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Rare molecular subtypes of lung cancer

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Abstract

While oncogenes that occur in ≤5% of non-small cell lung cancers have been defined as “rare”, this frequency can correspond to a substantial number of patients diagnosed annually. Within rare oncogenes, less commonly identified alterations (e.g., *HRAS*, *NRAS*, *RIT1*, *ARAF*, *RAF1*, and *MAP2K1* mutations, or *ERBB* family, *LTK*, and *RASGRF1* fusions) can share structural or oncogenic features with more commonly recognized alterations (e.g., *KRAS*, *BRAF*, *MET* and *ERBB* family mutations, or *ALK*, *RET*, and *ROS1* fusions). A surge in the identification of rare oncogene-driven lung cancers has challenged the boundaries of clinical-grade diagnostic assays and profiling algorithms. In tandem, the number of approved targeted therapies for patients with rare molecular subtypes of lung cancer has risen dramatically. Rational drug design has iteratively improved the quality of small molecule therapeutics and introduced a wave of large molecule therapeutics, expanding the list of actionable de novo and resistance alterations in lung cancer. Getting additional molecularly tailored therapeutics approved for rare oncogene-driven lung cancers in more countries will require ongoing stakeholder cooperation. Patient advocates, health care agencies, investigators, and diagnostic, therapeutic, and real-world evidence companies have already taken steps to surmount the challenges associated with research execution for low-frequency drivers.

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COMPETING INTERESTS

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INTRODUCTION

What constitutes a rare lung cancer? Rare is defined as “seldom occurring or found” – a definition that unfortunately fails to quantify the condition. In fact, no unified definition of rare lung cancer or even rare cancer exists[1]. In Europe and Asia, a cancer has been considered rare if it occurs in <6 out of 100,000 people annually[2,3]. In contrast, the National Cancer Institute of the United States considers a cancer rare if it occurs in <15 out of 100,000 people annually[4].

In the lung cancer community, molecular subsets of lung cancer have been loosely classified as rare based on percent frequency[5]. An upper frequency cutoff of 5% of non-small cell lung cancers (NSCLCs) has been used (Supplementary Table 1). Notably, the frequency of oncogene-driven lung cancers may vary by features, including race/ethnicity, age, and detection assay used (FIG. 1A-C, Supplementary Table 1-2, Supplementary Fig. 1). Molecular subsets of lung cancer that meet the ≤5% cutoff are expected to constitute ≤2 cases out of 100,000 people annually (Table S3).

While the 5% cutoff estimate satisfies definitions of a rare cancer, it makes it challenging to appreciate the true incident burden of rare molecular subtypes of lung cancer, some of which may affect >18,000-90,000 people annually worldwide (Supplementary Table 3)[6,7]. Furthermore, selected rare oncogene-driven NSCLCs are diagnosed annually with a frequency comparable to or exceeding that of other malignancies (e.g., acute lymphocytic leukemia, and vulvar, bone, and male genital cancers, FIG. 1D)[8,9].

MOLECULAR SUBTYPES

Molecular features

Mutations.—Rare mutations can be classified in terms of the proteins encoded by the affected genes. Receptor tyrosine kinase gene mutations represent one group (FIG. 2) and involve genes such as *MET*, *EGFR*, *ERBB2*, and *DDR2*. While a spectrum of mutations can affect these genes, the most common mutations are *MET* exon 14 alterations (4% of NSCLCs[10]), *EGFR* exon 20 mutations (1.5% of NSCLCs[11]), *ERBB2* exon 20 mutations (1.4% of NSCLCs[11]), and *DDR2* mutations (4% of squamous lung cancers[12] and 0.4% of lung adenocarcinomas [LUADs][13]).

MAPK pathway gene mutations represent another group (FIG. 3). These mutations involve genes such as *KRAS*, *NRAS*, *HRAS*, *RIT1*, *ARAF*, *BRAF*, *RAF1*, and *MAP2K1*. Mutations that affect RAS protein family members involve *KRAS* (non G12C/V/D mutations individually occur in less than 5% of NSCLCs[14]), *NRAS* (0.9% of NSCLCs), *HRAS* (0.1% of NSCLCs), and *RIT1* (~0.7% of LUADs). *KRAS* G12C, G12V, and G12D mutations exceed the frequency threshold for rare molecular subtypes and are excluded here. Mutations that affect downstream signaling proteins in LUADs involve *ARAF* (0.2%), *BRAF* (4.5%), *RAF1* (0.4%), and *MAP2K1* (0.7%) (Supplementary Table 2).

Rare mutations can also be classified by mutation type. Missense point mutations that result in amino acid substitutions commonly involve *KRAS*, *NRAS*, *HRAS*, *RIT1, ARAF*,

BRAF, *RAF1*, *MAP2K1* and *DDR2*. Insertions and/or deletions commonly affect *EGFR*, *ERBB2*, and *MET*. *EGFR* and *ERBB2* exon 20 insertions and *ERBB2* exon 20 insertions are structurally paralogous. Kinase domain duplication (KDD) of *ERBB* family members (0.2% NSCLC[15]) such as *EGFR* (i.e., in-tandem and in-frame duplication of exons 18-25) can also occur. Notably, KDD has been observed with other non-*ERBB* genes (e.g., *RET* and *MET*). For *MET* exon 14 alterations, insertions and/or deletions involve splice sites flanking exon 14.

Mutations in the above genes are not limited to the described mutation types. Insertions and/or deletions are identified in *KRAS*, *RIT1*, *BRAF*, and *MAP2K1*. Conversely, point mutations are identified in *MET* (kinase/semaphorin domains) and *ERBB2* (kinase, transmembrane, or extracellular domains)[13].

Fusions.—Fusions can be classified by the proteins encoded by the affected genes (FIG. 4). One group involves receptor tyrosine kinase (RTK) genes and includes *ALK* (3-4% LUADs), *RET* (1-2% LUADs), *ROS1* (1-2% LUADs), *NTRK1/2/3* (<1% LUADs), *FGFR1/2/3* (<1% LUADs), *EGFR* (<1% LUADs), *ERBB2* (<1% LUADs), *ERBB4* (<1% LUADs), and *LTK* fusions. An intact kinase domain is typically included. A second group involves MAPK pathway genes. These include *RASGRF1* (<0.1% in LUADs)[16] and *BRAF* (0.2% of LUADs)[17] fusions (Supplementary Table 2). While *BRAF* fusions are kinase domain inclusive and structurally similar to RTK fusions, *RASGRF1* fusions harbor the catalytically active C-terminal Ras-GEF domain of RASGRF1[16]. Another group involves RTK ligand genes and includes *NRG1* (0.3% of LUAD) and *NRG2* fusions[18]. Other fusions that do not belong to these three categories include *BRD4* (0.05% NSCLCs[19]) and *PKC* fusions. *PKC* fusions represent a separate entity as these are loss of function alterations[20].

A wide variety of fusion partners exist. Some partners predominantly fuse with a specific RTK (e.g., *EML4* with *ALK*[21]); others, like members of the TRIM protein family, can fuse with more than one RTK (e.g., *TRIM24-RET* and *TRIM24-NTRK2*)[22]. Some partners influence transmembrane (e.g., *NRG1* or *RASGRF1* fusions) or subcellular localization. Fusion partners can likewise affect ligand-independent dimerization ability by contributing dimerization domains (e.g., coiled-coil, zinc finger, LisH, WDR, or SAM domains)[22].

Copy number alterations.—RTK amplifications of *ERBB2* and *MET* occur in 0.9% and 1.4% of newly diagnosed LUADs, respectively (Supplementary Table 2). *FGFR* and *ARAF* amplifications have been identified in LUAD in 1-3% and 1% of cases, respectively[23,24]. Amplifications can occur on chromosomes or extrachromosomal DNA[25] (double minutes) and are also found as mechanisms of secondary resistance to EGFR tyrosine kinase inhibitor (TKI) therapy in *EGFR*-mutant lung cancers[26]. Higher levels of amplification and focality may correlate with increased dependence on the amplified gene[26].

Oncogenesis and signaling

RTK and RTK ligand alterations.—RTK gene mutations, fusions, and amplifications functionally converge on increased RTK activity and activate downstream signaling pathways; these preferentially include the MAPK, PI3K, PKC, and JAK/STAT pathways. Increased RTK activity can occur in ligand-dependent or ligand-independent manners.

Ligand-independent constitutive kinase domain activation can occur with mutations or fusions involving *EGFR, ERBB2, ERBB4, DDR2, ALK, RET, ROS1, NTRK1/2/3,* and *LTK*[12,27,28]. Mutant RTKs maintain their transmembrane localization. In contrast, whereas some RTK fusions localize to the cell membrane, many chimeric RTK fusions localize to the cytoplasm or other subcellular compartments (FIG. 4E). Localization differences may modify downstream pathway activation.

