The ACC lung project. Design and implementation of a nationwide genetic screening program in lung cancer
Luca Mazzarella1, Vanesa Gregoric2, Alessandro Guida1, Chiara Lazzari1, Gianmaria Frige1, Piergiuseppe Pelicci1, Ruggero Gero de Maria1, Alleanza contro il Cancro Working Group-genomics, Alleanza contro il Cancro Working Group-lung
1Istituto Universitario di oncologia, Milano; 2Ospedale San raffaele, Milano; 3Università Cattolica del Sacro Cuore, Roma; 4Alleanza contro il Cancro, Roma

Genetic characterization of non-small cell lung cancer (NSCLC) is essential for adequate treatment. Still, recent surveys revealed that most patients do not receive even the minimal molecular classification (EGFR and ALK status). Additional alterations predicting response to recently approved or experimental drugs (e.g. BRAF, MET, ROS, NTRK, FGFR) are even less frequently assessed, impeding access to targeted therapeutics with proven clinical benefit.

The Alleanza contro il Cancro (ACC)-Lung project was designed to foster the implementation of affordable, streamlined large-scale Next generation Sequencing (NGS)-based characterization in clinical practice.

Aims:
- Development of a national infrastructure to collect and homogenize genetic information from patients and literature
- Development of a bioinformatic tool to assist in the design of genomics-driven trials
- Development of a targeted sequencing panel to maximize clinical actionability in NSCLC

Technical validation of the panel by comparing hybridization/illumina-based vs PCR/Ion Torrent-based workflows

- Deployment of a multicentric trial to compare frequency of actionable EGFR and ALK fusions with standard methods
- Sample collection for translational studies (ACC-Immunotherapy, liquid biopsy)

1. The ACC IT infrastructure

The prescription database (left) was used to extract 163 genes whose molecular alteration may be actionable (actionability classes on the right)

2. Use of the ACC prescription database to identify 162 actionable genes

A centralised and well-structured computational core is key for adequate information integration in sequencing projects, and to make this information useful. The ACC IT infrastructure is being built together with the Elixir European network on the OINECA platform, and consists of:
- A mutational registry to collect and harmonize all genetic information, in compliance with privacy regulation
- A database, to digest literature- and trial-derived actionability information, and to make it available in user-friendly format to treating oncologists

3. Design of a targeted sequencing panel using Precision Trial Drawer

The prescription database (left) was used to extract 163 genes whose molecular alteration may be actionable (actionability classes on the right)

4. Validation of the ACC lung panel - PCR/Ion Torrent

5. Initiation of a clinical trial to test the ACC panel

Clinical trial was initiated by the ACC lung and genomics working groups

- Target sample size: 1000 cases
- 15 centres open to enrolment date

Inclusion criteria
- Advanced (stage IIIb/IV) NSCLC, ECOG PS 0-2

Primary objective
- Sample frequency of actionable EGFR and ALK fusions with standard methods

Secondary objectives
1. test feasibility (% pts w adequate amount and informative test, turnaround time)
2. compare frequency of oncogenic alterations with the literature. Focus on hotspot KRAS and BRAF, MET, ROS-1 fusions, EML4-ALK variant 3 and SLC34A2-ROS1 and many other of clinical relevance. Target fusions included EML4-ALK variant 3
3. proportion of patients carrying mutations for which targeted therapy is available
4. performance of each center.
5. correlate genotype with overall and progression-free survival