Continuing Professional Development

CPD

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60 Second Summary

Lung cancer is the single largest contributor to cancer-related death in Ireland. The majority of patients with lung cancer have non-small cell lung cancer (NSCLC) histology (80-85%), while a minority represent small-cell lung cancer.

The discovery of the Anaplastic Lymphoma Kinase (ALK) rearrangement is one of the major success stories of personalized medicine in NSCLC.

ALK rearrangements have also been identified in other cancer types including oesophageal, renal cell, serous ovarian and several haematologic malignancies, but it is in NSCLC that progress in ALK targeting has been greatest. Its role as an oncogenic driver in other cancers is less clearly understood.

The first targeted agent for this rare subtype of NSCLC to be clinically developed, was Crizotinib. The phase III PROFILE 1014 trial conducted in 2011 established Crizotinib as a new standard of care for ALK-rearranged NSCLC, by demonstrating a benefit in survival outcomes compared with chemotherapy in patients with ALK-rearranged NSCLC.

The side effect profile of each of the ALK inhibitors are distinct, and provide critical information to tailor treatment choice. Class side effects of ALK-TKIs include peripheral oedema and GI disturbance.

Unfortunately, most 'oncogene-addicted' tumours will 'acquire resistance' to targeted therapies over time through a number of mechanisms, leading to progressive disease.

1. REFLECT - Before reading this module, consider the following: Will this clinical area be relevant to my practice?

2. IDENTIFY - If the answer is no, I may still be interested in the area but the article may not contribute towards my continuing professional development (CPD). If the answer is yes, I should identify any knowledge gaps in the clinical area.

3. PLAN - If I have identified a knowledge gap - will this article satisfy those needs - or will more reading be required?

4. EVALUATE - Did this article meet my learning needs - and how has my practise changed as a result?Have I identified further learning needs?

5. WHAT NEXT - At this time you may like to record your learning for future use or assessment. Follow the 4 previous steps, log and record your findings.

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ALK–rearranged lung cancer: new treatments, better outcomes

Lung cancer is the single largest contributor to cancer-related death in Ireland. The majority of patients with lung cancer have non-small cell lung cancer (NSCLC) histology (80-85%), while a minority represent small-cell lung cancer. Historically, histological subtyping alone in NSCLC has guided prognosis and treatment selection for patients with this cancer type. However, in the last 10 years, it is now a widely accepted standard of care to perform a panel of genomic tests. These tests identify therapeutically actionable cancer-causing genes (oncogenes), which can guide selection of more focused and often more successful 'targeted therapies.' Broadly, the development and use of targeted therapies in cancer has been referred to as either "precision" or "personalized" oncology, as patients receive treatments that are tailored towards the specific genomic features of their cancer type. Genomic testing in

