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#	Author	Title	Study design	Study aim	Patients and patient characteristics	Targeted therapy line and regimen	Outcome categories	Outcomes
1	Li et al., 2017	Severe nivolumab-induced pneumonitis preceding durable clinical remission in a patient with refractory, metastatic lung squamous cell cancer: a case report.	Case Study	To discuss the clinical history, pathological evaluation, and genomic findings in a patient with metastatic lung squamous cell cancer (SCC) who developed severe nivolumab-induced pneumonitis preceding durable clinical remission after three doses of nivolumab.	1 patient with metastatic lung squamous cell cancer (SCC)	line: N/R nivolumab	CGP results & Targeted therapy	• Patient developed symptomatic pneumonitis by week 4 after nivolumab treatment, concurrently with onset of a potent antitumour response. Despite discontinuation of nivolumab after three doses and the use of high dose oral corticosteroids for grade 3 pneumonitis, continued tumour response to a complete remission by 3 months was evident by radiographic assessment. At the time of this submission, the patient has remained in clinical remission for 14 months. • High PD-L1 expression by IHC staining was seen in intra-alveolar macrophages and viable tumour cells in the pneumonitis and recurrent tumour specimens, respectively • CGP revealed a very high TMB corresponding to 95-96 percentile in lung SCC, i.e., 87.4-91.0 and 82.9 mut/Mb, respectively, in pre- and post-nivolumab tumour 7specimens. Except for 1, the 13 functional GAs remained the same in the diagnostic, recurrent, and post-treatment, relapsed tumour specimens
2	Lin et al., 2017	ROS1 Fusions Rarely Overlap with Other Oncogenic Drivers in Non-Small Cell Lung Cancer.	Observational retrospective	To test whether there is a significant overlap between ROS1 fusions and other oncogenic driver alterations, including mutations in EGFR and KRAS.	228 patients with ROS1-rearranged NSCLC (166 FoundationOne® 62 other genomic tests)	N/A	CGP results	• Analysis of an independent data set of 166 ROS1-rearranged NSCLCs identified by FoundationOne® demonstrated rare cases with co-occurring driver mutations in EGFR (one of 166) and KRAS (three of 166) and no cases with co-occurring ROS1 and ALK rearrangements. • Among 62 patients with ROS1-rearranged NSCLC evaluated with other tests none harbored concurrent ALK fusions (0%) or EGFR activating mutations (0%). KRAS mutations were detected in two cases (3.2%), one of which harbored a concurrent noncanonical KRAS I24N mutation of unknown biological significance. No concurrent mutations in BRAF, ERBB2, PIK3CA), AKT1, or MAP2K1 were detected
3	Rozenblum et al., 2017	Clinical Impact of Hybrid Capture-Based Next-Generation Sequencing on Changes in Treatment	Observational retrospective	to investigate the impact of hybrid capture-based NGS on treatment decisions and clinical outcomes	101 patients 53% females, 45% never-smokers, and 85% with adenocarcinoma	N/A	CGP results	• HC-based NGS identified clinically actionable genomic alterations in 50% of patients, EGFR (18%), Ret proto-oncogene (RET) (9%), ALK (8%), Mesenchymal-epithelial transition factor (MET) receptor tyrosine kinase gene (6%), and erb-b2 receptor tyrosine kinase 2 gene (ERBB2) (5%). • Treatment strategy was changed for 43 patients (42.6%) Immunotherapy was administered in 33 patients, mostly without an actionable driver, with a presenting disease control rate of 32%.

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		Decisions in Lung Cancer						
4	Ali et al., 2016	Comprehensive Genomic Profiling Identifies a Subset of Crizotinib-Responsive ALK-Rearranged Non-Small Cell Lung Cancer Not Detected by Fluorescence In Situ Hybridization.	Case Study	To report here a large series of NSCLC cases assayed by hybrid-capture-based comprehensive genomic profiling in the course of clinical care.	41 patients had EML4-ALK fusion 6 had other fusion partners	Second (one patient) Third (two patients) Crizotinib	CGP results & Targeted therapy	• Of 11 patients with false-negative FISH results, 9 received crizotinib based on the Comprehensive genomic profiling detection of an ALK fusion and 7 responded (6 partial responses and 1 complete response), as identified by investigator assessment of either radiographic and/or metabolic imaging. The response durations of these patients ranged from 5 to 28 (ongoing) mths, with the median exceeding 17 mths. • Three cases with ALK rearrangements identified by CGP was reported separately. Two ALK FISH-negative cases, one harbouring the previously undescribed EIF2AK3-ALK (case 1) and another harbouring the well-characterized EML4-ALK (case 2), were described. In both of these cases, the patient was switched to crizotinib after CGP results were received and experienced a durable partial response. The patient in case 3 harboured the novel fusion PRKAR1A-ALK and responded to crizotinib. Of the 47 patients with ALK rearrangements detected using CGP, 31 had FISH testing data available for review. Of these, 11 cases (35%) were FISH negative.
5	DiBardino et al., 2016	Yield and Clinical Utility of Next-Generation Sequencing in Selected Patients With Lung Adenocarcinoma.	Case Study	To investigate the diagnostic success and clinically relevant results of extensive sequencing in NSCLC patients	49 patients Female: 30 (61%), Median age: 62.9 (range: 42-93) years. Most common diagnosis: lung adenocarcinoma. Other final pathology included squamous cell carcinoma (4%), sarcomatoid carcinoma of the lung (2%), and unclassifiable none small-cell	N/R	CGP results & Targeted therapy	• The success of CGP according to the biopsy method, n/N: - Surgical Biopsy: 29/32 - Transthoracic CT-Guided Core Needle Biopsy: 0/5 (all had insufficient tissue to perform genomic sequencing) - Core Needle Biopsy of Liver: 1/1 - Percutaneous Ultrasound-Guided FNA: 2/2 - Endoscopic FNA: 2/2 - Endoscopic Forceps Biopsy: 1/1 - Effusion: 6/6 • Number of GAs found: 179 (average per tumour: 4.37), of which 63 were clinically relevant (average per tumour: 1.54). Number of samples with at least 1 genomic alteration: 40 of 41 analysed tumours. • Number of samples with a CRGA: 30 of 40 (all 30 having at least 1 FDA-approved drug available). Within the 10 tumours without CRGAs, 13 phase I or phase I/II trials were available with a range from 0 to 3. Two of the 41 tumours with genomic alterations had no available FDA-

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					carcinoma of the lung (2%).			approved targeted treatments, or actively enrolling targeted clinical trials. Specific genes affected by alterations are plotted by mutation type and percentage of patients affected in Figure 1. • The most frequent genomic alterations identified: TP53, CDKN2, MLC1, EGFR, SMARCA4, CDKN2B, PIK3CA, KRAS, ERBB2, STK11, NKX2-1. • Number of cases for whom the results of Comprehensive genomic profiling contributed to a change in lung cancer management, n/N (%): 7/49 (14.3%), including: - EGFR-directed therapy was discontinued: 2 patients - new targeted therapy initiated: 5 • Additionally, there were 10 patients with CGP results that could have been used to guide therapy: the patient with the EML4-ALK fusion gene found only on CGP, 3 patients with a PIK3CA mutation without additional options for targetable therapy who could have received a mammalian target of rapamycin inhibitor, 2 of the 3 patients with MET gene mutations who died without receiving crizotinib, a patient with a rearranged during transfection tyrosine kinase fusion mutation who could have received a tyrosine kinase inhibitor, and 3 of the 4 patients with ERBB2 mutations who died before receiving trastuzumab. • The results of simultaneous molecular testing with FISH assay (25 patient samples) was compared with the corresponding CGP, revealing 1 discrepancy in results. CGP identified EML4-ALK fusion, which was not identified in FISH analysis.
6	Goldstein et al., 2016	Recurrent Loss of NFE2L2 Exon 2 Is a Mechanism for Nrf2 Pathway Activation in Human Cancers.	Observational retrospective	To identify tumour-specific alterations that are missed by conventional sequencing and copy number approaches, and to explore the underlying mechanisms and consequences of these alterations.	113 patients	N/A	CGP results	• In KEAP1 mutant cell lines (26%), all but one of the genes identified showed increased expression, consistent with the evidence that the KEAP1 target Nrf2 is a positive regulator of gene transcription. • The set of genes regulated by NRF2 is highly conserved across different tissues and conditions. • Increased use of whole genome sequencing and integrative analysis with RNA sequencing will help identify oncogenes activated by a variety of mechanisms.

