ALK and *ROS-1* NSCLC patients treatment approach based on genomic profile by liquid biopsy

Lung cancer is the leading cause of cancer-related death in the world. Anaplastic lymphoma kinase (*ALK*) and *ROS-1* gene rearrangements occur in ~5% and 1–2% of patients with advanced NSCLC, respectively, mainly in lung adenocarcinomas.

ALK and ROS-1 tyrosine kinase inhibitors (TKIs) have become the new standard of care in the first-line treatment of advanced *ALK* and *ROS-1* positive NSCLC patients. As there are several TKIs available, the optimal sequential ALK and ROS-1 TKI strategy at progression is relevant, and this may have an impact on patients' outcome.

Almost one-third of advanced NSCLC patients do not have adequate tumor tissue for genomic profiling. Liquid biopsy as circulating tumor DNA analysis (ctDNA) may provide real-time information on the molecular evolution of the disease upon personalised therapy. Currently, next generation sequencing (NGS) is considered the optimal method for detecting *ALK* and *ROS-1* mutations from ctDNA.

Although intra-tyrosine kinase *ALK*-mutations are the main mechanism of acquired resistance (AR) to ALK TKIs, there is a preliminary specific resistance mutation profile with a subsequent therapeutic implication based on the ALK TKI chosen. In first generation ALK TKI crizotinib-refractory tumors, the efficacy of next generation ALK TKIs (brigatinib, ensartinib, ceritinib, lorlatinib) is independent of the occurrence of acquired *ALK*-mutations. However, the upfront administration of second generation ALK TKIs (alectinib, brigatinib) or third generation ALK TKI (lorlatinib), have challenged the current blinded sequential treatment strategy guided by clinicians.

AR to ROS-1 TKIs can occur through either pharmacological or biological mechanism, which consist mainly of acquisition of secondary point mutations in the *ROS1* kinase domain, activation of by pass tracks and phenotypic changes. After progression to first-line ROS-1 TKI crizotinib, secondary mutations can be overcome with repotrectinib or lorlatinib. However, the new first line entrectinib approval and other novel drugs under development, will require a more robust understanding of the resistance pattern that will have subsequent treatment impact.

Considering the crucial prognostic and predictive value of secondary *ALK* and *ROS-1* resistance mutations for the selection of the optimal sequential TKI, serial ctDNA analysis may provide real-time information on the disease molecular evolution upon ALK and ROS-1 TKI therapy. The characterization of mechanisms of AR will be clinically relevant relevant to develop new personalised treatment strategies to overcome resistance in the near future.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Precision Cancer Medicine* for the series "ALK and ROS-1 NSCLC Patients Treatment Approach Based on Genomic Profile by Liquid Biopsy". The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-36/coif). The series "ALK and ROS-1 NSCLC Patients Treatment Approach Based on Genomic Profile by Liquid Biopsy" was commissioned by the editorial office without any funding or sponsorship. JC, EN and LM served as the unpaid Guest Editors of the series. JC serves as an unpaid editorial board member of *Prevision Cancer Medicine* from April 2020 to March 2022. EN and LM serve as unpaid editorial board members of *Prevision Cancer Medicine* from March 2020 to February 2022. JC and EN receive consulting fees from AstraZeneca, Pfizer, Boehringer, MSD, Takeda, Roche, Lilly and Bristol-Myers. LM reports research grant/funding (self): Bristol Myers Squibb, Boehringer Ingelheim, Amgen, Stilla, Inivata; Advisory/Consultancy: Roche, Takeda; Honoraria (self): Bristol Myers Squibb, Roche, Takeda; Travel/

Accommodation/Expenses: Roche, BMS, AstraZeneca. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ernest Nadal

Laura Mezquita

Jesús Corral

Ernest Nadal
Department of Medical Oncology, Catalan Institute of Oncology, Barcelona, Spain.
(Email: esnadal@iconcologia.net)
Laura Mezquita
Thoracic Unit, Hospital Clinic, Barcelona, Spain.
(Email: LMEZQUITA@clinic.cat)
Jesús Corral, MD^
Department of Medical Oncology, Clínica Universidad de Navarra, Madrid, Spain.
(Email: jcorral@unav.es)
Received: 01 September 2021; Accepted: 23 September 2021; Published: 30 March 2022.
doi: 10.21037/pcm-21-36
View this article at: https://dx.doi.org/10.21037/pcm-21-36

doi: 10.21037/pcm-21-36
Cite this article as: Nadal E, Mezquita L, Corral J. *ALK* and *ROS-1* NSCLC patients treatment approach based on genomic profile by liquid biopsy. Precis Cancer Med 2022;5:1.

^ ORCID: 0000-0003-4377-2871.