
2. Cancer Facts & Figures 2022. Accessed March 13, 2022 at https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html#:~:text=The%20American%20Cancer%20Society's%20estimates,men%20and%2061%2C360%20in%20women)
3. Non-Small Cell Lung Cancer Treatment (PDQ®)-Health Professional Version - National Cancer Institute. Published March 26, 2021. Accessed June 2, 2021. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq
4. Facchinetti F, Rossi G, Bria E, Soria JC, et al. Oncogene addiction in non-small cell lung cancer: Focus on ROS1 inhibition. Cancer Treat Rev. 2017 Apr;55:83-95. doi: 10.1016/j.ctrv.2017.02.010
5. D'Angelo A, Sobhani N, Chapman R, et al. Focus on ROS1-Positive Non-Small Cell Lung Cancer (NSCLC): Crizotinib, Resistance Mechanisms and the Newer Generation of Targeted Therapies. Cancers (Basel). 2020;12(11):3293. doi:10.3390/cancers12113293
6. FDA approves crizotinib capsules. Accessed October 5, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-crizotinib-capsules
7. FDA approves entrectinib for NTRK solid tumors and ROS-1 NSCLC.Accessed October 5, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-entrectinib-ntrk-solid-tumors-and-ros-1-nsclc
8. Sehgal K, Piper-Vallillo AJ, Viray H, Khan AM, Rangachari D, Costa DB. Cases of ROS1 -rearranged lung cancer: when to use crizotinib, entrectinib, lorlatinib, and beyond? Precision Cancer Medicine. 2020;3(0). doi:10.21037/pcm-2020-potb-02
9. FDA Approves Mobocertinib for EGFR Exon 20 Insertion+ NSCLC. OncLive. Accessed September 15, 2021. https://www.onclive.com/view/fda-approves-mobocertinib-for-egfr-exon-20-insertion-nsclc

Presented at ISPOR Europe 2022; November 6-9, 2022; Vienna, Austria, and virtual

Email: andrew.shim@tptherapeutics.com