Advancing Cancer Research Together

NCRI Lung Group Priorities 2023 - 2026

NCRI Partners

NCRI is a UK-wide partnership between research funders working together to maximise the value and benefits of cancer research for the benefit of patients and the public. A key strength of NCRI is our broad membership with representation across both charity and government funders as well as across all four nations in the United Kingdom.

Contents

Introduction

The NCRI Groups bring the cancer research community together to develop practice-changing research, from basic to clinical research and across all cancer types, supporting NCRI's strategy. The NCRI Lung Group is a multi-disciplinary community of researchers and consumers focused on developing research to improve outcomes for cancer patients and identify areas of unmet need.

Each NCRI Group engages in a prioritisation process to identify the priority areas in its area of research (Appendix A). This process dictates the work of the group as well as providing an assessment of the state of research for the wider research community.

The NCRI Lung Group has identified its research priorities based on NCRI Lung Group's strategy setting sessions held in March 2022, review by the Group's Chair, and discussion in the Lung Group meeting held in December 2022.

There are multiple areas the NCRI Lung Group has identified as priorities, an overview of which can be seen below with full details on the following pages of this document. The Group will initially focus on 5 key priorities, forming time-limited working groups to address these priorities. When one working group finishes, capacity will be transferred to address the next priority. This is alongside a study group focused on mesothelioma and thymoma. An overview of the NCRI Lung Group structure can be found on page 6.

The strategies of NCRI Groups will be refreshed every three years. In addition, the research landscape will continue to be routinely assessed by NCRI to ensure the most pressing questions in the Lung research landscape are addressed over the course of this three-year strategy.

NCRI Lung Group strategic areas at a glance

1. Lung Cancer in Never Smokers (LCINS)
2. High grade neuroendocrine carcinomas of the lung
3. Immune related adverse events (irAEs) in people with lung cancer

Foreword from Prof. Gary Middleton, Chair of NCRI Lung Group

"We are pleased to present the strategic priorities and aligned working groups for the NCRI Lung Group. This document is the fruit of much work by many people who took part in dedicated priority setting sessions, and in the multiple ensuing discussions, to generate a list of priorities entirely aimed at improving the outcomes and the lives of people with lung cancer. The following document represents a distillation of this vital preparatory work. The final selection as it appears here was approved at a NCRI Lung Group meeting at the end of last year as being both representative of our stakeholders' major interests, needs and agendas and thus worthy of being offered as national strategic priorities in lung cancer research.

Some of the priorities are already well established as key areas of endeavour both in the NCRI and in our vital sister organisation the British Thoracic Oncology Group (BTOG) with whom we have a healthy and vibrant relationship which will continue to inform and invigorate the work of both organisations. We believe that the interaction of NCRI Lung

Group and BTOG will continue to maintain the UK as an important crucible for novel initiatives to enhance all aspects of those living with and beyond lung cancer.

The first strategic priority is Lung Cancer in Never Smokers (LCINs): this is a long-standing key theme for NCRI and was the focus of an all day meeting and survey on knowledge gaps in LCINS under Professor Matthew Hatton's leadership, outcomes of which will shortly be published. The gaps identified at that meeting lead naturally to the time-limited goal-oriented working groups that we here propose and which were voiced by many during priority setting. We firstly propose to identify whether a screening strategy for LCINS in the UK is feasible and appropriate, to develop a nomogram to predict those non-smokers most at risk in order to prioritise people for screening and determine the optimal screening modalities alongside the identification of potential prevention interventions for those at high risk of LCINS. The second aim is to scope a potential trial in epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) that will improve long term outcomes. Two options are proposed for this working group: to target the unique biology of drug-tolerant persisters and the persister-to-resister switch and to utilise strategies based on evolutionary game theory and evolutionary steering to prevent the outgrowth of resistant clones as a result of the standard treat-to-progression strategy employed using EGFR Tyrosine Kinase Inhibitors (TKIs).

