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#	Author	Title	Study design	Study aim	Patients and patient characteristics	Targeted therapy line and regimen	Outcome categories	Outcomes
1	Allen et al., 2017	Genomic Profiling of Circulating Tumour DNA in Relapsed EGFR-mutated Lung Adenocarcinoma Reveals an Acquired FGFR3-TACC3 Fusion	Case Study	To report a case of EGFR-mutated non-small-cell lung cancer (NSCLC) with progression during cetuximab plus afatinib treatment	1 patient • 66-year-old female former smoker	First line: Afatinib and cetuximab	Liquid biopsy results	• liquid biopsy of a mediastinal lymph node biopsy revealed EGFR L858R and E709K mutations (30% and 9% allele frequency, respectively), TP53 V272L mutation, and amplification of the NFKBIA, NKX2-1, and ZNF217 genes • "The ctDNA assay after progression revealed an emergent FGFR3-TACC3 fusion and CDKN2A mutation not present in the previous pre-treatment tissue analysis. The TP53 V272L and EGFR L858R mutations were also detected in the post-treatment ctDNA sample; however, the EGFR E709K mutation was not detected." • Owing to the lack of an available tissue biopsy specimen, a Clinical Laboratory Improvement Amendments-validated ctDNA assay (FoundationACT®) was performed to assess the potential resistance mechanisms to EGFR-targeted therapy
2	Dagogo-Jack et al., 2017	Circulating Tumour DNA Identifies EGFR Coamplification as a Mechanism of Resistance to Crizotinib in a Patient with Advanced MET-Amplified Lung Adenocarcinoma	Case Study	To report circulating Tumour DNA Identifying EGFR Co-Amplification as a Mechanism of Resistance to Crizotinib in a Patient with Advanced MET-Amplified Lung Adenocarcinoma	1 patient 70 year old female with metastatic adenocarcinoma	Crizotinib	Liquid biopsy results	Circulating Tumour DNA Identifies EGFR Coamplification as a Mechanism of Resistance to Crizotinib in a Patient with Advanced MET-Amplified Lung Adenocarcinoma.

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3	Dagogo-Jack et al., 2017	Genomic profiling of circulating tumour DNA (ctDNA) from patients with advanced non-small cell lung cancer (NSCLC).	Retrospective cohort	To perform a genomic profiling of circulating tumour DNA (ctDNA) from patients with advanced non-small cell lung cancer (NSCLC)	1019 patients Median age, years (range): 69 (8-94)	N/A	Liquid biopsy results	• NSCLC not otherwise specified (NSCLC NOS; n = 179), squamous cell (n = 57), LC NOS (n = 51), large cell (n = 6), and sarcomatoid (n = 6). ≥1 reportable genomic alteration was detected in 71% of all cases and in 83% of cases with evidence of ctDNA in the blood (MSAF > 0) • For 22 patients with paired blood and tissue samples collected within 30 days and MSAF > 0, 33/64 (52%) genomic alterations detected in tissue were also detected in ctDNA. In 55 patients for whom tissue was insufficient for analysis, ≥1 genomic alteration was detected in ctDNA in 43 (78%) cases. • For 856 cases with MSAF > 0, an average of 1.8 genomic alteration/sample were reported. genomic alterations were most frequently detected in TP53 (57%), EGFR (23%) and KRAS (17%). Comparative analysis with the tissue-based FoundationCORE™ database (n = 19,264) showed similar frequencies of genomic alteration per gene, although KRAS mutation was more frequent in tissue than ctDNA (27% vs 17%, P < 0.0001), and EGFR T790M was more frequent in ctDNA than tissue (7% vs 2%, P < 0.0001), likely reflecting use of liquid versus tissue biopsy after relapse on targeted therapy. • Kinase fusions (ALK, ROS1, RET, FGFR3, PDGFRA) were identified in 5% (39/856) of cases. Diverse and novel mechanisms of acquired resistance were detected in ctDNA including MET Y1230C and EGFR amplification post-crizotinib, FGFR3-TACC3 fusion post-EGFR inhibitor, and multiple EGFRAR mutations post-osimertinib. • Overall, 16% of amplifications that were observed in tissue were also observed in ctDNA; one amplification was detected in ctDNA only; 100% (4/4) kinase fusions (all EML4-ALK) that were observed in tissue were also observed in ctDNA; no fusions were detected in ctDNA only
4	Ou et al., 2016	Emergence of Preexisting MET Y1230C Mutation as a Resistance Mechanism to Crizotinib in NSCLC with MET	Case study	To report a clinically novel MET mutation after progression on crizotinib, in a patient with METex14+ NSCLC after a confirmed durable	1 patient 67-year-old Asian female never-smoker was diagnosed with stage IV metastatic adenocarcinoma of the lung when she presented with superior vena caval	Third: Crizotinib	Liquid biopsy results	• Comprehensive genomic profiling of the initial tissue biopsy performed as part of standard of care revealed a MET ex14 skipping alteration (MET D1010H) (44% MAF) but no concurrent MET amplification. • A retrospective analysis of the original CGP testing revealed that 2/762 (0.26%) sequencing reads showed the Y1230C mutation present well below reportable levels of the assay. • Patient achieved a confirmed PR after 2 mths of crizotinib treatment and maintained a PR for nearly 13 mths, at which point she developed metastasis to right cervical lymph nodes.

