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1 **Targeting Infrequent Driver Alterations in Non-Small Cell Lung Cancer**

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17

18 **Keywords:** NSCLC, infrequent drivers, targeted therapy, drug resistance

19

20 **Abstract**

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

31

32 **Glossary**

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

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

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

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

41 **Objective/overall response rate (ORR):** proportion of patients in a trial whose tumor is
42 significantly reduced by a drug.

43

44 **The challenge of targeted therapy in NSCLC driven by uncommon genetic alterations**

45 The expanding spectrum of oncogenic driver mutations and clinically available signaling
46 pathway inhibitors had a major impact on **non-small cell lung cancer (NSCLC)** (see Glossary)
47 patients management in the last decade [1]. Cancer driver mutations not only initiate the
48 disease but also sustain tumor progression and therefore their inhibition results in a
49 therapeutic benefit. Driver oncogenes are often identified due to their recurrence in
50 patients, a complicated feature when they appear with low prevalence as those covered in

51 this review. Yet the oncogenic nature and the addiction of cancer cells to this set of
52 infrequent drivers have been clearly established as well as their mutually exclusive pattern
53 with other oncogenes. With the exception of BRAF, all belong to the receptor tyrosine kinase
54 (RTK) family and when in the oncogenic form constantly activate essential downstream
55 signaling pathways, including the **MAPK** (see Glossary), PI3K and JNK, resulting in sustained
56 growth, increased survival and enhanced dissemination. Recently, Food and Drug
57 Administration (FDA) has approved specific inhibitors targeting infrequent NSCLC oncogenic
58 drivers (*ROS1*, *MET*, *RET*, *BRAF*, and *NTRK*). Beyond those, promising preliminary data with
59 compounds targeting other emerging driver alterations (e.g. *HER2*) have been reported [2].
60 Used as first or latter lines of treatment (after standard chemotherapy and/or
61 immunotherapy), these targeted therapies have greatly increased patients' outcome [3-9].
62 Unfortunately, as anticipated by the lessons learned from the clinical management of *EGFR*-
63 mutated and *ALK*-rearranged LUAD (**Box 1**), therapeutic resistance eventually appears in
64 most patients and, therefore, advanced NSCLC remains largely incurable (for review see
65 [10]). In the present review, we describe the biological relevance and the therapeutic
66 options of a series of infrequent drivers for which clinical treatments have been approved or
67 are under evaluation. Likewise, the clinical management of on-target resistance is discussed
68 per driver while that due to bypass signaling is collectively addressed given its pan-driver
69 conservation.

70 ***ROS1***

71 ***Biological and clinical features***

72 *ROS1* is a conserved orphan RTK initially identified in glioblastoma and was the first
73 chromosomal rearrangement described in NSCLC [11]. Since then, several *ROS1* breakpoints
74 have been described involving the entire *ROS1* kinase domain and accounting for 1-2% of
75 NSCLC. Twenty fusion partners (e.g. *SLC34A2*, *EZR* and *SDC4*) have been reported, among
76 which *CD74-ROS1* is the most common [12-14]. Whether distinct partners are functionally
77 equivalent is unknown, although *in vitro* data indicates that they impose changes in
78 subcellular localization affecting signaling and oncogenic properties [15]. Unlike *ALK*
79 rearrangements, most of the known *ROS1* fusion partners lack constitutive dimerization
80 domains and the mechanism of *ROS1* oncogenic activation remains unknown. Along with
81 *RET* and *NTRK*, *ROS1* rearrangements are associated with younger age at diagnosis, none or

82 low tobacco exposure and generally have adenocarcinoma histology [16, 17]. Diagnosis of
83 ROS1 fusions by immunohistochemistry (IHC) is the most cost-effective method requiring
84 confirmation by break-apart probe fluorescent *in situ* hybridization (FISH) or hybrid RNA-
85 based next-generation sequencing (NGS) if the RNA quality is optimal [18, 19].