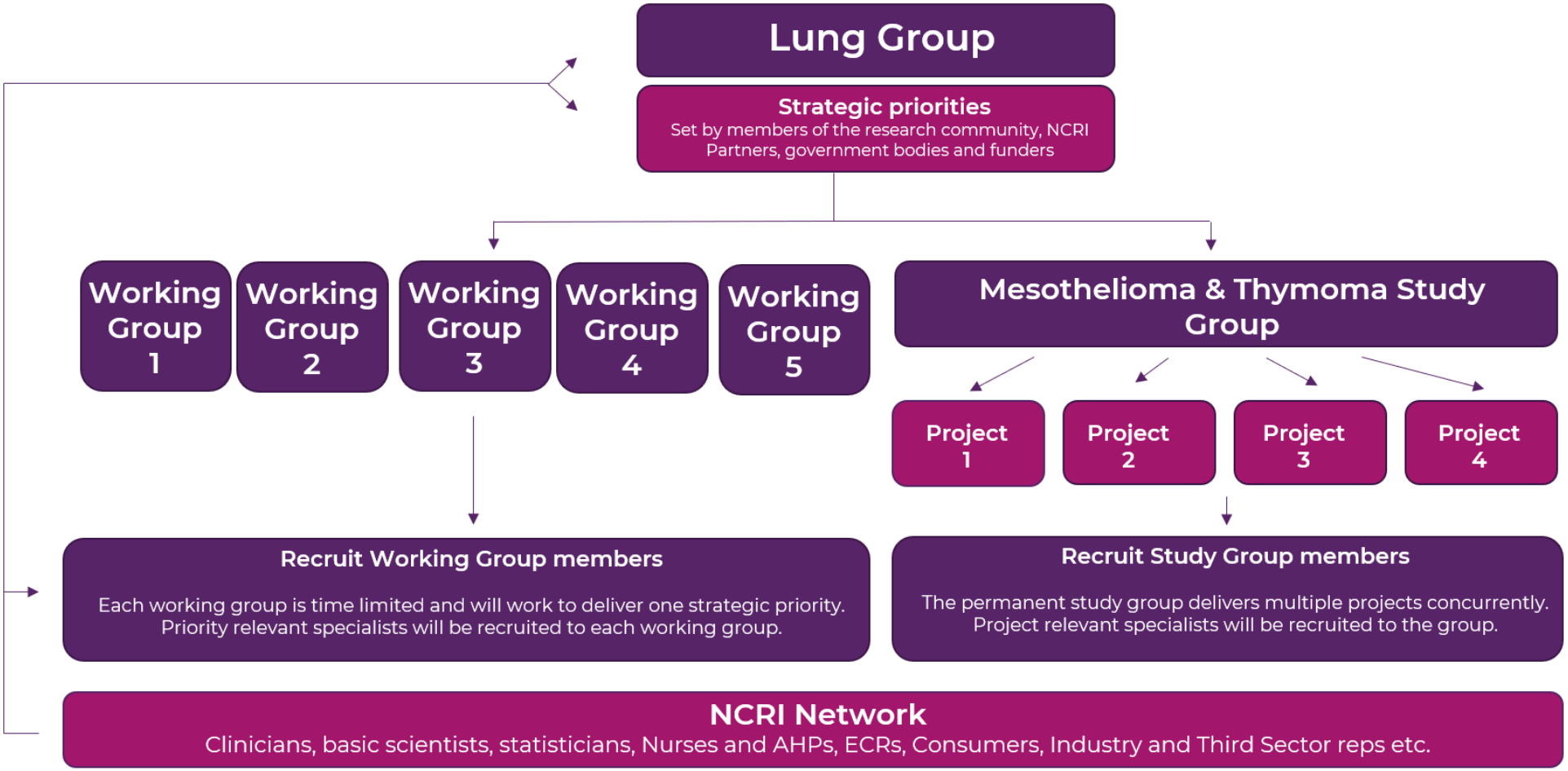
The second priority area is high grade neuroendocrine cancers. We must capitalise on the excellence of small cell lung cancer (SCLC) research in Manchester and we suggest a number of potential clinical trial options to be looked at in an SCLC working group. We also propose a working group to design and run a definitive standard of care trial in large cell neuroendocrine carcinoma (LCNEC), a long standing lung cancer of unmet need that BTOG has taken an important lead on.

Finally, we propose a working group to design and implement a series of predictive biomarkers for severe immune related adverse events alongside efforts to optimise the treatment of those with severe Immune related adverse events (irAEs). This is a huge issue for those for those living with and beyond lung cancer and the expertise that we have nationally in this space puts us in a good position to meaningfully contribute to this issue.

Some will naturally find the strategic priorities and the working groups proposed to address them do not reflect either their view of what constitute national priorities or indeed their areas of expertise. It will be seen that there is little mention of radiotherapy or surgery, two utterly pivotal therapeutic modalities in lung cancer. Part of this represents the majority view of the priority-setting stakeholders as to what were currently pressing needs, partly my own bias, I imagine, but it is in large part due to a real sense that what is needed is a new series of academic investigator-led systemic therapy national studies, of which there has been a down-turn of late. The radiotherapy trial portfolio nationally is broad and impressive and the surgical portfolio in both lung cancer and mesothelioma of global importance. However, it is critical to note that the working groups are frameworks in which to start multi- and trans-disciplinary conversations to enhance outcomes for the identified priority lung cancers and we feel surgical and radiotherapeutic input to those conversations is utterly essential. We are also still running grant clinic panels (proposal guidance meetings) to finesse nascent research concepts and in the latest of these 1 of the 3 reviewed was an oligometastatic SABR concept, an area of obvious UK strength.

Finally, we strongly feel that the national excellence, both clinically and translationally, in mesothelioma is world class and have strongly urged that mesothelioma should constitute a fully-fledged stand-alone study group. We are interested in views as to whether thymic malignancies should be incorporated under this banner, or given its distinct biology, represent a further separate study group. We will shortly be advertising for membership of each of the working groups and the study group."

NCRI Lung Group structure at a glance



NCRI Lung Working Groups and Study Group

Initial Working Groups and Study Group in set up

The NCRI Lung Group has identified seven strategic priorities, full details of which can be found on the following pages of this document. Time-limited working groups will be set up to firstly address 5 key priorities for the NCRI Lung Group, outlined below. Once one working group reaches completion, capacity will be transferred to the next priority. In contrast, the study group is a permanent standing group that sits under the NCRI Lung Group.

Working Group 1

To identify whether a screening strategy for Lung Cancer in Never Smokers (LCINS) in the UK is feasible and appropriate, develop a nomogram to predict those non-smokers most at risk in order to prioritise people for screening and determine the optimal screening modalities. To identify potential prevention interventions for those at high risk of LCINS.

Working Group 2

To scope a potential trial in epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) that will improve long term outcomes. Two options might be considered:

A) To target the unique biology of drug-tolerant persisters (DTPs) and the persister-to-resister switch.

B) To utilise strategies based on evolutionary game theory and evolutionary steering to prevent the outgrowth of resistant clones as a result of the standard treat-to-progression strategy employed using EGFR Tyrosine Kinase Inhibitors (TKIs).

Working Group 3

To design and implement a small cell lung cancer (SCLC) trial based on the molecular and immunological specificities and the plasticity of the recently described transcriptional subtypes of SCLC and which attempts to capitalise on the specific therapeutic vulnerabilities of each subtype.

To design and implement an immunotherapy trial in SCLC informed by the recent insights into the unique immunobiology of SCLC that factors in the transcriptional repression of Major Histocompatibility Complex-I (MHC-I) and consider trials of immune therapies that are not dependent on MHC-I presentation of neoantigens.

