Trends in Cancer

CellPress

Review

Targeting Infrequent Driver Alterations in Non-Small Cell Lung Cancer

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The discovery of oncogenic driver mutations led to the development of targeted therapies with non-small cell lung cancer (NSCLC) being a paradigm for precision medicine in this setting. Nowadays, the number of clinical trials focusing on targeted therapies for uncommon drivers is growing exponentially, emphasizing the medical need for these patients. Unfortunately, similar to what is observed with most targeted therapies directed against a driver oncogene, the clinical response is almost always temporary and acquired resistance to these drugs invariably emerges. Here, we review the biology of infrequent genomic actionable alterations in NSCLC as well as the current and emerging therapeutic options for these patients. Mechanisms leading to acquired drug resistance and future challenges in the field are also discussed.

Highlights

Lung cancer is responsible for around 1.8 million deaths per year worldwide and is widely the leading cause of cancer-related mortality.

The development of specific inhibitors is currently extending to less common oncogenic drivers (i.e., *ROS1*, *MET*, *RET*, *NTRK*, *HER2*, and *BRAF*) with an exponential growth of dedicated clinical trials.

While, individually, each of these drivers appears with low prevalence, altogether, they account for 15% of all lung cancer cases, thereby affecting a large population of patients worldwide.

Similar to what is observed with most targeted therapies directed against an oncogenic driver, the initial clinical response to targeted kinase inhibitors is almost always temporary and acquired resistance to these drugs invariably emerges, restricting their clinical utility.

The characterization of intrinsic and acquired resistance relies on tissue or liquid biopsy upon disease progression. However genomic testing does not always capture the underlying mechanism of resistance.

Both on-target and off-target resistance mechanisms to targeted therapies could be tackled in the clinic but the design of the most effective treatment still requires further evaluation.

The Challenge of Targeted Therapy in NSCLC Driven by Uncommon Genetic Alterations

The expanding spectrum of oncogenic driver mutations and clinically available signaling pathway inhibitors had a major impact on **non-small cell lung cancer (NSCLC)** (see Glossary) patient management in the past decade [1]. Cancer driver mutations not only initiate the disease but also sustain tumor progression and therefore their inhibition results in a therapeutic benefit. Driver oncogenes are often identified due to their recurrence in patients, a complicated feature when they appear with low prevalence, as those covered in this review. Yet the oncogenic nature and the addiction of cancer cells to this set of infrequent drivers have been clearly established, as well as their mutually exclusive pattern with other oncogenes. With the exception of BRAF, all belong to the receptor tyrosine kinase (RTK) family and, when in the oncogenic form, constantly activate essential downstream signaling pathways, including **MAPK**, PI3K, and JNK, resulting in sustained growth, increased survival, and enhanced dissemination. Recently, the FDA has approved specific inhibitors targeting infrequent NSCLC oncogenic drivers (*ROS1*, *MET*, *RET*, *BRAF*, and *NTRK*). Beyond those, promising preliminary data with compounds targeting other emerging driver alterations (e.g., *HER2*) have been reported [2]. Used as first or latter lines of treatment (after standard chemotherapy and/or immunotherapy), these targeted therapies have greatly increased patient outcome [3–9]. Unfortunately, as anticipated by the lessons learned from the clinical management of *EGFR*-mutated and *ALK*-rearranged lung adenocarcinoma (LUAD) (Box 1), therapeutic resistance eventually appears in most patients and, therefore, advanced NSCLC remains largely incurable (for review see [10]). In the present review, we describe the biological relevance and the therapeutic options of a series of infrequent drivers for which clinical treatments have been approved or are under evaluation. Likewise, the clinical management of on-target resistance is discussed per driver, while that due to bypass signaling is collectively addressed given its pan-driver conservation.

ROS1

Biological and Clinical Features

ROS1 is a conserved orphan RTK, initially identified in glioblastoma, and was the first chromosomal rearrangement described in NSCLC [11]. Since then, several *ROS1* breakpoints have

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Box 1. Targeting *EGFR* and *ALK* Alterations in NSCLC

EGFR mutations occur in 15% of NSCLC, in-frame deletion in exon 19 (19Del) or L858R mutation being the most frequent. Both first-generation (erlotinib and gefitinib) and second-generation (afatinib) inhibitors demonstrated more durable responses than chemotherapy [160–164], receiving FDA approval as first-line treatments in 2013 and 2014. In almost half of patients treated with these compounds, resistance is mediated by the T790M gatekeeper mutation (equivalent to those described in *ROS1*, *RET*, and *NTRK*; see Figure 2A in main text). Third-generation EGFR inhibitors such as osimertinib demonstrated impressive response in patients with EGFR T790M-positive NSCLC after progression on early-generation TKIs, receiving FDA approval in 2017 [165]. Due to its ability to spare wild type EGFR, inhibit EGFR 19Del/L858R/T790M, and CNS penetration, osimertinib has been approved as first-line treatment since 2018 [166]. Unfortunately, new resistance mechanisms have emerged, like the tertiary C797S mutation affecting the covalent binding of the drug [167,168] or the development of T790 wild type clones [169].

ALK rearrangements are observed in 5% of NSCLC, *EML4-ALK* being the most prevalent. At least 15 EML4-ALK variants have been identified so far, with some expressed as multiple isoforms [170]. All contain the ALK entire intracellular kinase domain (exons 20–29) but differ in the breakpoint with the *EML4* gene. First-generation crizotinib received FDA approval in 2011, becoming the first approved ALK inhibitor for NSCLC [171]. Almost one-third of crizotinib-treated patients acquire resistance by kinase domain mutations, with L1196M gatekeeper and G1269A mutations being the most frequent. In 2014, second-generation ALK inhibitor ceritinib was approved after confirmation of its efficacy in both crizotinib-naïve and crizotinib-resistant patients with L1196M and G1269A/S mutations [172,173]. In approximately half of cases, resistance is caused by emergence of additional *ALK* mutations, the most common being the solvent-front substitution G1202R. Therefore, two other second-generation ALK inhibitors, alectinib and brigatinib, were granted accelerated FDA approval for *ALK*-positive patients who had failed on crizotinib treatment, demonstrating superior inhibitory profile against all 17 known secondary *ALK* mutations [174,175]. Both alectinib and brigatinib were later also approved as first-line therapy in treatment-naïve patients, although alectinib has become the preferred agent. Recently, the third-generation ALK/ROS1 inhibitor lorlatinib, specifically designed to target resistance mutations and to penetrate the blood–brain barrier, received accelerated FDA approval for the treatment of patients with *ALK*-rearranged advanced NSCLC after progression on crizotinib and at least one other ALK inhibitor [176]. The Phase III trial CROWN, comparing lorlatinib with crizotinib as first-line therapy, is currently ongoing[vi].

been described involving the entire ROS1 kinase domain and accounting for 1–2% of NSCLC. Twenty fusion partners (e.g., *SLC34A2*, *EZR*, and *SDC4*) have been reported, among which *CD74-ROS1* is the most common [12–14]. Whether distinct partners are functionally equivalent is unknown, although *in vitro* data indicates that they impose changes in subcellular localization, affecting signaling and oncogenic properties [15]. Unlike *ALK* rearrangements, most of the known ROS1 fusion partners lack constitutive dimerization domains and the mechanism of ROS1 oncogenic activation remains unknown. Along with *RET* and *NTRK*, *ROS1* rearrangements are associated with younger age at diagnosis, none or low tobacco exposure, and generally have adenocarcinoma histology [16,17]. Diagnosis of ROS1 fusions by immunohistochemistry (IHC) is the most cost-effective method requiring confirmation by break-apart probe fluorescent *in situ* hybridization (FISH) or hybrid RNA-based next-generation sequencing (NGS) if the RNA quality is optimal [18,19].

Frontline Targeted Therapy

ROS1-positive lung cancer seems particularly sensitive to pemetrexed-based chemotherapy [20]. The ALK inhibitor crizotinib was supposed to efficiently target *ROS1*-rearranged tumors given that ROS1 and ALK belong to the insulin receptor superfamily [21], sharing >80% of amino acid sequence within their ATP-binding sites. Furthermore, crizotinib binds with high affinity to both kinases, inhibiting cell line proliferation. Indeed, this hypothesis was corroborated in the clinic, with crizotinib showing marked therapeutic effect in patients with *ROS1*-rearranged NSCLC [22]. Accordingly, crizotinib, first approved for the treatment of *ALK*-rearranged NSCLC, received FDA and European Medicines Agency (EMA) expanded approval in 2016 for *ROS1*-rearranged NSCLC [22–26] (Figure 1 and Table 1). Similarly, in 2020, entrectinib obtained FDA and EMA approval in this tumor type [8,27]. In addition, other kinase inhibitors, including ceritinib and lorlatinib, have been evaluated in *ROS1*-positive crizotinib naïve NSCLC [28,29] (Figure 1 and Table 1).

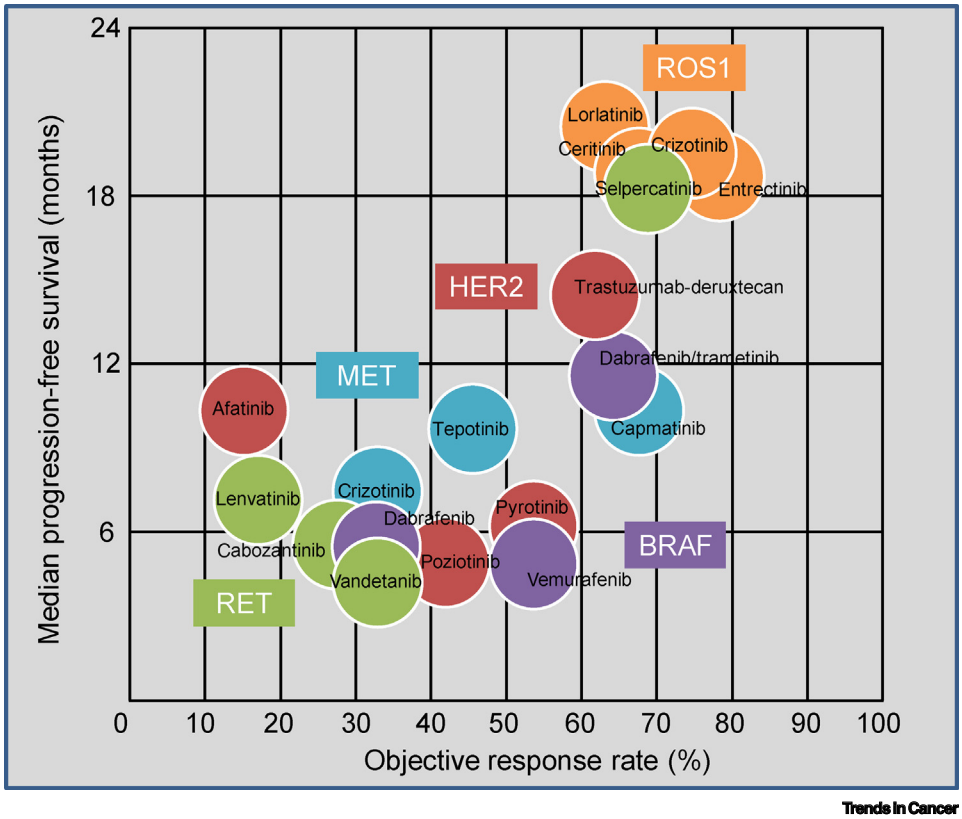

Figure 1. Comparative Clinical Efficacy of Targeted Therapies in *ROS1*-, *MET*-, *RET*-, *HER2*-, and *BRAF*-Altered Lung Cancers. Each circle on the plot represents the efficacy of the indicated inhibitor in patients for each specific driver (indicated with the different colors). Inspired by Figure 5 by Drilon and colleagues [57]. X and Y axis represent the objective response rate and the median progression-free survival duration, respectively, as reported from Phase I and II clinical trials (see main text and Table 1 for details and references).