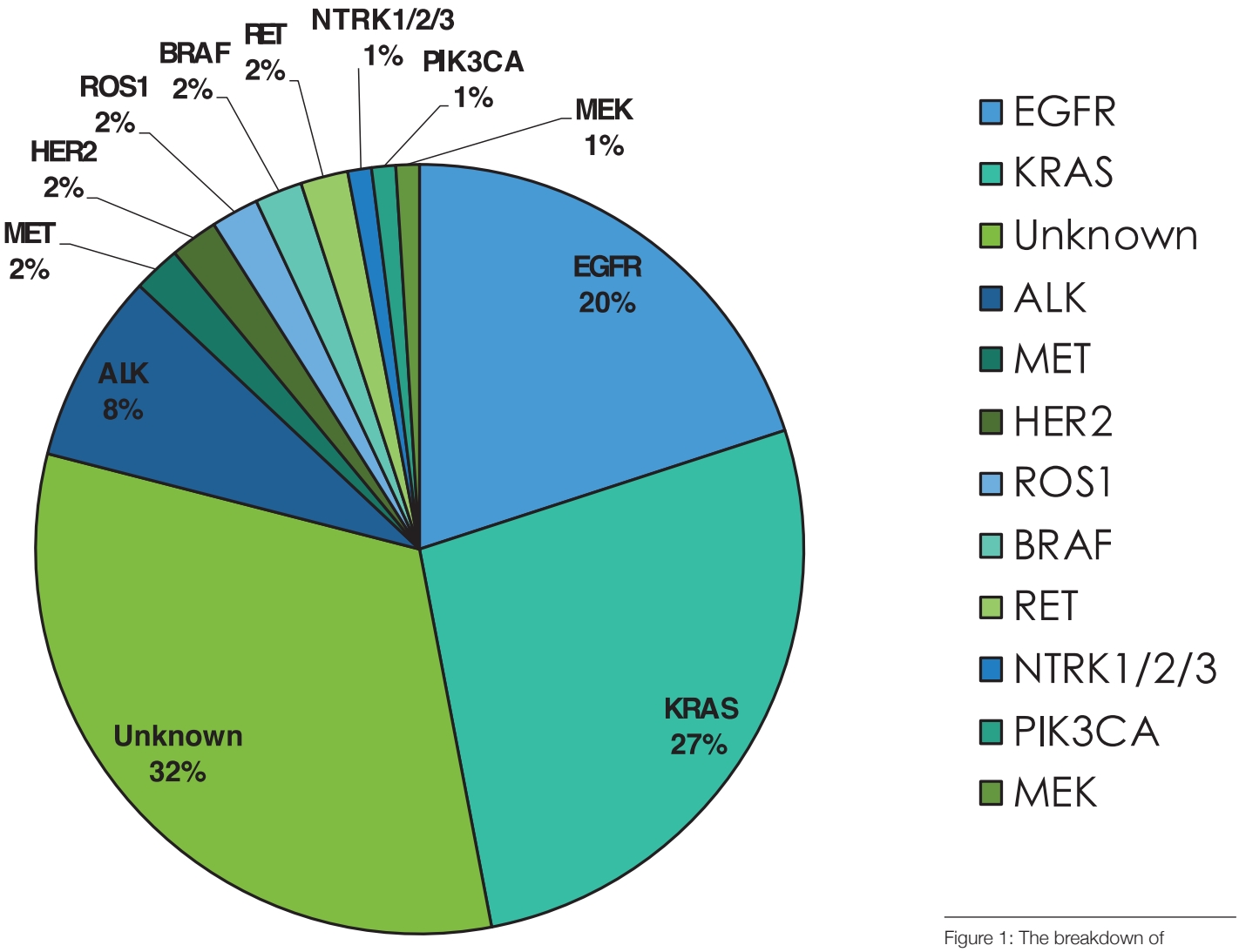


Figure 1: The breakdown of oncogenic mutations in Non-Small cell lung Cancer

NSCLC has led to the discovery of >10 oncogenes that can be therapeutically targeted (Figure 1), and thus led to significant benefits in patient quality and quantity of life.

ALK-rearranged NSCLC: A subset of NSCLC with rapidly expanding treatment options

The discovery of the Anaplastic Lymphoma Kinase (ALK) rearrangement is one of the major success stories of personalized medicine in NSCLC. Due to a number of successful clinical trials that led to approvals for >5 different ALK-targeting agents, patients with ALK-rearranged NSCLC now have a median survival of approximately 5-7 years. This is substantially longer, compared with the median survival of 12-18 months which is quoted for patients with NSCLCs that do not harbor an oncogenic driver mutation.

The oncogenic 'ALK-rearrangement' occurs in approximately 4-8% of NSCLC. Echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion is the most prevalent rearrangement, but ALK gene alterations including mutations, deletions and other rearrangements are also well described. Wild-type (ie 'normal') ALK protein is a transmembrane tyrosine kinase, however this oncogenic rearrangement leads to the uncontrolled growth of cancer cells.

ALK rearrangements have also been identified in other cancer types including oesophageal, renal cell, serous ovarian and several haematologic malignancies, but it is in NSCLC that progress in ALK targeting has been greatest. Its role as an oncogenic driver in other cancers is less clearly understood.

ALK-rearranged NSCLC is associated with certain clinical characteristics, in that patients with this subset of NSCLC are more likely to be young, of asian ethinicity, and either never smokers, or have a distant history of light smoking. ALK-rearranged NSCLC can also exhibit a unique biological behaviour, with a predisposition for intracranial spread.