Working Group 4

To design and implement a definitive large cell neuroendocrine carcinoma (LCNEC) trial of etoposide/cisplatin (EP) versus gemcitabine/platinum with prospective stratification by retinoblastoma (Rb) status/LCNEC subtype with or without anti- programmed death-1 (PD-1)/ ligand 1 (PD-L1) (anti-PD-1/PD-L1) immune checkpoint blockade (ICB) to determine the optimal chemo(immuno)therapy regimen for each subtype and the relative contribution of the addition of ICB in each subtype.

Such a trial will define the global standard of care in LCNEC in much the same way that the NCRI Hepato-pancreato-biliary (HPB) subgroup did for cholangiocarcinoma starting with ABC-02, a simple and pragmatic trial, which established gemcitabine/cisplatin as the global standard of care. LCNEC is also an important British Thoracic Oncology Group (BTOG) initiative.

Working Group 5

To design and implement a series of predictive biomarkers for Immune-Related Adverse Events (irAEs) alongside efforts to optimise the treatment of those with severe irAEs.

Mesothelioma and Thymoma Study Group

It is beyond the remit of this document to propose specific working groups for these areas. We strongly feel that a new chair be sought for this study group and following the NCRI over-arching strategy that the working groups should be generated as result of a strategy and priority setting workshop including all key stakeholders dedicated to defining key areas of interest and relevance to clinical and translational research in mesothelioma and thymic malignancies in the UK.

Detail on the strategic priorities

Strategic area 1: Lung Cancer in Never Smokers (LCINS)

Priority 1: To identify whether a screening strategy for Lung Cancer in Never Smokers in the UK is feasible and appropriate, to develop a nomogram to predict those non-smokers most at risk in order to prioritise people for screening and determine the optimal screening modalities. To consider the potential for prevention studies in those at particularly high risk. This will be the focus of Working Group 1.

LCINS is the 8th commonest cause of cancer death in the UK. In Japan 80% of all lung cancer in women is in never-smokers and 31% in men making death from LCINS the 5th commonest cause of death in men and the 3rd in women. Given that early detection is the only way to meaningfully impact lung cancer survival it becomes incumbent on the lung cancer community to consider possible screening programmes for LCINS.

This working group will consider the following:

Which people should be prioritised for screening?

- Those at high inheritable risk?

  Recently the largest gene-gene (G x G) interaction study examining the influence of these interactions on the risk of developing NSCLC was published and described an enhanced lung cancer screening model - the interaction-empowered polygenetic risk score (iPRS)[1]. The iPRS was externally validated in 162,316 never smokers in the UK Biobank, so highly pertinent to the development of a potential UK-wide LCINS screening programme. Each subject was assigned an iPRS score and categorised into 10 groups by deciles of scores. Never smokers in the top 10% decile were at much higher risk of lung cancer than those in the bottom 10% decile, with a gradual increase in risk across the deciles, with HR=5.31 (3.11-9.07).

- Those exposed to high levels of atmospheric pollution?

  In a Canadian study LCINS were more frequently seen in females (70.5% vs 48.2%) and those of Asian race (67.8% vs 16.7%)[2]. Outdoor air pollution levels (obtained from satellite geolocation estimates for each residential address for the past 20 years prior to cancer diagnosis), particularly particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) was significantly higher in LCINS compared with cancer in ever smokers. Multivariate analysis showed significantly increased risks according to: sex (female vs male) OR 4.01 (2.76-5.82); Asian vs other ethnicity OR 6.48 (4.42-9.50); greater air pollution (natural log transformed $PM_{2.5}$) OR 1.79 (1.10 – 7.29). In the ESCAPE study summating 17 separate cohort studies and over 4 million person-years at risk, in all participants the HR was 1.55 (1.05-2.29) per 5μg/m^3 $PM_{2.5}$ for adenocarcinoma rising to 1.65 (0.93-2.95) for participants that didn't change address[3].

  The likely mechanistic underpinning for these epidemiological findings has been elegantly demonstrated by Charlie Swanton's group who showed that $PM_{2.5}$ was associated with EGFR-mutant lung cancer[4]. Inhaled $PM_{2.5}$ significantly accelerated tumorigenesis in EGFR and KRAS mutant genetically engineered mouse models, an effect dependent on an intact immune response. PM resulted in enhanced

macrophage infiltration and the release of IL-1β from macrophages and lung epithelium which induced a primed AT2 stem-like cell state and which mimicked the enhanced tumorigenicity of PM. Blocking IL-1β blocked the tumorigenicity of PM leading to the proposal that PM induced IL-1β was promoting a pre-existing initiator mutation. Indeed, they found EGFR mutations in 15% and KRAS mutations in 53% of normal healthy lungs. Cancer associated mutations in the lung became more prevalent with age presumably due to clock signature mutations.

These data pose a huge public health challenge and raise immediate questions about how to screen for $PM_{2.5}$ exposure and crucially how exposure might be quantitated to select people for screening and what other supplemental factors beyond age, sex, ethnicity and iPRS scores (or other polygenic risk scores) need to be considered. It raises questions around prevention programmes based around anti-IL-1β in very high risk individuals and around what is the optimal screening tool – exhaled volatile compounds, low dose CT scanning, or liquid biopsy?

Priority 2: To scope a potential trial in epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) that will improve long term outcomes. This will be the focus of Working Group 2. Two options might be considered:

A) To target the unique biology of drug-tolerant persisters (DTPs) and the persister-to-resister switch.

B) To utilise strategies based on evolutionary game theory and evolutionary steering to prevent the outgrowth of resistant clones as a result of the standard treat-to-progression strategy employed using EGFR Tyrosine Kinase Inhibitors (TKIs).