Ligand-dependent RTK activation occurs with altered splicing. Many *MET* exon 14 alterations interfere with splice acceptor/donor sites, leading to exon 14 skipping. Without the CBL ubiquitin ligase binding domain encoded by exon 14, ligand-dependent MET is recycled to the cell surface rather than degraded[29]. *ERBB2* exon 16 skipping mutations (ERBB2Δex16) and *FGFR2* exon 18 truncated alterations (*FGFR2*$^{\Delta ex18}$) have also been identified[30,31]. These mutations eliminate HER2 and FGFR2 regulatory elements and induce receptor dimerization. Ligand-dependent RTK activation also occurs with RTK gene (e.g., *EGFR, ERBB2, MET, FGFR*) amplification. Amplification can increase the cell surface density of RTKs that remain influenced by ligand binding. Higher levels of amplification may correspond to higher RTK levels[26].

Fusions that involve NRG1/2 produce chimeric oncoproteins that maintain an EGF-like domain which binds ERBB3/4 in an autocrine or paracrine fashion. While more than 30 different *NRG1* isoforms exist, NRG1 fusions preferentially occur with the NRG1 IIIβ isoform, known to have higher affinity than the α isoform for ERBB3/4. Receptor dimerization (e.g., ERBB2-ERBB3) then occurs, activating the MAPK, PI3K, and FAK pathways[18].

MAPK pathway alterations.—RAS proteins are GTPases with biological activity governed by nucleotide binding states. The ratio of inactive RAS-GDP to active RAS-GTP is determined by the relative rates of GDP to GTP exchange and GTP hydrolysis. *KRAS*, *NRAS*, and *HRAS* mutations and *RASGRF1* fusions influence either or both activities[32]. Most *KRAS/NRAS/HRAS* codon 12 mutants affect GTP hydrolysis without changing the rate of GDP to GTP exchange while codon 13 mutants affect both activities. The C-terminal domain of *RASGRF1* fusions catalyzes the dissociation of GDP from RAS proteins[16]. Inactivating mutations involving *NF1* and *RASA1* have been identified; both genes encode RasGAPs that negatively control the RAS pathway[33].

RAF family gene mutations can be grouped by RAS dependency. RAS-independent activation of MEK1/2 occurs with *ARAF* S214X, *BRAF* class I (e.g., V600E) and II (e.g., G469A, K601E), and RAF1 mutations. *BRAF* class I mutations signal as monomers. *BRAF* fusions and *ARAF, BRAF* class II, and *RAF1* mutations signal as dimers[24,34,35].

RAS-dependent activation occurs with *BRAF* class III (e.g., G466V, D594G, N581S) mutations that have impaired kinase activity or are kinase-dead and bind more tightly to RAS-GTP than wild-type BRAF. This binding results in enhanced RAF1 activity and increased ERK signaling[34]; other RAS pathway alterations may co-occur. *ARAF* amplification can activate RAS in a kinase-independent manner by antagonizing NF1 binding.

MAP2K1 mutations can be grouped by RAF dependency. *MAP2K1* class I mutations (e.g., D67N, P124S) are RAF-independent, have low transforming capacity, and can co-occur with other ERK-activating alterations. *MAP2K1* class II (e.g., K57N, C121S) and III (e.g., E102_I103del, I103-K104del) are RAF-independent[36].

Other alterations.—BRD4 fusions are well described for NUT midline carcinoma. In lung cancer, fusions such as BRD4-NOTCH3 may sequester histone acetyltransferases and other transcriptional co-factors to chromatin regions that transcribed selected genes (e.g., *MYC*)[37] . Notably, the fusion includes the functional ankyrin domain of NOTCH3 and NOTCH fusions have been described as constitutive activators of NOTCH signaling in other tumors[38].

Clinicopathologic characteristics

Clinical and histologic features.—Most rare driver alterations in RTK/RAS/RAF/MEK are enriched in LUADs (Supplementary Table 4), the most common histologic subtype of NSCLC[8,39]. These alterations can also be found in non-LUAD histologies such as squamous cell, large cell neuroendocrine, or rarely small cell lung cancers. While no pathologic feature is specific for a molecular driver, unique morphologic patterns are associated with rare genomic subsets. For example, tumors with *ALK/ROS1/RET* fusions are often characterized by abundant extracellular mucin, a cribriform pattern, and signet-ring cell morphology[40,41].

NRG1 fusions are commonly found in invasive mucinous adenocarcinomas (IMAs), a variant of LUAD (found in 3% of cases) with distinct clinical, pathologic, and molecular features[42]. Despite their low prevalence, IMAs comprise a sizeable portion (28%) of *NRG1* fusion-positive lung cancers. *NRG1* fusion-positive IMAs tend to have higher-risk features and worse outcomes. IMAs lacking *NRG1* fusions harbor a wide range of *KRAS* mutations, especially G12D/V, and other driver alterations (e.g., non-*NRG1* fusions) found in non-mucinous LUADs.

In contrast to other mitogenic drivers, *MET* exon 14 skipping is associated with rare histologic subtypes of NSCLC, namely sarcomatoid carcinoma and adenosquamous carcinoma. Although most *MET* exon 14-altered tumors are LUADs, the frequency of sarcomatoid and adenosquamous histologies can be 4-6x higher in *MET* exon 14 altered compared to MET wildtype cases. These histologic variants are similarly enriched in highly *MET*-amplified lung cancers, suggesting a link to broader MET activation and addiction[43,44].

Many oncogenic alterations tend to occur in younger never smokers or former light smokers. Racial and ethnic differences may also occur, although these are less well studied for many rare oncogenes. *EGFR* and *ERBB2* exon 20 mutations are found commonly in never smoker women of Asian origin, phenocopying classical *EGFR* mutations[11]. Fusions are typically found in patients with little to no cigarette smoking history[45-47]. In contrast, *MET* exon 14 alterations are commonly diagnosed in older patients with more substantial smoking histories, including those who have smoked heavily[48]. Transversion mutations involving *KRAS* (e.g., G12A, G13C) and *MAP2K1*[36] (e.g., K57N) may be enriched in former/current smokers[49].

Chemotherapy and immunotherapy activity.—The overall activity of chemotherapy can be broadly divided into two groups. In the first group, chemotherapy can achieve durable benefit. Pemetrexed-inclusive chemotherapy results in high objective response rates (ORRs) and long progression-free survival (PFS) in *ALK/ROS1/RET* fusion-positive cancers compared to other alterations such as *KRAS/EGFR* mutations[50-52]. In the second group, more modest benefits are observed. This includes *BRAF*[53], *ERBB2*[54] and *EGFR* exon 20 mutations[55], and *NTRK*[56] and *NRG1*[57] fusions.

Single-agent immune checkpoint inhibitor (ICI) therapy does not achieve high ORRs (0% in *ALK* fusions to 26% in *KRAS* mutations) or durable PFS[58] (2.1 months in *RET* fusions to 3.4 months in *MET* exon 14 alterations) in the majority of oncogene-driven NSCLCs, possibly due to a poorly immunogenic microenvironment, lower tumor mutational burden, decreased CD8+ T cell infiltration, or other factors[59]. Selected situations may impart relatively increased benefit and long-term responders have been observed. Smokers with *BRAF*-mutant lung cancers have a longer median PFS compared to *BRAF*-mutant never smokers (4.1 vs. 1.9 months[58]). With first line pembrolizumab in PD-L1 ≥ 50% expressing *MET* exon 14-altered NSCLCs, an ORR of 43% and a median duration of response (DoR) of 13.9 months were achieved, although the median PFS was 3.5 months[60].

Concurrent or sequential ICI and TKI use may increase toxicity. With concurrent osimertinib use in *EGFR*-mutant NSCLCs, severe immune related adverse events such as pneumonitis are observed[61]. TKI therapy after immunotherapy results in increased transaminitis (crizotinib for *ALK* fusions[62]) and hypersensitivity (selpercatinib for *RET* fusions[63]). As such, should molecular testing not yet be available, chemotherapy could be reasonably considered over chemoimmunotherapy or single-agent ICI therapy for patients with suspected oncogene-driven lung cancers.

DIAGNOSTICS

Molecular profiling evolution

Rare oncogenic drivers have substantially transformed molecular testing practices in lung cancer over the past decade[64]. Genotyping previously focused on a few genes with sequential testing via single-gene assays (e.g., PCR, FISH, Sanger)[65]. The most commonly altered genes (e.g., *KRAS/EGFR*) were analyzed first, followed by less commonly altered genes; serial testing was performed until a positive result was found. With improvements in technology and the ever-growing list of actionable targets, diagnostic paradigms have converged on next-generation sequencing (NGS), a more comprehensive, economical, and tissue-efficient approach[66].