86 **Frontline targeted therapy**

87 ROS1-positive lung cancer seems particularly sensitive to pemetrexed-based chemotherapy
88 [20]. The ALK inhibitor crizotinib was supposed to efficiently target ROS1-rearranged tumors
89 given that ROS1 and ALK belong to the insulin receptor superfamily [21] sharing >80% of
90 amino acid sequence within their ATP-binding sites. Furthermore, crizotinib binds with high
91 affinity to both kinases and inhibiting cell line proliferation. Indeed, this hypothesis was
92 corroborated in the clinic with crizotinib showing marked therapeutic effect in patients with
93 ROS1-rearranged NSCLC [22]. Accordingly, crizotinib, first approved for the treatment of ALK-
94 rearranged NSCLC, received FDA and European Medicines Agency (EMA) expanded approval
95 in 2016 for ROS1-rearranged NSCLC [22-26] (**Figure 1 and Table 1**). Similarly, in 2020,
96 entrectinib has obtained FDA and EMA approval in this tumor type [8, 27]. In addition, other
97 kinase inhibitors including ceritinib and lorlatinib have been evaluated in ROS1-positive
98 crizotinib naïve NSCLC [28, 29] (**Figure 1 and Table 1**).

99 **Addressing on-target mechanisms of resistance**

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

108 Fortunately, also guided by the successful clinical management of resistant disease in EGFR-
109 and ALK-mutant patients (**Box 1**), new generation inhibitors have been identified or
110 purposely designed to combat drug resistance. **Figure 2B** summarizes pre-clinical and clinical
111 data regarding the sensitivities of the most common secondary mutations to a panel of
112 inhibitors for each driver. In the case of ROS1, resistance profiling studies using both *in vitro*

113 and *in vivo* models demonstrated that cabozantinib (and its structural analog foretinib) as
114 well as DS-6051b (a novel ATP-competitive ROS1/NTRK inhibitor) markedly inhibited the
115 growth of *ROS1* G2032R mutants [30-35]. Indeed, several case reports of *ROS1*-rearranged
116 LUAD patients resistant to crizotinib and ceritinib reported responses to cabozantinib [36,
117 37]. With similar efficacy, DS-6051b had better toxicity profile [38] and two ongoing clinical
118 trials are evaluating its efficacy in *ROS1*-rearranged NSCLCⁱⁱ. In addition, repotrectinib (TPX-
119 0005), a selective and highly potent TKI against ROS1, NTRK, and ALK, demonstrated potent
120 anti-proliferative activity against the G2032R and D2033N *ROS1* mutations in cellular
121 inhibitory assays and xenografts [39]. This has been tentatively confirmed in a clinical setting
122 (TRIDENT-1, NCT03093116) reporting that repotrectinib achieved tumor regression in 45% of
123 patients with *ROS1*-positive NSCLC resistant to prior TKI(s) [40, 41]. Interestingly, not all on-
124 target mutations are equally sensitive to new generation inhibitors and patient stratification
125 will be required. Indeed, each TKI is structurally distinct with varying degrees of activity
126 against the different resistance mutations, giving them unique activity profiles. This is
127 illustrated by lorlatinib that demonstrated promising activity in 40 patients with *ROS1*-
128 positive NSCLC who progressed to crizotinib with an **overall response rate (ORR**, see
129 Glossary) of 35% and a **median progression-free survival (mPFS**, see Glossary) of 8.5
130 months. While patients harboring K1991Q and S1986F *ROS1* mutations achieved durable
131 responses to lorlatinib, none of the patients with the more frequent G2032R mutation did
132 benefit [29].

133

134 ***NTRK***

135 ***Biological and clinical features***

136 The Neurotrophic Tropomyosin Receptor Kinase (NTRK) genes (*NTRK1*, 2 and 3) encode
137 TRKA, TRKB and TRKC, respectively. They are activated by a family of four ligands (NGF,
138 BDNF, NT-3 and NT-4) known as neurotrophins that display different affinities for each RTK
139 and play essential roles in the development and function of the nervous system. Activating
140 mutations in *NTRK* have been identified in NSCLC, yet their oncogenic role remains
141 controversial [42]. Similarly, activating splice variants and overexpression have been
142 reported in pan-cancer studies but, undoubtedly, the most frequent aberrations involve
143 intra- and inter-chromosomal gene-fusions implicating *NTRK* that occur at a frequency below
144 0.4% in NSCLC. The biology of *NTRK* oncogenes has been comprehensively reviewed

145 elsewhere [43, 44]. Of note, a *NTRK* fusion was the first non-*RAS* oncogene identified almost
146 40 years ago (indicated as OncD in [45]; for review see [46]). Of the three *NTRK*, pan-cancer-
147 related fusions more commonly affect *NTRK1* and *NTRK3*, and 48 different partners have
148 been reported [47]. In lung, the fusions involve *NTRK1* and *NTRK3* with five and two distinct
149 partners respectively, being *ETV6-NTRK3* the most prevalent [47, 48]. The NGS-based
150 FoundationOneCDx test has just received FDA-approval for the identification of *NTRK*
151 fusions.