Game theory conceptualises mathematically the contest between the physician as predator and the cancer as prey[5]. The oncologist has a distinct advantage in this "Stackelberg" game by being in the position of making the first move when initial treatment is applied. The cancer cells are at a major disadvantage as they cannot rationally predict their counter-strategies but must reactively inherit and evolve them and passively follow each move taken by the oncologist which cannot be anticipated. The ultimate desired end-point of targeted therapy is cure which will occur if the therapy causes the entire cancer cell population to become extinct. This end-point is pursued in clinical practice by using the recommended highest dose continuously. However, if there are sub-populations capable of evading death then this strategy will fail and which indeed, is the inevitable outcome of resistance to this strategy in the clinic. Continuous treatment with the same therapy allows the cancer at any point during this therapy in effect to adapt to future therapy because the subsequently administered one is the same one as is already being administered. As the leading proponent of adaptive therapy, Robert Gatenby pithily sums it up, with analogy to the rock-paper-scissors game "if the physician *only* plays "scissors" the cancer cells can evolve to the unbeatable resistance strategy of "rock"."

There are two alternatives to the standard treat-to-progression scissors-only approach in which the goal of therapy can be defined differently. Treatment with curative intent in the context of targeted therapy of oncogene addictions involves initial treatment to eliminate the bulk sensitive populations leaving a homogeneous minor fraction of DTPs which can then be targeted sequentially with a different treatment aimed specifically at DTPs, an active pre-meditated switch to a paper-strategy in response to the rock-strategy of the cancer.

A) Targeting DTPs – therapeutic avenues to consider

There are clear differences in gene signatures between cycling and non-cycling persisters[6]. Cycling persisters after osimertinib therapy express higher levels of glutathione and NRF2 signatures: proliferative persister capacity are strongly associated with antioxidant expression signatures. Accordingly, treatment with NAC significantly increase the fraction of cycling persisters whereas treatment with erastin which inhibits glutathione synthesis decreases the fraction of cycling persisters.

There is also a clear metabolic shift in cycling persisters. Cycling DTPs demonstrate increased fatty acid oxidation (FAO) with osimertinib treatment[6]. Blocking FAO with etomoxir at day 3 after sensitive cells had died reduces persister cell proliferation and co-treatment with osimertinib from day 1 significantly reduced cycling persister frequency at etomoxir concentrations that had little effect on untreated cells as single agent.

A recent study analysed the mechanisms of the persister-to-resister switch, that transformation of persisters to resisters[7]. AXL is the receptor for GAS6. The most significantly up-regulated gene in high-persistence subclones was *GAS6* and GAS6 was highly enriched in cycling compared to non-cycling persisters. In a clinical dataset residual disease displayed high GAS6. AXL-overexpression increased the proportion of cells surviving TKI therapy and AXL knockdown reduces this fraction. In vivo, the combination of osimertib+cetuximab+anti-AXL antibody completely abolishes relapse.

B) Evolutionary game theory

If cure is not deemed feasible then an *adaptive* approach is used which applies simple evolutionary principles of competition for scarce resources between competing populations in the cancer ecosystem and exploits the fitness costs of resistant clones. Here, a treatment sensitive population is deliberately *not* eliminated (which is always a cause of celebration when a particularly impressive response is seen on the first on-treatment scan) but is deliberately and pro-actively retained to out-compete the minor and less fit resistant population for access to restricted resources, precisely the population that can drive eventual treatment failure. In practice this involves drug-treatment holidays which allow partial re-growth of the readily drug-sensitive (and hence readily controllable) clones that can then drive back the less fit drug-resistant clones. A version of adaptive therapy is where the cancer is steered into repeatable periodic cycles of tumour composition, effectively coming back to the original composition at the start of therapy[8].

These data can be used as a launchpad for discussions around trial designs to improve outcomes in EGFR mutant NSLCC based on considerations of the biology of residual disease.

Strategic area 2: High grade neuroendocrine carcinomas of the lung

Priority 1: To design and implement a small cell lung cancer (SCLC) trial based on the molecular and immunological specificities and the plasticity of the recently described transcriptional subtypes of SCLC and which attempts to capitalise on the specific therapeutic vulnerabilities of each subtype. This will be the focus of Working Group 3 (part A).

A recent pivotal study proposes 4 distinct transcriptional subtypes of SCLC with distinct therapeutic vulnerabilities: ACLC-A (high *ASCL1,* 36%);SCLC-N (high *NEUROD1,* 31%); SCLC-P (high *POU2F3,* 16%) and SCLC-I (high expression of checkpoints, HLAs and with marked increases in T cells and NK cells)[9]. *YAP1* expression did not identify a discrete subtype and IHC could be used to accurately identify each subtype. SCLC-A and N have significantly higher expression of the neuroendocrine (NE) markers *CHGA* and *SYP* than the non-NE subtypes, SCLC-P and I, which have higher expression of *REST,* a negative repressor of NE genes. SCLC-A is the most epithelial subtype and SCLC-I the most mesenchymal. Most TTF1-positive SCLC are SCLC-A whilst SCLC-N is largely TTF1-negative.

In keeping with its much greater immune activation, in Impower133, the median OS in SCLC-I was 18 months for EP+atezo compared with 10 months for EP alone (which is the same as EP alone in SCLC-A and N, so therefore not prognostic). SCLC-P models were significantly more sensitive to PARP inhibitors independently of SLFN11 expression. SCLC-N have high expression of cMYC and accordingly are very sensitive to Aurora kinase inhibition[10]. Importantly, there is clinical proof of principle of high c-MYC expression predicting sensitivity to alisertib in SCLC[11]. In c-MYC positive patients the PFS HR for the addition of alisertib to paclitaxel was 0.29, a beneficial effect that was totally reversed in the setting of c-MYC negative SCLC where the HR=11.8. Some SCLC-A lines have high BCL2 expression and this subtype was most sensitive to BCL2 inhibition. SCLC-I have high level expression of Bruton's tyrosine kinase and were sensitive to ibrutinib. In terms of cell-surface protein targeting, DLL3 is high on SCLC-A and undetectable in SCLC-I and P, *SSTR2* is highly expressed in SCLC-N and *CECAM5* expression is significantly higher in SCLC-A.

