ORIGINAL ARTICLE

Genomic Landscape of NSCLC in the Republic of Ireland

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ABSTRACT

Introduction: The identification of genomic "targets" through next-generation sequencing (NGS) of patient's NSCLC tumors has resulted in a rapid expansion of targeted treatment options for selected patients. This retrospective study aims to identify the proportion of patients with advanced NSCLC in the Republic of Ireland whose tumors harbor actionable genomic alterations through broad NGS panel testing.

Methods: Institutional review board approval was obtained before study initiation. Patients with NSCLC whose tumors underwent genomic testing through the largest available NGS panel at a nationally funded Cancer Molecular Diagnostics laboratory (St. James's Hospital) between June 2017 and June 2022 were identified. Patient demographics and tumor-related data were collected by retrospective review from all cancer centers in Ireland, referring to the Cancer Molecular Diagnostics laboratory. A total of 203 (9%) tumor samples were excluded due to insufficient neoplastic cell content. Genomic data were collected through retrospective search of Ion Reporter software. The spectrum and proportion of patients with oncogenic driver mutations were evaluated using descriptive statistics (SPSS version 29.0).

Results: In total, 2052 patients were identified. Patients were referred from 23 different hospital sites and all four geographic regions (Leinster = 1091, 53%; Munster = 763, 37.2%; Connacht = 191, 9.3%; Ulster = 7, 0.3%). Median age was 69 (range: 26–94) years; 53% were male. The most common tumor histologic subtype was adenocarcinoma (77%, n = 1577). An actionable genomic alteration was identified in 1099 cases (53%), the most common of which was *KRAS* (n = 657, 32%). Less frequently, NSCLC tumors harbored the following: *MET* exon 14 skipping (n = 53, 2.6%), *MET* amplification (n = 26, 1.3%), *EGFR* (n = 181, 8.8%), *HER2* (n = 35, 1.7%), and *BRAF* (n = 72, 3.5%) mutations. Fusions were detected in 76 patients (3.7%) including *ALK* (n = 44, 58%), *RET* (n = 11, 14.5%), *ROS1* (n = 16, 21%), and *FGFR3* (n = 5, 6.6%), whereas no *NTRK* fusion was identified. Co-alterations were detected in 114 patients (5.6%), the most common of which was *KRAS/PIK3CA* (n = 19, 17%), *EGFR/PIK3CA* (n = 10, 8.5%), and *KRAS/IDH1* (n = 9, 8%). Other co-alterations of interest identified included *KRAS G12A/ROS1* fusion (n = 1) and *KRAS G12C/BRAF G469A* (n = 2).

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Conclusions: This is the first retrospective study to comprehensively characterize the genomic landscape of NSCLC in Ireland, using the broadest available NGS panel. Actionable alterations were identified in 53.4% of the patients, and *KRAS* was the most common oncogenic driver alteration. Our study revealed a lower prevalence of patients whose tumor harbors *ALK*, *ROS1*, and *RET* fusions, compared with similar data sets.

Keywords: Non–small cell lung cancer; Biomarkers; Genomic landscape; Ireland

Introduction

NSCLC is the leading cause of cancer-related mortality in men and women worldwide, including the Republic of Ireland.[1,2] Although there has been a notable lack of treatment options historically, this has dramatically changed since the discovery of driver oncogenes as biomarkers of response to "targeted" therapies in NSCLC. Sensitivity to these targeted treatments such as *EGFR* tyrosine kinase inhibitors (TKIs) or *ALK* inhibitors can differ between patients despite the presence of an oncogenic driver suggesting the presence of marked genomic and clinical heterogeneity.[3,4]

Advances in molecular profiling and sequencing techniques has catalyzed the discovery of oncogenic drivers and enhanced our improved understanding of the complex interplay between genomic alterations. In the Republic of Ireland, there are currently two laboratories supported by the National Cancer Control Programme aimed at delivering molecular testing nationally, the Cancer Molecular Diagnostics (CMD) Laboratory at St James's Hospital, Dublin, which has access to the broadest available next-generation sequencing (NGS) panel, and the Molecular Pathology Laboratory at Beaumont Hospital and Royal College of Surgeons in Ireland. Furthermore, the availability of targeted treatments is constantly evolving with a growing list of different targeted therapies currently reimbursed and others available through clinical trial or compassionate access programs.

