European Journal of Cancer 99 (2018) 20–27

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Review

KRAS: Reasons for optimism in lung cancer

C.R. Lindsay [a,b,c,*], M. Jamal-Hanjani [c,d], M. Forster [c,d], F. Blackhall [a,b,c]

[a] Division of Molecular and Clinical Cancer Sciences, University of Manchester, Manchester, UK
[b] Department of Medical Oncology, The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX, UK
[c] Cancer Research, Lung Cancer Centre of Excellence London and Manchester, UK
[d] Department of Oncology, University College of London Hospital and UCL Cancer Institute, London, UK

Received 30 November 2017; received in revised form 21 March 2018; accepted 13 May 2018

KEYWORDS
KRAS;
NSCLC;
RAS;
Non-small cell lung cancer;
G12C

Abstract Despite being the most frequent gain-of-function genetic alteration in human cancer, *KRAS* mutation has to date offered only limited potential as a prognostic and predictive biomarker. Results from the phase III SELECT-1 trial in non-small cell lung cancer (NSCLC) recently added to a number of historical and more contemporary disappointments in targeting *KRAS* mutant disease, including farnesyl transferase inhibition and synthetic lethality partners such as STK33. This narrative review uses the context of these previous failures to demonstrate how the knowledge gained from these experiences can be used as a platform for exciting advances in NSCLC on the horizon. It now seems clear that mutational subtype (most commonly *G12C*) of individual mutations is of greater relevance than the categorical evaluation of *KRAS* mutation presence or otherwise. A number of direct small molecules targeted to these subtypes are in development and have shown promising biological activity, with some in the late stages of preclinical validation.

RAS is the most common oncogene in cancer, with its mutation occurring in approximately 30% of all cases [1]. This rate of mutation can vary substantially in different cancer types, with its most frequent rates of modification found to affect *KRAS* in pancreatic, colorectal and lung adenocarcinomas [2–4]. Its function and importance as a GTPase is evidenced by its central coordinating role in the cell, where it connects upstream signals from cell surface receptors such as FGFR, EGFR and ERBB2-4 to downstream cancer-associated

* *Corresponding author*: Division of Molecular and Clinical Cancer Sciences, University of Manchester, Manchester, UK. Tel.: +44 (0)161 446 3745.
E-mail address: colin.lindsay@manchester.ac.uk (C.R. Lindsay).

https://doi.org/10.1016/j.ejca.2018.05.001
0959-8049/

pathways such as MAPK, PI3K and Ral [5]. Introduction of *RAS* mutations in mice using either chemical and/or environmental induction or genetic modification has been shown to induce cancers such as lung adenocarcinoma and melanoma, with perhaps the most well-characterised lung cancer model demonstrating that lung-specific *KRAS G12D* expression can allow mediation of both tumor initiation and multiplicity [6–9]. More recent studies of tumor heterogeneity have identified *RAS* mutations as both 'truncal' and 'branch' drivers, depending on genetic subtype and the cancer cell context [10].

Predominant isoforms and genetic subtypes of mutant *RAS* vary with cancer histology. In terms of isoforms, *NRAS* is the most frequently mutated in melanoma, whereas *KRAS* mutation occurs most frequently in adenocarcinomas [11]. Mutant HRAS occurs in a small percentage of head and neck squamous cancers [12]. Why certain cancers are driven by specific RAS isoforms remains unknown, and it is unclear whether this variation occurs as a consequence of cell lineage and/or other factors. In lung cancer, *KRAS* mutation occurs in 20–40% of adenocarcinomas, with codons 12 and 13 mutations being the most frequent, of which the most common subtypes are *G12C*, *G12V* and *G12D*. *G12C* and *G12V* have been epidemiologically associated with a smoking history, whereas the *G12D* subtype occurs more frequently in never smokers [13].