These data can be used as a launchpad for discussions around a trial design exploiting the specific therapeutic vulnerabilities of these discrete SCLC sub-types.

Priority 2: To design and implement an immunotherapy trial in SCLC informed by the recent insights into the unique immunobiology of SCLC that factors in the transcriptional repression of Major Histocompatibility Complex-I (MHC-I) and consider trials of immune therapies that are not dependent on MHC-I presentation of neoantigens. This will be the focus of Working Group 3 (part B).

In the Cancer Cell Line Encyclopedia, SCLC has the lowest expression of multiple MHC-I antigen presenting genes of any cancer[12]. EZH2 a core component of the polycomb repressor complex 2 (PRC2), which transcriptionally represses genes through H3K27 trimethylation and is highly expressed in SCLC. EZH2 expression is negatively correlated with both MHC-I expression and CD8+ T cells in clinical samples. EZH2 inhibition significantly reduces H32K27me3 levels thus upregulating MHC-I and dramatically upregulating IFNγ-induced MHC-I expression. EZH2 inhibition reverses the resistance of SCLC cells to antigen-specific T cell killing.

In line with the high MHC-I expression of the mesenchymal subtype SCLC-I, others demonstrate that a 15% frequency MHC-I high immune-enriched SCLC subset is also non-

neuroendocrine and enriched for EMT signatures and in particular for upregulation of the EMT marker AXL[13]. Importantly, MHC-I high cancers have dramatically more durable responses to ICB than MHC-I low SCLC and are the only variable predictive of survival. Both *TAP1* and *AXL* were among the top genes enriched for both H3K27me3 loss and H3K27ac gain in MHC-I high isogenic cells lines, alongside *TMEM173* that encodes STING. EZH2 inhibition triggered a neuroendocrine to non-neuroendocrine switch with upregulation of MHC-I and activation of dsRNA and dsDNA sensing. STING agonist therapy leads to long-term durable responses in vivo in EZH2 inhibitor treated SCLC cell models. This MHC-I high subtype thus appears to essentially phenocopy SCLC-I.

NK cells are not dependent for cancer cell recognition on neoantigens or MHC expression. In mouse models, whilst CD8+ T cell depletion had no effect on metastatic spread, an absence of NK cells resulted in enhanced metastatic spread[14]. *Cish*$^{-/-}$ mice have hyper-reactive NK cells and metastases were significantly reduced in *Cish*$^{-/-}$ mice harbouring SCLC. Anti-PD-1 treated *Cish*$^{-/-}$ mice had substantially greater tumour control compared with isotype treated *Cish*$^{-/-}$ mice.

These data can be used to support the design of a study to enhance the impact of chemoimmunotherapy standard of care in SCLC by upregulation of MHC-I via EZH2 inhibition and to target SCLC with immune based therapies that are not dependent on MHC-I expression and presentation.

Priority 3: To design and implement a definitive large cell neuroendocrine carcinoma (LCNEC) trial of etoposide/cisplatin (EP) versus gemcitabine/platinum with prospective stratification by retinoblastoma (Rb) status/LCNEC subtype with or without anti-programmed death-1 (PD-1)/ ligand 1 (PD-L1) (anti-PD-1/PD-L1) immune checkpoint blockade (ICB) to determine the optimal chemo(immuno)therapy regimen for each subtype and the relative contribution of the addition of ICB in each subtype.

Such a trial will define the global standard of care in LCNEC in much the same way that the NCRI Hepato-pancreato-biliary (HPB) subgroup did for cholangiocarcinoma starting with ABC-02, a simple and pragmatic trial, which established gemcitabine/cisplatin as the global standard of care. LCNEC is also an important British Thoracic Oncology Group (BTOG) initiative. <u>This will be the focus of Working Group 4.</u>

Two distinct subtypes of LCNEC have been defined – type I and II[15]. The most striking difference between them is that type I LCNEC harbours high level expression of NE genes and markers (*CHGA, SYP, ASCL1, DLL3*) and downregulation of NOTCH signalling whereas type II LCNEC demonstrate NOTCH pathway upregulation and low levels of *ASCL1* and *DLL3*. Type II LCNECs which have low NE gene expression harbour the canonical molecular aberrations of SCLC, p53 mutations and Rb loss, whereas type I LCNEC harbour loss of STK11 or KEAP1, mutations classically associated with NSCLC, as well as p53 mutations. Rb loss and KEAP1 alterations are mutually exclusive. Importantly, type II LCNEC have upregulation of immune related pathways with upregulation of *PDCD1LG2*, *TLR4* and *CTSB* and may thus be more likely to be poised to respond to ICB than type I LCNEC.

In a separate study that subdivided LCNEC by Rb status (Rb wild type (wt) is associated transcriptionally with type I NSCLC as noted above) and analysed outcome using diverse platinum-containing doublets[16]. LCNEC that harboured Rb wt showed significantly longer OS using gemcitabine- and taxane-containing doublets than in those treated with EP or

pemetrexed/platinum. There was no difference in outcome by regimen for LCNEC harbouring Rb1 mutations. In a Cox regression model the HR=2.37 favouring gem/tax over SCLC-EP therapy in those with Rb wt. Rb expression was assessed by IHC and 50% of those tumours with Rb wt had an H score of 0 with a median H score of 50. In patients with LCNEC with an H score ≥50. OS was significantly longer with gemcitabine or taxane doublets than with EP or pem/platinum (median OS 9.6 months, 1.9 months and 4.8 months respectively with HR=4.96 for gem/tax vs PE). No difference in outcome by regimen in LCNEC with Rb H score <50 was seen.