The frequency of driver oncogenes such as *ALK*, *ROS1*, *BRAF*, *RET*, *MET* amplification, *MET* exon 14 skipping, and *HER2* in the Republic of Ireland is not currently known. To the best of our knowledge, this is the first retrospective study to fully characterize the genomic landscape of NSCLC evaluated by the broadest available NGS panel in the Republic of Ireland.

Materials and Methods

Patients

Patients with NSCLC referred to the CMD laboratory for oncomine panel testing were included. Only tissue specimens with adequate tumor content for molecular profiling defined as greater than or equal to 10% were included. Each institution has an institution-specific workflow for genomic testing. For instance, in some locations, patients with a histologic NSCLC diagnosis will undergo a standard lung mutation panel (Supplementary Fig. 1). If no alteration is detected, samples are sent to St. James's Hospital CMD laboratory to undergo central oncomine panel testing, whereas other institutions send their NSCLC tumor samples directly to the CMD laboratory for genomic testing. Basic anonymized patient demographics and clinical information were collected through retrospective review such as tumor histology, age, sex, and referring hospital. Patients with NSCLC whose tumors underwent genomic testing through the largest available NGS panel (Oncomine: 35 hotspot genes, 23 fusion drivers, 19 copy number variants) at a nationally funded molecular laboratory were identified. The primary objective of the study is to report the prevalence of oncogenic driver alterations in the Irish population. We subclassified oncogenic alterations according to whether there was a targeted treatment available. The definition of lung cancer in the young is uncertain and ranges from 35 to 55 years in previously published studies.[5–13] We used a cutoff of less than or equal to 50 years to define young people with NSCLC in our cohort. The secondary objective was to explore subgroups and define co-alterations in a single tumor where present.

Ethical Considerations

Institutional approval by the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee (approved on September 27, 2022) for the secondary processing of anonymized genomic data was obtained before study initiation. A waiver for informed consent was obtained because anonymized data were collected retrospectively according to institutional guidelines. No information capable of identifying patients was collected.

Molecular Analysis

The Oncomine Focus Library Kit assay from Life Technologies follows the same clinically validated workflow as for standard-of-care individual gene assays.

Library preparation was performed according to the Oncomine Focus protocol (Thermo Fisher Scientific, Waltham, MA), with the following modifications. The input material uses either 10 ng of DNA or RNA from a total nucleic acid sample. Library preparation was

performed using the manual library preparation protocol automated on a robotic preparation system (Hamilton Robotics). Normalization was performed quantifying each library using the Ion Library TaqMan Quantitation kit (Thermo Fisher Scientific) and subsequently balancing to equimolar concentrations. Sequencing was performed using the Ion Torrent 530 sequencing chips and reagents with templating and sequencing using the Ion Chef and Ion Torrent S5 instruments, respectively. Analysis of mutations and fusions was performed using the Oncomine Focus version 2.7 DNA and Fusion workflow with Ion Reporter version 5.16.4.0 software (Thermo Fisher Scientific,). We note that the mutation analysis differs from standard laboratory analysis which uses validated protocols to analyze standard-of-care variants only.

Statistics

Statistical analysis was performed with genomic information from 2052 tumor samples. Descriptive statistics were used to describe the genomic landscape. Categorical variables were presented as total frequency and percentage with median and range used for continuous variables. Frequencies of mutations in different groups were compared using chi-square or Fisher exact tests, and a p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 29.0.

Results

From June 2017 to June 2022, NSCLC tumors from 2264 patients were identified. The primary reason for exclusion was insufficient tumor content for molecular profiling (Fig. 1). Patients were referred from 23 different hospital sites, and all four geographic regions (Leinster = 53.2%, n = 1091; Munster = 37.2%, n=763; Connacht = 9.3%, n = 191; Ulster = 0.3%, n = 7). Median age was 69 (range: 26–94) years; 53% were male. The most common tumor histology was adenocarcinoma (77%, n = 1577). Most common mutations identified were *KRAS*, *EGFR*, *BRAF*, *MET* exon 14 skipping, and *PIK3CA* with an overall prevalence of 32%, 8.8%, 3.5%, 2.6%, and 2.5%, respectively (Table 1). A clinically significant alteration was identified in 1096 cases (53.4%) (Fig. 2). The prevalence of oncogenic drivers was consistent across provinces except for a reduced prevalence of *KRAS* in the Connacht population compared with Leinster, Munster, and Ulster; however, this may have been influenced by smaller study numbers (23% versus 33.6% versus 31.4% versus 42.9%, $p < 0.001$) (Fig. 3).

