

100,000 Genomes Cancer Programme South London GMC Teaching Cases

Dr Katie Snape

Joint Lead Consultant for Clinical Genetics, St George's Hospital

Dr Nirupa Murugaesu

Consultant Oncologist, St George's Hospital

Cancer Lead, 100,000 Genomes Project

Overview

- Three patients enrolled in 100,000 Genomes cancer programme
- Paired tumour and cancer genome analysis
- Clinical and molecular information
- Impact on patient management

Case One

- Rectal adenocarcinoma (70) August 2016
 - Dukes A, pT1 25mm, EMVI negative, no LNs involved
 - Laparoscopic low anterior resection with loop ileostomy
 - Resection specimen showed loss of MSH2 and MSH6 on immunohistochemistry (IHC)
- Consented for 100,000 Genomes Project Cancer Programme
- Referred to clinical genetics

Case One

- Did not attend genetics appointment
- Results of cancer genome analysis
 - 10 Tier 1 variants
 - >100 Tier 2 variants
 - High mutational burden
 - Mutational signature = mismatch repair deficiency
 - Germline mutation in *MSH2* gene

100,000 Genomes report

Participant information

| Participant name | D.O.B | Gender | NHS number | Laboratory sample ID | GeL participant ID | GMC | Sample date | Date analysis issued |
|------------------|-------|--------|------------|----------------------|---------------------------|-----|-------------|----------------------|
| | | F | | 1018174223 | 212000082 | RJ1 | 24-08-2016 | 11-04-2017 |

Tumour information

| Tumour type | Tumour subtype | ICD10 code | Sample type | Reported tumour content | Tumour sample cross-contamination |
|-------------|----------------|------------|-------------|-------------------------|-----------------------------------|
| Colorectal | unknown | C189 | FF | High >60% | Pass |

Pathogenic germline cancer susceptibility variants

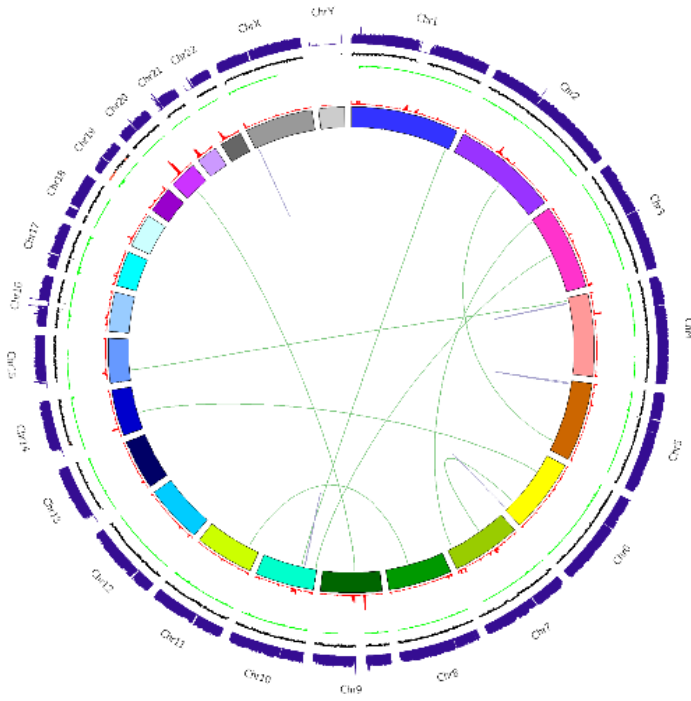
The following variants have been identified on analysis for pertinent germline findings (known pathogenic or likely pathogenic variants in cancer susceptibility genes relevant to the tumour type).

| Gene | GRCh38 coordinates ref/alt allele | Transcript | cDNA and protein change | Predicted consequences | Population germline allele frequency (1KG) | Alt allele/total read depth | Genotype | ClinVar ID | Gene mode of action |
|------|-----------------------------------|-----------------|--------------------------|------------------------|--|-----------------------------|----------|------------|---------------------|
| MSH2 | 2:47466756 A>T | ENST00000233146 | c.1609A>T p.(Lys537*) | stop_gained | N/A | 27/46 | 0/1 | N/A | N/A |