Many NGS assays interrogate hundreds of genes at once, including rare drivers often deprioritized due to their low incidence (e.g. *NTRK* fusions) or investigational status (e.g. *NRG1/FGFR* fusions)[67]. Given that stand-alone assays for rare drivers are not widely available and difficult to implement with limited tissue, NGS often represents the only screening method for these variants. Within commonly tested genes (e.g., *EGFR*), NGS can distinguish uncommon genotypes (e.g., exon 20 insertions not covered by hotspot

PCR-based assays[68]). NGS can also identify multiple alteration classes (e.g., amplifications, mutations, and fusions[29,69]) and novel alterations, fueling current and future research.

Optimizing driver identification

RNA-based testing.—While targeted DNA-based NGS is typically the primary/sole assay for genotyping, its sensitivity for fusions and alternatively spliced transcripts can be variable depending on assay design, gene coverage, and target enrichment[70,71]. Sequencing of introns (where most breakpoints occur) can be challenging due to size constraints (e.g., the sheer size of *NRG1* introns precludes adequate coverage[42,57,72]) and repetitive sequences (e.g., *ROS1* intron 31 is difficult to capture due to repetitive long interspersed nuclear elements [LINEs])[70].

In contrast, RNA-based methods directly assess oncogenic RNA transcripts lacking large intronic sequences, enabling more efficient and sensitive analyses. RNA-based NGS can detect occult kinase fusions[70,71] thus improving sensitivity. Furthermore, RNA-based testing optimizes specificity by confirming that some DNA-detected fusions of unknown significance do not transcribe into oncogenic fusions, while others produce novel chimeric transcripts[73].

For splice site alterations, DNA hybrid capture-based target enrichment outperforms amplicon-based methods; however, the intrinsic limitations associated with DNA sequencing remain[29,74]. Without adequate intronic coverage for *MET*, large deletions and cryptic splice site mutations deep within introns can be missed[75]. Furthermore, DNA-based NGS occasionally reveals deep intronic variants in *MET* introns 13/14 that have an unclear effect on splicing. In contrast, RNA sequencing can determine which variants lead to exon 14 skipping by directly capturing aberrant splicing byproducts[76].

A consensus approach to integrating DNA- and RNA-based workflows has yet to be established. While performing upfront dual DNA- and RNA-based NGS is one strategy[77], this may not be necessary for all cases and can be prohibitive in low-resource settings. An alternative strategy (Supplementary Fig. 2) uses DNA-based NGS as a primary screening assay with subsequent RNA-based NGS performed in select cases (e.g., DNA driver negative, fusions/intronic mutations of unknown significance[71]). This model focuses on DNA-based testing limitations and may facilitate a more judicious and cost-effective use of RNA-based testing, albeit with longer total turnaround times for cases requiring sequential testing.

Liquid biopsies.—Whereas adequate tumor tissue is foundational for NGS, samples acquired via invasive procedures are not always sufficient for comprehensive testing[78]. Liquid biopsies using circulating tumor DNA (ctDNA) have shorter turnaround times and can supplement tissue-based genotyping[79]. Despite the well-recognized utility of ctDNA testing, several important issues must be recognized.

Given the scarcity of plasma ctDNA and the need for ultra-deep sequencing, liquid biopsy panels include fewer genes than tissue-based panels to balance sequencing breadth and depth[80]. As a result, genes with highly recurrent alterations are often prioritized, and less

commonly altered genes are sometimes excluded. Compared to plasma, other body fluids (e.g., cerebrospinal fluid, pleural effusions) can be enriched in ctDNA, allowing analysis using tissue-based NGS assays with larger, more inclusive panels[81]. Regardless of fluid type, ctDNA testing has variable sensitivity and all negative results should be confirmed by tumor testing[79].

The limitations of DNA-based NGS from tissue also apply to ctDNA-based testing. While there are no routinely used clinical assays for RNA-based liquid biopsies in lung cancer (i.e. tissue is always required), there have been notable advances in circulating tumor cell[82], cell-free[83,84], and exosomal[85] RNA profiling that may be incorporated into clinical workflows in the future.

Novel driver discovery

Targeted DNA/RNA-based NGS may fail to identify a clear mitogenic driver. While a distinct unknown mitogenic driver phenotype (e.g., smoking-induced, complex genomics, high TMB, *TP53/STK11/KEAP1* alterations[39]) may exist, the absence of a driver could represent a false negative result and justify additional testing.

Whole transcriptome sequencing (WTS) of “driver-negative” cases enabled the discovery of *NRG2*[86,87], *RASGRF1*[16], and *LTK*[88] fusions and clinical-grade WTS may facilitate a more unbiased search for other rare/novel fusions. Whole genome sequencing (WGS) may similarly uncover recurrent oncogenic signatures. In the TCGA LUAD project, WGS of “driver-negative” tumors by WTS and whole exome sequencing (WES) revealed pathogenic copy number changes, complex rearrangements, and non-coding alterations including a candidate driver mutation in the *ILF2* promoter region[89]. Notably, WGS can identify canonical drivers missed by WES due to low tumor purity and poor coverage, highlighting the importance of pre-analytical factors and quality control metrics[89].

While WTS/WGS is not routinely used in the clinic, these studies suggest an emerging role for biomarker discovery in driver-negative tumors (Supplementary Fig. 2), especially those more likely to harbor occult drivers (e.g., low TMB, never smoker history). The potential utility of other multi-omic approaches (e.g., methylomics and proteomics) continues to evolve.

TARGETED THERAPY

Classes

Small molecules.—Kinase inhibitors are the leading representative of this group. Kinase substrates can be classified into tyrosine kinases (e.g., EGFR, ERBB2, MET, ALK, RET, ROS1), serine/threonine kinases (e.g., BRAF), and dual specificity kinases (e.g., MEK1/2). TKIs (e.g., mobocertinib, capmatinib, tepotinib, alectinib, brigatinib, lorlatinib, selpercatinib, pralsetinib, crizotinib, and entrectinib) are the most commonly approved agents (Table 1) for oncogene-driven lung cancers. Serine/threonine kinase (e.g., dabrafenib, vemurafenib) and dual specificity kinase (e.g., trametinib) inhibitors represent a minority of approved agents[90].

Kinase inhibitors can be classified by mechanism of action. Interestingly, all approved TKIs are ATP-competitive type I inhibitors that target the active kinase conformation. ATP-competitive type II inhibitors (e.g., cabozantinib) target the inactive conformation and are less common; none are approved for oncogene-driven lung cancers. Type III inhibitors (e.g. trametinib) are non-ATP competitive allosteric inhibitors[91]. Generations have also been assigned to kinase inhibitors that target a single molecular subset of lung cancers (e.g. *ALK* fusion-positive NSCLCs). Later-generation agents often harbor features such as improved central nervous system (CNS) activity and resistance mutation coverage.

Novel small molecules have entered or are set to enter clinical trials. While dabrafenib and vemurafenib target monomeric BRAF V600E-mutant BRAF, newer RAF inhibitors that target dimers (PLX8394[92], BGB-3245[93]) are being investigated in non-V600E (e.g., class II) BRAF mutants. Protein degradation agents (e.g., proteolysis targeting chimeras [PROTACs], molecular glues) are being explored in oncogene-driven lung cancers such as those with *KRAS*/*BRAF*[94]mutations or *RET* fusions.

Large molecules.—The most commonly explored large molecules in oncogene-driven lung cancers are antibody-based therapies. Naked antibodies can be monospecific or bispecific. Monospecific antibodies harbor specificity for one antigen/epitope (e.g., trastuzumab for ERBB2[95], seribantumab for ERBB3). Bispecific antibodies target two antigens/epitopes (e.g., amivantamab for MET and EGFR, zenocutuzumab for ERBB3 and ERBB2). These antibodies can serve a variety of functions including ligand binding interference, the inhibition of RTKs, and the induction of antibody-dependent cytotoxicity.

Expanding the scope of antibody-based targeting, antibody-drug conjugates (ADCs) have emerged as a new class of drugs. ADCs consist of an antibody (typically class 1 IgG), a payload (e.g., an auristatin, maytansinoid, calicheamicin, or camptothecin), and a linker (cleavable or non-cleavable) that connects both[96]. New warheads with putative immunomodulatory effects (e.g., TLR7/8 agonists[97], part of immune stimulating antibody conjugates) have entered the clinic. The drug-to-antibody ratio (DAR) is the average number of payloads for each antibody[96]. ADCs explored in oncogene-driven lung cancers include the anti-HER2 ADCs trastuzumab emtansine and trastuzumab deruxtecan[98], and the anti-MET ADC telisotumab vedotin[99].