These retrospective data strongly suggest that Rb positive LCNEC are optimally treated with an NSCLC-type regimen such as gemcitabine/platinum (rather than pemetrexed which is known to lack efficacy in NE cancers) and this finding requires urgent prospective validation. It is also imperative to understand the value of the addition of ICB to standard chemotherapy in LCNEC and whether this any benefit is sub-type specific. The definitive answer to these hypotheses can be best be answered in the context of a suitably designed clinical, the design and running of which is the focus of this working group.

Strategic area 3: Immune related adverse events (irAEs) in people with lung cancer

Priority 1: To design and implement a series of predictive biomarkers for severe irAEs alongside efforts to optimise the treatment of those with severe irAEs. This will be the focus of Working Group 5.

With the widespread use of ICB in a common cancer such as lung cancer, irAEs have become a significant burden on both lung cancer patients and the health care systems caring for them. In an analysis of a large nationwide US insurance database over 14,000 people the reported rate of severe irAEs requiring hospitalisation was 3.9% for lung cancer patients but which numerically represented 25% more patients than all other cancers put together (i.e. 55% of all those hospitalised)[17]. Using females with lung cancer on anti-PD-1/PD-L1 as the reference group (males gender was not predictive of irAE-related hospitalization), in regression analyses patients with melanoma and renal cell cancer were significantly less likely to require hospitalization for irAEs. Pneumonitis is a particular risk in lung cancer patients in part related to the high incidence of underlying interstitial lung disease[18]. Death from pneumonitis or infection related to the immunosuppression caused by its treatment are not uncommon outcomes.

This strategic area address the obvious gaps in our knowledge concerning diagnostic work-up, pathogenesis, risk factors, and management of pneumonitis, especially of steroid-refractory cases. We cannot put it any better than as stated in an excellent knowledge gaps and research priorities statement from the ATS: “Well-designed, accurately maintained, and accessible registry data are critically needed, as data from a relatively small number of patients with ICI-pneumonitis and extrapolated from treatment of other pulmonary toxicities and IRAEs are currently being used to define optimal treatment strategies for ICI-pneumonitis. In creating these registry data, care must be taken to include both ICI-pneumonitis and ICI-pneumonitis mimics, and data should be curated by a multidisciplinary team that includes at a minimum representation from immunology, oncology, pulmonology, infectious disease, pathology, and radiology. Careful design of ICI clinical trials, using similar diagnostic and outcome measures, with an effort to include diverse ethnic and racial enrolment, is essential to draw accurate conclusions on ICI pneumonitis from pooled data. This includes prioritization of multi-institutional studies with diverse, multidisciplinary involvement. Establishing new or increasing the accessibility of existing central databases…”[19].

Predictive biomarkers for those at high risk are essential and we can build on the expertise that the UK has already has on germline predisposition (IL-7 SNPs)[20,21] and immune based cell biomarkers (lack of pre-therapy Bregs)[22] to develop and validate clinical grade biomarkers for accurate irAE prediction.

Mesothelioma and Thymoma Study Group

The UK has an enviable clinical and translational track record in mesothelioma with previously a highly successful NCRI subgroup. We feel that this subgroup should constitute a separate study group within the NCRI. Whether this should incorporate thymic malignancies or whether the latter should constitute a discrete stand-alone group is up for discussion. It is beyond the remit of this document to propose specific working groups for these areas.

We strongly feel that a new chair be sought for this study group and following the NCRI over-arching strategy that the working groups should be generated as a result of a strategy and priority setting workshop including all key stakeholders dedicated to defining key areas of interest and relevance to clinical and translational research in mesothelioma and thymic malignancies in the UK.

NCRI Cross-cutting priority

Identify barriers resulting in a lack of diversity in clinical trials and propose solutions to improve equality, diversity, and inclusion.

Barriers resulting in a lack of diversity in clinical trials across cancer types has been raised as an issue in many of NCRI's discussions with researchers. For this reason, this priority will be addressed collaboratively in a working group comprising experts from across NCRI Groups. This priority aims to establish the reasons behind a lack of diversity in clinical trials and provide solutions to increase participation of a diverse cohort of patients in future studies. A working group will address the common issues across the NCRI, as well as identifying cancer-type specific barriers, and produce guidelines on the steps to take to improve the inclusion of patients from a range of backgrounds into clinical trials from their inception. More details on this working group will be decided in due course.

Next steps

Working groups addressing the highlighted tasks are currently being formed. These groups will be made up of the experts needed to address each research question. To be the first to hear about opportunities to join these working groups please sign up to the NCRI Lung Network. The progress of these working groups will be published in the annual reports and triennial review of NCRI Lung Group. These can be found on the NCRI website. Members of the NCRI Lung Network will also be updated periodically on the progress of the group.

Please get in touch if you have any questions or comments regarding this report or if you are interested in joining one of the NCRI Networks, the NCRI Consumer Forum or our NCRI Early Career Researcher Forum.