Less frequently, NSCLC tumors harbored *MET* amplification (n = 26, 1.3%), *HER2* (n = 35, 1.7%), and

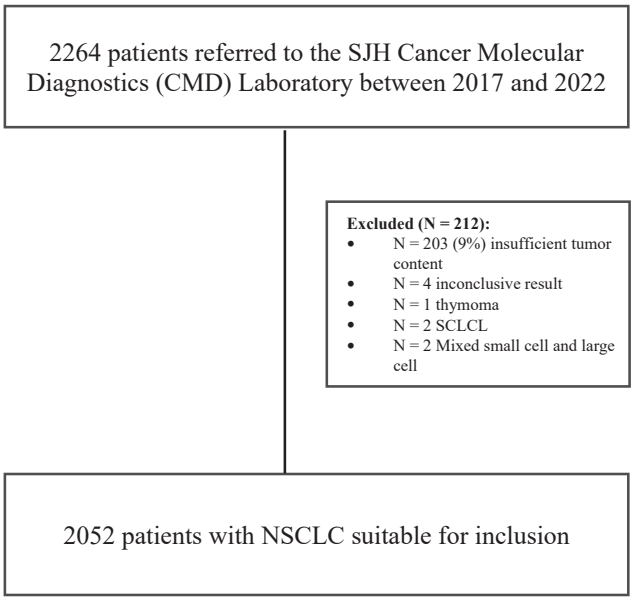

Figure 1. Overview of sample selection process. SCLCL, small cell lung cancer; SJH, St. James's Hospital.

NRAS (n = 11, 0.5%). Fusions were detected in 76 patients (3.7%), including *ALK* (n = 44, 58%), *RET* (n = 11, 14.5%), *ROS1* (n = 16, 21%), and *FGFR3* (n = 5, 6.6%), whereas no *NTRK* fusion was identified. In the adenocarcinoma cohort, most frequently identified mutations were *KRAS* and *EGFR* mutations with a prevalence of 34.6% and 10%, respectively. Of the 61 patients with squamous cell histology, the most common mutation detected was a *PIK3CA* mutation accounting for 9.8% (n = 6) of the cases.

Young patients (≤50 y old) accounted for 129 NSCLC tumor samples and were more likely to harbor a clinically significant alteration; however, this was not statistically significant (n = 78, 69%; $p = 0.097$) (Table 2). Frequently detected alterations included *KRAS* mutations, fusions/rearrangements (*ALK*, *RET*, *ROS1*), and *EGFR* mutations with an overall prevalence of 28.8%, 15.8% (9.4%, 3.6%, 2.9%), and 10.1%, respectively. *EGFR* mutations detected in young people with NSCLC included exon 19 deletion (n = 8, 6.2%), L858R (n = 4, 3.1%), and G719S (n = 1, 0.8%). Furthermore, 12 patients below or equal to 35 years old were diagnosed with having NSCLC. Of these, 11 (92%) had a genomic alteration, including fusion rearrangement at five (*ALK* = 4, *RET* = 1), *KRAS* at three (G12C = 1, G12D = 2), *EGFR* exon 19 del at two, and *MET* amplification at one (Supplementary Table 1). Patients above or equal to 80 years of age accounted for 229 (11%) tumors, 40% had no alteration detected, and KRAS accounted for 17.5%, with fusion rearrangements accounting for less than 1% (n = 2). Females were more likely to harbor a clinically significant alteration

Table 1. Prevalence of Genomic Aberrations by Histology and Overall Cohort

Genomic Alteration	Adenocarcinoma n = 1577 (77%)	Squamous n = 61 (3%)	Carcinoma Likely NSCLC n = 406 (20%)	Overall N = 2052 (%)
Wild type	592 (37.6)	48 (78.7)	199 (49)	853 (41.6)
KRAS	546 (34.6)	3 (4.9)	107 (26.4)	657 (32)
EGFR	157 (10)	-	24 (5.9)	181 (8.8)
Fusion (*ALK*/*ROS1*/*RET*/ *FGFR3*)	65 (4.1)	1 (1.6)	11 (2.7)	76 (3.7)
BRAF	55 (3.5)	1 (1.6)	16 (3.9)	72 (3.5)
MET exon 14 skipping	43 (2.7)	-	10 (2.5)	53 (2.6)
HER2/*ERBB2*	25 (1.6)	2 (3.3)	8 (2)	35 (1.7)
PIK3CA	28 (1.8)	6 (9.8)	16 (3.9)	51 (2.5)
JAK2	1 (0.1)	-	1 (0.2)	2 (0.1)
MET amplification	20 (1.3)	-	6 (1.5)	26 (1.3)
NRAS	9 (0.6)	-	2 (0.5)	11 (0.6)
ERBB3	4 (0.3)	-	-	4 (0.2)
FGFR2	3 (0.2)	-	1 (0.2)	4 (0.2)
HRAS	3 (0.2)	-	2 (0.5)	5 (0.2)
2 or more genes	93 (5.9)	1 (1.6)	20 (5)	114 (5.6)