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7	Hart et al., 2016	Missed Clinical Benefit due to False Negatives in Testing for EGFR T790M Mutations in Non-Small Cell Lung Cancer.	Case Study	To present three NSCLC patients with low frequency T790M mutations who initially received false negative results and the subsequent treatments and clinical outcomes.	3 patients with NSCLC who tested positive for an EGFR exon 19 deletion at diagnosis. Patient 1: 65 yrs male, never smoker, with stage IV NSCLC Patient 2: 63-year-old male, stage III NSCLC Patient 3: 54-year-old male, never smoker, stage IV NSCLC and brain metastases	line N/R Patient 1: Erlotinib for 12 mths, then 4 mths carboplatin/pemetrexed/bevacizumab, then 6 mths carboplatin/pemetrexed, then 10 mths pemetrexed maintenance therapy. Patient 2: Erlotinib for 8 mths, then afatinib for 5 mths, then alternate course of chemotherapy Patient 3: Erlotinib for 24 mths, then palliative carboplatin/pemetrexed	CGP results	• Factors contributing to false negative results for resistance mutations include tumour heterogeneity and insufficient assay sensitivity. • Treatments targeting EGFR are still effective even in patients with relatively low mutation frequency. • It is important to use sensitive, well-validated Comprehensive genomic profiling to ensure accurate detection of resistance mutations including EGFR T790M to allow for appropriate trial enrolment or access to appropriate treatments for patients to see clinical benefit.
8	Kodityal et al., 2016	A novel acquired ALK F1245C mutation confers resistance to crizotinib in ALK-positive NSCLC but is sensitive to ceritinib.	Case Study	To describe the emergence of an ALK F1245C mutation in an advanced ALK+ NSCLC patient (EML4-ALK variant 3a/b) who developed slow disease progression after a durable response to crizotinib.	1 patient 52-years old male Latin-American never-smoker diagnosed with stage IV NSCLC-adenocarcinoma of the lung at age 52 in 2010 after presenting with pleural nodules and abdominal lymph node metastases	Second and third Second line: crizotinib (based on FISH analysis results) Third line: ceritinib (based on NGS results)	CGP results & Targeted therapy	• NGS on the pleural nodule revealed EMl4-ALK variant 3 with an ALK F1245C mutation at a MAF of 2% with a tumour purity of 13% and three variants of unknown significance (IRS2 A694del, PIK3R2S273C, TSC1 K587R). No other known driver mutations and noTP53 alterations was detected. • Patient status rapidly improved clinically followed by a complete radiographic response after 3 months of ceritinib and continued without evidence of disease progression at 6 months at the time of submission of this report at reduced ceritinib dose due to gastrointestinal side effects. Of note, the patient had no brain metastasis throughout his disease course. • Given the low tumour burden, slow disease progression and

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								ongoing clinical benefit the patient was maintained on crizotinib for an additional 8 months after documentation of disease progression before transitioning to ceritinib.
9	Konduri et al., 2016	EGFR Fusions as Novel Therapeutic Targets in Lung Cancer.	[316]Case Study	To describe five patients with metastatic lung cancer (mLC) whose tumours harboured EGFR fusions, four of whom were treated with EGFR tyrosine kinase inhibitors (TKIs) with documented anti-tumour responses	5 mLC patients Case 1: female (35 yrs) presenting with generalized weakness and worsening vision Case 2: female (21 yrs) presenting with right shoulder pain and unintentional weight loss Case 3: female (42 yrs), presenting with right hip pain Case 4: male (38 yrs), presenting with dyspnoea and progressive weakness Case 5: female (60 yrs), presented with headache, slurred speech, and left foot drag	Second to fourth line Case 1 to 4: erlotinib Case 5: pemetrexed	CGP results & Targeted therapy	• Case 1: Within two weeks of erlotinib initiation, disseminated intravascular coagulation had resolved and the patient experienced clinical improvement with a noticeable decrease in supraclavicular lymphadenopathy and a hard palate metastatic lesion. After six months of treatment, the primary left lung mass and largest two liver lesions had decreased by 69% per RECIST, and the patient experienced an improvement in her functional status. Patient remained on erlotinib for 8 months, after which the disease progressed. • Case 2: Thrombocytopenia resolved within ten days after starting erlotinib, and the patient experienced symptomatic improvement. CT scans obtained 3 months after the initiation of erlotinib showed a significant regression of bilateral miliary nodules as well as a 43% decrease in the index lesions of the left lower lobe (LLL), subcarinal lymph node, and right apical soft tissue mass compared to baseline. The patient remained on erlotinib for 5 months with response, but patient stopped medication due to non-medical issues. • Case 3: At the time of disease progression on chemotherapy, the patient was treated with erlotinib, resulting in a 48% decrease in the LLL index lesion on-going for 20 months. • Case 4: At the time of disease progression, the patient was started on erlotinib, with PR after 2 cycles of therapy. The patient was receiving erlotinib for 6 months with continued response. • Case 5: Patient was treated with four cycles of carboplatin/pemetrexed with PR followed by pemetrexed maintenance therapy. The patient continued to receive benefit from pemetrexed therapy (patient was not treated with an EGFR TKI). • NGS testing identified: - EGFR-RAD51 gene fusion in patient 1, 2, 4, and 5. - EGFR-PURB gene fusion in patient 3. Four patients (1, 2, 3, and 4) received a EGFR TKI, erlotinib.

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10	Lim et al., 2016	Genomic profiling of lung adenocarcinoma patients reveals therapeutic targets and confers clinical benefit when standard molecular testing is negative.	Cross-sectional retrospective	To perform Comprehensive genomic profiling on tumour specimens from patients with lung adenocarcinomas who tested negative for EGFR, KRAS and ALK previously at our institution; to identify patients who were candidates for targeted therapy and expand treatment choices for apparently “wild type” patients.	51 patients Male sex: 35% Median age, yrs (range): 58 (29 to 77) Clinical stage III or IV, %: 74% Smoking status, %: - Never: 76% - Former or current smoker: 24%	N/A	CGP results	• Total number of identified GAs: - known: 190 - unknown: 601 Percentage of patients with at least one GA: 94% (average 3.7 alterations per patient [range: 1 to 10]) • Non-synonymous base substitutions comprised 50% (80/190) of the detected alterations: - insertions or deletions: 15% (29/190) - splice site mutation: 3% (5/190) Most commonly mutated gene among non-synonymous base substitutions: TP53 (30%, n=24/80), KRAS (10%, n=8/80) and EGFR (10%, 8/80). • Insertions or deletions commonly involved TP53 (17%, 5/29) and ERBB2 (14%, 4/29), and splice site mutations occurred in TP53, INPP4B, ATR, and MAP2K4. Gene amplification comprised 20% (39/190) of genomic alterations, and MDM2 amplification was identified most frequently (13%, 5/39). MDM2 amplification was frequently found with CDK4 amplification in 3 out of 5 cases observed. Homozygous loss comprised 5% (10/190) of all genomic alterations and all 10 cases were observed with CDKN2A. Fusion genes were found in 7% (n=14/190) and most commonly involved ROS1 fusion (50%, n=7/14). Alterations in the PI3K/mTOR pathway such as PIK3CA mutation, AKT1 mutation, PIK3R2 mutation, STK11 inactivating mutation, MTOR mutation and RICTOR amplification were detected in 17 cases (33%). • Sixteen patients (39%) had previously known driver alterations: - mutations in: BRAF (n=1), EGFR (n=8), ERBB2 (n=4), - amplification in MET (n=1), - rearrangement in: KIF5B-RET (n=2), CCDC6-RET (n=1), CD74-ROS1 (n=1), EZR-ROS1 (n=5), and SLC34A2-ROS1 (n=1). Genomic alterations for which targeted therapy could be considered in clinical trials were discovered in 14 patients (27%). These include the following alterations and the corresponding therapy: NF1 mutation (MEK inhibitor, NCT01885195), KRAS mutation (MEK inhibitor, NCT00890825) CDKN2A loss and CDK4 amplification (CDK4/6 inhibitor, NCT01237236), MDM2 amplification (MDM2 inhibitor, NCT01877382) and PIK3CA