Glossary

Epithelial to mesenchymal transition (EMT): process by which epithelial cells lose their epithelial phenotype and gain mesenchymal properties.

MAPK: signaling cascade (RAS-RAF-MEK-ERK) that mediates signals from cell surface receptors regulating cell growth, differentiation, and survival.

Median progression-free survival (mPFS): length of time during and after the treatment that a patient lives with the disease and does not get worse.

Non-small cell lung cancer (NSCLC): major subtype of lung cancer (accounts for 80–90% of all lung cancers) comprising both squamous neoplasms and adenocarcinoma (LUAD).

Overall response rate (ORR): proportion of patients in a trial whose tumor is significantly reduced by a drug.

Addressing On-Target Mechanisms of Resistance

The accumulated knowledge after a decade of using RTK inhibitor for the treatment of *ALK*- and *EGFR*-mutant LUAD (Box 1) anticipated that the selection of on-target mutations within the kinase domain would be the main mechanism of acquired resistance in ROS1 and the rest of infrequent drivers covered in this review. Indeed, several mutations have been reported affecting the solvent-front, the gatekeeper residue, the activation loop, or the DFG motifs and all are predicted to prevent drug binding due to steric hindrance. Figure 2A summarizes the different on-target mutations identified and their functional analogy among the different drivers, together with ALK and EGFR for comparative purposes.

Fortunately, also guided by the successful clinical management of resistant disease in EGFR- and ALK-mutant patients (Box 1), new generation inhibitors have been identified or purposely designed to combat drug resistance. Figure 2B summarizes preclinical and clinical data regarding the sensitivities of the most common secondary mutations to a panel of inhibitors for each driver. In the case of ROS1, resistance profiling studies using both *in vitro* and *in vivo* models demonstrated that cabozantinib (and its structural analog foretinib) as well as DS-6051b (a novel ATP-competitive ROS1/NTRK inhibitor) markedly inhibited the growth of *ROS1* G2032R mutants [30–35]. Indeed, several case reports of *ROS1*-rearranged LUAD patients, resistant to crizotinib and ceritinib, reported responses to cabozantinib [36,37]. With similar efficacy, DS-6051b had

Table 1. Comparative Clinical Efficacy of Targeted Therapies in *ROS1*-, *MET*-, *RET*-, *NTRK*-, *HER2*-, and *BRAF*-Altered Lung Cancers

Driver	Drug	Clinical trial identifier[a]/name (phase)	NSCLC (*n*)	ORR (%)	mPFS (months)	Intracranial disease control (*n*, %)	FDA approval	Refs
ROS1	Crizotinib	EUROS1 (retrospective)	32	80	9.1		2016	[24]
		NCT00585195/PROFILE 1001 (I)	50	72	19.2			[22]
		NCT01945021 (II)	127	71.7	15.9			[25]
		NCT02183870/EUCROSS (II)	34	70	20			[26]
		NCT02034981/AcSé (II)	78	47.2				[23]
	Ceritinib	NCT01964157 (II)	32 (30 crizotinib naïve)	62 (overall) and 67 (naïve)	9.3 (overall) and 19.3 (naïve)	5/8 (63%)		[28]
	Lorlatinib	NCT01970865 (I/II)	40 (previously treated) and 21 (TKI naïve)	35 (previously treated) and 62 (naïve)	8.5 (previously treated) and 21 (naïve)	Previously treated: 12/24 (50%) Naïve: 7/11 (64%)		[29]
	Entrectinib	NCT02097810/STARTRK-1 (I), NCT02568267/STARTRK-2 (II), and EudraCT 2012–000148–88/ALKA-372-001 (I)	53	77	19	11/20 (55%)	2019	[8,27]
MET	Crizotinib	NCT00585195/PROFILE 1001 (I)	65	32	7.3			[73]
	Tepotinib	NCT02864992/VISION (II)	99	46	8.5	6/11 (55%)		[74]
	Capmatinib	NCT02414139/GEOMETRY mono-1 study (II)	69 (previously treated) and 28 (naïve)	41 (previously treated) and 64 (naïve)	5.4 (previously treated) and 12.4 (naïve)	12/13 (92%)	2020	[9]
RET	Vandetanib	UMIN000010095/LURET (II)	19	47	4.7			[185]
		NCT01823068 (II)	17	18	4.5			[186]
	Cabozantinib	NCT01639508 (II)	25	28	5.5			[187]
	Lenvatinib	NCT01877083 (II)	25	16	7.3			[188]
	Cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib or regorafenib	GLORY (retrospective)	53	26	2.3			[54]
	RXDX-105	NCT01877811 (I/Ib)	31 (RET inhibitor naïve)	19 (0% with KIF5B-RET and 67% with non-KIF5B partners)				[189]
	Alectinib	UMIN000020628 (II) and NCT03131206 (II)	Ongoing					
	Pralsetinib	NCT03037385/ARROW (I/II)	116 (26 naïve)	65 (overall) and 73 (naïve)		5/9 (56%)	2020	[5]
		NCT04222972/AcceleRET (III)	Ongoing					
	Selpercatinib	NCT03157128/LIBRETTO-001 (I/II)	105 (previously treated) and 39 (naïve)	64 (previously treated) and 85 (naïve)	16.5 (previously treated)	10/11 (91%)	2020	[4]
		NCT04194944/LIBRETTO-431 (III)	Ongoing					

NTRK	Larotrectinib	NCT02122913 (I)	12	88 (pan cancer)			2018	[6]
		NCT02576431 (II)	Ongoing					
	Entrectinib	NCT02097810/STARTRK-1 (I), NCT02568267/STARTRK-2 (II), and EudraCT 2012–000148–88/ALKA-372-001 (I)	10	57 (pan cancer)	11.2 (pan cancer)		2019	[7]
HER2	Afatinib	Retrospective	10	33				[190]
		Retrospective	23	13				[191]
		NCT02369484/NICHE (II)	13	53.8	15.9			[192]
	Dacomitinib	NCT00818441 (II)	26	12	3			[193]
	Neratinib	NCT01953926/SUMMIT (II)	26	4	5.5			[194]
	Pyrotinib	NCT02535507 (II)	15	53.3	6.4			[195]
		NCT02834936 (II)	Ongoing					
	Mobocertinib (TAK-788)	NCT02716116 (I/II)	21					[95]
	Poziotinib	NCT03066206 (II)	12	42	5.6			[93,196]
	Trastuzumab-deruxtecan	NCT03505710/DESTINY-Lung 01 (II)	42	61.9	14			[96]
BRAF	Vemurafenib, dabrafenib, or sorafenib	European EURAF (retrospective)	35	53	5			[105]
	Vemurafenib	NCT01524978/VE-BASKET (II)	62 (8 naïve)	37.1 (overall), 37 (previously treated), and 37.5 (naïve)	6.5 (overall), 6.1 (previously treated), and 12.9 (naïve)			[107]
		NCT02304809/AcSé (II)	101	44.8	5.2			[106]
	Dabrafenib	NCT01336634 (II)	78 (previously treated) and 6 (naïve)	33 (previously treated) and 67 (naïve)	5.5 (previously treated)			[108]
	Dabrafenib and trametinib	NCT01336634 (II)	57 (previously treated) and 36 (naïve)	63.2 (previously treated) and 64 (naïve)	10.2 (previously treated) and 10.9 (naïve)		2017	[3,109]
	Encorafenib and binimetinib	NCT03915951/PHAROS (II)	Ongoing					
	Ulixertinib	NCT01781429 (I)	12 (BRAFi/MEKi naïve)	25		1/12 (8%)		[114]
	LXH254 and LLT462	NCT02974725 (I)	Ongoing					

[a]www.clinicaltrials.gov or www.umin.ac.jp

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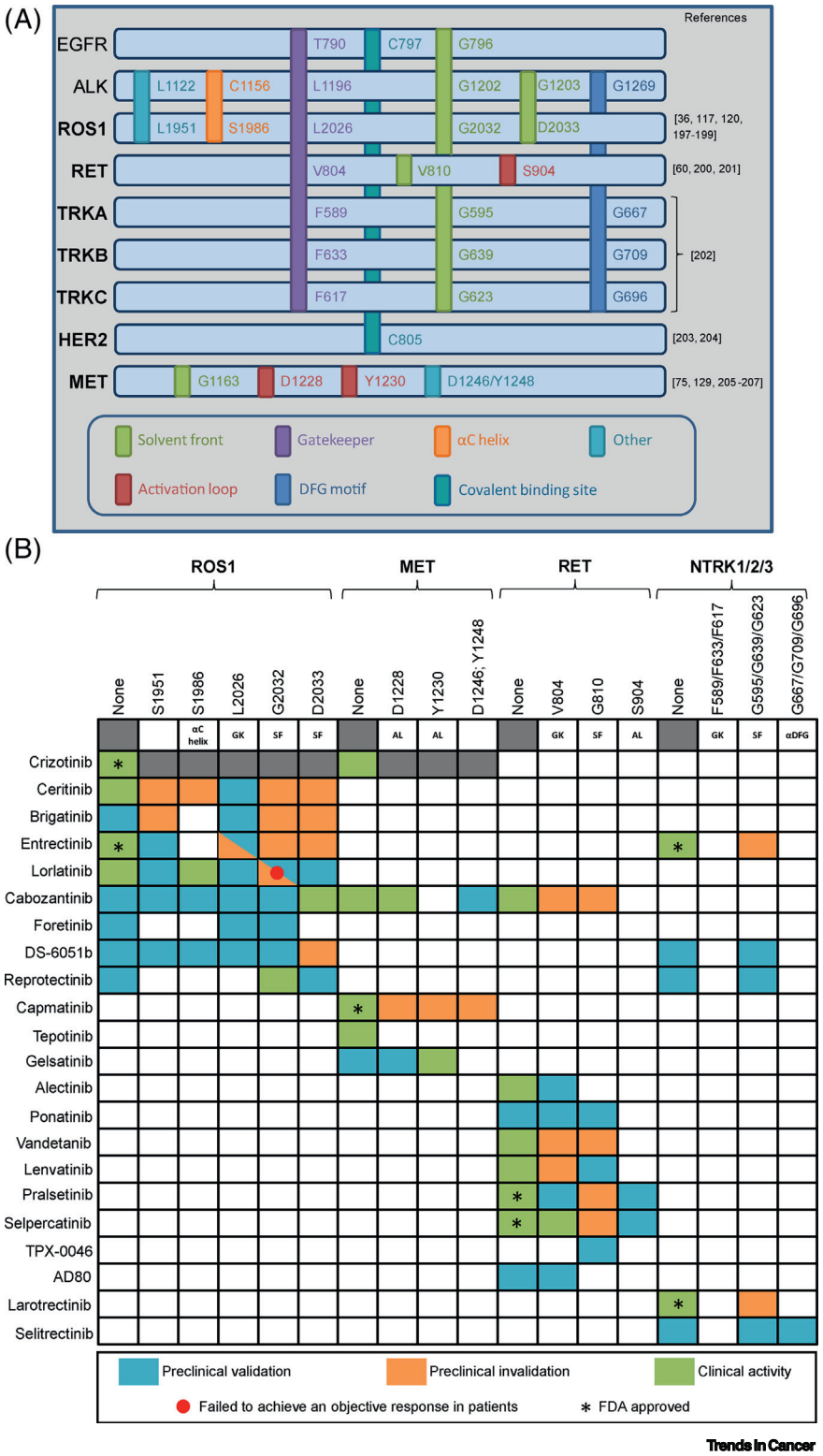

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better toxicity profile [38] and two ongoing clinical trials are evaluating its efficacy in *ROS1*-rearranged NSCLC[i,ii]. In addition, repotrectinib (TPX-0005), a selective and highly potent tyrosine kinase inhibitor (TKI) against ROS1, NTRK, and ALK, demonstrated potent antiproliferative activity against the G2032R and D2033N *ROS1* mutations in cellular inhibitory assays and xenografts [39]. This has been tentatively confirmed in a clinical setting (TRIDENT-1, NCT03093116) reporting that repotrectinib achieved tumor regression in 45% of patients with *ROS1*-positive NSCLC resistant to prior TKI(s) [40,41]. Interestingly, not all on-target mutations are equally sensitive to new generation inhibitors and patient stratification will be required. Indeed, each TKI is structurally distinct, with varying degrees of activity against the different resistance mutations, giving them unique activity profiles. This is illustrated by lorlatinib, which demonstrated promising activity in 40 patients with *ROS1*-positive NSCLC who progressed to crizotinib, with an **overall response rate (ORR)** of 35% and a **median progression-free survival (mPFS)** of 8.5 months. While patients harboring K1991Q and S1986F *ROS1* mutations achieved durable responses to lorlatinib, none of the patients with the more frequent G2032R mutation benefited [29].