All patients with newly diagnosed non-squamous NSCLC should have their cancers tested for the presence of an ALK rearrangement along with other genomic alterations, to inform potential targeted treatment. ALK-rearrangements may be tested for using next-generation sequencing, FISH (fluorescent in-situ hybridization) or immunohistochemical testing, however FISH is the accepted gold standard. If an ALK rearrangement is detected, several ALK-TKI treatment options may be appropriate treatment options.

Targeted therapy for ALK-rearranged NSCLC

The first targeted agent for this rare subtype of NSCLC to be clinically developed, was Crizotinib. The phase III PROFILE 1014 trial conducted in 2011 established Crizotinib as a new standard of care for ALK-rearranged NSCLC, by

ALK Inhibitor	Generation
Crizotinib (Xalkori®, Pfizer)	1st
Alectinib (Alcensa®, Roche) Brigatinib (Alunbrig®, Takeda)	2nd
Lorlatinib (Lorbrena®, Pfizer)	3rd

Figure 2 ALK inhibitors approved for use in Ireland

demonstrating a benefit in survival outcomes compared with chemotherapy in patients with ALK-rearranged NSCLC. Specifically, this trial showed a median progression-free survival (PFS) benefit of 7.7 months for Crizotinib vs 3.0 months for chemotherapy.

Second generation TKIs are more potent inhibitors of ALK. The development of 2nd generation ALK inhibitors, Alectinib, Ceritinib and Brigatinib, have brought further promise. Late phase clinical trials have elucidated that these agents confer a benefit in PFS compared with Crizotinib. Specifically, these studies include the ALEX trial (Alectinib versus Crizotinib in previously untreated ALK-rearranged NSCLC) and the ALTA-1L trial (Brigatinib versus Crizotinib in previously untreated ALK-rearranged NSCLC). These newer drugs also demonstrate superior intracranial disease control than that seen with Crizotinib. Ceritinib was demonstrated in the ASCEND-4 trial to have a superior PFS than platinum-based chemotherapy with pemetrexed (an anti-folate chemotherapeutic agent).

As mentioned earlier, ALK-rearranged NSCLC has a predilection for intracranial spread, making drugs which effectively cross the blood-brain barrier a focus of recent research. The most promising approved drug with regards to intracranial disease control is Lorlatinib, a 3rd generation TKI. Lorlatinib has an 82% intracranial response rate, compared to 23% with Crizotinib, in those with measurable disease at baseline. Impressively, Lorlatinib demonstrated that 71% of patients with brain metastases had a complete intracranial response - no visible disease in this area on subsequent imaging. Encouragingly, the 12-month PFS was 78% in the Lorlatinib arm compared to 39% in the Crizotinib arm.

What are the side effects of targeted therapy?

The side effect profile of each of the ALK inhibitors are distinct, and provide critical information to tailor treatment choice. Class side effects of ALK-TKIs include peripheral oedema, ECG changes (QT prolongation and bradycardia) and GI disturbance. Serious adverse events are rare. Side effects of Lorlatinib include but are not limited to: hypercholesterolemia, hypertriglyceridemia, oedema, weight gain, peripheral neuropathy, cognitive affects and hypertension. Indeed, 72% of patients had grade 3 or higher toxicity (although no deaths were reported) in the registration trial of Lorlatinib referenced above. Only 7% of patients experienced side effects requiring cessation of treatment. Cognitive effects were mainly grade 1 and respond to treatment interruption, and mainly consisted of inattention and memory impairment.

In contrast, there are side effects of particular interest with each ALK inhibitor. For example, Crizotinib requires careful monitoring of LFTs and can cause flashing lights, floaters or other mild visual phenomena that are mild and short-lived, but is otherwise well tolerated. Alectinib is known to cause anaemia, arthralgia and myalgia, and Brigatinib can lead to rises in CK, amylase and lipase, as well as a classic interstitial lung toxicity. Ceritinib causes GI disturbance, with diarrhea, nausea and vomiting. As a result of their slightly different side effect profiles, the choice of ALK inhibitor is individualized, while also taking into account patient preference, licensing and burden of intracranial disease.

It is also important to note, despite side effects being significantly higher in the Lorlatinib arm when compared head-to-head with Crizotinib, quality of life, as measured by validated patient reported outcome scores, was improved in the Lorlatinib arm, presumably due to a reduction in cancer related symptoms.