Following its description as a key cancer mutation in 1982, clinical investigation of *RAS* has been blighted by conflicting results regarding its prognostic relevance as well as unsuccessful clinical trial programmes, most recently evidenced by the large phase III SELECT-1 trial, which showed no improvement in progression-free or overall survival with the addition of selumetinib, an oral small molecule MEK inhibitor, to 2nd line docetaxel chemotherapy in advanced *KRAS* mutant NSCLC [14,15]. This is particularly disappointing as lung cancer is the most common cause of cancer-associated mortality in the UK and worldwide, with treatment for its most common histological category, NSCLC, offering only limited survival gains in both early and metastatic disease settings [16,17]. This translational review will argue that these past difficulties are by no means representative of *KRAS* irrelevance, but more a consequence of insufficient understanding of its biology coupled with sub-optimal study design. Here, strategies to improve delineation of the prognostic and predictive potential of *KRAS* as a biomarker will be presented, as well as reasons to be optimistic for the future success of its targeting in lung cancer.

1. Biomarker challenges

Within phase I of the Cancer Research UK Stratified Medicine Programme (SMP1), *KRAS* mutation was detected in 326 of 984 lung adenocarcinomas (33.1%) [personal communication], a figure which is higher than a prior large American study reporting *KRAS* mutations in 21% of 482 adenocarcinomas [18]; these percentages can reasonably be assumed to be the upper and lower limits of normal for *KRAS* mutation incidence in lung adenocarcinoma. In SMP1 non-squamous cases, *KRAS* mutations of codons 12 and/or 13 'not otherwise specified' were noted in 101 patients, leaving smoking-associated mutational subtypes to represent at least 56% of cases, most commonly *G12C* (77/225 samples, 34.2%) and *G12V* (48/225 samples, ~21.3%), while the *G12D* subtype (44/225 samples, ~19.6%) has been closely associated with never smokers [13]. The remaining cases can be constituted by a wide variety of mutational subtypes, involving usually codon 12 or codon 13 (Fig. 1).

Clinical reports from the past 5 years have progressively demonstrated the importance of interrogating *KRAS* mutation beyond a simple categorisation of whether it is present or not [19,20]. Its historical study as a prognostic biomarker in lung cancer frequently concluded, in line with its important biological context, that its presence conferred diminished survival. Many of these reports were limited by small numbers of patients, retrospective data and lack of a validation set and/or multivariate analysis, but subsequent meta-analyses offered similar conclusions [21,22]. However, an examination in 2013 by the LACE bio-collaborative group offered the most comprehensive single study assessment of this question with conflicting results. In greater than 1500 *KRAS*-tested patients recruited from four key lung

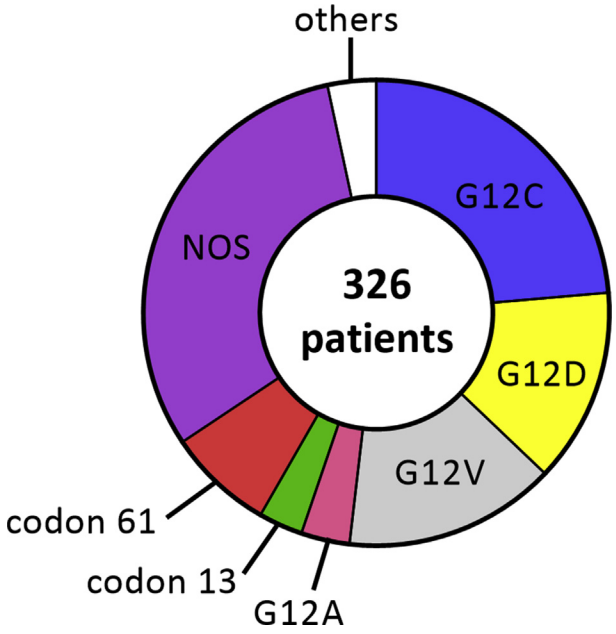

Fig. 1. *KRAS* mutational subtypes of lung adenocarcinomas analysed in phase I of the Cancer Research UK stratified medicine programme. NOS = mutation of KRAS codon 12 and/or 13 not otherwise specified.