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								mutation (PI3K inhibitor, NCT01570296). • Seven patients with ROS1 rearrangements were enrolled in an ongoing trial (NCT01964157) and received ceritinib.
11	Ou et al., 2016	High MET amplification level as a resistance mechanism to osimertinib (AZD9291) in a patient that symptomatically responded to crizotinib treatment post-osimertinib progression.	Case Study	To report a case of patient who developed resistance to osimertinib after a confirmed partial response for 9 mths	1 patient 73-year never-smoker Asian female who presented with stage IV lung adenocarcinoma harbouring exon 19 deletion	Multiple treatment lines Crizotinib	CGP results & Targeted therapy	• The Comprehensive genomic profiling revealed no MET amplification prior to start of osimertinib but a high level of MET amplification of 30 copies was observed post-therapy. EGFR T790M mutation was detected at 21% reads immediately prior to starting osimertinib but only present in about 3% of the sequencing reads in the post-osimertinib progression sample. • Once MET amplification was identified in the post-osimertinib sample, erlotinib was discontinued she was subsequently treated with crizotinib 250 mg twice daily and had significant symptoms improvement within 14 days: i.e. decreased shortness of breath; and repeat CT scan after 30 days of crizotinib treatment revealed stable size right lung mass and evidence of necrosis with non-enhancement and locules of air and liquefaction centrally. After 6 weeks treatment of single agent crizotinib treatment, patient had to hold crizotinib due to lower extremity oedema and fatigue. After patient had some relief of her lower extremity oedema, she was restarted on osimertinib in combination with crizotinib. However, the patient continued to experience fatigue and shortness of breath and passed away from her disease shortly thereafter after only 1 week of combined osimertinib and crizotinib treatment after declining further treatment.
12	Ou et al., 2016	ALK F1174V mutation confers sensitivity while ALK I1171 mutation confers resistance to alectinib. The importance of serial biopsy post progression.	Case Study	To describe a patient who developed an acquired ALK F1174V resistant mutation on progression from crizotinib that responded to alectinib for 18 mths but then developed an acquired ALK	1 patient 61-year-old Asian never-smoker male with stage IV ALK-rearranged NSCLC, who achieved PR with crizotinib with a 70% decrease in the primary tumour	Second: Alectinib	CGP results & Targeted therapy	• Two subsequent separate progressing pulmonary nodules developed after 34 mths of crizotinib treatment satisfying RECIST-defined progression (>1 cm). Comprehensive genomic profiling identified an acquired ALK F1174V mutation, and patient was enrolled onto a phase 2 alectinib trial. The larger of the two pulmonary nodules that harboured ALK F1174V mutation achieved a complete response. The other nodule achieved only a 44% decrease in the longest diameter. However, during the course of alectinib treatment, the same pulmonary nodule in the right lower lobe grew and eventually achieved progressive disease (PD) as defined by RECIST v1.1 at 18 mths. The pulmonary nodule was resected and a CGP analysis

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				I1171S mutation to alectinib				revealed an acquired ALK I1171S mutation in 31% of the sequencing runs. Patient continued on alectinib after resection of the right lower lobe metastatic pulmonary nodule as the primary tumour and the ALK F1174V metastatic pulmonary nodule continued to achieve complete remission with alectinib.
13	Papadimitrakopoulou et al., 2016	The BATTLE-2 Study: A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer.	RCT	To evaluate efficacy and identify predictive biomarkers for targeted therapies in the first stage, aiming at optimized patient selection for these therapies in the second stage	186 patients with pre-treated NSCLC who agreed to a baseline tumour biopsy, who had ECOG PS of 0 to 2, and who had multiple prior lines of therapy and stable or treated brain metastases Median age: 61 yrs (range: 26 to 82) Female: 53% ECOG PS of 0 or 1: 85% Smoking status: - Never smoker: 22% - Former smoker: 63% - Current smoker: 16% Tumour subtype: - Adenocarcinoma: 73.5% - Squamous cell carcinoma: 17.5% KRAS mutation: 54 patients	Patients received multiple prior treatment lines Group 1 (n=22): Erlotinib Group 2 (n=42): Erlotinib + MK-2206 Group 3 (n=75): MK-2206 + AZD6244 Group 4 (n=61): Sorafenib	Targeted therapy	• Overall 8-week disease control rate (DCR) in 186 patients eligible for this analysis: 48% Median PFS: 2.0 mth (95% CI: 1.9 to 2.8) Median OS: 6.5 mth (95% CI: 5.1 to 7.6) 1-year survival: 28% The median patient follow-up was 20 mths for PFS and 21 mths for OS. There were no complete responses and only six PR (three in group 3 and 4 each). • The overall 8-week DCRs among study groups: - Group 1: 32% - Group 2: 50%, p=NS vs. group 1 - Group 3: 53%, p=NS vs. group 1 - Group 4: 46%, p=NS vs. group 1 Only PS was associated with improved DCR; the 8-week DCR for PS 0 was 77% vs. 47% for PS 1 and 36% for PS 2 (p=0.03). PFS and OS were not statistically significantly different between study groups. • There was no significant association between 8-week DCR and KRAS mutation status. PFS and OS were not different for patients with KRAS mut+ vs. KRAS wt tumours for the whole study. In KRAS wt patients, there was no difference in PFS between therapy containing erlotinib or not containing erlotinib (p=0.13). Patients with KRAS mut+ tumours experienced a statistically significantly longer PFS if treated with therapy that did not contain erlotinib (HR=1.95; 95% CI: 1.00 to 3.77; p=0.04). There is a significant qualitative interaction between KRAS mutation and erlotinib-containing therapy (p=0.01). Patients with KRAS wt tumours treated with erlotinib-containing therapy had significantly better OS compared with those treated with therapy that did not contain erlotinib (HR=0.66; 95% CI: 0.45 to 0.97; p=0.03), yet no difference in OS was seen among KRAS mut+ patients between these two treatment groups (p=0.50), and the influence of the interaction

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								between KRAS mutation and erlotinib-containing therapy on OS was not significant (p=0.09). In Group 1, patients with KRAS mut+ tumours had a statistically significantly worse OS than those with KRAS wt tumours (median, 5.5 vs. 11.1 mths; p=0.02), but no significant differences were observed for KRAS mut+ compared with KRAS wt tumour-bearing patients in all other arms. • Epithelial mesenchymal transition (EMT) signature score was used to classify patient tumours as mesenchymal (EMT score>0; n = 68) or epithelial (EMT score<0; n = 73). There was no significant association between 8-week DCR and EMT score (p=0.72). EMT gene signature analysis revealed that PFS was not different in epithelial versus mesenchymal tumours, whereas analysis by arm revealed improved PFS for patients with mesenchymal tumours treated with the MEK inhibitor (Group 3; p=0.04). A statistically significantly improved OS was seen in patients with mesenchymal tumours (p=0.02) The most pronounced effect was found for patients treated with sorafenib and among KRASmut+ tumours (p=0.01).
14	Schrock et al., 2016	Comprehensive Genomic Profiling Identifies Frequent Drug-Sensitive EGFR Exon 19 Deletions in NSCLC not Identified by Prior Molecular Testing.	Case Study	To conduct a comprehensive review of NSCLC cases harbouring EGFR Δex19 assayed in the course of clinical using a hybrid-capture based comprehensive genomic profiling assay	400 patients 3 cases reported separately Case 1: female with lung adenocarcinoma with lymph node and intracranial metastases ("pan-negative" using a commercially available 'Hotspot' test) Case 2: male with lung adenocarcinoma (negative results for EGFR, ALK and KRAS using a commercially available 'Hotspot'	Case 1: Fourth Case 2: Seventh Case 3: Not applicable Case 1: third-generation EGRF TKI Case 2: Not reported Case 3: Patient died before therapy initiation	CGP results & Targeted therapy	In this series, hybrid-capture based Comprehensive genomic profiling utilizing next generation sequencing detected EGFR exon 19 deletions that were not identified by standard focused molecular testing, leading to changes in therapy. Pathology reports were available for 250 consecutive cases with classical EGFR Δex19 (amino acids 743-754) and were reviewed to assess previous non-hybrid capture-based EGFR testing. Twelve of 71 (17%) cases with EGFR testing results available were negative by previous testing, including 8 of 46 (17%) cases for which the same biopsy was analysed. Independently, five of six (83%) cases harboring C-helical EGFR Δex19 were previously negative. In a subset of these patients with available clinical outcome information, robust benefit from treatment with EGFR inhibitors was observed. 2 of 17 patients received EGFR targeted therapies (afatinib or erlotinib) which resulted in partial response.