152 ***Frontline targeted therapy***

153 Early phase basket trials of solid tumors harboring *NTRK* gene rearrangements were
154 performed with first-generation TKIs such as larotrectinib, which is selective for TRKA/B/C,
155 and entrectinib, which targets TRKA/B/C as well as ALK and ROS1. Both compounds have
156 demonstrated marked tumor-agnostic efficacy in pan cancer trials [6, 7] (**Figure 1 and Table**
157 **1**). Based on these results larotrectinib received accelerated FDA approval for the treatment
158 of TRK fusion-positive cancers in 2018 followed by entrectinib one year later. Both drugs also
159 obtained histology-independent approval in solid tumors harboring *NTRK* rearrangements by
160 EMA. Ongoing trials may help to better estimate efficacy and duration of response in NSCLC.

161 ***Addressing on-target mechanisms of resistance***

162 Next-generation TRK inhibitors, such as selitrectinib (LOXO-195) and repotrectinib (TPX-
163 0005), have been designed to combat on-target acquired resistance mutations and their
164 activity is being evaluated in phase I/II trials or compassionate use protocols for *NTRK*-
165 altered cancers. Indeed, selitrectinib was developed as a second-generation TRK inhibitor
166 using modeling studies even before acquired resistance appeared in the clinic. An initial
167 evaluation performed on a first-in-human basis proved its activity against solvent-front and
168 xDFG mutants inducing rapid tumor responses [49]. This has been extended in an ongoing
169 phase I/II trial upon enrolling patients with prior treatment with *NTRK* inhibitorsⁱⁱⁱ.
170 Preliminary results indicate an ORR of 45% in patients with mutations affecting the kinase
171 domain [50]. Similarly, repotrectinib evaluation in a phase I/II first-in-human dose-escalation
172 study (NCT03093116) demonstrated efficacy in patients harboring *NTRK3* solvent front
173 resistant mutations [39]. Whether these next-generation TRK inhibitors will exert a similar
174 benefit in resistant LUAD patients with kinase-domain acquired mutations is still unknown.

175

176 ***RET***

177 **Biological and clinical features**

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

193 **Frontline targeted therapy**

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

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

207 **Addressing on-target mechanisms of resistance**

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

216

217 ***MET***

218 ***Biological and clinical features***

219 In NSCLC, c-Mesenchymal-Epithelial Transition factor (c-MET) gene rearrangements, fusions
220 and somatic mutations have been identified but are rare [66]. MET overexpression,
221 however, is frequent in unselected NSCLC patients although its clinical value is unclear as this
222 criterion is largely dependent on the antibody assay and the determination of a positive
223 threshold. *MET* amplification is also a common mechanism of resistance to EGFR-TKIs in
224 NSCLC. Anyhow, increased expression is considered a causative driver only if co-occurring
225 with clinically relevant *MET* genomic alterations like *MET* gene amplification or mutations
226 resulting in exon 14 skipping (*METΔ14*). This alteration results in a MET protein lacking the
227 juxtamembrane domain with extended half-life after ligand stimulation and is considered an
228 oncogenic driver. *METΔ14* is predominantly associated to sarcomatoid carcinoma histology
229 [67, 68] and detected in 2-4% of NSCLC patients while *MET* amplification affects
230 approximately 2% of LUAD.

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

237 ***Frontline targeted therapy***

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

250 ***Addressing on-target mechanisms of resistance***

251 In the case of MET-resistant disease, mutations like those affecting the Y1230 and D1228
252 residues may predict response to type II MET inhibitors such as cabozantinib and glesatinib
253 [77]. Others, including substitutions implicating L1195 or F1200, may not be sensitive to
254 treatment with these compounds as they preclude binding to the DFG-out pocket [75]. In a
255 similar study, 7 out of 20 (35%) *METΔ14* patients who progressed to MET TKI had on-target
256 kinase domain mutations (H1094, G1163, L1195, D1228, Y1230) or elevated *MET*
257 amplification. Cabozantinib has also been shown to be active against the D1228V mutation
258 with concomitant MET amplification [78].

