Frequency of actionable alterations in *EGFR* wt NSCLC: experience of the Wide Catchment Area of Romagna (AVR)

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Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors have improved the outcome of *EGFR*-mutated lung adenocarcinoma (ADC) patients. However, other alterations are emerging as potential target of drugs. We analyzed the frequency of potentially targetable driver alterations in a series of advanced EGFR-wild type (wt) NSCLC patients.

Methods: 724 advanced *EGFR*-wt NSCLC patients enrolled from the Wide Catchment Area of Romagna were included in the study. *KRAS*, *BRAF*, *ERBB2*, *PIK3CA*, *NRAS*, *ALK*, *MAP2K1*, *RET* and *DDR2* mutations were analyzed by Myriapod®Lung Status kit (Diatech Pharmacogenetics) on MassARRAY® (SEQUENOM® Inc, California). *ERBB4* was evaluated by direct sequencing and *EML4-ALK* and *ROS1* rearrangements were assessed by immunohistochemistry or fluorescence in situ hybridization.

Results: 331 (45.7%) patients showed at least one alteration. Of these, 72.2%, 6.3%, 3.6%, 1.8%, 2.1% and 1.2% patients had mutations in *KRAS*, *BRAF*, *PIK3CA*, *NRAS*, *ERBB2* and *MAP2K1* genes, respectively. *EML4-ALK* and *ROS1* rearrangements were observed in 4.3% and 1.4% of all patients, respectively. The clinical characteristics of mutated patients are reported in Table 1. Overlapping mutations were observed in 7 *KRAS*-mutated patients: 2 (28.6%) patients were also mutated in *PIK3CA*, 4 (57.1%) showed also an *EML4-ALK* translocation and one (14.3%) had a ROS1 rearrangement. One (0.3%) patient showed both *BRAF* and *PIK3CA* alterations.

GENE	Mutated Patients N (%)	Gender		Smoking Habits*	
		Female (%)	Male (%)	Smoker (%)	Never Smoker (%)
KRAS	239 (33)	93 (39)	146 (61)	115 (48.1)	9 (3.8)
BRAF	21 (3)	11 (52.4)	10 (47.6)	11 (52.4)	1 (4.8)
NRAS	6 (0.8)	4 (66.7)	2 (33.3)	4 (66.7)	-
PIK3CA	12 (1.6)	4 (33.3)	8 (66.7)	5 (41.7)	-
MAP2K1	4 (0.5)	-	4 (100)	1 (25)	-
ERBB2	7 (0.9)	5 (71.4)	2 (28.6)	-	1 (14.3)
EML4-ALK	31 (4.3)	20 (64.5)	11 (35.5)	12 (38.7)	8 (25.8)
ROS1	10 (1.4)	7 (70)	3 (30)	3 (30)	5 (50)

Conclusions: Driver mutations were detected in about 50% of *EGFR*-wt lung ADC patients. Such alterations could represent potential targets for therapy and could be evaluated in routine multiplexed testing.