Increasing evidence supports complex subclonal relationships in solid tumours, manifested as intratumour heterogeneity. Our group and others are finding evidence for spatial heterogeneity within individual tumours and the temporal dynamics of tumour evolution. Parallel evolution of subclones, with distinct somatic events occurring in the same gene, signal transduction pathway or protein complex, suggests constraints to tumour evolution that might be therapeutically exploitable. Drivers of tumour heterogeneity appear to change during the disease course that contribute to the temporally distinct origins of cancer driver events. Genome doubling, occurring early or late in tumour evolution, exacerbates chromosomal instability contributing to intercellular heterogeneity and poor outcome. The finding of subclonal driver events is likely to limit the efficacy of targeted mono therapies, suggesting the need for new approaches to drug development and clinical trial design. TRACERx, a longitudinal lung cancer evolution study and DARWIN clinical trials aimed at deciphering the relevance of subclonal driver events to therapeutic outcome, will be discussed.

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