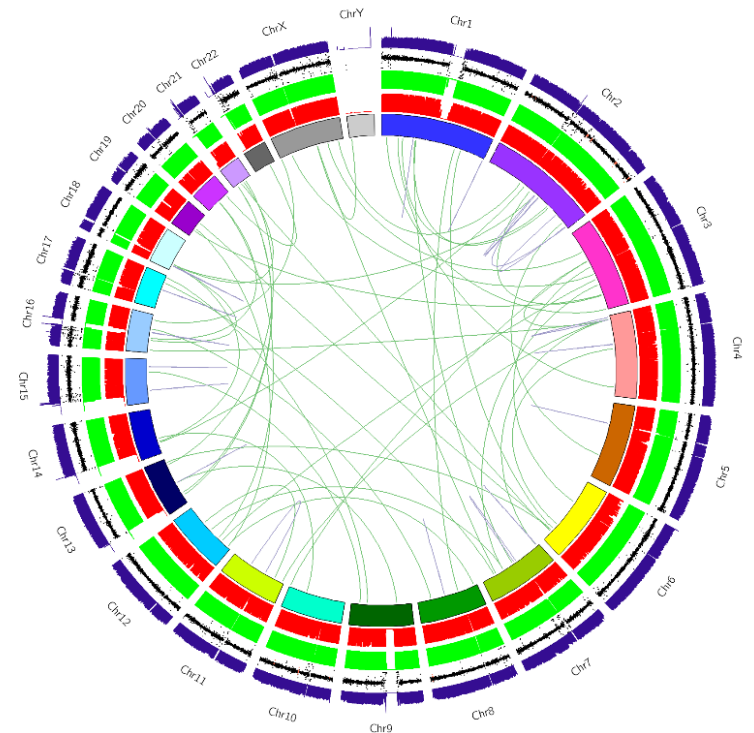
For more details of analysis and the genes included for pertinent germline findings, please refer to [Technical Information v1.4.main](#).

Comparison with MMR proficient colorectal tumour – Circus plot

MMR proficient



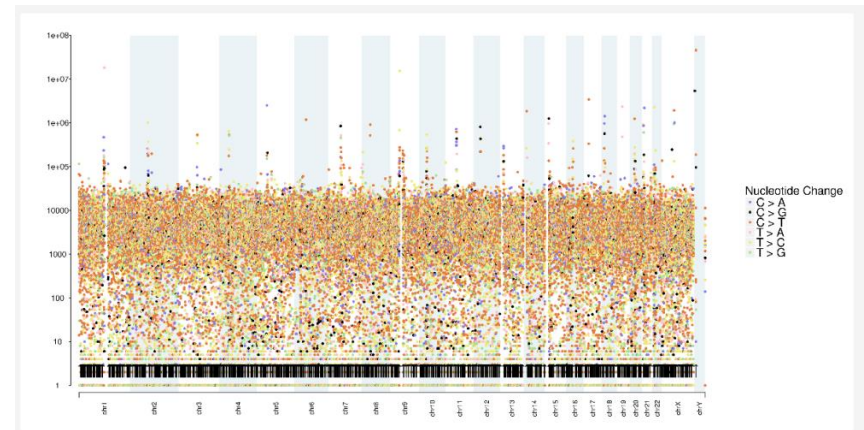
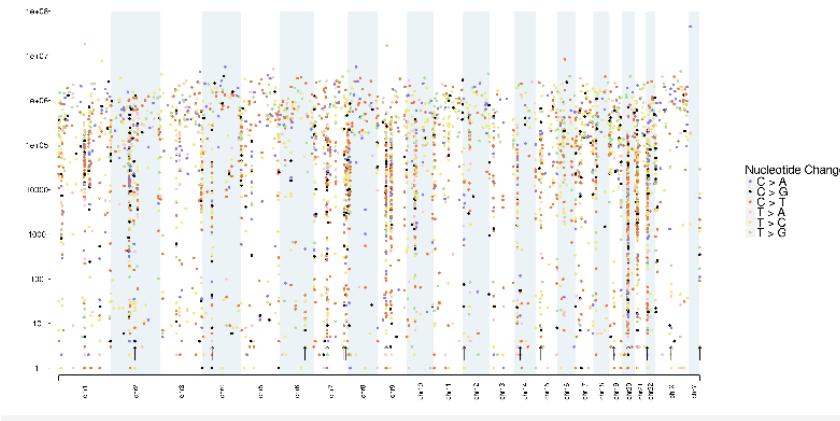
MMR deficient