259

260 ***HER2/ERBB2***

261 ***Biological and clinical features***

262 Human epidermal growth factor receptor 2 (HER2), also called ERBB2, is one of the four
263 members of the EGFR family. It remains an orphan receptor activated by heterodimerization
264 with other ERBB family members (for review see[79]). In NSCLC, HER2 dysregulations can be
265 caused by gene amplification, protein overexpression and mutations. Despite the efficacy of
266 anti-HER2 agents in breast and gastric cancer, clinical interest on HER2-positive NSCLC was
267 dampened when the first clinical trials evaluating trastuzumab, an anti-HER2 humanized
268 antibody reported negative results [80, 81]. In parallel, HER2 kinase domain mutations were

269 identified in NSCLC patients not associated with HER2 amplification/overexpression [82, 83].
270 These results were further confirmed [84] indicating that *HER2* amplification and mutations
271 represent two distinct oncogenic drivers and potential therapeutic targets. These findings,
272 coupled with the encouraging results of TKIs in EGFR mutants, launched the clinical
273 evaluation of anti-HER2 agents specifically in NSCLC patients bearing *HER2* mutations (90 %
274 of them are located in exon 20). *HER2* exon 20 alterations comprise point mutations (e.g.
275 L755S, V777L and G776C) or, more frequently, insertions [85]. The most prevalent (over
276 80%) is a 12 base pair in-frame insertion causing duplication of amino acids YVMA at codon
277 775 (A775_G776insYVMA) [86]. Mutations in exon 20 are analogous to *EGFR* exon 20
278 mutations and lead to HER2 constitutive activation [87-89]. Overall, *HER2* mutations account
279 for 2-4% of the NSCLC cases and tend to be women and light/never smokers with LUAD
280 histology [85].

281 ***Frontline targeted therapy***

282 HER2 targeted therapy is not yet standard of care in NSCLC and, currently, chemotherapies
283 remain the main strategy. Patients with *HER2*-mutant LUAD, especially YVMA insertion,
284 demonstrated a markedly inferior response to first line pemetrexed-based chemotherapy
285 compared to those harboring *ALK/ROS1* rearrangements, which strengthen the need for
286 effective anti-HER2 agents [90]. Retrospectives studies displayed encouraging disease
287 control rates in NSCLC patients bearing *HER2* exon 20 insertions treated with HER2-targeted
288 drugs [91, 92]. Several clinical studies have been carried out or are ongoing using both anti-
289 HER2 antibodies and small molecules (for review see [2]) (**Figure 1 and Table 1**). Among
290 these compounds, poziotinib, a pan-HER TKI, has structural features that can circumvent the
291 steric changes induced by exon 20 insertions and increase its affinity compared to larger TKIs
292 [93]. Next-generation TKIs with increased selectivity towards the EGFR and HER2 mutants
293 (such as TAK-788) are being developed to limit the toxicity associated to wild-type EGFR
294 inhibition [94, 95]. In addition, trastuzumab and its antibody-drug conjugate, trastuzumab-
295 emtansine (T-DM1), showed mixed results in the clinic due in part to the molecular
296 heterogeneity of *HER2*-altered NSCLC (for review see [2]). Trastuzumab-deruxtecan (DS-
297 8201a) showed promising efficacy among NSCLC patients with HER2 exon 20 mutations [96]
298 (**Figure 1 and Table 1**). In this context, patients with *HER2*-mutated NSCLC often develop
299 brain metastases with disease progression and trastuzumab would be inefficient due to its

300 inability to cross the blood-brain barrier. Therefore, monitoring and treatment of CNS
301 metastases may require specific approaches.

302

303 ***BRAF***

304 ***Biological and clinical features***

305 BRAF, together with ARAF and CRAF, constitute the RAF family of serine/threonine kinases, a
306 core component of the MAPK cascade. Since the first evidence in 2002 [97], almost 200
307 distinct *BRAF* mutations have been reported in around 8% of cancers. In NSCLC, they
308 represent 1.5-3.5% of the cases and affect the kinase domain, either in the glycine-rich loop
309 in exon 11 or in the activation segment in exon 15, resulting in increased ERK signaling (for
310 review see [98]). Clinical characteristics associated with *BRAF* mutations in lung cancer vary
311 without obvious segregation in specific parameters, except the significant association with
312 LUAD histology. Most patients with *BRAF* mutations are smokers, although patients with
313 V600 mutations are more likely to be light/never-smokers compared with patients with non-
314 V600 mutations [99-102]. *BRAF* mutations as well as *HER2* and *MET* alterations are generally
315 well covered by NGS gene panels. *BRAF* mutants are classified in three categories [103].
316 Class 1 (V600) and class 2 (G464, G469, L597 and K601) mutants are mutually exclusive, RAS-
317 independent and signal constitutively as active monomers or active dimers, respectively.
318 Class 3 (e.g. G466 and D594) have impaired/null kinase activity and activation of
319 downstream signaling is RAS- and CRAF-dependent and sensitive to ERK-mediated feedback.
320 In this case, RAS is generally activated by RTK signaling [103]. Notably, expression of an
321 endogenous class 3 *BRAF* mutant triggers LUAD in mice, indicating that kinase-inactive *BRAF*
322 isoforms are oncogenic drivers [104].