NTRK

Biological and Clinical Features

The neurotrophic tropomyosin receptor kinase (NTRK) genes (*NTRK1*, *2*, and *3*) encode TRKA, TRKB, and TRKC, respectively. They are activated by a family of four ligands (NGF, BDNF, NT-3, and NT-4), known as neurotrophins, that display different affinities for each RTK and play essential roles in the development and function of the nervous system. Activating mutations in *NTRK* have been identified in NSCLC, yet their oncogenic role remains controversial [42]. Similarly, activating splice variants and overexpression have been reported in pan-cancer studies but, undoubtedly, the most frequent aberrations involve intra- and inter-chromosomal gene-fusions implicating *NTRK* that occur at a frequency below 0.4% in NSCLC. The biology of *NTRK* oncogenes has been comprehensively reviewed elsewhere [43,44]. Of note, a *NTRK* fusion was the first non-*RAS* oncogene identified almost 40 years ago (indicated as OncD in [45]; for review see [46]). Of the three *NTRK*, pan-cancer-related fusions more commonly affect *NTRK1* and *NTRK3*, and 48 different partners have been reported [47]. In lung, the fusions involve *NTRK1* and *NTRK3* with five and two distinct partners, respectively, *ETV6-NTRK3* being the most prevalent [47,48]. The NGS-based FoundationOneCDx test has just received FDA approval for the identification of NTRK fusions.

Frontline Targeted Therapy

Early phase basket trials of solid tumors harboring *NTRK* gene rearrangements were performed with first-generation TKIs such as larotrectinib, which is selective for TRKA/B/C, and entrectinib, which targets TRKA/B/C as well as ALK and ROS1. Both compounds have demonstrated marked tumor-agnostic efficacy in pan cancer trials [6,7] (Figure 1 and Table 1). Based on these results, larotrectinib received accelerated FDA approval for the treatment of TRK fusion-positive cancers in 2018, followed by entrectinib 1 year later. Both drugs also obtained

Figure 2. Schematic Representation of the On-Target Resistance Mutations and Activity Profile of Kinase Inhibitors Targeting These Specific Resistance Mutations Among the Different Oncogenic Drivers in Non-Small Cell Lung Cancer. (A) The different types of mutations affecting the solvent-front, the gatekeeper residue, the activation loop, or the DFG motifs are represented. Most resistance mutations seen in uncommon driver oncogenes have analogous resistance mutations identified in EGFR and ALK. (B) Blue boxes indicate kinase inhibitor for which antitumoral activity against the indicated mutants has been reported in preclinical models (preclinical validation). Orange boxes designate kinase inhibitor that failed to show any inhibitory activity *in vitro* and/or *in vivo* (preclinical invalidation). Green boxes highlight reports of clinical activity (tumor shrinkage), while red dots indicate agents that failed to achieve an objective response in patients. Asterisks (*) indicate FDA approved drugs. Abbreviations: AL, activation loop; GK, gatekeeper; SF, solvent-front. (See [36,60,75,117,120,129,197–207].)

histology-independent approval by the EMA in solid tumors harboring NTRK rearrangements. Ongoing trials may help to better estimate efficacy and duration of response in NSCLC.

Addressing On-Target Mechanisms of Resistance

Next-generation TRK inhibitors, such as selitrectinib (LOXO-195) and repotrectinib (TPX-0005), have been designed to combat on-target acquired resistance mutations and their activity is being evaluated in Phase I/II trials or compassionate-use protocols for *NTRK*-altered cancers. Indeed, selitrectinib was developed as a second-generation TRK inhibitor using modeling studies even before acquired resistance appeared in the clinic. An initial evaluation performed on a first-in-human basis proved its activity against solvent-front and xDFG mutants inducing rapid tumor responses [49]. This has been extended in an ongoing Phase I/II trial enrolling patients with prior treatment with NTRK inhibitors[iii]. Preliminary results indicate an ORR of 45% in patients with mutations affecting the kinase domain [50]. Similarly, repotrectinib evaluation in a Phase I/II first-in-human dose-escalation study (NCT03093116) demonstrated efficacy in patients harboring *NTRK3* solvent front resistant mutations [39]. Whether these next-generation TRK inhibitors will exert a similar benefit in resistant LUAD patients with kinase-domain acquired mutations is still unknown.

RET

Biological and Clinical Features

Unlike other RTKs, rearranged during transfection (RET) does not directly bind to its ligands but requires an additional co-receptor. Indeed, ligands of the glial cell line-derived neurotrophic factor (GDNF) family bind to one of the four receptors of the GDNF family receptor-α (GFRα), which subsequently allow RET dimerization, autophosphorylation, and activation [51]. Despite a few studies reporting concomitant genomic alterations (for review see [52]), *RET* rearrangements are considered mutually exclusive with other alterations in NSCLC, indicating an independent carcinogenic role, and have been identified in 1–2% of cases. Chromosomal inversions or translocations involving *RET* results in a juxtaposition of its kinase domain and the coiled coil domain of the partner. Similar to the oncogenic activation of ALK fusions, this coiled coil domain is responsible for the ligand-independent homodimerization and constitutive RET activation [53]. In NSCLC, up to 12 fusion partners (e.g., *CCDC6*, *NCOA4*, *TRIM33*) have been described, with the most frequent being *KIF5B* [54]. Unlike *ALK* and *ROS1* rearrangements, *RET* fusion genes cannot be adequately detected by IHC due to low sensitivity and highly variable specificity [52]. Therefore, NGS is the most accurate option, as FISH and RT-PCR may lead to false negatives due to technical limitations.

Frontline Targeted Therapy

Similar to *ALK* and *ROS1*-positive tumors, durable benefits have been obtained with pemetrexed-based chemotherapy in *RET*-rearranged NSCLC [55]. Considering the structural similarities of both the kinase domain and the ATP-binding site with other RTKs [56], several multi-kinase inhibitors (MKIs; e.g., vandetanib, cabozantinib, lenvatinib, as well as alectinib, a VEGFR-sparing MKI) were initially used for the treatment of patients bearing *RET* fusions (for review see [52,57,58]) (Figure 1 and Table 1). Recently, more specific and potent RET inhibitors are under investigation. These include pralsetinib (BLU-667) and selpercatinib (LOXO-292), which have received FDA approval for *RET*-altered NSCLC [4,5,59–61] (Figure 1 and Table 1).

Treatment evolution of *RET*-driven disease is an illustrative example of the continuous need to design specific and potent inhibitors. New putative oncogenic fusions are being discovered [62,63] that could also require initial treatment with less efficient MKIs in parallel to the development of specific compounds.

Addressing On-Target Mechanisms of Resistance

The differential response of various on-target mutants has also been reported in *RET*-altered tumors. Whereas most MKIs are ineffective against resistant mutations, both ponatinib [64] and AD80 [65] showed preclinical efficacy against specific mutations (V804 and G810). Whether this may provide clinical benefit is under evaluation for ponatinib[iv]. In addition, while pralsetinib displayed inhibitor activity against V804M/L and S904F mutations but failed to inhibit G810 alterations [60], TPX-0046, a structurally different RET/SRC inhibitor, showed potent *in vitro* and *in vivo* activity against the *RET* solvent-front mutation G810R and is currently being tested in a Phase I/II trial[v].

MET

Biological and Clinical Features

In NSCLC, c-mesenchymal–epithelial transition factor (c-MET) gene rearrangements, fusions, and somatic mutations have been identified but are rare [66]. MET overexpression, however, is frequent in unselected NSCLC patients, although its clinical value is unclear as this criterion is largely dependent on the antibody assay and the determination of a positive threshold. *MET* amplification is also a common mechanism of resistance to EGFR-TKIs in NSCLC. Anyhow, increased expression is considered a causative driver only if co-occurring with clinically relevant *MET* genomic alterations like *MET* gene amplification or mutations resulting in exon 14 skipping (*METΔ14*). This alteration results in a MET protein lacking the juxtamembrane domain with extended half-life after ligand stimulation and is considered an oncogenic driver. *METΔ14* is predominantly associated with sarcomatoid carcinoma histology [67,68] and detected in 2–4% of NSCLC patients while *MET* amplification affects approximately 2% of LUAD.

Several MET inhibitors, including TKIs and monoclonal antibodies against MET or its ligand HGF, have been assessed in NSCLC (for review see [69,70]). Various agents have reached Phase III trials and failed in patients with *MET* alterations, illustrating the need for better stratification upfront. Indeed, a significant fraction of patients display coexisting oncogenes and only a small fraction of highly amplified tumors may actually be *bona fide* MET-addicted cases, which are associated with more effective responses to targeted therapies [71].

Frontline Targeted Therapy

Crizotinib received FDA approval for *ALK* and *ROS1* NSCLC patients but was initially developed as a MET inhibitor [72]. Significant clinical activity was reported in patients harboring *METΔ14* alterations, including complete responses. Yet, the ORR of crizotinib in this cohort was lower compared with those achieved with targeted therapies for other NSCLC drivers [73] (Figure 1 and Table 1). Neither variations in the mutation type or splice-site region nor the *MET* copy number appear to be major differentiating response factors, so the underlying causes of the heterogeneous clinical outcome are unknown. Novel and highly selective type Ib MET inhibitors, such as tepotinib and capmatinib, have been evaluated in Phase II trials [9,74] (Figure 1 and Table 1). In general, *METΔ14* tumors display lower initial response rates to TKIs compared with other RTK drivers in NSCLC. This could be due to high rate of coexisting genomic alterations inducing both MAPK and PI3K pathway activation, resulting in innate/primary resistance [75,76].

Addressing On-Target Mechanisms of Resistance

In the case of MET-resistant disease, mutations like those affecting the Y1230 and D1228 residues may predict response to type II MET inhibitors such as cabozantinib and glesatinib [77]. Others, including substitutions implicating L1195 or F1200, may not be sensitive to treatment with these compounds as they preclude binding to the DFG-out pocket [75]. In a similar study, seven out of 20 (35%) *METΔ14* patients who progressed to MET TKI had on-target kinase

domain mutations (H1094, G1163, L1195, D1228, Y1230) or elevated *MET* amplification. Cabozantinib has also been shown to be active against the D1228V mutation with concomitant MET amplification [78].