Activity

Mutations.—The only rare oncogene-driven lung cancers for which targeted therapies are approved or guidelines-listed are *EGFR* exon 20 mutant, *ERBB2*-mutant, *BRAF* V600E-mutant, *MET* exon 14-altered, and *MET*-amplified NSCLCs. While these drugs are clinically active and have benefitted many patients, no single-agent or combination drug class consistently and simultaneously achieves an ORR >50% and median PFS >1 year. Whereas in the treatment-naïve context, capmatinib has an ORR of 68% and a median PFS of 12.4 months[100], other members of the same drug class have lower activity (tepotinib: ORR 46%, median PFS 8.5 months[101]; crizotinib: ORR 32%, median PFS 7.3 months).

Among the most active approvals are that of trastuzumab deruxtecan in *ERBB2*-mutant lung cancers (ORR 55%, median PFS 8.2 months)[98] and dabrafenib plus trametinib in *BRAF*

V600E-mutant lung cancers (ORR 64%, median PFS 10.9 months[102]). The rest of the therapy-oncogene pairs achieve more modest ORRs of 30-50% and a median PFS of under a year: mobocertinib[103] or amivantamab[104] for *EGFR* exon 20 mutations, and capmatinib (in pre-treated patients)[100] or tepotinib[101] for *MET* exon 14 alterations.

In a field previously dominated by small molecules, proof of principle that large molecules can achieve comparable or improved activity is growing. Such is the case with *EGFR* exon 20 mutations for which amivantamab is active (in addition to the small molecule mobocertinib). Amivantamab has also demonstrated activity (ORR 64%, including MET TKI-treated patients) in *MET* exon 14 altered NSCLCs[105]. *ERBB2*-mutant NSCLCs represent an excellent example of an improvement in activity moving from TKIs (ORR 0-30% with HER2 TKIs[106,107]) to ADCs (trastuzumab emtasine ORR 44%, trastuzumab deruxtecan ORR 55%[98,108]).

Other mutation-driven lung cancers may be targeted based on preclinical data. *DDR2*-mutant tumors, thought to require SRC, have responded to the SRC inhibitor dasatinib[12]. Following the success of direct KRAS G12C inhibitors, other mutation specific or pan-RAS inhibitors are emerging for non-G12C *KRAS* mutations[109].

Beyond single-agent therapies, combination therapies may be effective for other RAS-MAPK pathway alterations (as was observed with BRAF-MEK compared to BRAF[110,111] inhibition in *BRAF* V600E mutants). *RIT1*-mutant cells/tumors[112] can respond to MEK and PI3K inhibition. Acknowledging their RAS dependence, class III *BRAF* alterations are being targeted with MEK and SHP2 inhibition[113].

Fusions.—As opposed to the mutation-driven lung cancers, fusion-driven lung cancers respond to approved targeted therapies with ORRs >50% and a median PFS >1 year in the TKI/treatment-naïve setting (Table 1). For *ALK/RET/ROS1/NTRK* fusion-positive lung cancers, approved TKIs achieve an ORR from 57-83%. Durability is equally impressive with a median PFS ranging from 13-35 months[114-126].

Sequential TKI therapy has demonstrated activity in fusion-positive cancers. While *ALK* fusion-positive NSCLC is the only subset for which this paradigm has corresponding drug approval (e.g., lorlatinib in TKI-pretreated patients, ORR 39%, median PFS 9.6 months)[127], clinical responses to next-generation TKI therapy in other fusion-positive lung cancers (e.g., repotrectinib for *ROS1* fusions, TPX-0046 for *RET* fusions, selitrectinib for *NTRK* fusions) have been documented after progression on initial TKI therapy.

NRG1 fusions demonstrate the utility of large molecule therapy for fusion-positive lung cancers that putatively harbor a chimeric oncoprotein on the cell surface. Although these tumors depend on ERBB3-ERBB2 dimers for growth, the pan-ERBB TKI afatinib has unimpressive overall activity (median PFS 2.8 months despite a 25% ORR)[57]. In contrast, the antibodies zenocutumab or seribantumab achieve ORRs of ~35% and a median DoR of 9.1 months (zenocutuzumab in *NRG1* fusion-positive cancers, including NSCLC)[128,129]. The utility of ADCs remains unclear, although ERBB3 ADCs (e.g. patritumab deruxtecan) have been explored in other ERBB3-expressing (i.e. *EGFR*-mutant) NSCLCs[130].

Other fusions may benefit from targeted therapy. *MET* fusion-positive NSCLCs, many of which harbor exon 14 exclusion in addition to an intact kinase domain, have clinically responded to crizotinib. A patient with an *FGFR* fusion-positive NSCLC responded to the FGFR inhibitor erdafitinib[131]. Fusions involving LTK (whose kinase domain is 80% identical to ALK) can respond to ALK TKIs (e.g. lorlatinib[88]). *RASGRF1* fusions can respond to MAPK pathway inhibition (e.g. sunitinib) preclinically and clinically[132]. *BRAF* fusions are considered class II *BRAF* alterations and are being treated on trials with RAF dimer/pan-RAF inhibitors[92].

Amplifications.—The least amount of clinical data on targeted therapy activity is available for amplification-driven NSCLCs. Crizotinib, capmatinib, and tepotinib have guidelines listing for the treatment of patients with lung cancers that harbor high-level *MET* amplification[100,133,134] (Table 1). As implied by the indication, higher levels of *MET* amplification or gene copy number have correlated with higher response rates to TKI therapy. Low/modest activity of TKI and antibody therapy has been described for *ERBB2*-amplified NSCLCs[135,136]. Other RTK amplifications can presumptively be targeted with TKI/antibody-based therapy, although the contribution of co-occuring alterations and amplification focality/level should be explored as it has been for RTKs like MET[137].

Contemporary features

Selectivity.—Several rational drug design improvements have improved clinical outcomes in oncogene-driven lung cancers (FIG. 5). Increased target selectivity is a favorable feature. In *RET* fusion-positive NSCLCs, the movement from multikinase inhibitors with anti-RET activity (e.g. cabozantinib[138], vandetanib[139]) to highly RET selective agents (e.g. selpercatinib[119], pralsetinib[120]) resulted in an increase in tolerability secondary to the avoidance of inhibition of non-RET kinases like VEGFR2[140] and activity, attributed in part to more meaningful plasma exposures and target coverage. Increasing ROS1 selectivity (e.g., with NVL-520) may avoid side-effects mediated by TRK inhibition such as dizziness, weight gain, and withdrawal pain observed with TRK/ROS1 inhibitors (entrectinib/repotrectinib)[141].

Increasing mutant selectivity is another favorable drug design feature. This was observed with mobocertinib[142] that is more selective for EGFR exon 20 mutant proteins compared to wild-type EGFR. Newer EGFR exon 20 mutant targeting agents such as CLN-081 combine both mutant selectivity and target selectivity (ERBB2 inhibition is avoided)[143].

While largely favorable, increasing kinase selectivity may result in clinical consequences for select agents. The move from type Ia (multikinase)[144] to more potent type Ib (selective) MET inhibitors for *MET*-mutant/amplified NSCLCs was associated with an increase in on-target MET inhibition mediated lower extremity edema[100,101]. A similar problem may present itself with isoform selectivity with novel FGFR2/3-selective TKIs that cannot avoid on-target cutaneous side-effects in patients with *FGFR*-amplified NSCLCs[131].

CNS coverage.—NSCLCs have a proclivity for metastasizing to the brain; the lifetime risk with oncogene-driven lung cancers can be substantial (35-50%)[145]. Rational drug design has moved to improve CNS coverage levels, particularly with small molecules.

TKIs for *ALK/RET/ROS1* fusion-positive lung cancers (e.g., alectinib[146], brigatinib[125], lorlatinib[147], entrectinib[118,147], selpercatinib[119], pralsetinib[120]) are the best examples, achieving intracranial ORRs between ~60-80% and activity even in leptomeningeal disease. In *ALK* fusion-positive NSCLCs, randomized phase 3 trials demonstrate the intracranial superiority of next-generation TKIs compared to crizotinib.

Large molecules can induce intracranial responses[148] but may suffer from an inability to cover the CNS as optimally as small molecules due to size constraints. Combining small and large molecules has been investigated in classical *EGFR* mutations (e.g., lazertinib plus amivantamab) and such a paradigm could be applied to rare oncogene-driven NSCLCs. In addition, developing nanoparticles conjugated to cytotoxic therapy[149], effectively smaller equivalents of ADCs, may improve CNS drug delivery.

Resistance anticipation.—Generational improvements in TKIs often include the addition of coverage for resistance mutations that emerge with earlier-generation TKIs. For fusion-positive NSCLCs, this can include activity against gatekeeper, solvent front, and other resistance mutations. Importantly, some mutations (i.e., xDFG) may result in conformational resistance that preclude the binding of any type I TKI, requiring the administration of a type II TKI[150].