Comparison with MMR proficient colorectal tumour – Rain plot

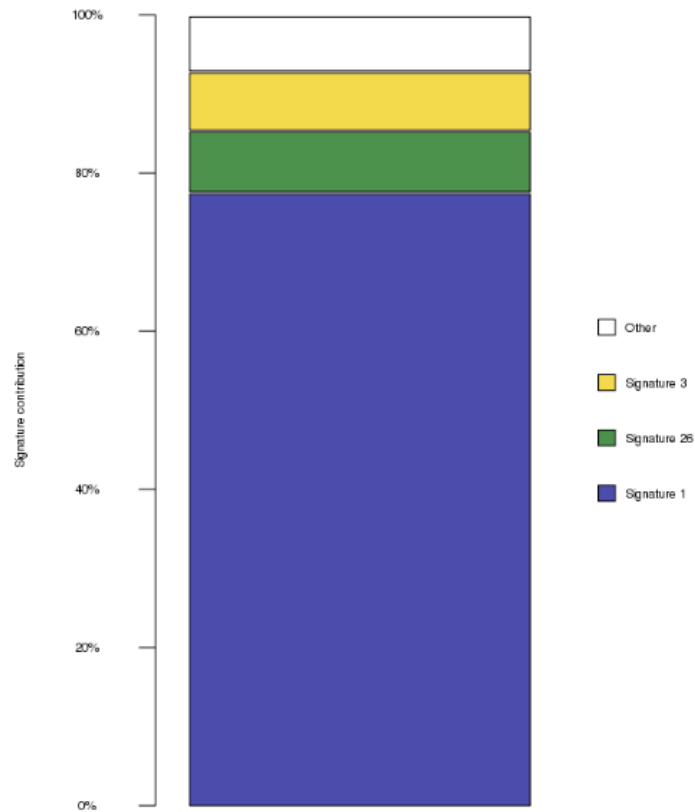
MMR proficient

MMR deficient

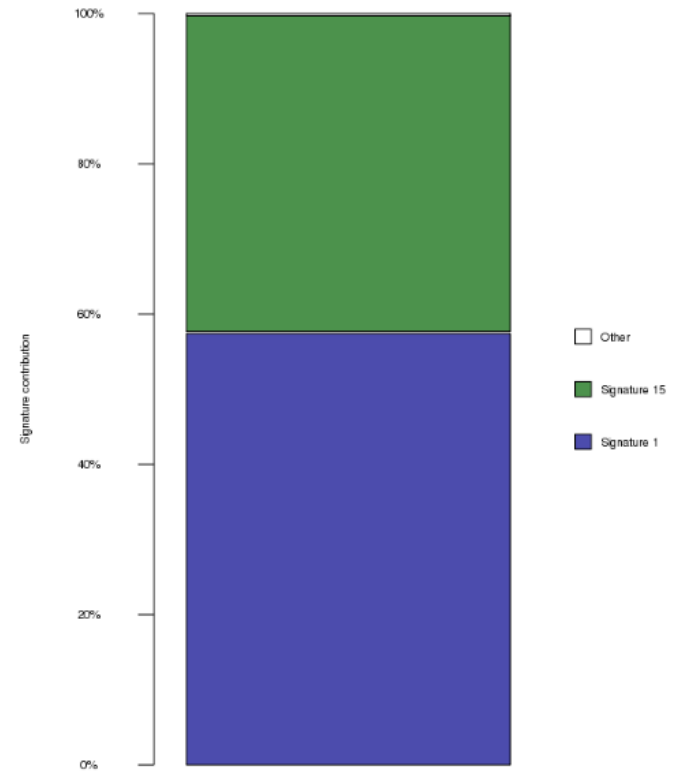


Comparison with MMR proficient colorectal tumour – Mutational signature

MMR proficient



MMR deficient



Clinical impact of germline MMR deficiency

- Treatment – limited benefit of single agent 5FU, doublet chemo regime with oxalaplatin and 5FU
- Less conservative surgery (significant second primary risk)
- Prophylactic aspirin reduces likelihood of second cancer
- Prophylactic gynaecological surgery – TAH and BSO greatly reduces risk of endometrial and ovarian cancers
- Cascade screening of relatives