323 ***Frontline targeted therapy***

324 Experience with *BRAF*-mutant melanoma has heavily influenced the management of NSCLC.
325 Targeted therapy has evolved from *BRAF* monotherapy to combined *BRAF*/MEK inhibition
326 showing superior efficacy and favorable safety profile in *BRAF* V600E-mutant NSCLC [3, 105-
327 109] (**Figure 1 and Table 1**). The combination of dabrafenib plus trametinib has received
328 both FDA and EMA approval for the treatment of metastatic NSCLC harboring the *BRAF*
329 V600E mutation regardless of previous therapies. Another pair of *BRAF* and MEK inhibitors,

330 encorafenib and binimetinib, is under investigation and has shown encouraging CNS activity
331 in a patient with *BRAF* V600E-mutated LUAD [110].

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

341

342 **Signaling bypass activation and other resistance mechanisms**

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

348 Alterations affecting the RAS-MAPK pathway or upstream receptors are the most frequent.
349 Notably, *EGFR* [116-119] and *HER2* [120, 121] activating mutations or amplification have
350 been reported in *ROS1*- and *MET*-altered patients after progressing to crizotinib.
351 Interestingly, EGFR activation may not only contribute to the resistant phenotype by
352 supporting bypass signaling but also by protein-protein interactions that reactivate drug-
353 inhibited ROS1 [118]. EGFR signaling has also been identified as a critical adaptive survival
354 mechanism to RET [118, 122, 123] and NTRK [118] blockade in NSCLC preclinical models.
355 Beside EGFR and HER2, other RTKs have been associated to drug resistance in lung cancer.
356 Particularly, *MET* amplification has been identified in afatinib-resistance cell lines harboring
357 *HER2* alterations [124], in pralsetinib resistant *RET*-rearranged tumors [125] and in
358 entrectinib resistant *NTRK*-rearranged biopsies [126]. Furthermore, FGFR autocrine pathway
359 activation through FGF1 secretion was shown to be associated with increased sensitivity to
360 FGFR inhibitor in resistant *BRAF* V600E LUAD [127].

361 In addition, *KRAS* and *NRAS* mutations on codons 12 and 61 have been identified both in
362 preclinical models of resistance to MKIs in *RET*-altered cells [123] and in *MET*, *NTRK* and
363 *BRAF*-altered patients after progressing to frontline targeted therapies [126, 128-132].
364 Similarly, *MEK1* activating mutations were described in case reports of *BRAF* V600E NSCLC
365 after progression to dabrafenib and trametinib [133] as well as in *NTRK*-rearranged patients
366 after TKIs treatment [126]. Furthermore, case-reports highlighted *BRAF* V600E mutation or
367 amplification in post-treatment biopsies of *ROS1*, *NTRK* and *METΔ14*-altered NSCLC patients
368 [126, 129, 134, 135]. Intriguingly, RTK-RAS-MAPK activating mutations tend to be mutually
369 exclusive in primary tumors, a finding justified due to functional redundancy and lack of
370 selective advantage. However, several studies have demonstrated that synthetic toxicity due
371 to excessive signaling could equally underlie oncogene incompatibility [136-138]. In this
372 context, intermittent therapy resulting in excessive signaling proves to be advantageous in
373 drug resistant melanoma harboring co-existing oncogenes [139]. Yet, in NSCLC, this
374 approach could only be applied to certain oncogenic combinations [140]. Additional clinical
375 support from both prospective and retrospective studies is required to validate this
376 therapeutic strategy.