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		Exon 14 Skipping.		response, using a plasma-based circulating tumour DNA (ctDNA) assay	(SVC) syndrome and 7-pound weight loss			Re-staging of the patient revealed progression of her brain metastases. • At this stage, a ctDNA assay confirmed the presence of the previously detected primary METex14 (D1010H) alteration at 10.9% MAF and also detected the MET Y1230C resistance mutation at a MAF of 3.5%.
5	Ou et al., 2017	Emergence of novel and dominant acquired EGFR solvent-front mutations at Gly796 (G796S/R) together with C797S/R and L792F/H mutations in one EGFR (L858R/T790M) NSCLC patient who progressed on osimertinib	Case Study	To report the emergence of novel EGFR solvent front mutations at Gly796 (G796S/R) in addition to a hinge pocket L792F/H mutations, and C797S/G all in cis with T790M in a single patient on progression on osimertinib as detected by plasma circulating tumour DNA (ctDNA) assay in the course of clinical care	1 patient 69 years-old former 15 pack-year smoker diagnosed with stage IV adenocarcinoma of the lung	First: Osimertinib	Liquid biopsy results	• Different secondary resistance mutations all in trans with each other including distinct mutations at the same codon producing different amino acid changes: G796S/R (mutant allele frequency [MAF]; 14.4%), C797S/G (MAF: 2.26%), L792F/H (MAF: 0.36%), and V802F (MAF: 0.40%), in addition to the pre-existing L858R (MAF:17.9%) and T790M (MAF:18.2%) but all in cis with T790M. • The G796S/R mutations are homologous with known reported solvent front mutations in ALK G1202R, ROS1 G2032R, TrkA G595R and TrkC G623R, all of which are associated with acquired resistance to type I TKIs • In silico modeling revealed mutation at G796 interferes with osimertinib binding to the EGFR kinase domain at the phenyl aromatic ring position as this residue forms a narrow "hydrophobic sandwich" with L718, while L792F/H mutation interferes with osimertinib binding at the methoxyl group on the phenyl ring. • Multiple resistance mutations at differing allele frequencies including novel EGFR solvent front mutations can emerge in a single patient with progression on osimertinib potentially due to tumour hetereogeneity and definitely present a significant therapeutic and drug development challenge.
6	Ou et al., 2017	Dual occurrence of ALK G1202R solvent front mutation and small cell lung cancer transformation as resistance mechanisms to second	Case Study	To report an ALK+ NSCLC patient who had disease progression after ceritinib andthen alectinib where an ALK G1202R mutation was detected on circulating tumour (ct) DNA prior to	1 patient 35 year-old Chinese male never-smoker who presented with extensive stage IV adenocarcinoma of the lung with central nervous system (CNS) and spine metastasis, pleural metastasis,	Multiple prior therapy lines: Ceritinib, loratinib	Liquid biopsy results	• Tumour tested positive for ALK rearrangement by fluorescence in situ hybridisation (FISH) (break apart signals positive in 100% of the cells tested) and immunohistochemistry (IHC) (100% positive by D5F3 antibody) but negative for chromogranin and synaptophysin by IHC • Patient underwent corpectomy, vertebroplasty, stereotactic radiation >> 8 months of ceritinib treatment, >> Alectinib treatment >> patient was then referred for a trial with a third-generation ALK inhibitor, lorlatinib • Next generation sequencing of circulating tumour (ct) DNA showing the presence of ALK G1202R mutations before (1A)

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		generation ALK inhibitors without prior exposure to crizotinib		enrollment onto a trial of another next generation ALK inhibitor, lorlatinib	and malignant pleural effusion			and disappearance of G1202R (1B) after treatment with lorlatinib. • Plasma based circulating tumour (ct) DNA sample using hybrid-capture base genomic profiling (FoundationACT®), performed as previously described, prior to starting lorlatinib, revealed the presence of ALK G1202R at 0.73% (Fig. 1A) as well as the original ALK rearrangement at an estimated allele frequency of 36–54%
7	Young et al., 2017	Kinase fusions in non-small cell lung carcinoma identified by hybrid capture based ctDNA assay	Prospective cohort	To describe kinase fusions in Non-Small Cell Lung Carcinoma identified by hybrid capture based ctDNA assay	288 patients Median age, years (range): 61 (41-81) Female gender, %: 59% Stage IV disease, %: 100% Adenocarcinoma histology, %: 85% Number of patients harbouring kinase fusions, n (%): 20 (6.9%)	Not reported: afatinib/cetuximab; crizotinib	Liquid biopsy results	• Number of cases harbouring ALK fusions, n (%): 13 (4.5%) • ALK fusion partners, n: - EML4: 9 (one each of novel partners PPFIBP1 and CACNB4), - unidentified partners: 2 • All but one case had breakpoints in ALK intron 19, the remaining harbouring a novel intron 17 breakpoint. • Three cases (1%) harboured KIF5B-RET (canonical breakpoint intron 12), three (1%) had CD74-ROS1 (breakpoints: ROS1 intron 33(2) and intron 32(1)), and one had FGFR3-TACC3. • ALK, RET, and ROS1 fusions were observed by tissue testing of NSCLC in the FoundationCore database with similar frequencies. • For one patient, EML4-ALK fusion was detected in both ctDNA and tissue, collected six days apart. For another, comprehensive genomic profiling identified EGFR L858R + EGFR L709K and the patient had a durable response to afatinib/cetuximab. • After progression, ctDNA assay identified FGFR-TACC3 as well as EGFR L858R. • For a pre-menopausal, therapy naïve never smoker, female of east Asian heritage, both assays detected a CD74-ROS1 fusion, whereas ROS1 rearrangement was not identified by the prior use of another commercially available ctDNA test. The patient had a major radiographic response by the second cycle of crizotinib treatment.