compared with males (60.6% versus 46.9%, $p < 0.001$) (Table 3). *KRAS* mutations were more common among females (35.8% versus 28.6%, $p = 0.001$) in addition to *EGFR* mutations (12.3% versus 5.7%, $p < 0.001$), including exon 19 deletion at 53 (5.6%), L858R at 3.4%, exon 20 insertion mutations at 18 (1.9%), and other at six (<1%).

For *KRAS*, the most frequently mutated alleles were G12C (n = 255, 38.6%) followed by G12V (n = 116, 17.7%) and G12D (n = 116, 17.7%). Other less

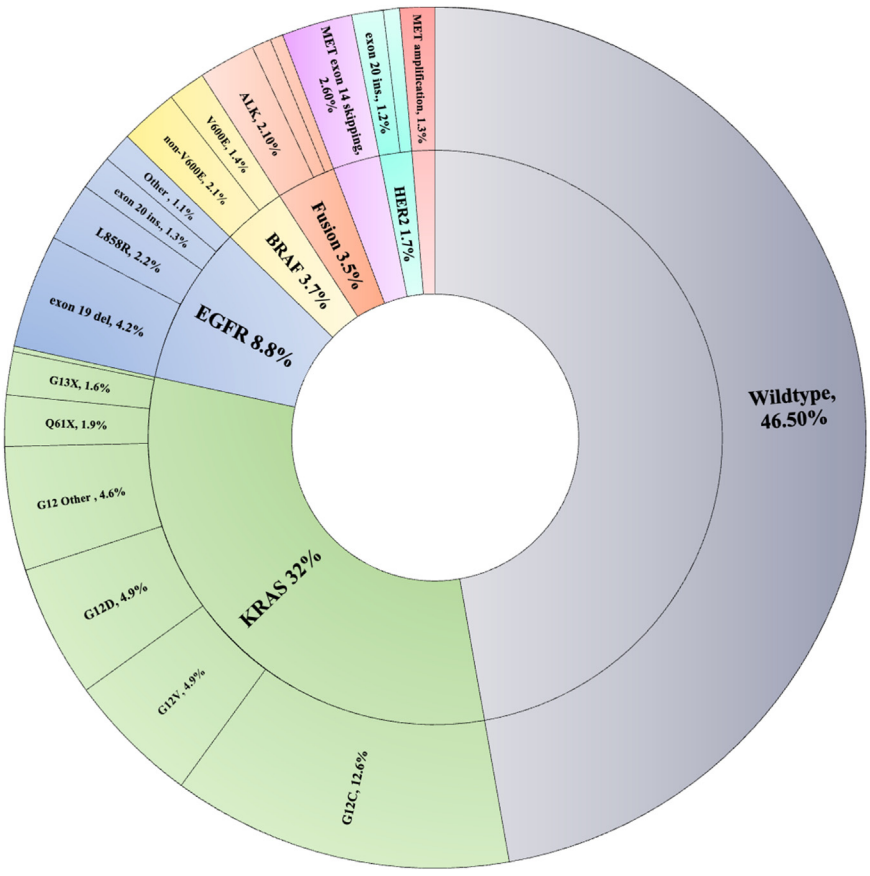

Figure 2. Prevalence of common oncogenic driver alterations in the Irish population with NSCLC (N = 2052).