In *ALK* fusion-positive lung cancers, improved mutational coverage is observed moving from second-generation TKIs (e.g., alectinib, ceritinib) to third-generation TKIs (e.g., lorlatinib); what could be considered as fourth-generation TKIs that additionally cover double mutations (e.g., TPX-0131[151], NVL-655[152]) are already in clinical trials. Next-generation TKIs with expanded mutation coverage are also being explored for *RET* (TPX-0046, HM06, LOXO-260), *ROS1* (repotrectinib, taletrectinib, NVL-520), and *NTRK1/2/3* (selitrectinib, repotrectinib, PBI-200). Notably, select programs (e.g., repotrectinib) have followed drug development paradigms in *ALK* fusions and moved next-generation TKI testing from TKI-pretreated to TKI-naïve patients.

RESEARCH EQUITY

A cancer population labeled “rare” may confront devaluation challenges like those faced by racial/ethnic minority groups. Research into rare populations may be deemed less important to that performed in people with more commonly diagnosed cancer subtypes. Therapeutic trials may be perceived as infeasible or of lower financial value to pharmaceutical companies. Fortunately, multiple stakeholders have mobilized to establish research equity for patients with less commonly diagnosed cancer subtypes (FIG. 6).

Advocacy

The number of biomarker-specific lung cancer patient advocacy groups has risen over the last decade (Supplementary Table 5)[153]. This paralleled the increasing recognition of rare molecular subtypes of lung cancer and the development of targeted therapies for patients with these cancers. These groups include: ALK positive (*ALK* fusions), BRAF Bombers (*BRAF* alterations), Exon 20 Group (*EGFR* and *ERBB2* exon 20 mutations), EGFR Resisters (including *EGFR* mutations beyond L858R and exon 19 deletion), KRAS

Kickers (*KRAS* mutations), MET Crusaders (*MET* alterations), NTRKers (*NTRK* fusions), RET Renegades (*RET* fusions), RET Positive (*RET* fusions), and ROS1ders (*ROS1* fusions). Initiatives have emerged such as the Biomarker Collaborative[154] that helps people find the most appropriate group for a specific molecular subtype of lung cancer.

Advocates have focused on increasing recognition of molecular subtypes of lung cancer, available standard of care and investigational therapies, treatment side effects, and physician experts. Research acceleration is another prime goal. As an example, the Global ROS1 initiative[155] promotes *ROS1* fusion-positive lung cancer research in several priority fields (education, basic science, real-world data, therapeutics, and survivorship). Under this initiative, the ROS1 Cancer Model Project allows patients to donate tumor specimens for the creation of patient-derived models.

Trials and regulation

Trial design.—Historical clinical trial designs heavily favored the exploration of more common molecular subtypes of cancer within a single histology[156]. Such strategies are not fit for function in rare cancer subtypes; various master protocols have been developed to address this challenge. Umbrella trials (e.g., BATTLE[157], Lung-MAP[158]) explore matched targeted therapy cohorts for different molecular subtypes of a single histology. Several (e.g., National Lung Matrix Trial[159]) have a central molecular screening effort. To date, many umbrella trials have been designed as signal finding studies; none of these trials have singularly supported targeted therapy approval.

Basket trial programs, in which patients are accrued by molecular alteration regardless of cancer type[160], have supported regulatory approval. The seminal tumor-agnostic approvals of TRK inhibitors demonstrate how basket trials address low frequency alterations[161]. Aggregating *NTRK* fusion-positive NSCLCs with other cancers established regulatory-grade data that resulted in TRK inhibitor approval in at least 40 countries[162]. Other design features (e.g., seamless clinical trials[163], contemporary statistical methods in adaptive designs[164]) have similarly hastened drug development (FIG. 6).

Regulatory support.—Various health care agencies have developed pathways (Supplementary Table 6) to support drug development for rare cancers. In the United States, investigational agents may gain orphan drug designation if developed for a population with a prevalence of <200,000 people[1]. This designation can provide research grant eligibility, trial tax credits, and fee waivers. In Europe, drugs may gain orphan medicinal product status if the treated condition is found in <50 out of 100,000 people. The US Food and Drug Administration (FDA) has approved more cancer drugs with orphan indications compared to the European Medicines Agency (EMA)[165].

The US FDA has several programs[166] that expedite drug approval: fast track, breakthrough therapy, priority review, and accelerated approval[167]. Drugs can receive fast-track designation (grants increased FDA interactions and rolling review) if intended to treat a serious condition and address an unmet need. In 2010, crizotinib was the first drug to receive fast-track status for a rare oncogene-driven NSCLC (Supplementary Table 6). Breakthrough therapy designation (BTD, established in 2012 with the added benefit of assigning an FDA

review committee) requires clinical evidence demonstrating substantially improved activity relative to existing treatments. In 2013, alectinib was the first drug to receive BTD for a rare oncogene-driven lung cancer.

Priority review, requested at the time of submission of a drug approval application, shortens review times to 6 months or less. Accelerated approval is a conditional approval that allows the use of surrogate endpoints for survival such as ORR; post-approval data must confirm benefit, after which a drug may receive full approval. In *ALK* fusion-positive NSCLCs, second- and third-generation TKIs first received accelerated approval for TKI-treated cancers, followed by a full approval that included TKI-naïve cancers. Trastuzumab deruxtecan was the first ADC to receive accelerated approval for a rare oncogene-driven NSCLC subtype.

Real-world evidence.—Real-world data (RWD) come from various sources[168] (e.g., wearables, electronic health records, claims, billing activities) and can be analyzed to produce real-world evidence (RWE). RWE is prospectively or retrospectively curated clinical evidence regarding the use, benefits (response, durability), and risks (adverse effects) of a medical product.

Rare cancer stakeholders have put a premium on RWE generation. Academic investigators have formed global registries for rare oncogene-driven NSCLCs (e.g., GLORY[169] for *RET* fusions, eNRGy1[57] for *NRG1* fusions). Patient-powered research networks leverage social media and online websites/applications to collate patient-reported outcomes. Commercial companies have aggregated large, deidentified RWD data sets.

Health care agencies have signaled an increased adoption of RWE to support regulatory decision making[170], owing to movements such as the 21st Century Cures Act. In rare oncogene-driven NSCLCs for which mounting a randomized trial is challenging, single-arm targeted therapy trial data may be compared to synthetic standard of care cohorts in a molecularly-enriched population. The digitalization of structured health care data, natural language processing, and artificial intelligence are likely to accelerate these efforts.

CONCLUSIONS

Lung cancer remains an archetype of a tumor enriched for rare oncogenes. These molecular subtypes of lung cancer have challenged our conceptions of mechanisms of oncogenesis and reshaped our approach to molecular diagnostics. Importantly, multiple stakeholders have responded to the increasing clinical identification of these rare alterations by putting a premium on advocacy, expanded data generation, rational drug discovery, and global regulatory openness to expediting therapeutic approvals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

• Many “rare” molecular lung cancer subtypes can individually account for a substantial number of patients diagnosed annually around the world.

• An incredible diversity of molecular subtypes exists. Mechanistically, these can be classified into mutations, fusions, and copy number changes.

• Alterations involving receptor tyrosine kinases and MAPK pathway members can share structural or oncogenic features. Conversely, other alterations function distinctly and can impact splicing or epigenetic processes.

• Optimizing the identification of rare driver oncogenes requires both clinicopathologic feature agnostic and tailored approaches to patient selection, tumor and plasma interrogation, DNA and RNA sequencing, and more unbiased profiling.

• Targeted therapy approvals were previously class saturated and dominated by small molecule tyrosine kinase inhibitors. Approved and investigational antibody-based large molecule therapies are now on the rise.

• Oncogene-driven advocacy, contemporary trial design adoption, expedited regulatory pathways for drug development, and real-world evidence generation represent crucial steps toward promoting research and drug approval for rare oncogene-driven lung cancers.