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					test) Case 3: male with advanced lung adenocarcinoma (negative for mutation of EGFR and KRAS and ALK rearrangement using a commercial laboratory Hotspot test)			
15	Schrock et al., 2016	Characterization of 298 Patients with Lung Cancer Harboring MET Exon 14 Skipping Alterations.	Observational prospective	To comprehensively characterize patients with lung cancer by patient characteristics, tumour pathology, mutational burden, and co-amplification of MET, murine double minute gene (MDM2), and EGFR.	11,205 patients Cancer histologic subtypes types among 298 patients with METex14 alterations, n (%): - Adenocarcinoma: 205 (68.6%) - Adenosquamous: 8 (2.7%) - Squamous: 25 (8.4%) - Large cell: 2 (0.7%) - Sarcomatoid: 8 (2.7%) - SCLC: 1 (0.3%) - NSCLC (NOS): 49 (16.4%)	line: N/R 8 cases treated with Crizotinib	CGP results & Targeted therapy	• Alteration types identified (total 298): - base substitutions: 51.6% - indels: 47.7% - whole exon deletions of MET exon 14: 0.6% • Average TMB in cases with METex14: 6.9 mutations per MB (range: 0 to 197.9) Mutational load (mutations per MB), n (%): - Low (0-5): 168 (56.4%) - Intermediate low (6-10): 95 (31.9%) - Intermediate high (11-20): 31 (10.4%) - High (>20): 4 (1.3%) TMB was comparable among histologic subtypes. • Number of patients who achieved disease control, n/N (%): 8/8 (100%): - PR: 4 - CR: 2 - SD: 2 Responses to MET TKIs were seen in patients with METex14 and concurrent METamp, MDM2amp, or CDK4amp. In one patient, (white never-smoking woman who presented with unresectable stage IIIB METex14-positive lung adenocarcinoma), who received neoadjuvant crizotinib for 2 mths, achieved excellent symptomatic and radiographic response that allowed her to undergo a complete tumour resection and mediastinal lymph node dissection, which revealed only extensive fibrosis and no viable cancer.
16	Suh et al., 2016	Comprehensive Genomic Profiling Facilitates Implementation of the	Observational retrospective	To describe our series of all NSCLC cases submitted to Foundation Medicine for	6832 clinical samples Lung adenocarcinoma: 5,380 cases (79%) NSCLC-NOS (not	N/A	CGP results	• 4,876 patients (71%) harboured at least one genetic alteration involving EGFR (20%), ALK (4.1%), BRAF (5.7%), ERBB2 (6.0%), MET (5.6%), ROS1 (1.5%), RET (2.4%), or KRAS (32%) • CGP identified multiple, additional, potentially targetable GAs involving the same driver oncogenes, including 401

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		National Comprehensive Cancer Network Guidelines for Lung Cancer Biomarker Testing and Identifies Patients Who May Benefit From Enrollment in Mechanism-Driven Clinical Trials.		Comprehensive genomic profiling over a 33-mth period to demonstrate its clinical utility	otherwise specified): 1,345 (20%) ADSQ (adenosquamous carcinoma): 72 (1%) LCC (large cell carcinoma): 35 (0.5%)			cases (5.9%)with EGFR amplification, 203 cases (3.0%) with BRAF non-V600E point mutations, 12 cases (0.2%) with BRAF rearrangement, and 208 cases (3.0%) with ERBB2 amplification. EGFR T790M resistance mutations were identified in 221 cases (3.2%), and ALK resistance mutations were identified in 9 cases (0.1%). • In cohort of patients with lung adenocarcinoma (AD), genetic alterations involving previously known lung AD oncogenes NF1 (13%), PIK3CA (5.4%), NRAS (2.3%), MAP2K1 (1.2%), and HRAS (0.7%) were detected.
17	Tchekmedyian et al., 2016	Acquired ALK L1152R Mutation Confers Resistance to Ceritinib and Predicts Response to Alectinib.	Case Study	To report a patient with anaplastic lymphoma receptor tyrosine kinase gene (ALK)-rearranged lung cancer who acquired resistance to crizotinib and ceritinib mediated by an L1152R mutation	1 patient A 36-yr old female with left scapular pain and dyspnoea, diagnosed with adenocarcinoma	Second: Crizotinib, ceritinib, alectinib	CGP results & Targeted therapy	• Comprehensive genomic profiling identified an ALK intron 19 rearrangement with an unidentified partner gene, tumour protein 53 gene (TP53) G154V and R158C mutations, and retinoblastoma-1 gene (RB1) loss of exons 3 to 17. • Treatment with crizotinib resulted in a PR lasting 4 mth, and ceritinib resulted in a PR lasting another 4 mth, after which the disease progressed. • Six weeks after alectinib was started, imagining of the chest, abdomen, and brain showed a PR in all areas of disease.
18	Zhu et al., 2016	TPD52L1-ROS1, a new ROS1 fusion variant in lung adenosquamous cell carcinoma identified by comprehensive genomic profiling.	Case Study	To report a novel ROS1 fusion variant generated by rearrangement of a cell cycle-regulated protein, TPD52L1, and ROS1 in a patient with lung adenosquamous cell carcinoma.	1 patient Caucasian male (74 yrs) >100 pack year smoking history referred to Lung Nodule Program for a right upper lobe 2 cm spiculated lung nodule found on chest CT	N/A	CGP results	• CGP identified a novel TPD52L1-ROS1 fusion variant

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19	Cheng et al., 2015	RICTOR Amplification Defines a Novel Subset of Patients with Lung Cancer Who May Benefit from Treatment with mTORC1/2 Inhibitors.	Case Study	To determine the prevalence of RICTOR amplification in two independent series of human lung carcinoma cases, test the effects of blockade of RICTOR signalling in lung cancer cells both in vitro and in vivo, and demonstrate clinical benefit in a RICTOR-amplified lung carcinoma patient when treated with dual mTOR1/2 inhibitors	1 patient with RICTOR amplification	Fourth: mTOR1/2 inhibitor (CC223)	CGP results & Targeted therapy	• NGS assay identified RICTOR amplification as the sole actionable genomic alteration in an 18-year old lung cancer patient. • The initial clinical data presented in the study suggest that RICTOR-amplified NSCLC patients may benefit from treatment with dual mTOR1/2 inhibitors, especially in cases where RICTOR is the sole oncogenic driver. • Previous studies have shown limited clinical benefit from mTOR1/2 inhibitors in unselected lung cancer patients. Study findings suggest that stratifying patients by genomic profiles, specifically RICTOR amplification, for future incarnations of these trials may lead to better patient selection.
20	Drilon et al., 2015	Broad, Hybrid Capture-Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches.	Observational prospective	To determine the frequency of genomic alterations via NGS in tumours in which previous extensive non-NGS testing had not yielded a targetable driver alteration	47 patients with lung adenocarcinomas who harboured no evidence of a genomic alteration via focused non-NGS testing, of which in 16 cases non-NGS testing exhausted the tissue leaving 31 cases who underwent NGS testing patients with a ≤15 pack-year smoking history	line: N/R 6 of 8 patients received targeted therapy with crizotinib (3 pt.), cabozantinib (2 pt.), erlotinib (1 pt.)	CGP results & Targeted therapy	• % of patients with a genomic alteration with a corresponding targeted therapeutic (NCCN guidelines): 26% (8/31); % of patients with an actionable genomic alteration for which targeted therapy was available through an ongoing trial at the institution or off-protocol: 39% (12/31); • Two patients demonstrated a partial response (RECIST v1.1) to targeted therapy: HIP1-ALK with crizotinib and KIF5B-RET with cabozantinib. Both patients remain on therapy and are progression-free at 5 and 7 mths, respectively. Disease shrinkage < 30% (stable disease by RECIST v1.1) and a clinical response to therapy were noted in 2 others: SOCS5-ALK with crizotinib and KIF5B-RET with cabozantinib. The former patient died from disease progression, whereas the latter remains progression-free on cabozantinib at 3 mths. Two additional patients have begun targeted therapy but are pending a response evaluation: erlotinib for EGFR G719A and crizotinib for CD74-ROS1. • % of patients in whom non-NGS testing with multiple assays resulted in tissue exhaustion and a repeat biopsy was either