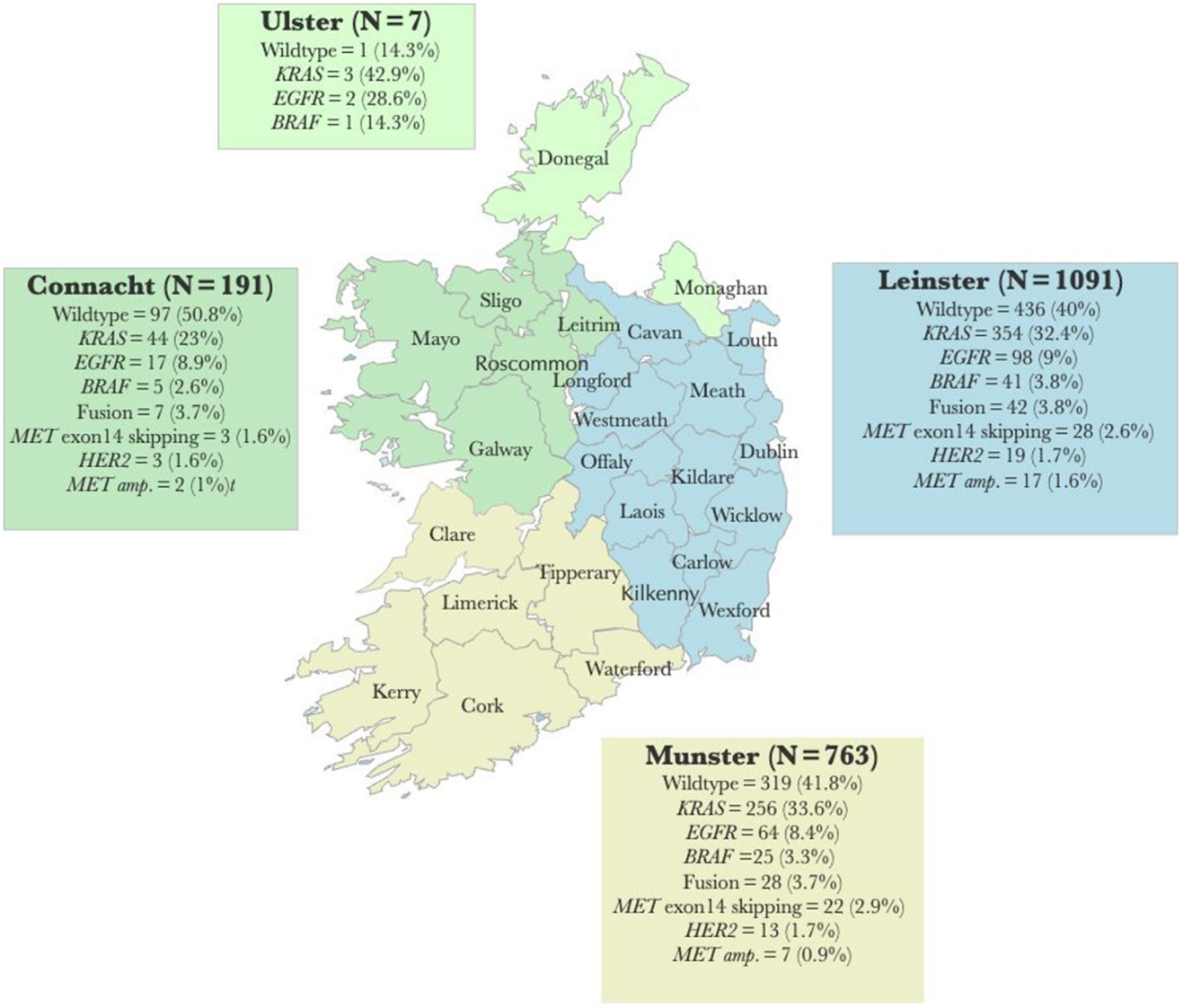

Figure 3. Patient population (N) according to province and prevalence of common driver oncogenes by province.

frequently affected codons included 13 (n = 33, 5%, G13C = 20, 3.3%, G13D = 11, 1.7%, G13V = 2, 0.3%) and 61 (n = 39, 6%, Q61H = 30, 4.6%, Q61L = 9, 1.4%). The most common mutation for *EGFR* was an exon 19 deletion (n = 87, 48.1%) followed by L858R (n = 45, 24.9%) and exon 20 insertion (n = 26, 14.4%). Rare sensitizing *EGFR* mutations including L861Q, G719X, and S768I were detected in 10, nine and two cases, respectively. Of the 76 *BRAF* mutations detected, class I mutations accounted for 28 cases (38.9%), class II for 20

Table 2. Prevalence of Oncogenic Drivers by Age

	<=50 years old n = 129 (%)	>50 years old n = 1923 (%)	*P*-value
Clinically significant alteration	78 (60.5)	1018 (52.9)	0.097
KRAS	37 (28.7)	620 (32.2)	0.402
EGFR	13 (10.1)	168 (8.7)	0.603
BRAF	4 (3.1)	68 (3.5)	0.795
MET exon 14 skipping	-	53 (2.8)	0.076
MET amplification	2 (1.6)	24 (1.2)	0.677
HER2	3 (2.3)	32 (1.7)	0.480
Fusions (ALK/ROS1/RET/FGFR)	19 (14.7)	57 (3)	<0.001