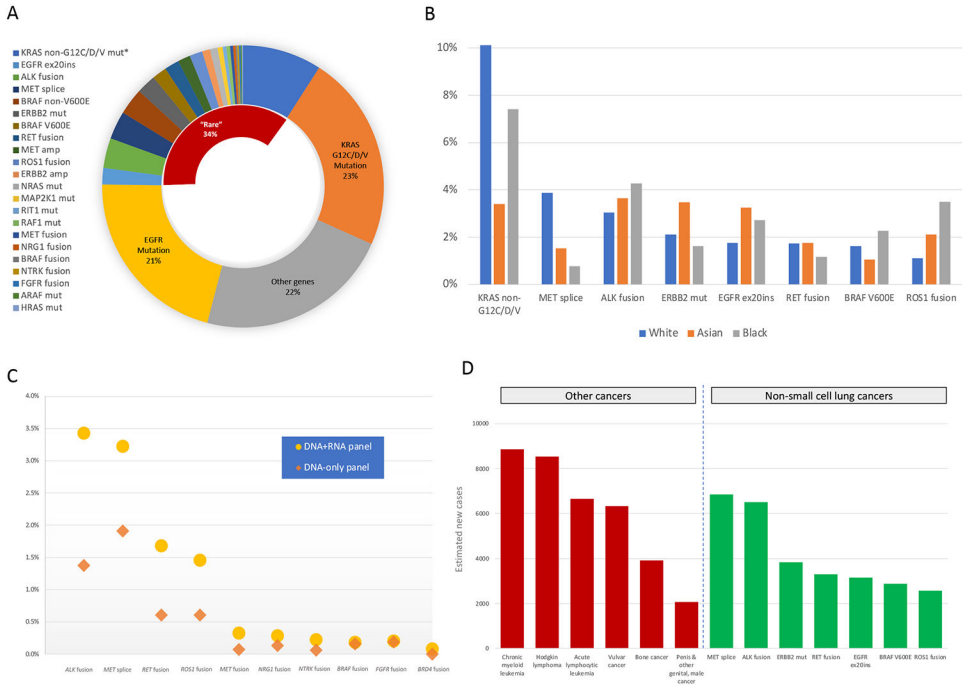

FIGURE 1. Frequency of "rare" lung cancers.

The percent prevalence of oncogenic driver alterations in lung adenocarcinoma was based on two aggregated cohorts. The first cohort, used to calculate the prevalence of non-fusion and non-*MET* exon 14 alterations, was derived from the GENIE database (v12; n=16,913)[13], the PanCancer Atlas cohort of The Cancer Genome Atlas (TCGA, n=566)[177], and the OncoSG cohort (n=305)[178]. The percent prevalence of fusions and *MET* exon 14 alterations was based on cohorts with both DNA and RNA sequencing: MSK-IMPACT 468 and 505 (Genie v.12.0)[13], TCGA[177], and OncoSG[178]. All data were extracted from and visualized via the cBioPortal[179,180]. **A.** The prevalence of oncogene-driven lung adenocarcinomas is shown, rare lung cancers comprising over a third of cases. *The KRAS non-G12C/D/V group is comprised of mutations that individually represent less than 5% of non-small cell lung cancers (NSCLCs). **B.** Prevalence can vary by race or ethnicity. Using the same dataset, the prevalence of oncogenic drivers in Caucasian, Asian, and Black patients is shown. **C.** Prevalence can also vary by the type of assay used. A comparison of the prevalence of fusions and *MET* exon 14 alterations between panels with DNA sequencing only (all panels at Genie v.12.0 except for MSK IMPACT 468 and 505[13]) and panels with both DNA and RNA sequencing (MSK-IMPACT 468 and 505[13], TCGA[177], OncoSG[178]) is shown. **D.** Estimates for the annual incidence of each molecular subtype of NSCLC in the United States are derived from the GENIE database (v12; n=19,777 NSCLCs[13]) and statistics from Cancer.Net[181] that summarized data from the American Cancer Society, Cancer Facts & Figures 2022, and the International Agency for Research on Cancer.

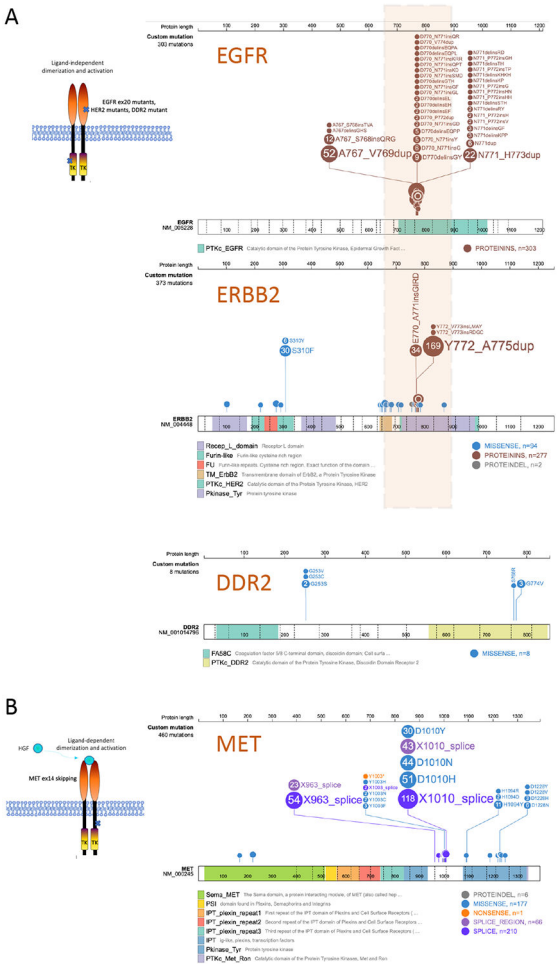

FIGURE 2. Receptor tyrosine kinase gene mutations.

A. Mutations involving *EGFR*, *ERBB2*, and *DDR2* that result in constitutively active oncogenic kinases that are putatively ligand independent are shown. *EGFR* insertions (e.g., the 9 base-pair insertions SVD or NPH, or the 12 base-pair insertion FQEA) typically occur between residues 769 and 775 while *ERBB2* insertions (e.g., the 12 base-pair insertion YVMA) occur between residues 775 and 881. *DDR2* mutations affect extracellular (e.g., *DDR2* G253S) and intracellular domains (e.g., *DDR2* G774V). **B.** *MET* mutations can similarly occur at various extracellular and intracellular domains. *MET* exon 14 alterations are thought to be ligand dependent. These mutation types are not intuitively annotated and can be missed by clinicians when reviewing reports. The *MET* exon 14 alteration c.2888-40_2888-19del20 is an example. This represents a 20-base-pair deletion in the intronic region adjacent to the splice acceptor site at the 5’ boundary of *MET* exon 14; the deletion involves positions −40 to −19 preceding the start of the exon 14 coding sequence at position 2888. The variants were selected from lung adenocarcinomas in the GENIE database (v12)[13] and represent driver mutations as annotated by OncoKB and hotspot recurrence[182].

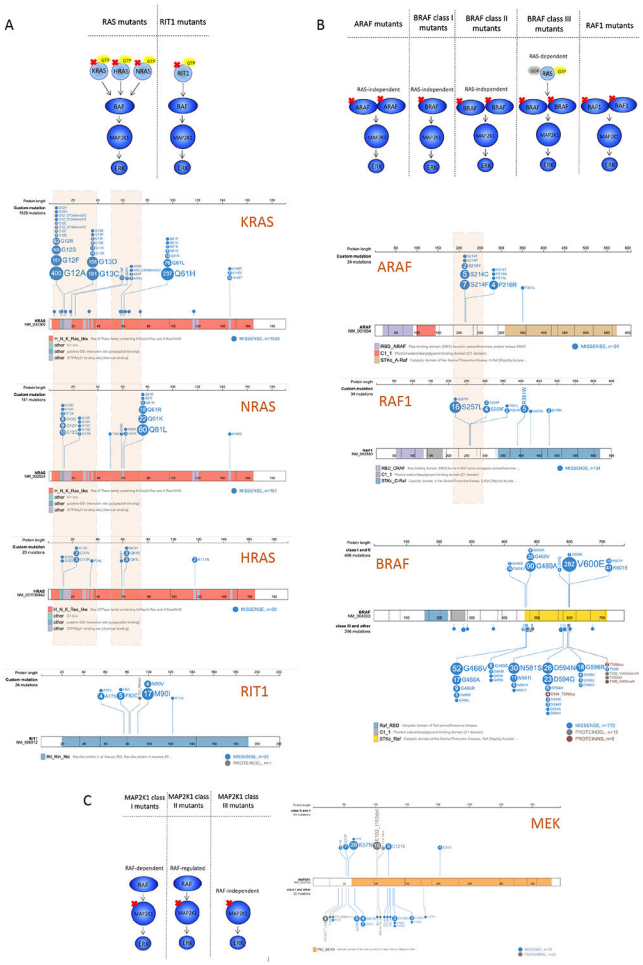

FIGURE 3. RAS and MAPK family mutations.