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								not feasible or declined by the patient: 34% (16 of 47) of cases
21	Gallant et al., 2015	EGFR Kinase Domain Duplication (EGFR-KDD) Is a Novel Oncogenic Driver in Lung Cancer That Is Clinically Responsive to Afatinib.	Observational retrospective	To describe the case of a 33-year-old male never smoker with metastatic lung adenocarcinoma whose tumour lacked all previously described actionable genomic alterations in this disease	1 patient 33-year-old male never smoker, diagnosed with stage IV lung adenocarcinoma after presenting with cough and fatigue. Determination of the frequency of EGFR-KDD domain duplication: >38,000 clinical cases	Second: Afatinib	CGP results & Targeted therapy	• Immediately after beginning afatinib, the patient reported feeling markedly better with improvements in his symptoms of cough and fatigue. After two cycles of afatinib, the patient showed a partial radiographic response (~50% tumour shrinkage) per RECIST criteria. After 7 cycles of therapy, the patient developed acquired resistance to afatinib. Molecular profiling was performed on the afatinib resistant tumour biopsy sample, and this testing uncovered significant amplification of the EGFR-KDD allele as the only genomic alteration that differed from his pre-treatment tumour sample. • The EGFR-KDD was detected in 5 tumours from ~7,200 total lung cancers tested. In addition, EGFR-KDD was identified in 3 gliomas, 1 sarcoma, 1 peritoneal carcinoma, and 1 Wilms' tumour. Among samples in The Cancer Genome Atlas (TCGA), authors found previously unreported cases of the EGFR-KDD in lung adenocarcinoma and glioblastoma multiforme. • The data show that the EGFR-KDD is a recurrent mutation in lung cancer, glioma, and other human malignancies. It is important to note, however, that since most conventional (exomic) sequencing platforms would not routinely detect this particular EGFR alteration (due to its intronic breakpoints), these numbers are likely an underestimate, and the true prevalence of the EGFR-KDD remains unknown.
22	Klempner et al., 2015	The Clinical Use of Genomic Profiling to Distinguish Intrapulmonary Metastases From Synchronous Primaries in Non-Small-Cell Lung	Review	To highlight the potential clinical incorporation of sequencing-based technologies to discriminate independent primaries in the same lobe in resected NSCLC	2 patients Case 1: Asian female (57 yrs) never-smoker with incidental pulmonary nodule confirmed as a 1.6-cm right lower lobe (RLL) nodule Case 2: Caucasian male (73 yrs) former smoker with	line: N/R Case 1: platinum-based doublet chemotherapy Case 2: Not reported	CGP results & Targeted therapy	• Case 1: Patient underwent Comprehensive genomic profiling of the dominant and smaller nodule, which revealed that both nodules harboured the same exon 19 E746 et al., A750 EGFR mutation. The patient was staged as pT3N0, overall stage IIB disease and underwent adjuvant therapy with platinum-based doublet chemotherapy. Patient completed 4 cycles of therapy and remained disease-free at the time of submission of this report. • Case 2: Patient underwent lobectomy of 2 separate right upper lobe nodules. EGFR genotyping of both tumours was performed.

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		Cancer: A Mini-Review.			a 40 pack-year history with 2 separate incidental right upper lobe nodules			The larger tumour nodule was found to have an exon 18 G719A EGFR mutation and the smaller lesion harboured different EGFR mutations: a S768I and a V769L exon 20 EGFR mutation. Thirty mths after the initial resection, multiple pulmonary nodules, and cervical and mediastinal adenopathy were identified. A lung biopsy of 1 of the growing pulmonary lesions confirmed lung adenocarcinoma and the recurrent tumour harboured the EGFR-S7681 + V769L mutations seen in the initial smaller tumour focus.
23	Klempner et al., 2015	Emergence of RET rearrangement co-existing with activated EGFR mutation in EGFR-mutated NSCLC patients who had progressed on first- or second-generation EGFR TKI.	Case Study	To report the emergence of RET rearrangement in post EGFR TKI progression EGFR-mutated NSCLC patients while retaining the original activating EGFR mutation	2 patients Case 1: 55-year-old Asian male never-smoker with de-novo metastatic NSCLC Case 2: 73-year-old Asian female never-smoker with a metastatic recurrence 12 mths after neoadjuvant chemoradiation and lobectomy for NSCLC adenocarcinoma	Both patients received multiple regimens	CGP results & Targeted therapy	• At the time of diagnosis, EGFR mutation testing did not demonstrate the presence of any activating EGFR mutations (both patients). - Case 1: Patient achieved a PR to erlotinib lasting 9 mths. A Comprehensive genomic profiling of biopsy of a progressing liver metastasis identified an EGFR exon 19 deletion in both the original diagnosis sample and the liver metastasis at a mean allelic frequency (MAF) of 53% and 54% respectively. Additionally CCDC6-RET (C1; R12) fusion was detected from the liver biopsy obtained after progression on erlotinib therapy but not from the sample at the time of diagnosis. However, patient developed rapid hepatic progression and was not treated with any anti-RET targeted treatment. - Case 2: Patient developed disease progression in the left neck and lung parenchyma after 12 mths of cytotoxic therapy. A comprehensive genomic profiling of mediastinal lymph node biopsy revealed an EGFR exon 19 deletion mutation at a MAF of 75%. Patient received fourth line erlotinib for 10 mths prior to developing progressive disease. A post erlotinib progression biopsy from a left cervical lymph node was found to harbour the original exon 19 EGFR deletion at a MAF of 62% and a novel acquired CCDC6-RET (C1; R12) fusion. • Retrospective analysis of Foundation Medicine database revealed an addition case of NCOA4-RET (N6; R12) co-existing with EGFR L858R mutation (MAF 18%) in an EGFR-mutated NCLCL patient who had progressed on afatinib. However, the pre-afatinib sample was not subjected to CGP and the study authors were not able to confirm NCOA4-RET was an acquired mutation arising in the context of resistance to erlotinib.

