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Conclusion

We have recently witnessed a remarkable progress in our understanding of molecular biology and signalling pathways of NSCLC cells which resulted in ErbB targeted therapies, ALK inhibitors and other targeted agents being now in clinical trials. However, a substantial number of NSCLC patients remain non-responsive or relapse early on these targeted therapies. Improved understanding of the functioning of ErbB receptor family have led to second generation active anti-ErbB therapies. It is clear from different preclinical and clinical studies that combined anti-ErbB therapies have a superior efficacy to single agent therapies.

In future it will be essential to characterize mutations of resistance in each line of treatment. Circulating tumour cells and plasma DNA analysis could enable us to obtain this information easier. The development of the resistance can be clonal/thus not present at all the tumour sites, supporting a concept of continuing the targeted treatment even beyond tumour progression. Co-targeting molecular pathways such as P13K-AKT and/or RAS-ERK and/or T790M or c-Met along with ErbB receptors may result in more optimal anti-cancer effects.

We need to better understand the interplay between various oncogenes and tumour suppressors and thus identify key molecular pathways for the treatments. Understanding the reasons for toxicities of targeted therapies will be important for our future rational approaches in combining or sequencing different targeted agents. Co-targeting receptors and their ligand synthesis might help eliminating more effectively receptor activation and downstream oncogenic signalling. New insights of autocrine activation of receptors might lead to new therapeutic approaches.

The past successes and failures of therapies led to development of new generation irreversible ErbB family inhibitors and the discovery of new targets, i.e. EML4—ALK fusion gene, ROS, RET and others, which offer significant improvements in clinical outcome for a specific group of patients. The combined regimen strategies of first generation ErbB family inhibitors with anti c-MET inhibitors are being tested in ongoing clinical trials in hope to further improve therapeutic effect. We have to target multiple pivotal players of malignant cells on individual basis and in each line of treatment, in order to replace ''chemotherapy to fit all'' by personalized medicine and thus conquer NSCLC.

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