A. Mutations in *KRAS*, *NRAS*, and *HRAS* can affect a variety of residues, including the paralogous G12, G13, and Q61 residues. *RIT1* encodes a small GTPase. *RIT1* mutations can affect the A77, F82, and M90 residues close to the switch II pocket. **B.** *ARAF* mutations commonly affect S214 in addition to other residues. To date, mutations in the S214 codons are the only mutations in ARAF that have been proved to be oncogenic in lung cancer. *RAF1* mutations involve S257 and S259 (an ARAF S214 paralogue). *BRAF* mutations affect V600 and a wide variety of non-V600 residues (e.g., G466, G469, N581, D594, G596, and K601) in the serine/threonine kinase domain. *BRAF* V600E is considered a class I (RAS-independent) alteration, while class II (RAS-independent) and class III (RAS-dependent) alterations are comprised of many non-V600 substitutions. **C.** *MAP2K1* class I mutations (e.g. D67N) are RAF-independent. Class II mutations (e.g. K57N, a common *MAP2K1* mutation) can be modulated when phosphorylated by RAF and may occur in isolation or co-occur with ERK-activating alterations. Class III mutations are both RAF and phosphorylation independent, constitutively active, and highly oncogenic. The variants were selected from lung adenocarcinomas in the GENIE database (v12)[13] and represent driver mutations as annotated by OncoKB and hotspot recurrence[182].

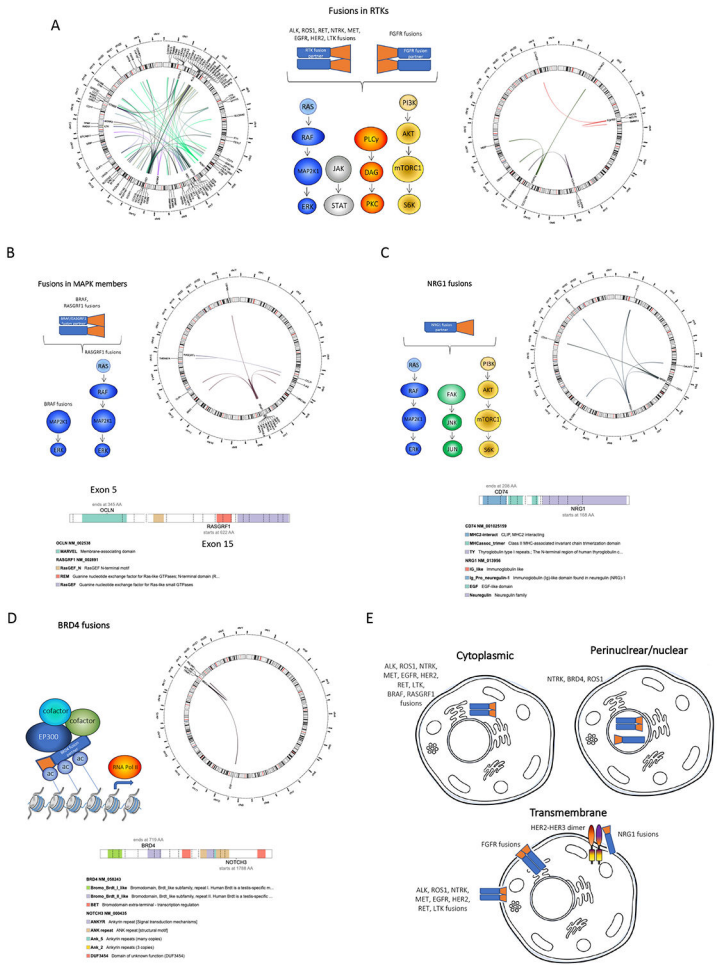

FIGURE 4. Fusions.

A. Intrachromosomal and interchromosomal fusions involving receptor tyrosine kinase genes are shown. Classical 3’ fusions harbor the RTK in the downstream position. These include *ALK*, *RET*, *ROS1*, *NTRK* (more commonly *NTRK1*/3 than *NTRK2*), *ERBB1/2/4*, *MET*, and *LTK* (e.g., *CLIP1-LTK*) fusions. 5’ fusions harbor the RTK upstream; *FGFR1/2/3* fusions are examples. MAPK, JAK-STAT, PLCγ, and PI3K-AKT pathways signaling occurs. Upstream partners are shown in the flanking Circos plots. Common fusions in lung cancer include *EML4-ALK*, *KIF5B-RET*, and *CD74-ROS1*; 5’ partner preference may be influenced by intrinsic genome stability, susceptible loci and transcriptional activation. **B.** Fusions involving MAPK pathway members (RASGRF1 and BRAF) are shown. These putatively signal through MEK-ERK. Many *RASGRF1* fusions (e.g. *OCLN-RASGRF1*) feature a transmembrane domain that anchors the RAS-GEF domain to the cell membrane, facilitating RAS activation. *BRAF* fusions (e.g. *TRIM24-BRAF, LIMD1-BRAF*) often include the BRAF kinase in the 3’ position. **C.** *NRG* fusions can additionally signal through FAK-JNK-JUN. NRG1 (commonly CD74-NRG1/SLC3A2-NRG1) and NRG2 (CD74-NRG2α) serve as ligands for ERBB family members; NRG2 fusions may preferentially activate ERBB4. **D.** BRD4-NOTCH3 includes bromo/extraterminal domains that sequester histone acetyltransferases and other transcriptional co-factors to chromatin

regions that transcribe pro-proliferative and anti-differentiation genes. **E.** The cellular localization of specific fusions is shown.

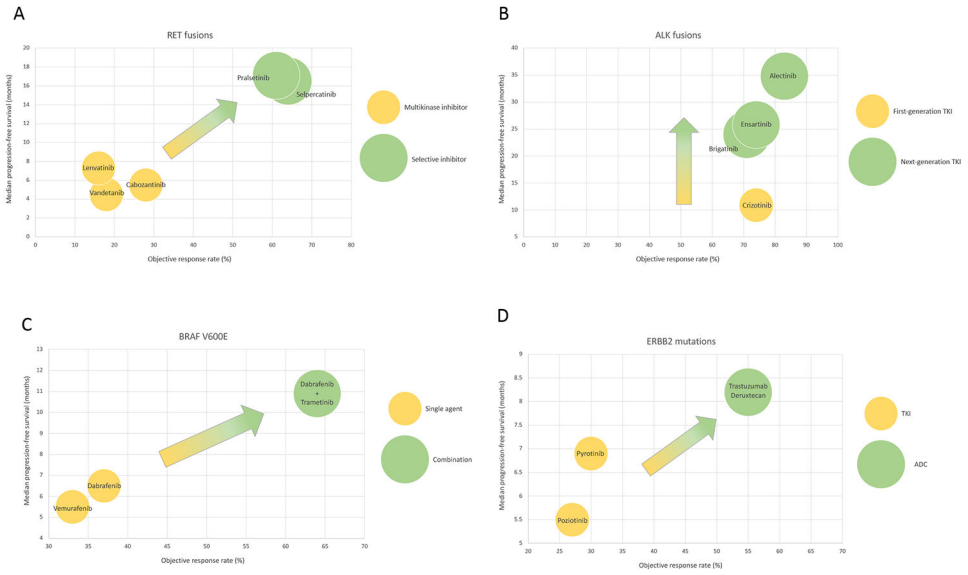

FIGURE 5. Rational drug design trends.

The improvements in clinical outcomes accompanied by advancements in rational drug design are depicted in these bubble plots. The objective response rate (ORR) is shown on the x-axes. The median progression-free survival (PFS) is shown on the y-axis. Each circle represents a specific targeted therapy strategy, including single agents and combination therapies. **A.** In *RET* fusion-positive lung cancers, both ORR and median PFS improved with the move from multikinase inhibitors[138,139,183] with anti-RET activity to the highly selective RET inhibitors, selpercatinib and pralsetinib[119,120], that entered clinical testing in 2017. **B.** Generational changes in tyrosine kinase inhibitor (TKI) use can result in substantial improvements in median progression-free survival. Specifically, later generation ALK TKIs (e.g. alectinib, brigatinib, ensartinib, and lorlatinib [not shown due to the median PFS not yet being reached][125,126,146,174]) with improved central nervous system and resistance mutation coverage have replaced the first-generation ALK TKI crizotinib based on randomized phase 3 clinical trial data[121]. **C.** The utility of combination small molecule therapies was demonstrated by the move from single-agent BRAF inhibition with dabrafenib or vemurafenib[110,111], to the combination of a BRAF inhibitor and a MEK inhibitor (dabrafenib and trametinib)[102]. **D.** Finally, the increase in both ORR and median PFS with trastuzumab deruxtecan[98] compared to pyrotinib and poziotinib[106,107] underscore the meaningful entry of a new wave of large molecules into the clinic.