Table 3. Prevalence of Oncogenic Drivers by Sex

	Male N = 1092 (%)	Female N = 950 (%)	*P*-value
Clinically significant alteration	511 (46.8)	577 (60.7)	<0.001
KRAS	312 (28.6)	340 (35.8)	0.001
EGFR	62 (5.7)	117 (12.3)	<0.001
BRAF	439 (3.6)	33 (3.5)	0.827
MET exon 14 skipping	30 (2.7)	22 (2.3)	0.274
MET amplification	18 (1.6)	8 (0.8)	0.250
HER2	15 (1.4)	20 (2.1)	0.407
Fusions (ALK/ROS1/RET/FGFR)	39 (3.6)	37 (3.9)	0.765

Note: In ten cases, sex was not specified in ten cases (wild type = 2, *EGFR* exon 20 insertion = 2, *KRAS* = 5, *MET* exon 14 skipping = 2).

(27.8%), class III for 22 (30.6%), and other for two (2.8%). Among the 44 *ALK*-positive patients, *EML4-ALK* fusion rearrangements included 17 (38.6%) variant 3a/b (*E6, A20*), 15 (34.1%) variant 1 (*E13, A20*), five (11.4%) variant 2 (*E20, A20*), five (11.4%) variant 5' (*E18, A20*), one variant 5a (E2, A20), and one case of *HIP1-ALK*.

Co-alterations were detected in 114 patients (5.6%), the most common of which was a *KRAS/PIK3CA* (n = 19, 17%), *KRAS/IDH1* (n = 9, 8%), and *EGFR/PIK3CA* (n = 10, 8.5%) (Supplementary Fig. 2). Other co-alterations of interest included one case of *KRAS G12A/ROS1* fusion and two cases of *KRAS G12C/BRAF G469A* co-alterations. *EGFR T790M* mutations were detected in four patients with an *EGFR* mutation (L858R = 2, Exon 19 del = 2).

Discussion

This is the largest retrospective study exploring the genomic landscape of NSCLC in the Republic of Ireland. Consistent with prior data, *KRAS* and *EGFR* were the most frequently mutated alterations with an overall prevalence of 32% and 9%, respectively. The genomic profile across all four provinces was similar except for Connacht where there was a reduced prevalence of *KRAS*. Females were more likely to harbor a clinically significant alteration ($p < 0.001$). In patients below or equal to 50 years old, the most common oncogenic driver was a fusion rearrangement including *ALK*, *ROS1*, and *RET*. Co-alterations were present in 119 (5.2%) cases and likely represent passenger mutations or bypass mechanisms of therapeutic resistance in the case of oncogene-driven NSCLC.

KRAS is the most common oncogenic driver in NSCLC accounting for approximately 25% of cases and represents a biologically distinct subtype of NSCLC.[14] *KRAS* mutations are ubiquitous, likely driving the evolutionary process of lung cancer carcinogenesis.[15] They are typically associated with a smoking history and a high mutation burden.[16,17] *KRAS* prevalence generally differs according to geographic distribution with a reduced frequency in Asian populations compared with Western populations.[18] The prevalence of *KRAS* mutations in our study, particularly in the adenocarcinoma cohort, was higher than previously reported data sets from Western populations.[14,19,20] The cause of this is not fully understood. Judd et al.[21] analyzed 17,095 NSCLC tumor samples and found a *KRAS* prevalence of 27.5%. Consistent with our findings, the most frequently mutated allele was G12C (40%) followed by G12V (19%) and G12D (15%). *KRAS* was also more frequently detected in females than males, and there was no difference across age groups. Interestingly, we report a reduced prevalence in Connacht in the West of Ireland compared with other provinces (44 of 191, 23% versus 354 of 1091, 32.4% versus 256 of 763, 33.6% versus three of seven, 42.9%). One potential explanation for this is a reduced smoking prevalence in Connacht and Ulster[22]; however, caution should be exercised when interpreting the results owing to the small sample size. Of note, G12D was the more frequently mutated allele in the Connacht population compared with Leinster and Munster (15 of 191, 7.9% versus 51 of 1091, 4.7% versus 48 of 763, 6.3%, respectively).