Case Two

- 55 year old diagnosed with triple negative breast cancer (right breast) July 2016
- No family history or Jewish ancestry
- Referred to Genetics August 2016
- Not offered germline *BRCA1/BRCA2* testing as outside standard Pan-Thames BRCA testing criteria

Clinical management

- Right mastectomy Sept 2016
- Chemotherapy 6# FEC complicated by co-existing COPD and cellulitis
- Radiotherapy June 2017
- Enrolled in 100,000 genome study and consented to receive germline results

100,000 Genome Report

Whole Genome Analysis

100,000 Genomes Project Cancer Programme

Preliminary analysis: somatic small non-synonymous variants and pertinent germline findings in cancer susceptibility genes v1.4



Participant information

| Participant name | D.O.B | Gender | NHS number | Laboratory sample ID | GeL participant ID | GMC | Sample date | Date analysis issued |
|------------------|-------|--------|------------|----------------------|---------------------------|-----|-------------|----------------------|
| | | F | | 1018173889 | 212000085 | RJ1 | 09-09-2016 | 24-04-2017 |

Tumour information

| Tumour type | Tumour subtype | ICD10 code | Sample type | Reported tumour content | Tumour sample cross-contamination |
|-------------|----------------|------------|-------------|-------------------------|-----------------------------------|
| Breast | ductal | C509 | FF | High >60% | Pass |

Pathogenic germline cancer susceptibility variants

The following variants have been identified on analysis for pertinent germline findings (known pathogenic or likely pathogenic variants in cancer susceptibility genes relevant to the tumour type).

| Gene | GRCh38 coordinates ref/alt allele | Transcript | cDNA and protein change | Predicted consequences | Population germline allele frequency (1KG) | Alt allele/total read depth | Genotype | ClinVar ID | Gene mode of action |
|-------|-----------------------------------|-----------------|--------------------------|------------------------|--|-----------------------------|----------|--|---------------------|
| BRCA2 | 13:32340432 C>CA | ENST00000544455 | c.6079dupA p.(Arg2027fs) | frameshift_variant | N/A | 21/36 | 0/1 | RCV000044837 RCV000076953 RCV000132018 | tumour suppressor |

For more details of analysis and the genes included for pertinent germline findings, please refer to [Technical Information v1.4.main](#).

Pathogenic variant in BRCA2

Confirmed in diagnostic lab, seen in clinic August 2017 with result

Change in management

- Now eligible for Olaparib - PARPi (tablet chemotherapy that specifically targets cancers in BRCA carriers) via OLYMPIA trial
- Increased lifetime risk ovarian cancer (10-30%)
 - recommend bilateral salpingo-oophorectomy
- Predictive genetic testing for specific *BRCA2* mutation can be offered to children
 - daughter is a carrier and is now due for MRI breast screening

Case Three

- Lung adenocarcinoma

100,000 Genome Report

Whole Genome Analysis

100,000 Genomes Project Cancer Programme

Preliminary analysis: somatic small non-synonymous variants and pertinent germline findings in cancer susceptibility genes v1.3