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24	Le et al., 2015	Detection of Crizotinib-Sensitive Lung Adenocarcinomas With MET, ALK, and ROS1 Genomic Alterations via Comprehensive Genomic Profiling.	Observational retrospective	To describe use of CGP to identify tumours responsive to crizotinib	3 patients Case 1: 38 years-old white male, former smoker (5 pack-years) with recurrent/ metastatic adenocarcinoma Case 2: 41 years-old Asian male, never smoker with stage IV adenocarcinoma Case 3: 72 years-old white female, former smoker (12 pack-years) with stage IV adenocarcinoma	Case 1: Sixth Cases 2 and 3: Second Crizotinib	CGP results & Targeted therapy	• Case 1: CGP identified EML4-ALK-E13;A20 alteration. Within a mth of crizotinib, his baseline cardio-pulmonary symptoms improved and he attained radiographic improvement of his cancer-related lesions. Using RECIST v1.1, sum of target lesion diameters decreased by 14.2% and non-target lesions improved significantly (a scenario best classified as stable disease). This clinical and radiographic response was sustained for 17 mths of crizotinib, upon which the patient experienced central nervous system and systemic progression. • Case 2: CGP identified SDC4-ROS1 alteration. Within weeks of crizotinib therapy, patient baseline cardio-pulmonary status and performance status improved remarkably. This improvement was accompanied by radiographic improvement of lymphangitic tumour spread (non-target lesion) and a decreased of 26.8% in RECIST target lesions; classified as stable disease (and just under the threshold for a partial response). The response lasted for 4 mths when the patient experienced acquired resistance with worsening dyspnoea and pathologically-confirmed malignant pericardial effusion. • Case 3: CGP revealed MET-amplification (all 20 exons were amplified to an estimated copy number of 10) as the main oncogenic driver. Within a week of crizotinib therapy, patient noted improvement in baseline cardio-pulmonary complaints, hoarseness and previously palpable lymphadenopathy had diminished in size. Radiographic assessment after 1 and 2 mths of therapy disclosed significant improvement of nodal and pulmonary tumour burden, with a decrease in 38.7% of target lesions; a partial response by RECIST. This response was ongoing for over 5 mths of clinical follow-up after initiation of crizotinib.
25	Lee et al., 2015	MET 14 Deletion in Sarcomatoid Non-Small-Cell Lung Cancer Detected by Next-Generation Sequencing	Case Study	To describe a case of a patient with MET 14 deletion in sarcomatoid NSCLC detected by NGS and successfully treated with a MET Inhibitor	1 patients 61-year-old male never smoker who first presented with pain in his left hip and right-sided chest pain in 2014	Second: Crizotinib	CGP results & Targeted therapy	• Comprehensive genomic profiling found that the tumour harboured two MET alterations predicted to result in skipping of exon 14 (c.2888-5_2890TTAAGATC>A and c.3028+2T>G) and a known activating point mutation in MET (p.H1094Y, c.3280C>T) • Patient experienced a partial response by RECIST 1.0 criteria, which was accompanied by the patient reporting symptomatic improvement in activity level and pain. Most notably, a dominant right-sided chest mass decreased from 8.2 to 6.1 cm, but there was no clear change in bony

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		and Successfully Treated with a MET Inhibitor.						lesions. This lasted for more than 5 months until he experienced progressive pain. Imaging confirmed progression both in the lung and in bony lesions. At the time submitting the publication, the patient was on hospice care. • Based on identified MET alterations, patient was treated on a clinical trial of the MET inhibitor crizotinib
26	Ou et al., 2015	I1171 missense mutation (particularly I1171N) is a common resistance mutation in ALK-positive NSCLC patients who have progressive disease while on alectinib and is sensitive to ceritinib. Lung Cancer.	Case Study	To report the presence of an ALK I1171N resistance mutation from CGP from a liver biopsy of a progressing metastatic lesion in an ALK+ patient on alectinib after an initial partial response	1 patient Caucasian female (51 yrs) never-smoker who was diagnosed with stage IV non-small cell lung cancer (left hilar tumour primary and liver metastases)	Third: Ceritinib	CGP results & Targeted therapy	• Patient was treated with alectinib at 600 mg twice daily without a recurrence of transaminitis and achieved PR within 3 mths. However 5 mths after starting alectinib patient developed jaundice, grade 3 alkaline phosphatase elevations, and grade 2 liver enzymes elevations and recurrence of her right upper quadrant pain. CT of the abdominal revealed several new liver metastasis. Repeat surveillance CT scans revealed disease progression in the primary tumour but no brain metastasis. Patient was started on ceritinib at 750 mg once daily two weeks after documented disease progression with resolution of her abdominal symptoms. • An ALK I1171N missense mutation was detected by CGP one week after starting ceritinib with approximately 5% of the sequencing runs by NGS recording the T -> A transition indicating ~33% of the tumour harboured the resistant I1171N mutation. Despite the regular use of anti-emetics patient experienced persistent nausea and occasional vomiting that required dose reduction to 600 mg once daily. Follow up CT scan 6 weeks after starting ceritinib showed regression of the liver lesions and the primary lung lesion and patient remained on ceritinib at 600 mg once daily with an on-going response of 3 mths.
27	Ou et al., 2015	Identification of a novel TMEM106B-ROS1 fusion variant in lung adenocarcinoma by comprehensive genomic profiling.	Case Study	To report a novel ROS1-rearranged NSCLC fusion generated by fusion of 5'-end of the transmembrane protein 106 (TMEM106B) to the 3' end-kinase domain of ROS1	1 patient Greece female (70 yrs) never-smoker who was diagnosed with stage IV (malignant pleural effusion) NSCLC	N/A	CGP results	• Comprehensive genomic profiling assay revealed that the tumour harboured a novel TMEM106-ROS1 fusion variant involving the translocation of exons 1-3 of TMEM106B to exons 35-43 of ROS1. Patient had disease progression and decreased performance status and could not be enrolled onto a ROS1 inhibitor trial before passing.

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				in a patient who presented with stage IV adenocarcinoma of the lung				
28	Pekar-Zlotin et al., 2015	Fluorescence in situ hybridization, immunohistochemistry, and next-generation sequencing for detection of EML4-ALK rearrangement in lung cancer.	Cross-sectional retrospective	To test 51 patients consecutively for ALK rearrangement by FISH and IHC and further sequenced any discordant specimens by NGS	57 patients Mean age: 63.5 Male sex: 28/51 Tumour histology: adenocarcinoma Disease stage: IV Smoking status, n: - Never smoker: 26 - Previous or current smoker: 21 - Unknown: 4 IHC TTF1 staining, n: - Positive: 32 - Negative: 10 - Unknown: 4 51 patients had sufficient tissue for ALK FISH and IHC testing	line: N/R Two cases treated with crizotinib	CGP results & Targeted therapy	Among all discordance cases, only two patients were treated with crizotinib. One case showed a complete response to therapy, with progression-free survival of 18 months, whereas the other case presented stable disease. • Number of patients with positive ALK tested with: - FISH: 4/51 - IHC: 8/51 Three had concordant results (i.e., positive with both FISH and IHC). One sample was positive with FISH and negative with IHC, and five were positive with IHC and negative with FISH. • The six cases with discordant results were sequenced by the FoundationOne® assay. Of 5 cases that were FISH-negative and IHC-positive, 4 harboured ALK rearrangements. The one case that was positive with FISH and negative with IHC did not harbour an ALK rearrangement. The final incidence of EML4-ALK rearrangement in study cohort: 13.7% (not 7.8%, as was defined previously by FISH) • Accuracy of FISH and IHC for EML4-ALK based on 51 cases with next-generation sequencing as the gold standard (sensitivity, specificity, PPV, NPV; respectively), %: - IHC: 100%, 97.7%, 87.5%, 100% - FISH: 42.9%, 97.7%, 75%, 91.4%
29	Capelletti et al., 2014	Identification of recurrent FGFR3-TACC3 fusion oncogenes from lung adenocarcinoma.	Observational retrospective	To identify additional oncogenic alterations from patients with NSCLC to define additional treatment options	576 patients of Asian and Caucasian ethnicity	N/A	CGP results	• FGFR3–TACC3 rearrangements occur in a subset of patients with lung adenocarcinoma • Many of genetic alterations, including ALK, ROS1, RET, and NTRK1, are chromosomal inversions or translocations that would not have been detected using more conventional methods such as Sanger sequencing.

