ReWARD Study: Real World ALK Resistance Data: A single center experience

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INTRODUCTION

ALK rearranged NSCLC has emerged as a distinct entity with growing number of potent ALK tyrosine kinase inhibitors. However, resistance mechanisms ensue and newer generation alectinib and ceritinib were developed to overcome these.
Resistance to TKIs can broadly be categorized as on target alterations which include ALK kinase domain alterations and ALK amplification; and the second category includes off-target mechanisms involving upregulation of other bypass pathways (EGFR, SRC, MEK/ERK, KIT, and others). .

In this study, we present the largest series of repeat biopsies (tissue and/or liquid) from patients of ALK positive NSCLC who have progressed on ALK directed therapy from this part of the world. Using a combinatorial approach of genomics, histology we describe the spectrum of various resistance mechanisms encountered as patients relapse on ALK TKIs

METHODS AND MATERIALS

All patients of ALK positive NSCLC treated with any ALK TKI in any line and progressed on the same during their disease course were considered for enrolment in this study. Only those patients with a rebiopsy (tissue) or frozen plasma sample at the time of progression on TKI were recruited. Those with insufficient tissue in the FFPE block/ suboptimal nucleic acid quantity or quality were excluded from the study.
Genomic Sequencing
Comprehensive Genomic Profiling (tissue) :
Comprehensive genomic profiling was done using Oncomine Focus Assay encompassing 52genes, including both DNA and RNA based alterations.
The libraries were prepared, and the templates were enriched on Ion Chef using Ion One Touch 2. The prepared libraries were quality checked on TapeStation. The final libraries were optimised and equalized and then sequenced on Ion Torrent S5 platform
Comprehensive Genomic Profiling- Liquid

RESULTS

Between 2015-2021, a total of 32 patients with ALK-positive NSCLC, progressed on TKI were enrolled in this study. The median age was 53 years (range:36-75 years) with a male predilection (male: female- 1.3:1). ALK IHC was positive in all the 32 cases at diagnosis, whereas on NGS an ALK fusion was detected in 30 out of the 32 cases. The 2 cases which did not reveal a fusion on NGS, were confirmed on FISH and showed break apart signals
Of these 32 cases, 27 (84.4%) cases were known to harbor an additional resistance mechanism. Eighteen of these 27 cases harbored an on-target ALK alteration, with L1196M gatekeeper mutation being the most common, seen in 11 cases, G1202 alteration seen in 3 cases. In 9 cases a potential off-target alteration was detected, the most frequent being TP53 mutation in 8 cases, followed by KRAS mutation in 4 cases and MET amplification in 3 cases. Figure 1 depicts the spectrum of resistance alterations detected along with their frequencies and related drugs.

Characteristics	Number	%
Age: Median	53	
Range	36-75 years	
Gender		
Male	18	56.3
Female	14	43.7
Pre-enrolment TKI		
Crizotinib	12	37.5
Ceritinib	11	34.4
Alectinib	9	28.1
Post Resistance treatment given		
Ceritinib	9	28.1
Alectinib	7	21.9
Lorlatinib	16	50

RESULTS

A total of four patients underwent rebiopsy after subsequent lines of treatment. Three out of these four patients were treated with crizotinib in the first-line setting, of which 2 developed L1196M solvent front mutation, 1 patient developed a G1202del and 1 patient was treated with alectinib developed KRAS mutation and MET dysregulation. The two patients who developed L1196M were offered ceritinib, and post ceritinib progression NGS revealed additional D1203N mutation in one patient along with increase allele frequency of the existing L1196M mutation, and the other developed an ALK amplification with a copy number of 8.4. The patient with G1202del was offered alectinib, and post alectinib progression revealed stable allele frequency of the G1202del mutation, with an additional TP53 alteration (allele frequency:2.3%, possibly indicative of clonal hematopoiesis of indeterminate potential) on liquid biopsy-based NGS profiling. The patient with KRAS, MET, and G1202del showed a reduction in G1202del mutation, with an increase in VAF of the KRAS alteration.
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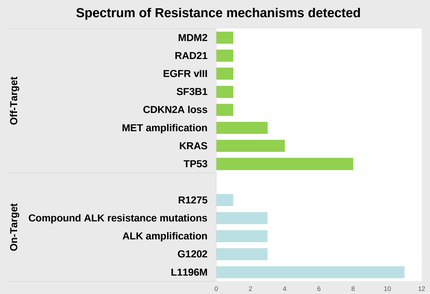

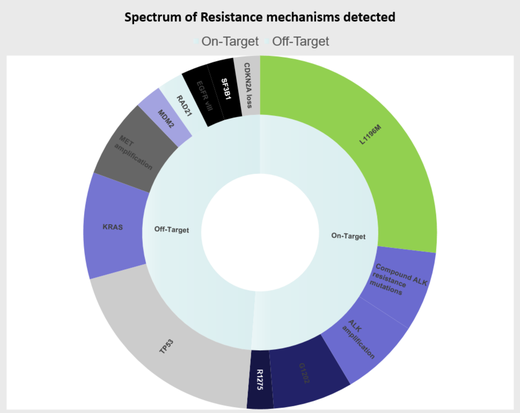

DISCUSSION

The current therapeutic paradigm for advanced *ALK*-positive NSCLC is to treat with sequential ALK inhibitors, nowadays starting with one of the second-generation ALK TKIs as the first-line treatment then follow by third-generation ALK inhibitor, instead of starting with first-generation ALK TKI. This study reveals real world evidence on various resistance mechanisms encountered on treatment with ALK TKIs These are different from controlled trials, and is one of its kind from this part of the world, with a good sized cohort
Although the numbers are small, this is by far the largest real world evidence from Indian peninsula.

CONCLUSIONS

Although this treatment approach has dramatically improved the survival of patients, third-generation acquired resistance invariably develops and leads to clinical progression. As lorlatinib has been approved into the first-line setting, rebiopsy to characterize resistance mechanisms might be necessary to determine the role of earlier generation ALK TKIs in this setting.

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