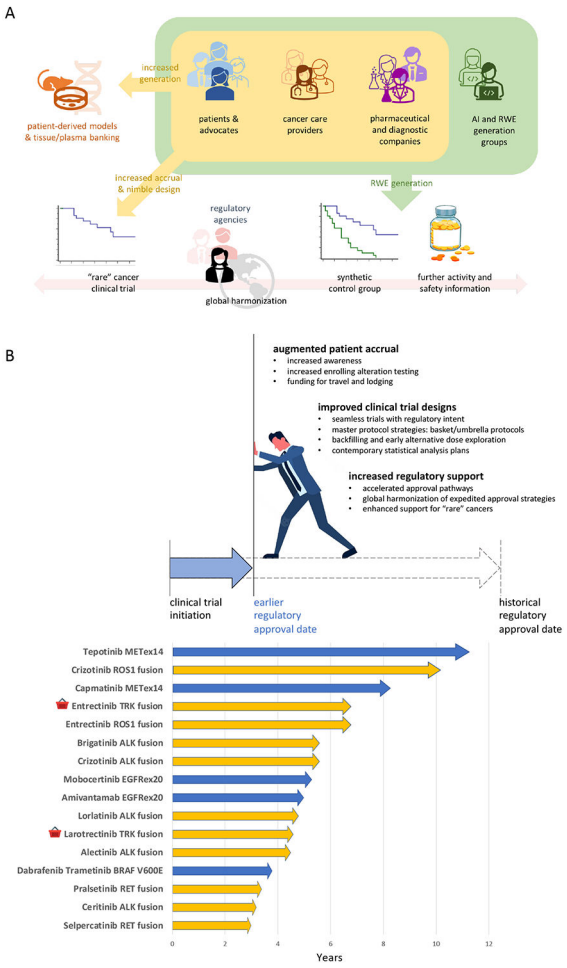

FIGURE 6. Stakeholder cooperation.

A. In the field of rare cancer research, multiple stakeholders have come together to generate an increasing amount of data. These stakeholders include patients and their advocates, cancer care providers, pharmaceutical and diagnostic companies, and artificial intelligence (AI) and real-world evidence (RWE) groups. Efforts to increase model/tissue/plasma generation, trial accrual, and global targeted therapy approvals are critical. **B.** Factors that are poised to increase the speed with which molecularly-matched therapeutics are approved are shown above. Below, the time to the approval of various targeted therapies in oncogene-driven lung cancers is shown relative to the date the first phase 1 trial was launched.

Table 1.

Clinical activity of targeted therapies.

The patient population, objective response rate (ORR), median progression-free survival (PFS) and median overall survival (OS) of various targeted therapies in “rare” lung cancers are summarized.

Molecular alteration	Agent name	Patient Population	Mechanism of action	ORR	Median DoR	Median PFS	Median OS
EGFR exon 20 insertions	Amivantamab *,^[104]	Pretreated	EGFR-MET BiAb	40%	11.1 months	8.3 months	22.8 months
	Mobocertinib *,^[103]	Pretreated	EGFR TKI	28%	17.5 months	7.3 months	24 months
	Poziotinib[107]	Treatment-naïve and pretreated	EGFR and ERBB2 TKI	32%	8.6 months	5.5 months	19.2 months
	CLN-081 **[143]	Pretreated	EGFR TKI	38%	10 months	10 months	Not mature
BRAF V600E mutations	Dabrafenib + Trametinib *,^[102]	Treatment-naïve	BRAF S/TKI and MEK1/2 inhibitor	64%	10.4 months	10.9 months	24.6 months
	Dabrafenib ^[110]	Treatment-naïve and pretreated	BRAF S/TKI	33%	9.9 months	5.5 months	12.7 months
	Vemurafenib ^[111]	Treatment-naïve and pretreated	BRAF S/TKI	37%	7.2 months	6.5 months	15.4 months
ERBB2 mutations	Trastuzumab deruxtecan *,^[98]	Pre-treated	ERBB2 ADC	55%	9.3 months	8.2 months	17.8 months
	Trastuzumab emtansine ^[108]	Treatment-naïve and pretreated	ERBB2 ADC	44%	4 months	5 months	Not reported
	Trastuzumab + Pertuzumab + Docetaxel[171]	Pretreated	ERBB2 mAb and chemo	29%	11 months	6.8 months	17.6 months
	Poziotinib **[107]	Treatment-naïve and pretreated	EGFR and ERBB2 TKI	27%	5 months	5.5 months	15 months
	Pyrotinib[106]	Pretreated	Pan-ERBB TKI	30%	6.9 months	6.9 months	14.4 months
ERBB2 copy number increases	Pyrotinib[136]	Treatment-naïve and pretreated	Pan-ERBB TKI	22%	7.2 months	6.3months	12.5 months
	Pertuzumab + Trastuzumab[135,172]	Pretreated (included ERBB2 amplification/ overexpression	ERBB2 mAb	13%	Not reported	Not reported	Not reported
MET exon 14 alterations	Capmatinib *,^[100]	Treatment-naïve	Type Ib MET TKI	68%	12.6 months	12.4 months	Not reported
		Pretreated	Type Ib MET TKI	41%	9.7 months	5.4 months	Not reported
	Tepotinib *,^[101]	Treatment-naïve and pretreated	Type Ib MET TKI	46%	11.1 months	8.5 months	17.1 months
	Crizotinib ^[133,144]	Treatment-naïve and pretreated	Type Ia MET TKI	32%	9.1 months	7.3 months	20.5 months
	Savolitinib[173]	Treatment-naïve and pretreated	Type Ib MET TKI	47%	Not reported	6.8 months	12.5 months
	Amivantamab[105]	Treatment-naïve and pretreated	EGFR-MET BiAb	33%	Not reached	Not reported	Not reported

Molecular alteration	Agent name	Patient Population	Mechanism of action	ORR	Median DoR	Median PFS	Median OS
MET copy number increases	Capmatinib[^100]	Treatment-naïve (GCN ≥10)	Type Ib MET TKI	40%	7.5 months	4.2 months	Not reported
		Pretreated (GCN ≥10)	Type Ib MET TKI	29%	8.3 months	4.1 months	Not reported
	Tepotinib[^134]	Treatment-naïve and pretreated (MET gene copy number ≥2.5)	Type Ib MET TKI	42%	Not reached	4.2 months	Not reported
	Crizotinib[^133]	Treatment-naïve and pretreated (MET/CEP7 ≥4)	Type Ia MET TKI	38%	5.2 months	6.7 months	11.4 months
ALK fusions	Crizotinib[*^121]	Treatment-naïve	1st gen ALK TKI	74%	11.3 months	10.9 months	Not reached
	Ceritinib[*^122]	Treatment-naïve	2nd gen ALK TKI	73%	23.9 months	16.6 months	Not reached
	Alectinib[*^124,146]	Treatment-naïve	2nd gen ALK TKI	83%	28.1 months	34.8 months	Not reached
	Brigatinib[*^125]	Treatment-naïve	2nd gen ALK TKI	71%	33.2 months	24 months	Not reached
	Ensartinib[174]	Treatment-naïve	2nd gen ALK TKI	74%	Not reached	25.8 months	Not reached
	Lorlatinib[*^126]	Treatment-naïve	3rd gen AK TKI	76%	Not reached	Not reached	Not reached
RET fusions	Selpercatinib[*^119]	Treatment-naïve	RET TKI	85%	Not reached	Not reached	Not reached
		Pretreated	RET TKI	64%	17.5 months	16.5 months	Not reached
	Pralsetinib[*^120]	Treatment-naïve	RET TKI	70%	9 months	9.1 months	Not reached
		Pretreated	RET TKI	61%	Not reached	17.1 months	Not reached
ROS1 fusions	Crizotinib[*^117]	Treatment-naïve and pretreated	ROS1 TKI	72%	24.7 months	19.3 months	51.4 months
	Ceritinib[^175]	Pretreated	ROS1 TKI	62%	21 months	9.3 months	24 months
	Entrectinib[*^118]	Treatment-naïve	ROS1 TKI	68%	20.5 months	15.7 months	47.8 months
	Lorlatinib[^147]	Treatment-naïve and pretreated	ROS1 TKI	62%	25.3 months	21 months	Not reached
	Repotrectinib[**^176]	Treatment-naïve	ROS1 TKI	79%	Not reported	Not reported	Not reported
NTRK1/2/3 fusions	Larotrectinib[*^114]	Treatment-naïve and pretreated	NTRK TKI	83%	Not reached	Not reached	40.7 months
	Entrectinib[*^141]	Treatment-naïve and pretreated	NTRK TKI	64%	19.9 months	14.9 months	Not reached
NRG1 fusions	Zenocutuzumab[**^128]	Treatment-naïve and pretreated	ERBB2-ERBB3 BiAb	35%	9.1 months (pan-tumor; not reported in the NSCLC cohort)	Not reported	Not reported
	Seribantumab[**^129]	Pretreated	ERBB3 mAb	36%	Not reached	Not reported	Not reported

ADC, antibody-drug conjugate; BiAb, bispecific antibody; chemo, chemotherapy; DoR, duration of response; mAb, monoclonal antibody; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; S/TKI, serine/threonine kinase inhibitor; TKI, tyrosine kinase inhibitor

* FDA-approved

^ included in the NCCN guidelines

** Fast Track/ Breakthrough designation by FDA