The prevalence of *EGFR* mutations varies across ethnic groups with an incidence in a western population of 15% in the Br.21 study compared with 59.7% in the seminal Iressa Pan-Asia Study (IPAS).[23,24] Melowsky et al. conducted a meta-analysis evaluating the prevalence of EGFR mutations worldwide and estimated a European prevalence of 12.8% for all EGFR mutations with exon 19 deletions and L858R substitutions accounting for 48.4% and 29.9% of the overall cohort, respectively.[25] Other large-scale genomic studies have also found an increased prevalence of *EGFR* mutations.[20,26] We report an overall prevalence of 9% in our cohort; however, this is largely consistent with a previous study which detected an *EGFR* prevalence of 9% in the South of Ireland.[27] In contrast to this, Shikhrakab et al.[28] revealed an *EGFR* prevalence of 13.8% among

209 Irish patients tested for the mutation. Differences may be related to availability of genomic testing, and it is important to note that *EGFR* prevalence may be underestimated in our cohort as patients may have undergone local testing.

The frequency of fusion rearrangements in our population was lower than previously published data with an overall prevalence for *ALK*, *ROS1*, and *RET* of 2.2%, 0.8%, and 0.5%, respectively, whereas no *NTRK* fusion was identified.[20,29,30] Compared with other studies, we did not identify a significant difference in *ALK* prevalence between males and females (1.9% versus 2.5%, $p = 0.581$).[31] *ALK* variants were consistent with the literature, and *EML4-ALK V3 a/b* was the most common accounting for 38.6% followed by *EML4-ALK v1*. Of note, one novel *ALK* fusion variant was detected, *HIP1-ALK*, which may also be sensitive to ALK inhibitors as previously described[32] and has also been implicated as a potential resistance mechanism to second-generation *ALK* inhibitors.[33] *ROS1* prevalence has previously been reported in the region of 1% to 2%[34,35]; however, a recently reported study by Steel et al. identified an overall prevalence of 0.2% more in keeping with our findings.[36]

Activation of the fibroblast growth factor receptor (*FGFR*) through fusion with various partners has been described in a number of solid malignancies, including NSCLC.[37]

FGFR3 fusions (0.2%) were detected in five cases of lung adenocarcinoma in our study population. Qin et al.[38] molecularly profiled 26,054 NSCLC cases and detected an overall *FGFR* fusion prevalence of 0.2%. *FGFR* fusions were more common in squamous cell carcinoma and were often present with other mutations and have been associated with bypass resistance mechanisms to *EGFR* inhibitors.[39–41] In contrast, we identified no co-alterations and all five cases were detected in lung adenocarcinoma. *FGFR* fusions are rare but of particular interest as there are emerging data that suggest they may be sensitive to *FGFR* inhibitors.[42]

Significant clinical and molecular diversity exists within the subclass of oncogene-addicted NSCLC.[14] This intratumoral heterogeneity can lead to variable sensitivity to targeted treatments and points toward potential mechanisms to overcome therapeutic resistance. In our study, co-alterations were detected in 114 cases (5.6%). In oncogene-addicted NSCLC cases, the most common co-alterations were *KRAS/PIK3CA*, *EGFR/PIK3CA*, *KRAS/IDH1*, and *EGFR/CTNNB1*. In contrast to oncogenes that play a crucial in tumorigenesis and are largely exclusive, other mutations are frequently referred to as passenger mutations. Consistent with previously published literature, *PIK3CA* was the most often detected co-mutation in *EGFR*-mutant and *KRAS*-mutant NSCLC.[43–45] The impact of *PIK3CA* co-mutations is not fully understood. Activation of phosphatidylinositol 3-kinases (PI3K) triggers the PI3K/AKT/mTOR pathway, leading to cell survival, transformation, metastasis, and tumor growth. Eng et al.[46] found that *PIK3CA* co-mutation was associated with poor prognosis in patients with *EGFR*-mutant and *KRAS*-mutant NSCLC. Despite preclinical data to suggest *PIK3CA* co-mutations may confer therapeutic resistance in EGFR-mutant cancer cell lines,[47] this does not seem to translate clinically.[48,49] Both *PIK3CA* and beta-catenin (*CTNNB1*) mutations are preferentially detected in advanced-stage disease.[50,51] *CTNNB1* mutations lead to aberrant accumulation of the encoded beta-catenin protein and may be implicated in therapeutic resistance.[52–55] Isocitrate dehydrogenase 1 and 2 (IDH1/2) are important metabolic enzymes and are associated with a number of malignancies, including gliomas, cholangiocarcinoma, leukemia,[56–58] and rarely NSCLC.[59–61] They are typically found in high grade, *KRAS*-mutant tumors and likely represent branch mutations promoting subclonal evolution.[60] Other frequently reported co-mutations in NSCLC such as *TP53*, *STK11*, *KEAP1*, *RB1*, and *CDKN2A/B* are not reported by the Oncomine Focus assay.