References

Working Group 1

1. **Zhang R**, Shen S, Wei Y, Zhu Y, Li Y, Chen J, et al. A Large-Scale Genome-Wide Gene-Gene Interaction Study of Lung Cancer Susceptibility in Europeans With a Trans-Ethnic Validation in Asians. J Thorac Oncol. 2022 Aug;17(8):974-990.
2. **Myers R**, Brauer M, Dummer T, Atkar-Khattra S, Yee J, Melosky B, Ho C, McGuire AL, Sun S, Grant K, Lee A, Lee M, Yuchi W, Tammemagi M, Lam S. High-Ambient Air Pollution Exposure Among Never Smokers Versus Ever Smokers With Lung Cancer. J Thorac Oncol. 2021 Nov;16(11):1850-1858.
3. **Beelen R**, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, et al. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. Lancet. 2014 Mar 1;383(9919):785-95.
4. **C. Swanton,** W. Hill, E. Lim, C. Lee, C.E. Weeden, M. Augustine, K. Chen, F. Kuan, F. Marongiu, F. Rodrigues, H. Cha, T. Jacks, M. Luchtenborg, I. Malanchi, J. Downward, C. Carlsten, A. Hackshaw, K.R. Litchfield, J. DeGregori, M. Jamal-Hanjani. LBA1 - Mechanism of action and an actionable inflammatory axis for air pollution induced non-small cell lung cancer: Towards molecular cancer prevention. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Working Group 2

5. **Stanková K**, Brown JS, Dalton WS, Gatenby RA. Optimizing Cancer Treatment Using Game Theory: A Review. JAMA Oncol. 2019 Jan 1;5(1):96-103.
6. **Oren Y**, Tsabar M, Cuoco MS, Amir-Zilberstein L, Cabanos HF, Hütter JC, et al. Cycling cancer persister cells arise from lineages with distinct programs. Nature. 2021 Aug;596(7873):576-582.
7. Noronha A, Belugali Nataraj N, Sang Lee J, Zhitomirsky B, Oren Y, et al. AXL and error-prone DNA replication confer drug resistance and offer strategies to treat EGFR-mutant lung cancer. Cancer Discov. 2022 Jul 27:CD-22-0111.
8. **West J**, You L, Zhang J, Gatenby RA, Brown JS, Newton PK, Anderson ARA. Towards Multidrug Adaptive Therapy. Cancer Res. 2020 Apr 1;80(7):1578-1589.

Working Group 3

9. **Gay CM**, Stewart CA, Park EM, Diao L, Groves SM, Heeke S, et al. Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. Cancer Cell. 2021 Mar 8;39(3):346-360.e7.
10. **Mollaoglu G**, Guthrie MR, Böhm S, Brägelmann J, Can I, Ballieu PM, et al. MYC Drives Progression of Small Cell Lung Cancer to a Variant Neuroendocrine Subtype with Vulnerability to Aurora Kinase Inhibition. Cancer Cell. 2017 Feb 13;31(2):270-285.
11. **Owonikoko TK**, Niu H, Nackaerts K, Csoszi T, Ostoros G, Mark Z, et al. Randomized Phase II Study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line Therapy for SCLC: Primary and Correlative Biomarker Analyses. J Thorac Oncol. 2020 Feb;15(2):274-287.
12. **Burr ML**, Sparbier CE, Chan KL, Chan YC, Kersbergen A, Lam EYN, et al. An Evolutionarily Conserved Function of Polycomb Silences the MHC Class I Antigen Presentation Pathway and Enables Immune Evasion in Cancer. Cancer Cell. 2019 Oct 14;36(4):385-401.e8.
13. **Mahadevan NR**, Knelson EH, Wolff JO, Vajdi A, Saigí M, Campisi M, et al. Intrinsic Immunogenicity of Small Cell Lung Carcinoma Revealed by Its Cellular Plasticity. Cancer Discov. 2021 Aug;11(8):1952-1969.

14. **Best SA**, Hess JB, Souza-Fonseca-Guimaraes F, Cursons J, Kersbergen A, Dong X, Rautela J, Hyslop SR, Ritchie ME, Davis MJ, Leong TL, Irving L, Steinfort D, Huntington ND, Sutherland KD. Harnessing Natural Killer Immunity in Metastatic SCLC. J Thorac Oncol. 2020 Sep;15(9):1507-1521.

Working Group 4

15. **George J**, Walter V, Peifer M, Alexandrov LB, Seidel D, Leenders F, et al. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. Nat Commun. 2018 Mar 13;9(1):1048.
16. **Derks JL**, Leblay N, Thunnissen E, van Suylen RJ, den Bakker M, Groen HJM, Smit EF, Damhuis R, van den Broek EC, Charbrier A, Foll M, McKay JD, Fernandez-Cuesta L, Speel EM, Dingemans AC; PALGA-Group. Molecular Subtypes of Pulmonary Large-cell Neuroendocrine Carcinoma Predict Chemotherapy Treatment Outcome. Clin Cancer Res. 2018 Jan 1;24(1):33-42.

Working Group 5

17. **Kalinich M**, Murphy W, Wongvibulsin S, Pahalyants V, Yu KH, Lu C, Wang F, Zubiri L, Naranbhai V, Gusev A, Kwatra SG, Reynolds KL, Semenov YR. Prediction of severe immune-related adverse events requiring hospital admission in patients on immune checkpoint inhibitors: study of a population level insurance claims database from the USA. J Immunother Cancer. 2021 Mar;9(3):e001935.
18. **Chen X**, Li Z, Wang X, Zhou J, Wei Q, Jiang R. Association of pre-existing lung interstitial changes with immune-related pneumonitis in patients with non-small lung cancer receiving immunotherapy. Support Care Cancer. 2022 Aug;30(8):6515-6524.
19. **Sears CR**, Peikert T, Possick JD, Naidoo J, Nishino M, Patel SP, Camus P, Gaga M, Garon EB, Gould MK, Limper AH, Montgrain PR, Travis WD, Rivera MP. Knowledge Gaps and Research Priorities in Immune Checkpoint Inhibitor-related Pneumonitis. An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med. 2019 Sep 15;200(6):e31-e43.
20. **Taylor CA**, Watson RA, Tong O, Ye W, Nassiri I, Gilchrist JJ, de Los Aires AV, Sharma PK, Koturan S, Cooper RA, Woodcock VK, Jungkurth E, Shine B, Coupe N, Payne MJ, Church DN, Naranbhai V, Groha S, Emery P, Mankia K, Freedman ML, Choueiri TK, Middleton MR, Gusev A, Fairfax BP. IL7 genetic variation and toxicity to immune checkpoint blockade in patients with melanoma. Nat Med. 2022 Dec;28(12):2592-2600.
21. **Chin IS**, Khan A, Olsson-Brown A, Papa S, Middleton G, Palles C. Germline genetic variation and predicting immune checkpoint inhibitor induced toxicity. NPJ Genom Med. 2022 Dec 24;7(1):73.
22. **Patel AJ**, Willsmore ZN, Khan N, Richter A, Naidu B, Drayson MT, Papa S, Cope A, Karagiannis SN, Perucha E, Middleton GW. Regulatory B cell repertoire defects predispose lung cancer patients to immune-related toxicity following checkpoint blockade. Nat Commun. 2022 Jun 7;13(1):3148.