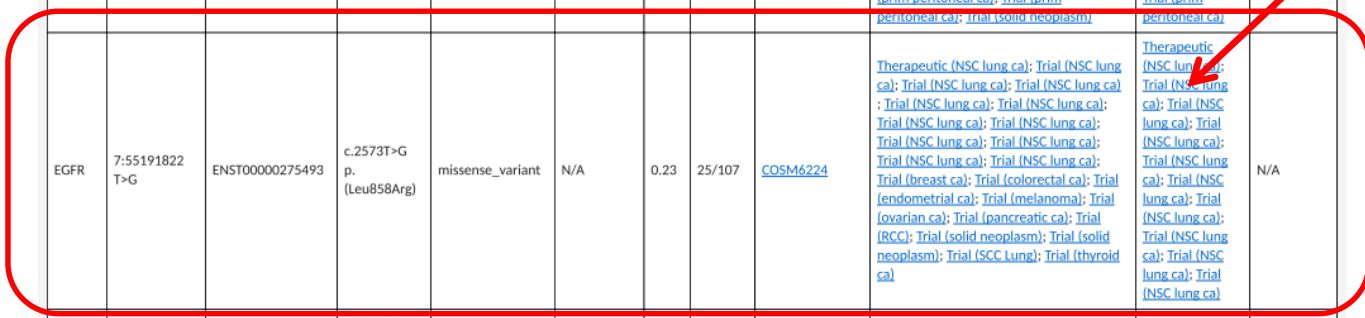
Participant information

| Participant name | D.O.B | Gender | NHS number | Laboratory sample ID | GeL participant ID | GMC | Sample date | Date analysis issued |
|------------------|-------|--------|------------|----------------------|---------------------------|-----|-------------|----------------------|
| | | F | | 1023650796 | 212000226 | RJ1 | 22-11-2016 | 24-03-2017 |

Tumour information

| Tumour type | Tumour subtype | ICD10 code | Sample type | Reported tumour content | Tumour sample cross-contamination |
|-------------|----------------|------------|-------------|-------------------------|-----------------------------------|
| Lung | adenocarcinoma | N/A | FF | High >60% | Pass |

| Gene | GRCh38 coordinates ref/alt allele | Transcript | cDNA and protein change | Predicted consequences | Population germline allele frequency (1KG) | VAF | Alt allele/ total read depth | COSMIC ID | Gene-level actionability | Variant-level actionability | Gene mode of action |
|-------|-----------------------------------|-----------------|--------------------------|------------------------|--|------|------------------------------|--|--|--|---------------------|
| BRCA2 | 13:32338167 C>A | ENST00000544455 | c.3812C>A p. (Ser1271*) | stop_gained | N/A | 0.06 | 7/123 | N/A | Therapeutic (ovarian ca); Therapeutic (fallopian tube ca); Therapeutic (peritoneal ca); Trial (fallopian tube ca) ; Trial (fallopian tube ca) ; Trial (ovarian ca) ; Trial (ovarian ca) ; Trial (ovarian ca) ; Trial (prim peritoneal ca) ; Trial (prim peritoneal ca) ; Trial (solid neoplasm) | Therapeutic (ovarian ca); Trial (fallopian tube ca) ; Trial (ovarian ca) ; Trial (prim peritoneal ca) | tumour suppressor |
| EGFR | 7:55191822 T>G | ENST00000275493 | c.2573T>G p. (Leu858Arg) | missense_variant | N/A | 0.23 | 25/107 | COSM6224 | Therapeutic (NSC lung ca); Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (breast ca) ; Trial (colorectal ca) ; Trial (endometrial ca) ; Trial (melanoma) ; Trial (ovarian ca) ; Trial (pancreatic ca) ; Trial (RCC) ; Trial (solid neoplasm) ; Trial (solid neoplasm) ; Trial (SCC Lung) ; Trial (thyroid ca) | Therapeutic (NSC lung ca); Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (NSC lung ca) | N/A |
| FGF3 | 11:69816341 C>G | ENST00000334134 | c.303G>C p. (Lys101Asn) | missense_variant | N/A | 0.06 | 5/89 | N/A | Trial (solid neoplasm) | | N/A |
| FGFR4 | 5:177090544 G>C | ENST00000292408 | c.246G>C p. (Trp82Cys) | missense_variant | N/A | 0.05 | 5/101 | N/A | Trial (solid neoplasm) ; Trial (urothelial ca) | | N/A |
| NF1 | 17:31219095 G>C | ENST00000358273 | c.1618G>C p. (Glu540Gln) | missense_variant | N/A | 0.06 | 7/127 | COSM5963097 COSM5963098 | Trial (breast ca) ; Trial (colorectal ca) ; Trial (endometrial ca) ; Trial (melanoma) ; Trial (NSC lung ca) ; Trial (NSC lung ca) ; Trial (ovarian ca) ; Trial (pancreatic ca) ; Trial (RCC) ; Trial (solid neoplasm) ; Trial (solid neoplasm) ; Trial (SCC Lung) ; Trial (thyroid ca) ; Trial (glioma) ; Trial (glioma) ; Trial (MPNST) ; Trial (neuroblastoma) ; Trial (neurofibroma) ; Trial (rhabdoid tu) ; Trial (rhabdomyosarcoma) ; Trial (schwannoma) ; Trial (sarcoma-ST) | | N/A |