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30	Falchook et al., 2014	Effect of the RET Inhibitor Vandetanib in a Patient With RET Fusion-Positive Metastatic Non-Small-Cell Lung Cancer.	Case Study	To describe a patient with NSCLC with a known RET fusion who was treated with the RET inhibitor vandetanib and achieved a dramatic response that has continued for more than 5 mths	1 patient Asian female with lung adenocarcinoma	Fourth: Vandetanib	CGP results & Targeted therapy	• NGS assay identified CCDC6-RET fusion • Patient underwent a therapy with vandetanib, a multikinase inhibitor targeting RET, EGFR, and VEGFR • The first restaging CT scans after 6 weeks of treatment demonstrated a dramatic response in the patient's large left supraclavicular mass and her innumerable pulmonary nodules. • The patient continued to receive vandetanib at the time of article submission, 4 mths after the treatment was initiated
31	Janjigian et al., 2014	Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations.	Observational prospective	To assess the efficacy of combination therapy with afatinib and cetuximab in heavily pre-treated patients with advanced EGFR-mutant lung cancer who acquired resistance to erlotinib/gefitinib	126 patients (71 with T790M mutation) Median age: 59 yrs Male sex, %: 26% Baseline ECOG PS: - 0: 21% - ≥1: 79%	48% of patients received 0 to 1 prior chemotherapies; 52% ≥2 Afatinib+cetuximab	Targeted therapy	• Number of patients with confirmed objective response, n (%): 39 (29%) (all PRs), of which 22 (18%) had ≥50% tumour shrinkage from baseline Median PFS: 4.7 months (95% CI: 4.3 to 6.4) Median duration of confirmed objective response: 5.7 months (range: 1.8–24.4). ORR: - T790M-positive tumours: 32% (95% CI: 21.8 to 44.5) - T790M-negative tumours: 25% (95% CI: 13.8 to 38.3; p=0.341 vs T790M-positive group)
32	Jia et al., 2014	Successful treatment of a patient with Li-Fraumeni syndrome and metastatic lung adenocarcinoma harboring synchronous EGFR L858R and ERBB2 extracellular domain S310F	Case Study	To report the case of a young, never-smoker woman with Li–Fraumeni syndrome and advanced lung adenocarcinoma refractory to multiple lines of conventional chemotherapy and negative for actionable alterations by routine testing	1 patient 46-y-old, never smoker, Hispanic woman with Li–Fraumeni syndrome (LFS) who was diagnosed with recurrent, metastatic lung adenocarcinoma	Sixth: Afatinib	CGP results & Targeted therapy	• NGS profiling revealed the presence of both an EGFR L858R mutation (estimated 27% of reads) and an ERBB2 extracellular domain S310F mutation (estimated 25% of reads). • Based on NGS results, patient was enrolled into an ongoing compassionate use program of afatinib, a dual inhibitor of EGFR and ERBB2. • After two weeks of afatinib monotherapy, patient fatigue, right-sided chest pain and dyspnoea improved dramatically, and all symptoms resolved completely after 2 months. Repeat fused PET-CT scans revealed complete anatomic and metabolic response with minimal residual FDG avidity in the right pleura consistent with prior talc pleurodesis. Twelve months afterwards, complete response was maintained, both clinically and by repeated imaging.

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		mutations with the pan-HER inhibitor afatinib						
33	Mukhopadhyay et al., 2014	RET-rearranged lung adenocarcinomas with lymphangitic spread, psammoma bodies, and clinical responses to cabozantinib.	Case Study	To describe the clinical, radiologic, and histologic findings in five patients with RET-rearranged lung adenocarcinoma presenting with metastatic disease to draw attention to an unusual constellation of clinical and histologic findings in these tumours, and to add further evidence of clinical responses of these tumours to RET-targeting inhibitor therapy.	5 patients Case 1: 77-year-old woman diagnosed with adenocarcinoma with extensive lymphangitic spread, psammoma bodies, and a mucinous cribriform pattern Case 2: 67-year-old man diagnosed with metastatic lung cancer Case 3: 57-year-old woman diagnosed with metastatic lung cancer Case 4: 48-year-old woman diagnosed with metastatic adenocarcinoma Case 5: 47-year-old woman diagnosed with metastatic adenocarcinoma	Case 1: First Case 2: Second Case 3: Third Case 4: Third Case 5: Fourth Cases 1 to 3: cabozantinib	CGP results & Targeted therapy	• NGS profiling revealed: - KIF5B-RET fusion in patient 1, 3 and 5 - CCDC6-RET fusion in patient 2 Patient 4 did not undergone NGS profiling • Patient 1: After starting targeted treatment, patient symptoms improved and she had a radiologically confirmed partial response by RECIST criteria. However, after 4 weeks of therapy she developed significant grade 3 stomatitis requiring dose reduction to 100 mg. However, her stomatitis continued to worsen and cabozantinib was discontinued. Given her poor performance status she was transitioned to hospice care and subsequently expired. • Patient 2: The patient had significant improvement in dyspnoea and exercise tolerance accompanied by a radiographic partial response by RECIST criteria after 4 weeks of therapy. He continued to have PR on most recent scans at 8 weeks and the response was ongoing. • Patient 3: A PET scan 2 months post therapy showed slight shrinkage of tumour. Although the response was classified as stable disease by RECIST measures, many of the lesions became PET-negative posttreatment and she felt much better symptomatically. The dose was reduced due to severe stomatitis. Overall, she was on cabozantinib for a total of 4 months. Therapy was stopped after the 4-month restaging scan showed progression, and she died one month after stopping the drug (3 years after the initial diagnosis). • Patient 4: Patient did not receive targeted therapy • Patient 5: Patient did not receive targeted therapy, however, RET inhibitor therapy was planed in the event of disease progression • Based on NGS results, patients 1 to 3 received cabozantinib
34	Ou et al., 2014	Identification of a novel HIP1-ALK fusion variant in Non-Small-Cell Lung Cancer	Case Study	To describe a patient with NSCLC harbouring a novel HIP1-ALK fusion variant together with	2 patients Case 1: Dutch-Indonesian female (58 yrs) never smoker with de novo stage IV NSCLC	Second: Alectinib (both patients)	CGP results & Targeted therapy	• Comprehensive genomic profiling analysis identified: - Case 1: HIP1-ALK fusion variant involving rearrangement and fusion of exons 1 to 30 of HIP1 to exons 20 to 29 of ALK (H30; A20) - Case 2: EML4-ALK 3a/b variant and a base substitution occurring at 36% frequency in the codon encoding amino acid residue 1171 that resulted in the substitution of isoleucine to

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		(NSCLC) and discovery of ALK I1171 (I1171N/S) mutations in two ALK-rearranged NSCLC patients with resistance to Alectinib.		another patient with EML4-ALK variant 3a/b both of whom have been treated with crizotinib and then alectinib in which secondary mutations at amino acid residue 1171 in the hydrophobic regulatory-spine (R-spine) of the ALK kinase domain were identified	adenocarcinoma Case 2: Caucasian male (38 yrs) never-smoker with stage IV ALK-rearranged NSCLC			serine (I1171S) • Targeted therapy effectiveness: - Case 1: Patient achieved a confirmed CR after 2 mths on alectinib that lasted for 12 mths after starting alectinib when several new liver lesions were noted - Case 2: Patient achieved a PR with alectinib treatment after 6 weeks but after 12 mths of alectinib treatment a new 18-fluorodeoxyglucose-avid liver lesion was identified
35	Ignatius Ou et al., 2014	Next-generation sequencing reveals a Novel NSCLC ALK F1174V mutation and confirms ALK G1202R mutation confers high-level resistance to alectinib (CH5424802/ RO5424802) in ALK-rearranged NSCLC patients who progressed on crizotinib.	Case Study	To report a case of two patients with NSCLC who acquired secondary mutations	2 patients Case 1: Asian man (61 yrs) never-smoker with stage IV NSCLC Case 2: Asian woman (60 yrs) never-smoker with stage IV adenocarcinoma of the lung NSCLC	Case 1: Third Case 2: Fourth Crizotinib followed by alectinib (both patients)	CGP results & Targeted therapy	• Case 1: Patient achieved a confirmed PR after 3 mths on crizotinib that lasted 21 mths. A new 1.8 cm right upper lobe (RUL) pleural nodule that was fluorodeoxyglucose (FDG)-avid was detected in February 2013. The patient continued on crizotinib for ongoing clinical benefit as he remained asymptomatic. Over the next 6 mths, the RUL lobe lesion continued to grow with appearance of a new FDG-avid right lower lobe nodule. CGP revealed the presence of EML4-ALK variant 3 (E6; A20) and identified the presence of a novel ALK F1174V mutation. The patient was enrolled in a phase 2 trial of alectinib for crizotinib-resistant ALK+ NSCLC patients. • Case 2: Patient achieved a confirmed PR after 3 mths of crizotinib treatment (RECIST 1.0). Twenty mths into crizotinib treatment, she developed RECIST-defined disease progression of 20% increase in aggregate tumour measurement from the lowest achieved baseline achieved due to an enlarging right hilar lymph node. Simultaneously, a right axillary lymph node demonstrated increasing FDG avidity with a standardized uptake value (SUV) of 2.0 but was still normal in size (<1 cm). She was continued on crizotinib post progression due to ongoing clinical benefit as she was asymptomatic and her aggregate tumour measurement was still at 63% reduction from the precrizotinib treatment level. The right axillary lymph node (LN) continued to grow in size to