Appendix A - NCRI Lung Group priority setting process

Agenda setting

- After engaging with the wider community, the NCRI sets the agenda along with people in leadership roles within NCRI Lung Group for the following discussions.

Discussion

- Virtual sessions are held with participants from a range of locations, sectors and disciplines.
- The sessions allow for discussion of the overarching challenges, opportunities and gaps as well as specific issues and areas of unmet need in the field.

Prioritisation

- NCRI and the group Chair use the intelligence collected from the discussions to identify the research priorities.
- NCRI and the Group Chair decide which priorities will be addressed first through the establishment of working groups for the Lung Group. For the Mesothelioma and Thymoma study group, priorities will be established and worked on as concurrent projects.

Launch

- The priorities for the overall Lung Group are disseminated to the research community by NCRI.

Working groups

- Working groups are established to address the first five priorites.
- A chair for each working group is recruited, followed by working group members with the skills and expertise needed to address the specific priority.
- When one working group finishes, capacity is transfered to the next task.
- The Mesothelioma and Thymoma study group projects will be delivered concurrently by specialists recruited to the study group.

Monitoring progress

- Working groups and the Study Group will complete an implementation plan detailing how they will achieve the aims of the priority including information on inputs, activities, outputs, outcomes and impact.
- Working groups and the study group will regularly update a progress report using SMART principles.
- Implementation plans will be fed through to a review panel every year to review and monitor progress.
- NCRI Lung Group will complete a triennial review which will be assessed by an expert panel.

Appendix B - NCRI Lung Group priority discussion contributors

The NCRI Lung Group developed their strategic priorities through discussions with professionals from a range of sectors and disciplines, including NCRI Consumer Forum members, early career researchers and NCRI Partners, as well as members of the NCRI Strategy Advisory Group (SAG). We thank all contributors for their invaluable input into these discussions and the subsequent priorities addressing the most pressing needs in Lung research today.

Strategy session contributors

Abbie Fearon
Acacio Maia
Alastair Greystoke
Alexander Renziehausen
Alexis Barr
Alexis Webb
Alison Finall
Amanda Skinner
Amit Grover
Ana Julett
Andrea Corkhill
Andrew Mumford
Andrew Wight
Ane Appelt
Animesh Saha
Anna Minchom
Anshuman Chaturvedi
Arjun Nair
Azeem Saleem
Babu Naidu
Barry Laird
Caroline Kelly
Catriona Mayland
Cheryl Routley
Christopher Barton
Christy Toms
Clare Gardiner
Corinne Finn
Daniel Murphy
David Baldwin
David Farrugia
Debra Josephs
Debra Montague
Edmond Murphy
Ella Daniels
Emma Kinloch
Emma Odowd
Evangelos Katsampouris
Fergus Gleeson
Fiona Blackhall
Fiona Parker
Frank McCaughan
Frank McDermott
Gary Cook
Gary Middleton
Geoffrey Higgins
George Ntentas
Georgiou Alexandros
Gerry Hanna
Gillian Prue
Glenn Edge
Graham Nicoll
Helen Pitman
Iain Phillips
Igor Vivanco
Ik Shin Chin
Janette Rawlinson
Joshua Savage
Julian Dunnett
Kam Zaki
Kamalram Thippu Jayaprakash
Karen Clayton
Kate Quirk
Kathleen Bodey
Katy Shearer
Kevin Franks
Khamael Al-Battat
Kieran Prior
Laura Chambers
Laura Farrelly
Lauren Marks
Leah Holtam
Leanne Ashrafian
Leanne Harlign
Lee Campbell
Leqi Tang
Louise Medley
Lucinda Billingham
Lynn Calman
Magenta Black
Mary O'Brien
Matthew Callister
Matthew Hatton
Matthew Johnson
Michael Davies
Michael Lind
Mulyati Mohamed
Nanita Dalal
Nichola Gale
Nicholas Counsell
Nicola Keat
Peter Henley
Philip Crosbie
Raj Shrimali
Rebecca Landy
Richard Ballerand
Richard Marais
Riyaz Shah
Robert Rintoul
Robin Wickens
Rowena Sharpe
Rupesh Robinson-Vyas
Ruth Haley
Ryan Langdon
Sally Hayton
Sam H Ahmedzai
Sam Janes
Samantha Harrison
Samavia Raza
Sandy Jack
Sanjay Popat
Sarah Jevons
Siva Tharshini Ramalingam
Tara McKay
Thi Vu
Timothy Mitchell
Virginia Sherborne
Yolanda Thompson
Yvonne Summers

Advancing Cancer Research Together

Report produced by:

Gary Middleton, Chair of the NCRI Lung Group
Abbie Fearon, Senior Programme Manager (Strategic Projects), NCRI
Anna Fry, Programme Manager, NCRI
Nicola Keat, Head of Groups, NCRI

National Cancer Research Institute
2 Redman Place,
London, E20 1JQ

T: +44 (0)20 3469 8798
F: +44 (0)20 3014 7658

info@ncri.org.uk
www.ncri.org.uk