HER2/ERBB2

Biological and Clinical Features

Human epidermal growth factor receptor 2 (HER2), also called ERBB2, is one of the four members of the EGFR family. It remains an orphan receptor activated by heterodimerization with other ERBB family members (for review see [79]). In NSCLC, HER2 dysregulations can be caused by gene amplification, protein overexpression, and mutations. Despite the efficacy of anti-HER2 agents in breast and gastric cancer, clinical interest on HER2-positive NSCLC was dampened when the first clinical trials evaluating trastuzumab, an anti-HER2 humanized antibody, reported negative results [80,81]. In parallel, HER2 kinase domain mutations were identified in NSCLC patients not associated with HER2 amplification/overexpression [82,83]. These results were further confirmed [84], indicating that *HER2* amplification and mutations represent two distinct oncogenic drivers and potential therapeutic targets. These findings, coupled with the encouraging results of TKIs in EGFR mutants, launched the clinical evaluation of anti-HER2 agents specifically in NSCLC patients bearing *HER2* mutations (90% of them are located in exon 20). *HER2* exon 20 alterations comprise point mutations (e.g., L755S, V777L, and G776C) or, more frequently, insertions [85]. The most prevalent (over 80%) is a 12-base pair in-frame insertion causing duplication of amino acids YVMA at codon 775 (A775_G776insYVMA) [86]. Mutations in exon 20 are analogous to *EGFR* exon 20 mutations and lead to HER2 constitutive activation [87–89]. Overall, *HER2* mutations account for 2–4% of the NSCLC cases and tend to be women and light/never smokers with LUAD histology [85].

Frontline Targeted Therapy

HER2 targeted therapy is not yet standard of care in NSCLC and, currently, chemotherapies remain the main strategy. Patients with *HER2*-mutant LUAD, especially YVMA insertion, demonstrated a markedly inferior response to first-line pemetrexed-based chemotherapy compared with those harboring *ALK/ROS1* rearrangements, which strengthen the need for effective anti-HER2 agents [90]. Retrospectives studies displayed encouraging disease control rates in NSCLC patients bearing *HER2* exon 20 insertions treated with HER2-targeted drugs [91,92]. Several clinical studies have been carried out or are ongoing using both anti-HER2 antibodies and small molecules (for review see [2]) (Figure 1 and Table 1). Among these compounds, poziotinib, a pan-HER TKI, has structural features that can circumvent the steric changes induced by exon 20 insertions and increase its affinity compared with larger TKIs [93]. Next-generation TKIs with increased selectivity towards the EGFR and HER2 mutants (such as TAK-788) are being developed to limit the toxicity associated with wild type EGFR inhibition [94,95]. In addition, trastuzumab and its antibody–drug conjugate, trastuzumab–emtansine (T-DM1), showed mixed results in the clinic due, in part, to the molecular heterogeneity of *HER2*-altered NSCLC (for review see [2]). Trastuzumab–deruxtecan (DS-8201a) showed promising efficacy among NSCLC patients with HER2 exon 20 mutations [96] (Figure 1 and Table 1). In this context, patients with *HER2*-mutated NSCLC often develop brain metastases with disease progression and trastuzumab would be inefficient due to its inability to cross the blood–brain barrier. Therefore, monitoring and treatment of central nervous system (CNS) metastases may require specific approaches.

BRAF

Biological and Clinical Features

BRAF, together with ARAF and CRAF, constitute the RAF family of serine/threonine kinases, a core component of the MAPK cascade. Since the first evidence in 2002 [97], almost 200 distinct

BRAF mutations have been reported in around 8% of cancers. In NSCLC, they represent 1.5–3.5% of the cases and affect the kinase domain, either in the glycine-rich loop in exon 11 or in the activation segment in exon 15, resulting in increased ERK signaling (for review see [98]). Clinical characteristics associated with *BRAF* mutations in lung cancer vary without obvious segregation in specific parameters, except the significant association with LUAD histology. Most patients with *BRAF* mutations are smokers, although patients with V600 mutations are more likely to be light/never-smokers compared with patients with non-V600 mutations [99–102]. *BRAF* mutations as well as *HER2* and *MET* alterations are generally well covered by NGS gene panels. *BRAF* mutants are classified in three categories [103]. Class 1 (V600) and class 2 (G464, G469, L597, and K601) mutants are mutually exclusive, RAS-independent, and signal constitutively as active monomers or active dimers, respectively. Class 3 (e.g., G466 and D594) have impaired/null kinase activity and activation of downstream signaling is RAS- and CRAF-dependent and sensitive to ERK-mediated feedback. In this case, RAS is generally activated by RTK signaling [103]. Notably, expression of an endogenous class 3 BRAF mutant triggers LUAD in mice, indicating that kinase-inactive BRAF isoforms are oncogenic drivers [104].

Frontline Targeted Therapy

Experience with *BRAF*-mutant melanoma has heavily influenced the management of NSCLC. Targeted therapy has evolved from BRAF monotherapy to combined BRAF/MEK inhibition showing superior efficacy and favorable safety profile in *BRAF* V600E-mutant NSCLC [3,105–109] (Figure 1 and Table 1). The combination of dabrafenib plus trametinib has received both FDA and EMA approval for the treatment of metastatic NSCLC harboring the *BRAF* V600E mutation, regardless of previous therapies. Another pair of BRAF and MEK inhibitors, encorafenib and binimetinib, is under investigation and has shown encouraging CNS activity in a patient with *BRAF* V600E-mutated LUAD [110].

Next-generation RAF inhibitors have been reported to be active in *BRAF*-mutant NSCLC in the clinic (for review see [111]). Notably, the pan-RAF inhibitor PLX8394 selectively disrupts both BRAF homo- and BRAF-CRAF heterodimers [112,113]. Furthermore, a Phase I study evaluating ulixertinib, a first-in-class ERK inhibitor, reported partial responses in NSCLC patients bearing both V600 and non-V600 mutations as well as CNS activity [114]. In addition, *BRAF*-mutant NSCLC is likely to have high level of PD-L1 expression [115]. When treated with immune checkpoint inhibitors, no significant differences in ORR and mPFS were reported among V600E and non-V600E mutants. The optimal therapeutic sequence has yet to be established in both V600 and non-V600 (Box 2) *BRAF*-mutated LUAD patients.

Signaling Bypass Activation and Other Resistance Mechanisms

In accordance with *EGFR*- and *ALK*-driven NSCLC (Box 1), the development of resistance to targeted therapies in lung cancer bearing infrequent alterations also implicates signaling bypass tracks, although the underlying molecular mechanisms are less understood. The activation of bypass pathways described so far in both preclinical and clinical studies are depicted for each uncommon driver in Figure 3.

Alterations affecting the RAS-MAPK pathway or upstream receptors are the most frequent. Notably, *EGFR* [116–119] and *HER2* [120,121] activating mutations or amplification have been reported in *ROS1*- and *MET*-altered patients after progressing to crizotinib. Interestingly, EGFR activation may not only contribute to the resistant phenotype by supporting bypass signaling but also by protein–protein interactions that reactivate drug-inhibited ROS1 [118]. EGFR signaling has also been identified as a critical adaptive survival mechanism to RET [118,122,123] and NTRK [118] blockade in NSCLC preclinical models. Beside EGFR and HER2, other RTKs have

Box 2. BRAF Non-V600 Mutations in NSCLC

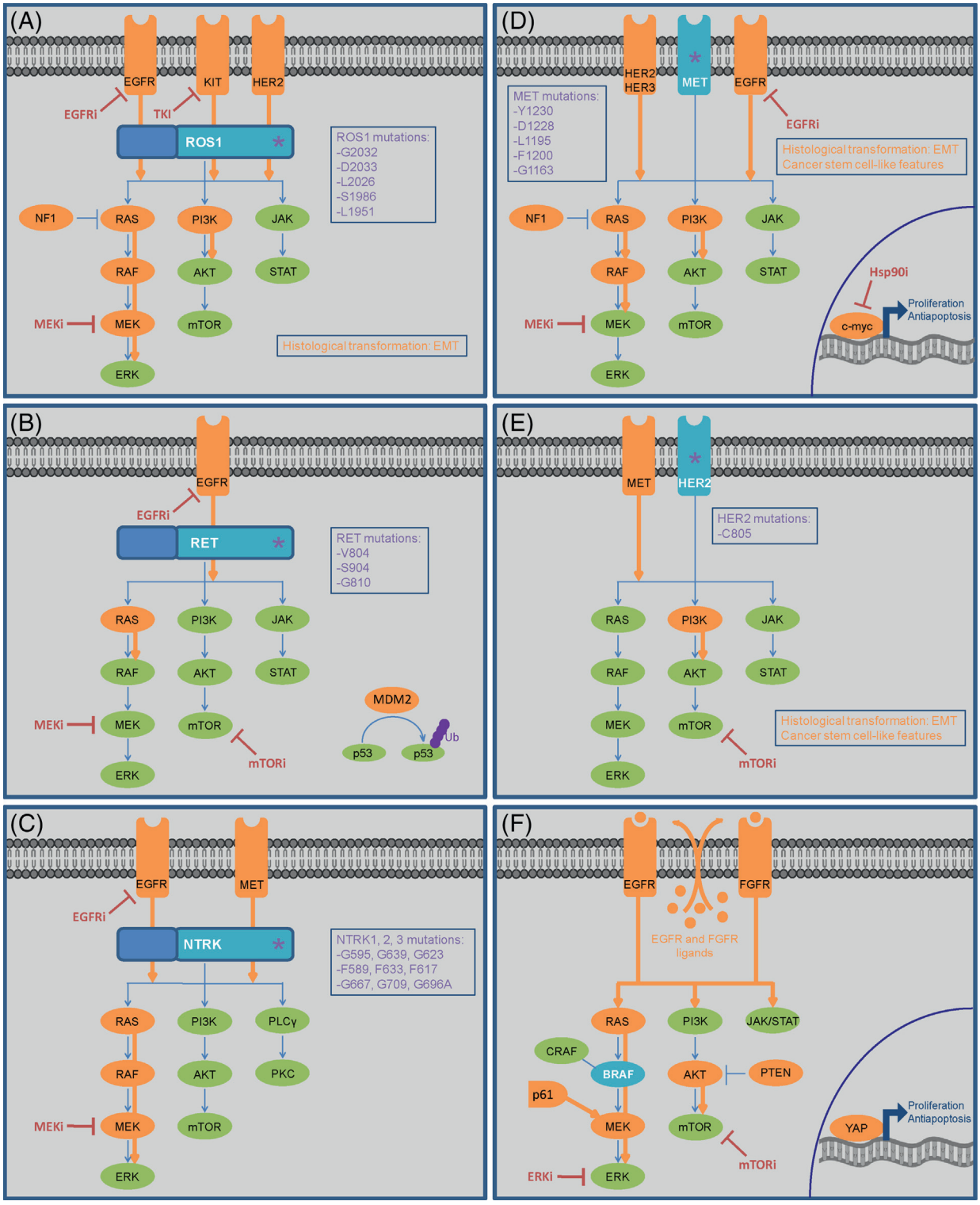
While more than 90% of *BRAF*-altered melanoma bear a V600 mutation, *BRAF*-positive NSCLC are equally divided into V600 and non-V600 mutations and, therefore, represent one of the cancers with the higher proportion of non-V600 mutations. The tumor-initiating potential of many of the rare BRAF mutations has yet to be demonstrated *in vivo*. In addition, data demonstrating clinical activity of MAPK-directed therapies in non-V600 *BRAF*-mutant lung cancers are lacking. Therefore, there is currently no consensus on how to optimally manage patients with class 2 and 3 *BRAF* mutations. In the EURAF retrospective series that included six NSCLC patients with *BRAF* mutations other than V600E, only one patient (G596V) achieved a partial response to vemurafenib [105]. These findings are consistent with the statement that class 2 and 3 mutants signal as RAF dimers rather than monomers [103], making them resistant to the BRAF monomer inhibitors. However, *in vitro*, both class 2 and 3 mutated cell lines are sensitive to MEK inhibition [177]. Additionally, the combination of BRAF and MEK inhibitors enhanced MAPK inhibition and cell proliferation reduction in both class 2 and 3 *BRAF*-mutant NSCLC preclinical models compared with MEK inhibitor alone [178–181]. Interestingly, oncogenic signaling triggered by class 3 BRAF mutants depends on a variety of RTKs that should be identified per patient [103]. Alternatively, the inhibition of SHP2, a scaffold protein downstream of RTKs promoting RAS activation, or the use of pan-RTK inhibitors (such as afatinib) could be considered [182]. Incidentally, concomitant SHP2 and BRAF/MEK inhibition showed synergistic effects in a class 3 *BRAF*-mutant cell line [183]. Additionally, allosteric inhibitors targeting the heterodimer interface between BRAF class 3 mutants with CRAF may represent an alternative approach [184]. Further studies are required to: (i) determine the precise the molecular mechanisms of each *BRAF* mutant (i.e., homo versus heterodimer); (ii) define the importance of the additional molecular determinants that may play a role in modulating therapeutic response (i.e., expression level of CRAF and concomitant genetic alterations); and (iii) identify the most promising strategies with potential drug combination to achieve successful clinical response in patients with non-V600 *BRAF* mutations.