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								1.1 cm and the SUV increased to 7.8. Crizotinib was discontinued and patient was enrolled onto the same alectinib trial as patient 1. The disease progression continued after 5 weeks on alectinib, as evidence the right axillary LN had increased in size to 2.0 cm with a SUV of 11.9. RECIST progression was confirmed 9 weeks after starting alectinib due to continued growth of the right axillary LN to 2.2 cm with a SUV of 11.0. Comprehensive genomic profiling assay revealed the presence of an EML4-ALK rearrangement (E6; A20) (variant 3) and an ALK G1202R mutation with an estimated allele frequency of 23% in a background of 60% tumour purity, consistent with a near clonal heterozygous substitution. In addition, loss of CDKN2A/B and ARFRP1 amplification (9X) were identified. No EGFR or KRAS alterations or ALK amplification was identified. Patient's right chest pain was resolved post axillary lymph node excision and continued on alectinib post progression as allowed by protocol but had continued disease progression.
36	Ross et al., 2014	Next-generation sequencing reveals frequent consistent genomic alterations in small cell undifferentiated lung cancer.	Observational retrospective	To test the hypothesis that CGP of clinical small cell lung cancer (SCLC) samples by NGS could identify genomic-derived drug targets of therapy for patients diagnosed with this aggressive malignancy in a single diagnostic test.	98 patients Female: 60/98 Mean age: 60.7 yrs All tumours were high grade Tumour stage at the time of sequencing, n (%): - Stage I: 1 (1%) - Stage II: 2 (2%) - Stage III: 22 (23%) - Stage IV: 72 (74%)	N/A	CGP results	• All specimens harboured at least one GA. Total number of GAs: 386, of which: - base substitutions: 200 - short insertions and deletions: 55 - gene amplifications: 99 - homozygous deletions: 26 - rearrangements/fusions: 6 • Number of GAs considered to be actionable with the potential to personalise targeted treatment, n (%): 96 (25%) Number of cases harbouring at least one actionable alteration, n (%): 52 (53%) (0.98 actionable alterations per the entire cohort of SCLC) including base substitutions, amplifications or homozygous deletions in RICTOR (10%), KIT (7%), PIK3CA (6%), EGFR (5%), PTEN (5%), KRAS (5%), MCL1 (4%), FGFR1 (4%), BRCA2, (4%), TSC1 (3%), NF1 (3%), EPHA3 (3%) and CCND1 (3%). Of the seven most commonly altered genes, only one gene (RICTOR) was considered to be actionable. The most common non-actionable genomic alterations were alterations in TP53 (86% of SCLC cases), RB1 (54%) and MLL2 (17%).

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37	West et al., 2014	Unique metastases of ALK mutated lung cancer activated to the adnexa of the uterus.	Case Study	To describe a case of 50 year-old-woman diagnosed with stage IV NSCLC, T2N3M1b, ALK fusion positive disease	1 patient 50-yr old female, with metastatic lung cancer	Second: Crizotinib	CGP results & Targeted therapy	• FISH assay revealed ALK fusion. Systemic therapy with crizotinib resulted in decreased tumour burden, except of adnexal mass lesion. Patient underwent an abdominal hysterectomy with bilateral salpingo-oophorectomy and following surgery the therapy with crizotinib was restarted. • Molecular analysis (FoundationOne®) of a tissue sample from ovarian metastases were performed to identify treatment options, however no additional treatment specific genomic alterations were noted.
38	Drilon et al., 2013	Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas	Case Study	To report preliminary data for the first three patients treated with the RET inhibitor cabozantinib on a prospective phase II trial for patients with RET fusion-positive NSCLCs	3 cases Case 1: female with metastatic adenocarcinoma with papillary morphology Case 2: female with lung adenocarcinoma (stage IIIA; T4N1M0) Case 3: female with metastatic mixed-subtype adenocarcinoma with multiple bilateral pulmonary nodules and no evidence of distant disease	Three patients who underwent targeted therapy received prior treatments Cabozantinib	CGP results & Targeted therapy	• Therapy with cabozatinib was chosen on the basis of the observation that the drug was most effective at inhibiting proliferation in a CCDC6-RET (RET/PTC1) fusion-positive papillary thyroid cancer cell line compared with vandetanib, sunitinib, and axitinib. • Two patients remained progression-free at 4 or 5 mth One patient had a stable disease which had been maintained clinically and radiographically at 8 mth • RET fusions were found in five patients, and three underwent treatment with cabozantinib within clinical trial
39	Vaishnavi et al., 2013	Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.	Observational prospective	To perform a targeted NGS assay on tumour samples from 36 patients with lung adenocarcinoma whose tumours did not contain known genetic alterations using standard clinical assays	36 patients A patient who was treated with crizotinib harboured a MPRIP-NTRK1 fusion	line: N/R Crizotinib (one received targeted therapy)	CGP results & Targeted therapy	• NGS assay revealed an in-frame gene fusion in two patients (MPRIP-NTRK1 and CD74-NRTK1 fusions). • Patient experienced a minor radiographic response with a decrease in serum levels of CA125, but experienced disease progression after ~3 mths. • The patient with MPRIP-NTRK1 fusion had no standard therapies and no clinical trials of potentially effective TRKA inhibitors available; therefore the patient consented to treatment with crizotinib outside of a clinical trial.

#	Author	Title	Study design	Study aim	Patients and patient characteristics	Targeted therapy line and regimen	Outcome categories	Outcomes
40	Vignot et al., 2013	Next-generation sequencing reveals high concordance of recurrent somatic alterations between primary tumour and metastases from patients with non-small-cell lung cancer.	Observational prospective	To compare genomic alterations identified in archived primary tumours from patients with NSCLC with those identified in metachronous or synchronous metastases.	15 patients (30 samples: primary and matched metastatic tumour pairs) - Adenocarcinoma: 8 patients - Squamous cell carcinoma: 3 - Large-cell carcinoma: 2 - Basaloid carcinoma: 2 No patient received molecularly targeted therapy before biopsy of metastatic lesions	N/A	CGP results	• 311 somatic alterations were identified among the 189 evaluated genes: - primary tumours: 161 - metastases: 150 • The comparative analysis between primary tumour and matched metastasis includes 170 unique mutations and 21 large structural changes. No gene fusions were identified in this study. The global rate of concordance was 63.9% (64.5% for mutations, 59.0% for large structural changes). • The comparative analysis between primary tumour and matched metastasis for 33 recurrent alterations compared with 159 likely passenger alterations revealed a concordance of 94%for all recurrent alterations compared with 63% for likely passenger alterations. No discrepancy was observed for the five large structural recurrent alterations, and concordance was 93% for recurrent mutations versus 61% for likely passenger mutations ($p<0.001$).
41	Peled et al., 2012	Next-generation sequencing identifies and immunohistochemistry confirms a novel crizotinib-sensitive ALK rearrangement in a patient with metastatic non-small-cell lung cancer.	Case Study	To report a novel crizotinib sensitive ALK rearrangement in a patient with metastatic non-small cell lung cancer	1 patient 43 yrs never-smoker male presented with pericardial tamponade	line: N/R Crizotinib	CGP results & Targeted therapy	• Genomic profiling revealed a EML4-ALK fusion. Based on that result, crizotinib was started. • Within 2 weeks, the patient reported an improvement in pain in the pubic area and in exercise tolerance. Significant improvement was seen on initial CT-PET scans and after 4 mths, the PET was negative and the chest CT scan showed further shrinkage of the primary lesion (RECIST 75%). • NGS identified a complex ALK rearrangement. FISH testing was negative using standard criteria