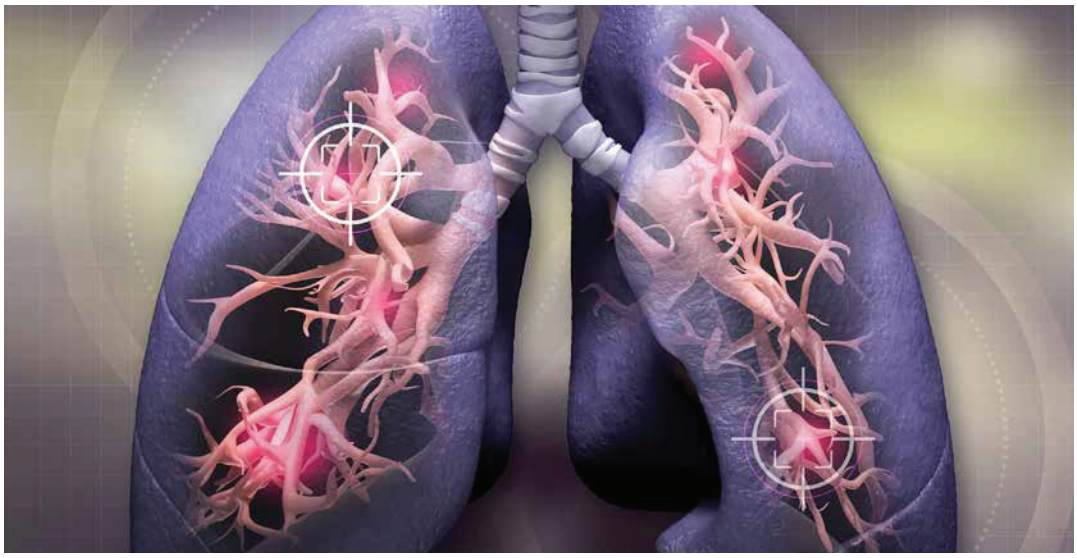
The management of side effects of ALK-inhibitors often consists of dose interruption or dose reduction. Use of statins for hypercholesterolemia and hypertriglyceridemia is common, as is the use of diuretics for fluid retention. It is important given the average life expectancy of patients is 5-7 years to treat this subset of lung cancer patients as we would patients with any other chronic disease. The overall health of patients is monitored, with optimization of chronic disease management for any co-existing illnesses. The NCCP protocols for these agents give clear guidance for when to consider introducing lipid-lowering therapy for example. The NCCP protocols also outline baseline evaluations required prior to initiation of therapy (ECG, biochemical evaluation, haematological evaluation etc) and for monitoring of therapy on a monthly basis thereafter.

Importantly, if severe side effects do develop, amelioration of this adverse events is possible with cessation of therapy.

Future efforts in drug development seek not only to maximize the efficacy of anti-cancer therapies, but also minimize side effect profiles.

Acquired resistance to targeted therapy

While direct targeting of the defective protein often leads to tumour shrinkage and control, unfortunately, most 'oncogene-addicted' tumours will 'acquire resistance' to targeted therapies over time through a number of mechanisms, leading to progressive disease. Acquired resistance in ALK-rearranged NSCLC may be due to development of secondary ALK mutations, activation of 'bypass' signaling pathways, development of alternative mutations e.g. cMET/HER2, epigenetic changes or transformation to different subtypes e.g. small cell transformation. The most common secondary mutations to develop after initial treatment with an ALK-TKI include L1196M and G1269A. These alterations can be identified via conventional tumour biopsy of a progressing area, or assessment by 'liquid biopsy,' a test that detects circulating tumour DNA in the blood. This also has the ability to account for heterogeneity of tumour cell clones – and is both quicker and less invasive. It also allows for repeated assessment over time which can be correlated with radiological and clinical response.



Treatment beyond ALK Inhibitors

Interestingly, patients with ALK-rearranged NSCLC typically have a poor response to immunotherapy. This is thought to be due to an immune-suppressive microenvironment in ALK-rearranged NSCLC which leads to immune evasion. As a result of known poor response to immunotherapy in oncogene-addicted NSCLC, these patients are now routinely excluded from first-line trials of immunotherapy in NSCLC. There is biological rationale for overcoming this immune refractory tumour microenvironment in ALK-rearranged NSCLC in the future, but for now the treatment paradigm of ALK-rearranged NSCLC is firmly established, with TKIs and chemotherapy playing the largest role.