been associated with drug resistance in lung cancer. Particularly, *MET* amplification has been identified in afatinib-resistance cell lines harboring *HER2* alterations [124], in pralsetinib-resistant *RET*-rearranged tumors [125], and in entrectinib-resistant *NTRK*-rearranged biopsies [126]. Furthermore, FGFR autocrine pathway activation through FGF1 secretion was shown to be associated with increased sensitivity to FGFR inhibitor in resistant *BRAF* V600E LUAD [127].

In addition, *KRAS* and *NRAS* mutations on codons 12 and 61 have been identified both in preclinical models of resistance to MKIs in *RET*-altered cells [123] and in *MET*-, *NTRK*-, and *BRAF*-altered patients after progressing to frontline targeted therapies [126,128–132]. Similarly, *MEK1* activating mutations were described in case reports of *BRAF* V600E NSCLC after progression to dabrafenib and trametinib [133] as well as in *NTRK*-rearranged patients after TKI treatment [126]. Furthermore, case-reports highlighted *BRAF* V600E mutation or amplification in post-treatment biopsies of *ROS1*-, *NTRK*-, and *METΔ14*-altered NSCLC patients [126,129,134,135]. Intriguingly, RTK-RAS-MAPK activating mutations tend to be mutually exclusive in primary tumors, a finding justified due to functional redundancy and lack of selective advantage. However, several studies have demonstrated that synthetic toxicity due to excessive signaling could equally underlie oncogene incompatibility [136–138]. In this context, intermittent therapy resulting in excessive signaling proves to be advantageous in drug-resistant melanoma harboring coexisting oncogenes [139]. Yet, in NSCLC, this approach could only be applied to certain oncogenic combinations [140]. Additional clinical support from both prospective and retrospective studies is required to validate this therapeutic strategy.

Another frequently altered pathway upon TKI treatment is PI3K-AKT-mTOR. Indeed, activating mutations of *PIK3CA* have been reported in both *ROS1*-altered [135,141] and *HER2* exon 20-mutated patients [142] after progression to targeted therapies.

Finally, other alterations potentially contributing to drug resistance have been reported, such as KIT [143] and c-myc [144] in preclinical models of *ROS1*- and *MET*-altered NSCLC, respectively. Additionally, acquired amplification of *MDM2*, which encodes the E3 ubiquitin-protein ligase MDM2, has been identified in *RET*-rearranged cabozantinib-resistant patients [145]. Likewise, the Hippo pathway with its effector YAP has been recognized as a mechanism of resistance to BRAF- and MEK-targeted therapy in both preclinical and clinical samples bearing BRAF



Trends in Cancer

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V600 mutations [146]. Yet, given their low prevalence, their clinical significance requires further confirmation.

Importantly, the activation of bypass signaling pathways often results in the acquisition of vulnerabilities that could be therapeutically exploited. In a recent study, novel activating MAPK alterations (deletions of several nucleotides in *MAP3K1* and *MAP2K1* as well as *NF1* loss-of-function mutations) were acquired in patients harboring *ROS1*-rearranged tumors being treated with ROS1 inhibitors. Cells bearing these alterations are resistant to ROS1-TKIs but sensitive to a combination of ROS1 and MEK inhibitors *in vitro* and *in vivo* [147]. Importantly, a *METΔ14*-altered patient who acquired a *KRAS* gain after crizotinib treatment achieved clinical response upon addition of trametinib [75].

The identification of *PIK3CA* or *PTEN* mutations suggests that activation of the PI3K-AKT-mTOR pathway could represent an acquired vulnerability and supports the potential use of mTOR inhibitors for the treatment of resistant NSCLC. In a Phase I clinical trial, a *BRAF* V600E-mutated NSCLC patient who progressed to single-agent dabrafenib and multiple lines of chemotherapy achieved a partial response with the combination vemurafenib plus everolimus, a mTOR inhibitor [148]. Preliminary results from a clinical trial (NCT01582191) combining vandetanib and the mTOR inhibitor everolimus showed significant activity in *RET*-positive NSCLC [149] as well as CNS responses [150]. Overall, combined inhibition of uncommon drivers and bypass signaling pathway (either with mTOR inhibitors or MEK inhibitors) could be a promising therapeutic strategy that should be assessed in resistant patients lacking on-target resistance mutations.

Finally, phenotypic changes such as **epithelial to mesenchymal transition (EMT)** have been reported in one ROS1 crizotinib-resistant patient lacking resistant *ROS1* mutations or alternative pathway mutations [117]. EMT along with acquisition of cancer stem cell-like properties have been identified in both TKI resistant *MET*- and *HER2*-altered cell lines [124,151]. No cases of histological transformation to a small-cell lung cancer, a phenomenon observed in EGFR and ALK TKI-resistant tumors, has been reported so far in the context of uncommon drivers.

Concluding Remarks and Future Perspectives

Alongside *EGFR*- and *ALK*-driven NSCLC, patients bearing infrequent drivers display limited benefit from targeted therapies due to the onset of resistance. Despite the growing body of evidence about their clinical management, many key knowledge gaps remain (see Outstanding Questions). First, lung cancers genomes display substantial heterogeneity and complex branching evolution that can be influenced by treatment-imposed selective pressure [152–154]. The understanding of the subclonal origin of resistance in the context of rare drivers will require deep sequencing studies of either multiregional biopsies or single tumor cells that are currently missing. This information could help develop tailored treatments to tackle resistance by anticipating the emergence of on-target or bypass mechanisms. Interestingly, recent preclinical evidence has demonstrated enhanced therapeutic benefit and delayed onset of resistance upon multiple low dosing of different nodes within the same pathway [155]. Beside targeted therapies, these patients may benefit from combining chemotherapy and immunotherapy, but further information is needed. Recent retrospective studies highlighted that immune checkpoint inhibitors may provide an

Outstanding Questions

Is it ethical to have an approved targeted treatment against an uncommon driver and not implement the diagnostic tests as routine to identify the patients?

Are large randomized clinical trials comparing targeted agents with platinum-based chemotherapy needed in patients with rare oncogenic drivers?

How could we design and validate combination treatments in the clinic that would outperform single agent therapies? Could we develop in parallel predictive biomarkers for stratifying patients?

How can we improve the early identification of emergent on-target mutations? Could multiple samplings along the treatment through liquid biopsies and circulating DNA represent an alternative option to monitor resistance onset?

Could concomitant low dosing therapies targeting different effectors within the RTK-RAS-MAPK pathway be implemented in the clinic?

Figure 3. Signaling Pathways Driving Resistance to Targeted Therapies in *ROS1* (A), *RET* (B), and *NTRK* (C) Fusions-Positive Non-Small Cell Lung Cancer (NSCLC) and *MET* (D), *HER2* (E), and *BRAF* (F) Mutated NSCLC. Oncogenic drivers and their downstream signaling pathways are represented in blue and green, respectively. On-target resistance mutations as well as histological transformation are indicated (boxes). Protein alterations that have been implicated in the resistance to targeted agents are shown in orange. Potential therapeutic strategies are also highlighted in red. Abbreviation: EMT, epithelial to mesenchymal transition.

effective option for NSCLC patients with certain infrequent alterations, especially in those associated with smoking, such as *BRAF* mutations [115,156,157]. Future clinical trials should determine the ideal regimen of combination therapies, including dosing and nature of targeted agents, antiangiogenic drugs, and/or chemotherapy plus immunotherapy. When defining the ideal clinical regimen, caution should be applied if transposing information from other cancer types harboring the same infrequent driver. For example, the extended survival upon combinatorial treatments in *BRAF* V600E mutant melanoma has also been achieved in LUAD patients. However, the therapeutic response of colorectal carcinoma patients bearing the same alteration was disappointing due to EGFR-mediated intrinsic resistance [158]. In any case, an ideal clinical regimen would require radiological and molecular monitoring of disease progression. Resistance mechanisms could be captured by noninvasive methods like liquid biopsy [119,125,159] (see Outstanding Questions). A recurrent and important problem is the occurrence of brain metastases, thereby requiring the use of compounds with good intracranial activity. In conclusion, a better understanding of the alterations underlying the development of resistance and the design of tailored treatments will allow delaying tumor progression and achieving improved clinical outcomes in NSCLC patients bearing infrequent alterations.

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Resources

[i]https://clinicaltrials.gov/ct2/show/NCT02279433

[ii]https://clinicaltrials.gov/ct2/show/NCT02675491

[iii]https://clinicaltrials.gov/ct2/show/NCT03215511

[iv]https://clinicaltrials.gov/ct2/show/NCT01813734

[v]https://clinicaltrials.gov/ct2/show/NCT04161391

[vi]https://clinicaltrials.gov/ct2/show/NCT03052608

References

1. Rosell, R. and Karachaliou, N. (2016) Large-scale screening for somatic mutations in lung cancer. *Lancet* 387, 1354–1356
2. Baraibar, I. *et al.* (2020) Novel drugs targeting EGFR and HER2 exon 20 mutations in metastatic NSCLC. *Crit. Rev. Oncol. Hematol.* 148, 102906
3. Planchard, D. *et al.* (2016) Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol.* 17, 984–993
4. Drilon, A. *et al.* (2020) Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. *N. Engl. J. Med.* 383, 813–824
5. Gainor, J.F. *et al.* (2020) Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion+ non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* 38, 9515
6. Hong, D.S. *et al.* (2020) Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol.* 21, 531–540
7. Doebele, R.C. *et al.* (2020) Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* 21, 271–282
8. Drilon, A. *et al.* (2020) Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. *Lancet Oncol.* 21, 261–270
9. Wolf, J. *et al.* (2020) Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N. Engl. J. Med.* 383, 944–957
10. Rotow, J. and Bivona, T.G. (2017) Understanding and targeting resistance mechanisms in NSCLC. *Nat. Rev. Cancer* 17, 637–658
11. Rikova, K. *et al.* (2007) Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 131, 1190–1203
12. Liu, Y. *et al.* (2019) Identification of a novel WNK1-ROS1 fusion in a lung adenocarcinoma sensitive to crizotinib. *Lung Cancer* 129, 92–94