Although typically *KRAS* mutations and other driver alterations are mutually exclusive,[62,63] we identified one case of *KRAS G12A/ROS1* and two cases of *KRAS/BRAF* class II alterations. There have been rare reported cases of co-occurring *ROS1* rearrangements and *KRAS* mutations.[64,65] *KRAS* and *ROS1* co-alteration may be associated with therapeutic resistance to ROS1 inhibitors.[66,67] Several studies have supported the theory that KRAS and BRAF co-mutations are mutually exclusive[68–71]; however, other studies found the presence of *KRAS* and *BRAF* co-mutations which seem to be rare events typically with class II/III *BRAF* mutations.[72–75]

There are a number of limitations to the current study. First, only basic clinical and demographic data were available for analysis. It was not possible therefore to test for associations between alteration and tumor stage, smoking history, and survival. We did not have access to treatment history, and thus, it was not possible to determine whether genomic alterations were present in treatment-naive patients or as a result of secondary resistance mechanisms. As we relied on the clinical information from referral hospitals, we were unable to confirm histologic subtype except for NSCLC in 19.8% of cases, and therefore, these were reported as carcinoma likely NSCLC. Many patients undergo local testing for *EGFR*, *ALK*, and *ROS1* in their respective institutions, and so, these alterations may be underestimated in our cohort. The exact impact of this is unknown. If we look at patients referred from the local institution St. James's Hospital, our results seem to be largely consistent (n =

433 [21%], *KRAS* = 145 [33.5%], *EGFR* = 36 [8.3%], *ALK* = 7 [1.6%], *ROS1* = 5 [1.2%], and *RET* = 3 [0.7%]). A previous study by Kelly et al.[27] also reported a prevalence of 9% for EGFR mutations in the South of Ireland. Broader molecular testing such as whole exome, genome, or transcriptome sequencing may identify other alterations that contribute to lung cancer pathogenesis that are missed using targeted NGS, such as alterations in tumor suppressor genes *STK11* and *TP53*.

Conclusion

This is the first retrospective study to fully characterize the genomic landscape of NSCLC in Ireland, using the broadest available NGS. Actionable driver oncogenes were detected in 53% of patients, and KRAS was the most common oncogenic driver identified.

Our study revealed a lower prevalence of *EGFR* and fusion rearrangements, *ALK*, *ROS1*, and *RET*, compared with previously published data sets. This study highlights the need to prospectively collect genomic data for patients in the Republic of Ireland to inform treatment prioritization and clinical trial selection.

CRediT Authorship Contribution Statement

Rachel J. Keogh: Data curation, Investigation, Methodology, Formal analysis, Writing—original draft, Writing—review and editing, Project administration.

Martin P. Barr: Resources, Data curation, Methodology, Writing—review and editing.

Anna Keogh, David McMahon: Data curation, Investigation, Writing—review and editing.

Cathal O'Brien, Stephen P. Finn: Investigation, Resources, Writing—original draft, Writing—review and editing, Supervision.

Jarushka Naidoo: Conceptualization, Investigation, Resources, Writing—original draft, Writing—review and editing, Supervision.

Disclosures

R Keogh has received support for attending meetings from Janssen and Merck Sharp & Dohme. McMahon has received grants or contracts from Pfizer and Roche; consulting fees, payments, or honoraria from Pfizer; and support for attending meetings and/or travel from Pfizer and Takeda. Finn has participated on a data safety monitoring board or advisory board for Amgen, Illumina, Pfizer, and Roche; received consulting fees, payments, or honoraria from Amgen, AstraZeneca, Pfizer, and Revolution Medicines; have stocks/shares from Revolution Medicines; and received institutional support from Roche. Naidoo has received research funding from AstraZeneca, Amgen, Bristol-Myers Squibb, Mirati, Roche/Genentech, Pfizer, Novartis, Takeda, and Bayer; consulting fees, payments, or honoraria from AstraZeneca, Amgen, Bristol-Myers Squibb, Mirati, Roche/Genentech, Pfizer, Novartis, Takeda, NGM Pharmaceuticals, Kaleido Biosciences, Elevation Oncology, and Daiichi Sankyo; and having participation on a data safety monitoring board or advisory board for Bristol-Myers Squibb, AstraZeneca, and Daiichi Sankyo. The remaining authors declare no conflict of interest.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100627.

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