Acquired resistance in EGFR mutated oncogene-addicted NSCLC
DISCLOSURE OF INTEREST

- I have no conflicts of interest to disclose
Initial presentation

- 52 year old Caucasian male
- He had never visited a doctor’s office before 2010
- He was a life long smoker: seventy (70) pack year
- No history of cancer in the family

He developed shortness of breath on exercise and a chest X-ray showed total white out of the left lung.

- **CT chest**: Mass 4x5cm LLL, LT pleural effusion
  - mediastinal LNs
  - hilar LNs
- **Bone Scan**: (-), CT brain: (-)
- **CT abdomen**: peritoneal seedings
He underwent a thoracoscopy: about 7 litres of bloody stained pleural fluid were aspirate and biopsy and adenocarcinoma was diagnosed (positivity for TTF1/CK7).

February 2010 commenced on chemotherapy Cisplatin + Pemetrexed with very good response after 3 cycles. Further response after 6 cycles of chemotherapy. July 2010 he then underwent successful omentectomy.

Results of genetic testing on original biopsy sample: Deletion in exon 19 of EGFR, ALK gene rearrangement negative

Started on Erlotinib 150mg once daily

Did not experience any adverse events

January 2011 continued response - rising creatinine → lowered Erlotinib dose to 100mg o.d., he was also referred to a nephrologist

February 2012 good partial response → August 2012 wedge excision of lesion in the left lower lobe of lung revealing completely resected pT2 lung adenocarcinoma mixed acinar and papillary histology
November 2015 significant progressive pulmonary disease:
- Recurrent mass at the resection margin and left hilum of the lung with a metastatic deposit measuring 1cm in the apicoposterior segment of the left upper lobe, mediastinum LNs

1. Continuation of first-line EGFR TKI, or local therapy followed by continuation of the first-line EGFR TKI?
   - Continuation of first-line EGFR TKI may be beneficial in patients with slowly progressive disease, although frequent follow-up is needed.
   - Local therapy followed by continuation of first-line EGFR TKI may be beneficial in patients with oligoprogression (eg, single metastasis).

2. Perform a repeat biopsy.
   - Particularly important in patients with rapidly progressive disease and whenever a change in therapy is considered
Further bronchoscopy was undertaken which showed the initial exon 19 deletion but no T790M mutation.

CT scans in February and April suggested slow progression and the patient was asymptomatic → continued erlotinib.

June 2016 further disease progression: A liquid biopsy was therefore undertaken which confirmed the presence of a secondary resistance T790M mutation, in the EGFR gene.

In view of this he was enrolled in July 2016 on the global expanded access program for Osimertinib.

He displayed significant radiological response to Osimertinib as evidenced by serial radiological imaging.
Whilst on treatment he developed increase in the QTc from a baseline QTc of 434 to over 500msec on at least two occasions and one episode of loss of consciousness in view of this the Osimertinib was reduced to 40mg - Also started on bisoprolol.

He remain well until October 2018 when he developed epileptic seizures.

November 2018: MRI with contrast has confirmed the presence of brain metastases the largest being 23mm in the frontoparietal lobe and also evidence of leptomeningeal disease.

CT chest/abdomen: SD.
Progressive disease with 3rd generation EGFR TKI

- Discussed in the thoracic MDT and the decision was made to treat him with whole brain radiotherapy. He received 3000Gy in 10 fractions.

- Consideration for further treatment?
- Patient maintains an excellent performance status of WHO 0
What would you suggest?

- RT and continuation of Osimertinib
- Platinum Doublet
  - IMpower 150 regimen with Carboplatin, Paclitaxel, Bevacizumab, Atezolizumab
- Clinical Trial
Thank you for your attention!