13. Xu, S. *et al.* (2019) ROS1-ADGRG6: a case report of a novel ROS1 oncogenic fusion variant in lung adenocarcinoma and the response to crizotinib. *BMC Cancer* 19, 769
14. Lin, J.J. and Shaw, A.T. (2017) Recent advances in targeting ROS1 in lung cancer. *J. Thorac. Oncol.* 12, 1611–1625
15. Neel, D.S. *et al.* (2019) Differential subcellular localization regulates oncogenic signaling by ROS1 kinase fusion proteins. *Cancer Res.* 79, 546–556
16. Lin, J.J. *et al.* (2017) ROS1 fusions rarely overlap with other oncogenic drivers in non-small cell lung cancer. *J. Thorac. Oncol.* 12, 872–877
17. Wang, R. *et al.* (2012) RET fusions define a unique molecular and clinicopathologic subtype of non-small-cell lung cancer. *J. Clin. Oncol.* 30, 4352–4359
18. Lindeman, N.I. *et al.* (2018) Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J. Thorac. Oncol.* 13, 323–358
19. Davies, K.D. *et al.* (2018) Comparison of molecular testing modalities for detection of ROS1 rearrangements in a cohort of positive patient samples. *J. Thorac. Oncol.* 13, 1474–1482
20. Chen, Y.F. *et al.* (2016) Efficacy of pemetrexed-based chemotherapy in patients with ROS1 fusion-positive lung adenocarcinoma compared with in patients harboring other driver mutations in East Asian populations. *J. Thorac. Oncol.* 11, 1140–1152
21. Robinson, D.R. *et al.* (2000) The protein tyrosine kinase family of the human genome. *Oncogene* 19, 5548–5557
22. Shaw, A.T. *et al.* (2014) Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N. Engl. J. Med.* 371, 1963–1971
23. Moro-Sibilot, D. *et al.* (2019) Crizotinib in c-MET- or ROS1-positive NSCLC: results of the AcSe phase II trial. *Ann. Oncol.* 30, 1985–1991
24. Mazieres, J. *et al.* (2015) Crizotinib therapy for advanced lung adenocarcinoma and a ROS1 rearrangement: results from the EUROS1 cohort. *J. Clin. Oncol.* 33, 992–999
25. Wu, Y.L. *et al.* (2018) Phase II study of crizotinib in East Asian patients with ROS1-positive advanced non-small-cell lung cancer. *J. Clin. Oncol.* 36, 1405–1411
26. Michels, S. *et al.* (2019) Safety and efficacy of crizotinib in patients with advanced or metastatic ROS1-rearranged lung cancer (EUCROSS): a European phase II clinical trial. *J. Thorac. Oncol.* 14, 1266–1276
27. Drilon, A. *et al.* (2017) Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov.* 7, 400–409
28. Lim, S.M. *et al.* (2017) Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. *J. Clin. Oncol.* 35, 2613–2618
29. Shaw, A.T. *et al.* (2019) Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. *Lancet Oncol.* 20, 1691–1701
30. Davare, M.A. *et al.* (2015) Structural insight into selectivity and resistance profiles of ROS1 tyrosine kinase inhibitors. *Proc. Natl. Acad. Sci. U. S. A.* 112, E5381–E5390
31. Davare, M.A. *et al.* (2013) Foretinib is a potent inhibitor of oncogenic ROS1 fusion proteins. *Proc. Natl. Acad. Sci. U. S. A.* 110, 19519–19524
32. Zou, H.Y. *et al.* (2015) PF-06463922 is a potent and selective next-generation ROS1/ALK inhibitor capable of blocking crizotinib-resistant ROS1 mutations. *Proc. Natl. Acad. Sci. U. S. A.* 112, 3493–3498
33. Chong, C.R. *et al.* (2017) Identification of existing drugs that effectively target NTRK1 and ROS1 rearrangements in lung cancer. *Clin. Cancer Res.* 23, 204–213
34. Katayama, R. *et al.* (2015) Cabozantinib overcomes crizotinib resistance in ROS1 fusion-positive cancer. *Clin. Cancer Res.* 21, 166–174
35. Katayama, R. *et al.* (2019) The new-generation selective ROS1/NTRK inhibitor DS-6051b overcomes crizotinib resistant ROS1-G2032R mutation in preclinical models. *Nat. Commun.* 10, 3604
36. Drilon, A. *et al.* (2016) A novel crizotinib-resistant solvent-front mutation responsive to cabozantinib therapy in a patient with ROS1-rearranged lung cancer. *Clin. Cancer Res.* 22, 2351–2358
37. Sun, T.Y. *et al.* (2019) Lengthy progression-free survival and intracranial activity of cabozantinib in patients with crizotinib and ceritinib-resistant ROS1-positive non-small cell lung cancer. *J. Thorac. Oncol.* 14, e21–e24
38. Fujiwara, Y. *et al.* (2018) Safety and pharmacokinetics of DS-6051b in Japanese patients with non-small cell lung cancer harboring ROS1 fusions: a phase I study. *Oncotarget* 9, 23729–23737
39. Drilon, A. *et al.* (2018) Repotrectinib (TPX-0005) is a next-generation ROS1/TRK/ALK inhibitor that potently inhibits ROS1/TRK/ALK solvent-front mutations. *Cancer Discov.* 8, 1227–1236
40. Ou, S. *et al.* (2018) OA09 preliminary clinical activity of repotrectinib (TPX-0005) in advanced ROS1 fusion-positive non-small cell lung cancer. *J. Thorac. Oncol.* 13, S1047
41. Cho, B.C. *et al.* (2019) Safety and preliminary clinical activity of repotrectinib in patients with advanced ROS1 fusion-positive non-small cell lung cancer (TRIDENT-1 study). *J. Clin. Oncol.* 37, 9011
42. Harada, T. *et al.* (2011) Role and relevance of TrkB mutations and expression in non-small cell lung cancer. *Clin. Cancer Res.* 17, 2638–2645
43. Vaishnavi, A. *et al.* (2015) TRKing down an old oncogene in a new era of targeted therapy. *Cancer Discov.* 5, 25–34
44. Cocco, E. *et al.* (2018) NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat. Rev. Clin. Oncol.* 15, 731–747
45. Pulciani, S. *et al.* (1982) Oncogenes in solid human tumours. *Nature* 300, 539–542
46. Barbacid, M. (2019) On the right TRK: from oncogene discovery to cancer therapeutics. *Ann. Oncol.* 30, viii3–viii4
47. Rosen, E.Y. *et al.* (2020) TRK fusions are enriched in cancers with uncommon histologies and the absence of canonical driver mutations. *Clin. Cancer Res.* 26, 1624–1632
48. Farago, A.F. *et al.* (2018) Clinicopathologic features of non-small-cell lung cancer harboring an NTRK gene fusion. *JCO Precis. Oncol.* 2018, PO.18.00037
49. Drilon, A. *et al.* (2017) A next-generation TRK kinase inhibitor overcomes acquired resistance to prior TRK kinase inhibition in patients with TRK fusion-positive solid tumors. *Cancer Discov.* 7, 963–972
50. Hyman, D. *et al.* (2019) Abstract CT127: phase I and expanded access experience of LOXO-195 (BAY 2731954), a selective next-generation TRK inhibitor (TRKi). *Cancer Res.* 79, CT127
51. Mulligan, L.M. (2014) RET revisited: expanding the oncogenic portfolio. *Nat. Rev. Cancer* 14, 173–186
52. Ferrara, R. *et al.* (2018) Clinical and translational implications of RET rearrangements in non-small cell lung cancer. *J. Thorac. Oncol.* 13, 27–45
53. Ju, Y.S. *et al.* (2012) A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. *Genome Res.* 22, 436–445
54. Gautschi, O. *et al.* (2017) Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET registry. *J. Clin. Oncol.* 35, 1403–1410
55. Drilon, A. *et al.* (2016) Clinical outcomes with pemetrexed-based systemic therapies in RET-rearranged lung cancers. *Ann. Oncol.* 27, 1286–1291
56. Knowles, P.P. *et al.* (2006) Structure and chemical inhibition of the RET tyrosine kinase domain. *J. Biol. Chem.* 281, 33577–33587
57. Drilon, A. *et al.* (2018) Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. *Nat. Rev. Clin. Oncol.* 15, 150
58. Bronte, G. *et al.* (2019) Targeting RET-rearranged non-small-cell lung cancer: future prospects. *Lung Cancer (Auckl)* 10, 27–36
59. Subbiah, V. *et al.* (2018) Precision targeted therapy with BLU-667 for RET-driven cancers. *Cancer Discov.* 8, 836–849
60. Solomon, B.J. *et al.* (2020) RET solvent front mutations mediate acquired resistance to selective RET inhibition in RET-driven malignancies. *J. Thorac. Oncol.* 15, 541–549

