Role of *TP53* mutations in determining primary resistance to first-line tyrosine kinase inhibitors in *EGFR*-mutated NSCLC patients

Paola Ulivi[1], Matteo Canale[1], Angelo Delmonte[2], Elisabetta Petracci[3], Elisa Chiadini[1], Claudio Dazzi[4], Maximilian Papi[5], Laura Capelli[1], Claudia Casanova[4], Nicoletta De Luigi[2], Marita Mariotti[2], Alessandro Gamboni[6], Rita Chiari[7], Chiara Bennati[7], Daniele Calistri[1], Vienna Ludovini[7], Lucio Crinò[8], Dino Amadori[2]

[1] Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola,Italy; [2] Department of Medical Oncology, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy;[3] Unit of Biostatistics and Clinical Trials, Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [4]S. Maria delle Croci Hospital, Ravenna, Italy; [5]Infermi Hospital, Rimini, Italy; [6]Degli Infermi Hospital, Faenza, Italy; [7]Medical Oncology, Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia, Italy; [8] University of Perugia, Perugia, Italy

Background: Patients with non-small-cell lung cancer (NSCLC) carrying specific mutations at epidermal growth factor receptor (EGFR) gene are usually sensitive to tyrosine kinase inhibitors (TKIs). However, approximately 20-30% of patients show primary resistance, the mechanisms of which are scarcely understood. In this study we aimed to assess the role of *TP53* mutations in relation to response to TKIs .

Methods: We analyzed 136 patients with advanced *EGFR*-mutated NSCLC treated with first-line TKIs. Exons 5-8 of *TP53* gene were analyzed by direct sequencing. Disease Control Rate (DCR) was defined as the sum of complete response, partial response and stable disease. The survival endpoints examined were Progression Free Survival (PFS) and Overall Survival (OS).

Results: *TP53* mutations were observed in 37 (30.1%) patients. DCR was 70% in *TP53*-mutated patients compared to 88% in *TP53*-wt patients (relative risk, RR: 3.17, p=0.019). In particular, a 42% DCR was observed in patients with *TP53* exon 8 mutation compared to 87% in wt patients (RR 9.6, p<0.001). Shorter median PFS and OS were observed in patients with *TP53* exon 8 mutations compared to other patients (4.2 vs 12.5 months [p=0.058] and 16.2 vs 32.3 months [p=0.114], respectively); these differences became significant in the subgroup of patients with *EGFR* exon 19 deletion (4.2 vs 16.8 months [p<0.001] and 7.6 months vs not reached [p=0.006], respectively), hazard ratio (HR) 6.99, p<0.001) and HR 4.75, p=0.013), respectively.

Conclusions: *TP53* mutations, in particular exon 8 mutations, reduce responsiveness to TKI treatment and induce a worse prognosis in *EGFR*-mutated NSCLC patients, especially in those carrying exon 19 deletions.