EGFR mutations in lung cancer

- **EGFR inhibitors used in NSCLC with *EGFR* gene mutations**
- **Erlotinib (Tarceva)**
- **Afatinib (Gilotrif)**
- **Gefitinib (Iressa)**
- These drugs can be used alone (without chemo) as the first treatment for advanced NSCLCs that have certain mutations in the *EGFR* gene. These are more common in women and people who haven't smoked. Erlotinib can also be used for advanced NSCLC without these mutations if chemo isn't working. All of these medicines are taken as pills.
- **EGFR inhibitors that also target cells with the T790M mutation**
- EGFR inhibitors can often shrink tumors for several months or more. But eventually these drugs stop working for most people, usually because the cancer cells develop another mutation in the *EGFR* gene. One such mutation is known as T790M. But some newer EGFR inhibitors also work against cells with the T790M mutation, including **osimertinib (Tagrisso)**.
- Doctors now commonly get another tumor biopsy when EGFR inhibitors have stopped working to see if the patient has developed the T790M mutation.
- **EGFR inhibitors used for squamous cell NSCLC**
- **Necitumumab (Portrazza)** is a monoclonal antibody (a man-made version of an immune system protein) that targets EGFR. It can be used along with chemotherapy as the first treatment in people with advanced squamous cell NSCLC. This drug is given as an infusion into a vein (IV).

Clinical trial links

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Trial record 2 of 15 for: matrix lung cancer

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National Lung Matrix Trial: Multi-drug Phase II Trial in Non-Small Cell Lung Cancer

This study is currently recruiting participants.

See [▶ Contacts and Locations](#)

Verified October 2016 by University of Birmingham

Sponsor:

University of Birmingham

ClinicalTrials.gov Identifier:

NCT02664935

First Posted: January 27, 2016

Last Update Posted: October 26, 2016

Clinical trial links

CT <https://clinicaltrials.gov/ct2/show/NCT02013219>

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A Phase 1b Study of Atezolizumab in Combination With Erlotinib or Alectinib in Participants With Non-Small Cell Lung Cancer (NSCLC)

This study is ongoing, but not recruiting participants.

Sponsor:
Hoffmann-La Roche

ClinicalTrials.gov Identifier:
NCT02013219

First Posted: December 17, 2013
Last Update Posted: July 17, 2017

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

Information provided by (Responsible Party):
Hoffmann-La Roche

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Purpose

This open-label, multicenter study will assess the safety, tolerability, and pharmacokinetics of intravenous (IV) dosing of atezolizumab in combination with oral erlotinib or alectinib in participants with NSCLC.

This study has two stages. In the erlotinib group, the combination treatment will be given to participants with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) -treatment-naïve, advanced (nonresectable) NSCLC in a safety-evaluation stage and to participants with previously untreated EGFR mutation-positive, advanced NSCLC in an expansion stage (Stage 2). In the alectinib group, for both the safety-evaluation and expansion stages (Stages 1 and 2), the combination will be given to participants who are treatment-naïve with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC.

In Stage 1, erlotinib will be given at a starting dose of 150 milligrams (mg) by mouth (PO) once daily (QD) and the starting dose of alectinib will be 600 mg twice daily (BID), for 28 consecutive days during Cycle 1 and on Days 1 through 21 of each cycle thereafter. The starting dose of atezolizumab will be 1200 mg, administered every 3 weeks (q3W) starting on Day

08:49
27/09/2017