61. Evans, E. *et al.* (2019) P2.03-44 BLU-667 demonstrates robust activity in RET fusion-driven intracranial tumor models. *J. Thorac. Oncol.* 14, S701
62. Zhuo, M. *et al.* (2020) Analysis of MET kinase domain rearrangement in NSCLC. *Lung Cancer* 145, 140–143
63. Reddy, V.P. *et al.* (2017) BRAF fusions in clinically advanced non-small cell lung cancer: an emerging target for anti-BRAF therapies. *J. Clin. Oncol.* 35, 9072
64. Huang, Q. *et al.* (2016) Preclinical modeling of KIF5B-RET fusion lung adenocarcinoma. *Mol. Cancer Ther.* 15, 2521–2529
65. Plenker, D. *et al.* (2017) Drugging the catalytically inactive state of RET kinase in RET-rearranged tumors. *Sci. Transl. Med.* 9, eaah6144
66. Campbell, J.D. *et al.* (2016) Distinct patterns of somatic genome alterations in lung adenocarcinomas and squamous cell carcinomas. *Nat. Genet.* 48, 607–616
67. The Cancer Genome Atlas Research Network (2014) Comprehensive molecular profiling of lung adenocarcinoma. *Nature* 511, 543–550
68. Tong, J.H. *et al.* (2016) MET amplification and exon 14 splice site mutation define unique molecular subgroups of non-small cell lung carcinoma with poor prognosis. *Clin. Cancer Res.* 22, 3048–3056
69. Pasquini, G. and Giaccone, G. (2018) C-MET inhibitors for advanced non-small cell lung cancer. *Expert Opin. Investig. Drugs* 27, 363–375
70. Liang, H. and Wang, M. (2020) MET oncogene in non-small cell lung cancer: mechanism of MET dysregulation and agents targeting the HGF/c-Met axis. *OncoTargets Ther.* 13, 2491–2510
71. Noonan, S.A. *et al.* (2016) Identifying the appropriate FISH criteria for defining MET copy number-driven lung adenocarcinoma through oncogene overlap analysis. *J. Thorac. Oncol.* 11, 1293–1304
72. Cui, J.J. *et al.* (2011) Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). *J. Med. Chem.* 54, 6342–6363
73. Drilon, A. *et al.* (2020) Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. *Nat. Med.* 26, 47–51
74. Paik, P.K. *et al.* (2020) Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. *N. Engl. J. Med.* 383, 931–943
75. Rotow, J.K. *et al.* (2020) Co-occurring alterations in the RAS-MAPK pathway limit response to MET inhibitor treatment in MET exon 14 skipping mutation-positive lung cancer. *Clin. Cancer Res.* 26, 439–449
76. Jamme, P. *et al.* (2020) Alterations in the PI3K pathway drive resistance to MET inhibitors in NSCLC harboring MET exon 14 skipping mutations. *J. Thorac. Oncol.* 15, 741–751
77. Engstrom, L.D. *et al.* (2017) Glesatinib exhibits antitumor activity in lung cancer models and patients harboring MET exon 14 mutations and overcomes mutation-mediated resistance to type I MET inhibitors in nonclinical models. *Clin. Cancer Res.* 23, 6661–6672
78. Bahcall, M. *et al.* (2016) Acquired METD1228V mutation and resistance to MET inhibition in lung cancer. *Cancer Discov.* 6, 1334–1341
79. Yarden, Y. and Sliwkowski, M.X. (2001) Untangling the ErbB signalling network. *Nat. Rev. Mol. Cell Biol.* 2, 127–137
80. Gatzemeier, U. *et al.* (2004) Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. *Ann. Oncol.* 15, 19–27
81. Clamon, G. *et al.* (2005) Lack of trastuzumab activity in nonsmall cell lung carcinoma with overexpression of erb-B2: 39810: a phase II trial of Cancer and Leukemia Group B. *Cancer* 103, 1670–1675
82. Shigematsu, H. *et al.* (2005) Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. *Cancer Res.* 65, 1642–1646
83. Stephens, P. *et al.* (2004) Lung cancer: intragenic ERBB2 kinase mutations in tumours. *Nature* 431, 525–526
84. Li, B.T. *et al.* (2016) HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers. *J. Thorac. Oncol.* 11, 414–419
85. Pillai, R.N. *et al.* (2017) HER2 mutations in lung adenocarcinomas: a report from the Lung Cancer Mutation Consortium. *Cancer* 123, 4099–4105
86. Arcila, M.E. *et al.* (2012) Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. *Clin. Cancer Res.* 18, 4910–4918
87. Perera, S.A. *et al.* (2009) HER2YVMA drives rapid development of adenosquamous lung tumors in mice that are sensitive to BIBW2992 and rapamycin combination therapy. *Proc. Natl. Acad. Sci. U. S. A.* 106, 474–479
88. Shimamura, T. *et al.* (2006) Non-small-cell lung cancer and Ba/F3 transformed cells harboring the ERBB2 G776insV_G/C mutation are sensitive to the dual-specific epidermal growth factor receptor and ERBB2 inhibitor HKI-272. *Cancer Res.* 66, 6487–6491
89. Wang, S.E. *et al.* (2006) HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors. *Cancer Cell* 10, 25–38
90. Wang, Y. *et al.* (2018) Outcomes of pemetrexed-based chemotherapies in HER2-mutant lung cancers. *BMC Cancer* 18, 326
91. Mazieres, J. *et al.* (2016) Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. *Ann. Oncol.* 27, 281–286
92. Mazieres, J. *et al.* (2013) Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J. Clin. Oncol.* 31, 1997–2003
93. Robichaux, J.P. *et al.* (2018) Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat. Med.* 24, 638–646
94. Chouitar, J. *et al.* (2018) P2.13-32 TAK-788 is a novel and potent tyrosine kinase inhibitor with selective activity against EGFR/HER2. *J. Thorac. Oncol.* 13, S811
95. Neal, J. *et al.* (2018) P1.13-44 safety, PK, and preliminary antitumor activity of the oral EGFR/HER2 exon 20 inhibitor TAK-788 in NSCLC. *J. Thorac. Oncol.* 13, S599
96. Smit, E.F. *et al.* (2020) Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01. *J. Clin. Oncol.* 38, 9504
97. Davies, H. *et al.* (2002) Mutations of the BRAF gene in human cancer. *Nature* 417, 949–954
98. Holderfield, M. *et al.* (2014) Targeting RAF kinases for cancer therapy: BRAF-mutated melanoma and beyond. *Nat. Rev. Cancer* 14, 455–467
99. Leonetti, A. *et al.* (2018) BRAF in non-small cell lung cancer (NSCLC): pickaxing another brick in the wall. *Cancer Treat. Rev.* 66, 82–94
100. Auliac, J.B. *et al.* (2018) Patients with non-small-cell lung cancer harbouring a BRAF mutation: a multicentre study exploring clinical characteristics, management, and outcomes in a real-life setting: EXPLORE GFPC 02-14. *Curr. Oncol.* 25, e398–e402
101. Litvak, A.M. *et al.* (2014) Clinical characteristics and course of 63 patients with BRAF mutant lung cancers. *J. Thorac. Oncol.* 9, 1669–1674
102. Tissot, C. *et al.* (2016) Clinical characteristics and outcome of patients with lung cancer harboring BRAF mutations. *Lung Cancer* 91, 23–28
103. Yao, Z. *et al.* (2017) Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. *Nature* 548, 234–238
104. Nieto, P. *et al.* (2017) A Braf kinase-inactive mutant induces lung adenocarcinoma. *Nature* 548, 239–243
105. Gautschi, O. *et al.* (2015) Targeted therapy for patients with BRAF-mutant lung cancer: results from the European EURAF Cohort. *J. Thorac. Oncol.* 10, 1451–1457
106. Mazieres, J. *et al.* (2020) Vemurafenib in non-small-cell lung cancer patients with BRAF(V600) and BRAF(nonV600) mutations. *Ann. Oncol.* 31, 289–294

107. Subbiah, V. *et al.* (2019) Efficacy of vemurafenib in patients with non–small-cell lung cancer with BRAF V600 mutation: an open-label, single-arm cohort of the histology-independent VE-BASKET study. *JCO Precis. Oncol.* 3, PO.18.00266
108. Planchard, D. *et al.* (2016) Dabrafenib in patients with BRAF (V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 17, 642–650
109. Planchard, D. *et al.* (2017) Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol.* 18, 1307–1316
110. McLoughlin, E.M. *et al.* (2019) Clinical and radiographic response of leptomeningeal and brain metastases to encorafenib and binimetinib in a patient with BRAF V600E-mutated lung adenocarcinoma. *J. Thorac. Oncol.* 14, e269–e271
111. Karoulia, Z. *et al.* (2017) New perspectives for targeting RAF kinase in human cancer. *Nat. Rev. Cancer* 17, 676–691
112. Okimoto, R.A. *et al.* (2016) Preclinical efficacy of a RAF inhibitor that evades paradoxical MAPK pathway activation in protein kinase BRAF-mutant lung cancer. *Proc. Natl. Acad. Sci. U. S. A.* 113, 13456–13461
113. Yao, Z. *et al.* (2019) RAF inhibitor PLX8394 selectively disrupts BRAF dimers and RAS-independent BRAF-mutant-driven signaling. *Nat. Med.* 25, 284–291
114. Sullivan, R.J. *et al.* (2018) First-in-class ERK1/2 inhibitor ulixertinib (BVD-523) in patients with MAPK mutant advanced solid tumors: results of a phase I dose-escalation and expansion study. *Cancer Discov.* 8, 184–195
115. Dudnik, E. *et al.* (2018) BRAF mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. *J. Thorac. Oncol.* 13, 1128–1137
116. Davies, K.D. *et al.* (2013) Resistance to ROS1 inhibition mediated by EGFR pathway activation in non-small cell lung cancer. *PLoS One* 8, e82236
117. Song, A. *et al.* (2015) Molecular changes associated with acquired resistance to crizotinib in ROS1-rearranged non-small cell lung cancer. *Clin. Cancer Res.* 21, 2379–2387
118. Vaishnavi, A. *et al.* (2017) EGFR mediates responses to small-molecule drugs targeting oncogenic fusion kinases. *Cancer Res.* 77, 3551–3563
119. Dagogo-Jack, I. *et al.* (2017) Circulating tumor DNA identifies EGFR coamplification as a mechanism of resistance to crizotinib in a patient with advanced MET-amplified lung adenocarcinoma. *J. Thorac. Oncol.* 12, e155–e157
120. McCoach, C.E. *et al.* (2018) Resistance mechanisms to targeted therapies in ROS1(+) and ALK(+) non-small cell lung cancer. *Clin. Cancer Res.* 24, 3334–3347
121. Ding, G. *et al.* (2019) Case report: HER2 amplification as a resistance mechanism to crizotinib in NSCLC with MET exon 14 skipping. *Cancer Biol. Ther.* 20, 837–842
122. Chang, H. *et al.* (2017) EGF induced RET inhibitor resistance in CCDC6-RET lung cancer cells. *Yonsei Med. J.* 58, 9–18
123. Nelson-Taylor, S.K. *et al.* (2017) Resistance to RET-inhibition in RET-rearranged NSCLC is mediated by reactivation of RAS/MAPK signaling. *Mol. Cancer Ther.* 16, 1623–1633
124. Torigoe, H. *et al.* (2018) Therapeutic strategies for afatinib-resistant lung cancer harboring HER2 alterations. *Cancer Sci.* 109, 1493–1502
125. Lin, J.J. *et al.* (2020) Mechanisms of resistance to selective RET tyrosine kinase inhibitors in RET fusion-positive non-small cell lung cancer. *Ann. Oncol.* Published online September 29, 2020. https://doi.org/10.1016/j.annonc.2020.09.015
126. Cocco, E. *et al.* (2019) Resistance to TRK inhibition mediated by convergent MAPK pathway activation. *Nat. Med.* 25, 1422–1427
127. Wang, V.E. *et al.* (2019) Adaptive resistance to dual BRAF/MEK inhibition in BRAF-driven tumors through autocrine FGFR pathway activation. *Clin. Cancer Res.* 25, 7202–7217
128. Riedel, R. *et al.* (2019) Acquired KRAS mutation and loss of low-level MET amplification after durable response to crizotinib in a patient with lung adenocarcinoma. *Lung Cancer* 133, 20–22
129. Recondo, G. *et al.* (2020) Molecular mechanisms of acquired resistance to MET tyrosine kinase inhibitors in patients with MET exon 14-mutant NSCLC. *Clin. Cancer Res.* 26, 2615–2625
130. Rudin, C.M. *et al.* (2013) Molecular characterization of acquired resistance to the BRAF inhibitor dabrafenib in a patient with BRAF-mutant non-small-cell lung cancer. *J. Thorac. Oncol.* 8, e41–e42
131. Abravanel, D.L. *et al.* (2018) An acquired NRAS Q61K mutation in BRAF V600E-mutant lung adenocarcinoma resistant to dabrafenib plus trametinib. *J. Thorac. Oncol.* 13, e131–e133
132. Niemantsverdriet, M. *et al.* (2018) KRAS mutation as a resistance mechanism to BRAF/MEK inhibition in NSCLC. *J. Thorac. Oncol.* 13, e249–e251
133. Facchinetti, F. *et al.* (2020) Molecular mechanisms of resistance to BRAF and MEK inhibitors in BRAF(V600E) non-small cell lung cancer. *Eur. J. Cancer* 132, 211–223
134. Watanabe, J. *et al.* (2018) Appearance of a BRAF mutation conferring resistance to crizotinib in non-small cell lung cancer harboring oncogenic ROS1 fusion. *J. Thorac. Oncol.* 13, e66–e69
135. Dagogo-Jack, I. *et al.* (2019) Molecular analysis of plasma from patients with ROS1-positive NSCLC. *J. Thorac. Oncol.* 14, 816–824
136. Ambrogio, C. *et al.* (2017) In vivo oncogenic conflict triggered by co-existing KRAS and EGFR activating mutations in lung adenocarcinoma. *Oncogene* 36, 2309–2318
137. Unni, A.M. *et al.* (2015) Evidence that synthetic lethality underlies the mutual exclusivity of oncogenic KRAS and EGFR mutations in lung adenocarcinoma. *eLife* 4, e06907
138. Cisowski, J. *et al.* (2016) Oncogene-induced senescence underlies the mutual exclusive nature of oncogenic KRAS and BRAF. *Oncogene* 35, 1328–1333
139. Hong, A. *et al.* (2018) Exploiting drug addiction mechanisms to select against MAPKi-resistant melanoma. *Cancer Discov.* 8, 74–93
140. Sale, M.J. *et al.* (2019) MEK1/2 inhibitor withdrawal reverses acquired resistance driven by BRAF(V600E) amplification whereas KRAS(G13D) amplification promotes EMT-chemoresistance. *Nat. Commun.* 10, 2030
141. Xu, C.W. *et al.* (2017) Patient harboring a novel PIK3CA point mutation after acquired resistance to crizotinib in an adenocarcinoma with ROS1 rearrangement: a case report and literature review. *Thoracic Cancer* 8, 714–719
142. Chuang, J.C. *et al.* (2017) ERBB2-mutated metastatic non-small cell lung cancer: response and resistance to targeted therapies. *J. Thorac. Oncol.* 12, 833–842
143. Dziadziuszko, R. *et al.* (2016) An activating KIT mutation induces crizotinib resistance in ROS1-positive lung cancer. *J. Thorac. Oncol.* 11, 1273–1281
144. Shen, A. *et al.* (2015) c-Myc alterations confer therapeutic response and acquired resistance to c-Met inhibitors in MET-addicted cancers. *Cancer Res.* 75, 4548–4559
145. Somwar, R. *et al.* (2016) MDM2 amplification (Amp) to mediate cabozantinib resistance in patients (Pts) with advanced RET-rearranged lung cancers. *J. Clin. Oncol.* 34, 9068
146. Lin, L. *et al.* (2015) The Hippo effector YAP promotes resistance to RAF- and MEK-targeted cancer therapies. *Nat. Genet.* 47, 250–256
147. Sato, H. *et al.* (2020) MAPK pathway alterations correlate with poor survival and drive resistance to therapy in patients with lung cancers driven by ROS1 fusions. *Clin. Cancer Res.* 26, 2932–2945
148. Subbiah, V. *et al.* (2018) Phase I study of the BRAF inhibitor vemurafenib in combination with the mammalian target of rapamycin inhibitor everolimus in patients with BRAF-mutated malignancies. *JCO Precis. Oncol.* 2, PO.18.00189
149. Subbiah, V. *et al.* (2018) Multi-kinase RET inhibitor vandetanib combined with mTOR inhibitor everolimus in patients with RET rearranged non-small cell lung cancer. *J. Clin. Oncol.* 36, 9035
150. Subbiah, V. *et al.* (2015) Systemic and CNS activity of the RET inhibitor vandetanib combined with the mTOR inhibitor everolimus in KIF5B-RET re-arranged non-small cell lung cancer with brain metastases. *Lung Cancer* 89, 76–79

