Contribution of *KRAS* mutations and c.2369C > T (p.T790M) *EGFR* to acquired resistance to EGFR-TKIs in *EGFR* mutant NSCLC: a study on circulating tumor DNA

M. Del Re[1], M. Tiseo[2], P. Bordi[2], I. Petrini[3], M. Lucchesi[4], E. Vasile[4], V. Citi[1], S. Gori[5], A. Falcone[4], D. Amoroso[6], A. Chella[7], F. Cappuzzo[8], A. Ardizzoni[2], A. Scarpa[9], R. Danesi[1]

1 Department of Clinical and Experimental Medicine, University of Pisa
2 Medical Oncology Unit, Azienda Ospedaliero-Universitaria, Parma
3 Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa 6 Medical Oncology Unit 2, Azienda Ospedaliero-Universitaria, Pisa
4 Medical Oncology Unit 2, Azienda Ospedaliero-Universitaria, Pisa
5 Medical Oncology Unit, Ospedale Sacro Cuore, Negrar
6 Medical Oncology Unit, AUSL12, Istituto Toscano Tumori, Lido di Camaiore
7 Lung Diseases Unit, Azienda Ospedaliero-Universitaria, Pisa
8 Medical Oncology Unit, AUSL6, Istituto Toscano Tumori, Livorno
9 ARC-NET Research Centre and Department of Pathology and Diagnostics, Azienda Ospedaliero-Universitaria, Verona 10 Lung Diseases Unit, Azienda Ospedaliero-Universitaria, Pisa

Introduction: KRAS oncogene mutations (MUTKRAS) drive resistance to EGFR inhibition by providing alternative signaling as demonstrated in colo-rectal cancer. In non-small cell lung cancer (NSCLC), the ef cacy of treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs) depends on activating EGFR mutations (MUTEGFR). However, inhibition of EGFR may select resistant cells displaying alternative signaling, i.e., KRAS, or restoration of EGFR activity due to additional MUTEGFR, i.e., the c.2369C > T (p.T790MEGFR).

Aim: The aim of this study was to investigate the appearance of MUTKRAS during EGFR-TKI treatment and their contribution to drug resistance.

Methods: This study used cell-free circulating tumor DNA (cftDNA) to evaluate the appearance of codon 12 MUTKRAS and p.T790MEGFR mutations in 33 advanced NSCLC patients progressing after an EGFR-TKI.

Results: p.T790MEGFR was detected in 11 (33.3%) patients, MUTKRAS at codon 12 in 3 (9.1%) while both p.T790MEGFR and MUTKRAS codon 12 were found in 13 (39.4%) patients. Six patients (18.2%) were KRAS wild-type (WTKRAS) and negative for p.T790MEGFR. In 8 subjects paired tumor re-biopsy/plasma samples were available; the percent concordance of tissue/plasma was 62.5% for p.T790MEGFR and 37.5% for MUTKRAS. The analysis of time to progression (TTP) and overall survival (OS) in WTKRAS vs. MUTKRAS were not statistically different, even if there was a better survival with WTKRAS vs. MUTKRAS, i.e., TTP 14.4 vs. 11.4 months ($p = 0.97$) and OS 40.2 vs. 35.0 months ($p = 0.56$), respectively.

Conclusions: MUTKRAS could be an additional mechanism of escape from EGFR-TKI inhibition and cftDNA is a feasible approach to monitor the molecular development of drug resistance.