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Sommario/riassunto

Lung cancer still remains a challenging disease with a higher mortality rate in comparison to other cancers. The discovery of oncogene addicted tumours and targeted therapies responsive to these targets lead to a meaningful change in the prognosis of these diseases. Unfortunately, these newer therapeutic options are reserved to a minor part of lung cancer patients harbouring specific mutations. In the so called wild type population, the first line options bring the median overall survival to go beyond 1 year, and in the population receiving the maintenance therapy over 16 months. Given these results, more than 60% of patients may receive a second line therapy with further opportunities to improve the length and quality of life. For patients not harbouring targetable DNA mutations newer options will be available for second line therapeutic schemes and two major assets seem to be promising: immune modulation and anti-angiogenetic agents. In particular, anti PD1/PDL1 antibodies, VEGFR antibodies and TKIs, these latter combined with standard chemotherapy docetaxel advance the median overall survival of 12 months. These drugs have a different mechanism of action, various adverse events and their activity is different depending on the types of population. However, the biomarkers' activity and efficacy prediction are not fully or totally understood. In addition, also for patients with DNA targetable mutations new drugs seems to be promising for the use in the second line therapeutic protocols. In particular, drugs selectively directed

against ALK translocation and mutational events and EGFR T790M secondary mutations seems to be very promising. In this Research Topic we critically discuss the older therapies and the historical development of second line, putting in to perspective the new agents available in clinical practice. We discuss their importance from a clinical point of view, but also consider and exploit the complex molecular mechanisms responsible of their efficacy or of the subsequently observed resistance phenomena. In this perspective, the undercovering and characterization of novel predictive biomarkers by NGS technology, the characterization of novel actors in the signal transduction pathway modulating the response of the cells, the optimization of new diagnostic tool as the evaluation of liquid biopsy and the implementation of more suitable pre-clinical models are crucial aspects dissected too. Nivolumab, nintedanib and ramucirumab probably will give the opportunity to improve the efficacy outcomes for the treatment of wild type tumours in second line therapeutic schemes, but many aspects should be debated in order that these agents are made available to patients, planning ahead a therapeutic strategy, beginning from the first line therapy, to the subsequent ones in a logical and affordable manner. As well, for treatment of mutated tumours, mutated EGFR irreversible inhibitors such as rociletinib and AZD9291, and ALK targeting drugs ceritinib and alectinib will also play an important role in the immediate future. Probably the right way is to give all the available opportunities to patients, but challenges and pitfalls should be carefully debated, and by launching this Research Topic we tried to give some practical insights in this changing landscape.