151. Sugano, T. *et al.* (2015) Inhibition of ABCB1 overcomes cancer stem cell-like properties and acquired resistance to MET inhibitors in non-small cell lung cancer. *Mol. Cancer Ther.* 14, 2433–2440
152. Nahar, R. *et al.* (2018) Elucidating the genomic architecture of Asian EGFR-mutant lung adenocarcinoma through multi-region exome sequencing. *Nat. Commun.* 9, 216
153. Maynard, A. *et al.* (2020) Therapy-induced evolution of human lung cancer revealed by single-cell RNA sequencing. *Cell* 182, 1232–1251
154. Negrao, M.V. *et al.* (2020) Molecular landscape of BRAF-mutant NSCLC reveals an association between clonality and driver mutations and identifies targetable non-V600 driver mutations. *J. Thorac. Oncol.* 15, 1611–1623
155. Fernandes Neto, J.M. *et al.* (2020) Multiple low dose therapy as an effective strategy to treat EGFR inhibitor-resistant NSCLC tumours. *Nat. Commun.* 11, 3157
156. Mazieres, J. *et al.* (2019) Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann. Oncol.* 30, 1321–1328
157. Guisier, F. *et al.* (2020) Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J. Thorac. Oncol.* 15, 628–636
158. Corcoran, R.B. *et al.* (2018) Combined BRAF, EGFR, and MEK inhibition in patients with BRAF(V600E)-mutant colorectal cancer. *Cancer Discov.* 8, 428–443
159. Ortiz-Cuaran, S. *et al.* (2020) Circulating tumor DNA genomics reveal potential mechanisms of resistance to BRAF-targeted therapies in patients with BRAF-mutant metastatic non-small cell lung cancer. *Clin. Cancer Res.* Published online August 28, 2020. https://doi.org/10.1158/1078-0432.CCR-20-1037
160. Maemondo, M. *et al.* (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N. Engl. J. Med.* 362, 2380–2388
161. Mitsudomi, T. *et al.* (2010) Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* 11, 121–128
162. Rosell, R. *et al.* (2012) Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol.* 13, 239–246
163. Sequist, L.V. *et al.* (2013) Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J. Clin. Oncol.* 31, 3327–3334
164. Zhou, C. *et al.* (2011) Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol.* 12, 735–742
165. Mok, T.S. *et al.* (2017) Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N. Engl. J. Med.* 376, 629–640
166. Soria, J.C. *et al.* (2018) Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N. Engl. J. Med.* 378, 113–125
167. Niederst, M.J. *et al.* (2015) The allelic context of the C797S mutation acquired upon treatment with third-generation EGFR inhibitors impacts sensitivity to subsequent treatment strategies. *Clin. Cancer Res.* 21, 3924–3933
168. Thress, K.S. *et al.* (2015) Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat. Med.* 21, 560–562
169. Piotrowska, Z. *et al.* (2015) Heterogeneity underlies the emergence of EGFRT790 wild-type clones following treatment of T790M-positive cancers with a third-generation EGFR inhibitor. *Cancer Discov.* 5, 713–722
170. Choi, Y.L. *et al.* (2008) Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. *Cancer Res.* 68, 4971–4976
171. Kwak, E.L. *et al.* (2010) Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N. Engl. J. Med.* 363, 1693–1703
172. Shaw, A.T. *et al.* (2014) Ceritinib in ALK-rearranged non-small-cell lung cancer. *N. Engl. J. Med.* 370, 1189–1197
173. Soria, J.C. *et al.* (2017) First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 389, 917–929
174. Shaw, A.T. *et al.* (2016) Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol.* 17, 234–242
175. Camidge, D.R. *et al.* (2018) Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N. Engl. J. Med.* 379, 2027–2039
176. Solomon, B.J. *et al.* (2018) Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol.* 19, 1654–1667
177. Pratilas, C.A. *et al.* (2008) Genetic predictors of MEK dependence in non-small cell lung cancer. *Cancer Res.* 68, 9375–9383
178. Noeparast, A. *et al.* (2017) Non-V600 BRAF mutations recurrently found in lung cancer predict sensitivity to the combination of trametinib and dabrafenib. *Oncotarget* 8, 60094–60108
179. Kim, S.Y. *et al.* (2019) Patient-derived cells to guide targeted therapy for advanced lung adenocarcinoma. *Sci. Rep.* 9, 19909
180. Joshi, M. *et al.* (2015) Trametinib with or without vemurafenib in BRAF mutated non-small cell lung cancer. *PLoS One* 10, e0118210
181. Noeparast, A. *et al.* (2018) Type II RAF inhibitor causes superior ERK pathway suppression compared to type I RAF inhibitor in cells expressing different BRAF mutant types recurrently found in lung cancer. *Oncotarget* 9, 16110–16123
182. Nichols, R.J. *et al.* (2018) RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers. *Nat. Cell Biol.* 20, 1064–1073
183. Bracht, J.W.P. *et al.* (2019) BRAF mutations classes I, II, and III in NSCLC patients included in the SLLIP trial: the need for a new pre-clinical treatment rationale. *Cancers* 11, 1381
184. Cope, N.J. *et al.* (2020) Analyses of the oncogenic BRAF (D594G) variant reveal a kinase-independent function of BRAF in activating MAPK signaling. *J. Biol. Chem.* 295, 2407–2420
185. Yoh, K. *et al.* (2017) Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *Lancet Respir. Med.* 5, 42–50
186. Lee, S.H. *et al.* (2017) Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring RET rearrangement: a phase II clinical trial. *Ann. Oncol.* 28, 292–297
187. Drilon, A. *et al.* (2016) Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol.* 17, 1653–1660
188. Hida, T. *et al.* (2019) A phase 2 study of lenvatinib in patients with RET fusion-positive lung adenocarcinoma. *Lung Cancer* 138, 124–130
189. Drilon, A. *et al.* (2019) A phase I/Ib trial of the VEGFR-sparing multikinase RET inhibitor RXDX-105. *Cancer Discov.* 9, 384–395
190. Peters, S. *et al.* (2018) Activity of afatinib in heavily pretreated patients with ERBB2 mutation-positive advanced NSCLC: findings from a global named patient use program. *J. Thorac. Oncol.* 13, 1897–1905
191. Lai, W.V. *et al.* (2019) Afatinib in patients with metastatic or recurrent HER2-mutant lung cancers: a retrospective international multicentre study. *Eur. J. Cancer* 109, 28–35
192. Dziadziuszko, R. *et al.* (2019) Afatinib in NSCLC with HER2 mutations: results of the prospective, open-label phase II NICHE trial of European Thoracic Oncology Platform (ETOP). *J. Thorac. Oncol.* 14, 1086–1094
193. Kris, M.G. *et al.* (2015) Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. *Ann. Oncol.* 26, 1421–1427
194. Hyman, D.M. *et al.* (2018) HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature* 554, 189–194

195. Wang, Y. *et al.* (2019) HER2 exon 20 insertions in non-small-cell lung cancer are sensitive to the irreversible pan-HER receptor tyrosine kinase inhibitor pyrotinib. *Ann. Oncol.* 30, 447–455
196. Robichaux, J.P. *et al.* (2019) Pan-cancer landscape and analysis of ERBB2 mutations identifies poziotinib as a clinically active inhibitor and enhancer of T-DM1 activity. *Cancer Cell* 36, 444–457
197. Awad, M.M. *et al.* (2013) Acquired resistance to crizotinib from a mutation in CD74-ROS1. *N. Engl. J. Med.* 368, 2395–2401
198. Gainor, J.F. *et al.* (2017) Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non-small-cell lung cancer. *JCO Precis. Oncol.* 2017, PO.17.00063
199. Facchinetti, F. *et al.* (2016) Crizotinib-resistant ROS1 mutations reveal a predictive kinase inhibitor sensitivity model for ROS1- and ALK-rearranged lung cancers. *Clin. Cancer Res.* 22, 5983–5991
200. Dagogo-Jack, I. *et al.* (2018) Emergence of a RET V804M gatekeeper mutation during treatment with vandetanib in RET-rearranged NSCLC. *J. Thorac. Oncol.* 13, e226–e227
201. Nakaoku, T. *et al.* (2018) A secondary RET mutation in the activation loop conferring resistance to vandetanib. *Nat. Commun.* 9, 625
202. Drilon, A. *et al.* (2018) Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N. Engl. J. Med.* 378, 731–739
203. Koga, T. *et al.* (2018) Activity of a novel HER2 inhibitor, poziotinib, for HER2 exon 20 mutations in lung cancer and mechanism of acquired resistance: an in vitro study. *Lung Cancer* 126, 72–79
204. Kosaka, T. *et al.* (2017) Response heterogeneity of EGFR and HER2 exon 20 insertions to covalent EGFR and HER2 inhibitors. *Cancer Res.* 77, 2712–2721
205. Heist, R.S. *et al.* (2016) Acquired resistance to crizotinib in NSCLC with MET exon 14 skipping. *J. Thorac. Oncol.* 11, 1242–1245
206. Ou, S.I. *et al.* (2017) Emergence of preexisting MET Y1230C mutation as a resistance mechanism to crizotinib in NSCLC with MET exon 14 skipping. *J. Thorac. Oncol.* 12, 137–140
207. Schrock, A.B. *et al.* (2017) Mutation of MET Y1230 as an acquired mechanism of crizotinib resistance in NSCLC with MET exon 14 skipping. *J. Thorac. Oncol.* 12, e89–e90