These cancers respond similarly to other subtypes of NSCLC when treated with chemotherapy, which remains an option in later lines of therapy or in rare cases where patients may be unsuitable for treatment with ALK-TKIs. It is common for patients with an ALK rearrangement to undergo treatment with 2-3 ALK inhibitors before requiring treatment with chemotherapy. Chemotherapy is rarely associated with the longer duration of response seen with ALK inhibition, and is also less likely to achieve intracranial disease control. There is always also a role for radiotherapy as an option in patients with a limited number of areas of progressive cancer ('oligoprogressive disease') or areas causing clinically meaningful symptoms e.g., pain or mass effect, throughout the treatment course of patients with this disease.

Conclusions and Future Directions

ALK-rearranged lung cancer is an example of how bench to bedside (and back again) research has led to several new treatment options, that have translated into tangible benefits in survival for patients. The story of target oncogene identification, drug development, clinical trials and real-world efficacy and tolerability is the foundation for personalized medicine. Long may lung cancer reign, as the poster-child of this approach in oncology.

References on request

Beating Cancer: Reclaim Lost Momentum to Deliver Measurable Advances

February 2020 marked a unique turning point in the fight against cancer. Cancer stakeholders – including oncology experts, patients and industry – stepped up collaboration on cancer policy at EU level. It was a key moment: the European Commission had just opened a consultation that promised a new era in cancer care. Optimism was in the air.

Then COVID-19 struck. Within weeks, the world had changed. People with cancer found their appointments cancelled or moved online. Treatment and clinical trials were disrupted. Screening was paused.

However, at the policy level, momentum never stopped. An intensive one-year consultation period led to the publication of Europe's Beating Cancer Plan – an impressive achievement under challenging circumstances. We applauded the Plan, while stressing the importance of measuring progress.

This year's European Health Forum Gastein (EHFG) offered an opportunity to reflect on the impact of the COVID-19 pandemic and the opportunities of the new Beating Cancer Plan. At a session organised by the EFPIA Oncology Platform, the European Cancer Patient Coalition and European Cancer Organisation there was a strong sense that the Plan provides a platform on which to build back to a "new better" the cancer care system. Cancer care could – to borrow the theme of this year's EHFG – rise like a Phoenix in the post-pandemic world.

Building a Data-driven Cancer Service

However, the event also heard some worrying data that made us sit up and take notice. There have been 100 million missed screening tests in the EU during the pandemic. This means that 1 million people may be walking around unaware that they have cancer.

There is also deep concern that the advances in patient outcomes gained in the decade before the pandemic could be lost. Not only could the pace of progress slow, but there is also a real risk of going backwards.

Despite this well-founded fear, we remain optimistic that Europe has an unprecedented opportunity for progress. If we unite and act now in unison, we can create a future that is far better than anything that has gone before. We can revert the current trend that sees cancer becoming the leading cause of death in the EU by 2035.

At the heart of this will be data and the ability to use them. Europe's Beating Cancer Plan includes an inequalities registry, designed to bridge the gap between Member States. The OECD has been appointed to explore this, and we look forward to engaging on this key topic.

But we also see the need to go further. The Plan cannot be a success unless we demonstrate progress. A public-facing measurement system displaying key indicators would empower patients and policymakers with the information required to drive change. We trust in plans but what gets measured gets done.

We need a jointly agreed set of indicators, defined by an expert group with input from all stakeholders. This does not take years to be developed – it can be built from existing indicators and introduced as swiftly as possible.

Tracking key indicators is not to name, shame or blame. It is to have an up-to-date picture of progress on the core areas of cancer, to learn what works and what doesn't, and provide an early warning system in case implementation is in danger of drifting off course. It is for citizens to understand and be involved.

Seizing the Moment – Together

Europe has never had a better chance than this to get cancer services right. Key policymaking institutions are on board while experts, patients and industry are ready to play their part. But cancer cannot wait – and neither can we. Now is the moment to ensure that the Beating Cancer Plan is a success.