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

380 Finally, other alterations potentially contributing to drug resistance have been reported such
381 as *KIT* [143] and *c-myc* [144] in preclinical models of *ROS1* and *MET*-altered NSCLC,
382 respectively. Additionally, acquired amplification of *MDM2*, which encodes the E3 ubiquitin-
383 protein ligase MDM2, has been identified in *RET*-rearranged cabozantinib-resistant patients
384 [145]. Likewise, the Hippo pathway with its effector YAP has been recognized as a
385 mechanism of resistance to *BRAF* and *MEK* targeted therapy in both preclinical and clinical
386 samples bearing *BRAF* V600 mutations [146]. Yet, given their low prevalence, their clinical
387 significance requires further confirmation.

388 Importantly, the activation of bypass signaling pathways often results in the acquisition of
389 vulnerabilities that could be therapeutically exploited. In a recent study, novel activating
390 MAPK alterations (deletions of several nucleotides in *MAP3K1* and *MAP2K1* as well as *NF1*
391 loss-of-function mutations) were acquired in patients harboring *ROS1*-rearranged tumors
392 being treated with *ROS1* inhibitors. Cells bearing these alterations are resistant to *ROS1*-TKIs

393 but sensitive to a combination of ROS1 and MEK inhibitors *in vitro* and *in vivo* [147].
394 Importantly, a *MET* Δ 14-altered patient who acquired a *KRAS* gain after crizotinib treatment
395 achieved clinical response upon addition of trametinib [75].

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

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

414

415 **Concluding remarks and future perspectives**

416 Alongside *EGFR*- and *ALK*-driven NSCLC, patients bearing infrequent drivers display limited
417 benefit from targeted therapies due to the onset of resistance. Despite the growing body of
418 evidence about their clinical management many key knowledge gaps remain (see
419 Outstanding Questions). First, lung cancers genomes display substantial heterogeneity and
420 complex branching evolution that can be influenced by treatment-imposed selective
421 pressure [152-154]. The understanding of the subclonal origin of resistance in the context of
422 rare drivers will require deep sequencing studies of either multiregional biopsies or single
423 tumor cells that are currently missing. This information could help develop tailored
424 treatments to tackle resistance by anticipating the emergence of on-target or bypass

425 mechanisms. Interestingly, recent preclinical evidence has demonstrated that enhanced
426 therapeutic benefit and delayed onset of resistance upon multiple low dosing of different
427 nodes within the same pathway [155]. Beside targeted therapies, these patients may benefit
428 from combining chemotherapy and immunotherapy, but further information is needed.
429 Recent retrospective studies highlighted that immune checkpoint inhibitors may provide an
430 effective option for NSCLC patients with certain infrequent alterations, especially in those
431 associated with smoking such as *BRAF* mutations [115, 156, 157]. Future clinical trials should
432 determine the ideal regimen of combination therapies including dosing and nature of
433 targeted agents, anti-angiogenic drugs and/or chemo plus immunotherapy. When defining
434 the ideal clinical regimen caution should be applied if transposing information from other
435 cancer types harboring the same infrequent driver. For example, the extended survival upon
436 combinatorial treatments in *BRAF* V600E mutant melanoma has also been achieved in LUAD
437 patients. However, the therapeutic response of colorectal carcinoma patients bearing the
438 same alteration was disappointing due to EGFR-mediated intrinsic resistance [158]. In any
439 case, an ideal clinical regimen would require radiological and molecular monitoring of
440 disease progression. Resistance mechanisms could be captured by non-invasive methods like
441 liquid biopsy [119, 125, 159] (see Outstanding Questions). A recurrent and important
442 problem is the occurrence of brain metastases, thereby requiring the use of compounds with
443 good intracranial activity. In conclusion, a better understanding of the alterations underlying
444 the development of resistance and the design of tailored treatments will allow delaying
445 tumor progression and achieving improved clinical outcomes in NSCLC patients bearing
446 infrequent alterations.

447

448 **Box 1. Targeting *EGFR* and *ALK* alterations in NSCLC**

449 *EGFR* mutations occur in 15% of NSCLC, being in-frame deletion in exon 19 (19Del) or L858R
450 mutation the most frequent. Both first-generation (erlotinib and gefitinib) and second-
451 generation (afatinib) inhibitors demonstrated more durable responses than chemotherapy
452 [160-164], receiving FDA-approval as first-line treatments in 2013 and 2014. In almost half of
453 patients treated with these compounds, resistance is mediated by the T790M gatekeeper
454 mutation (equivalent to those described in *ROS1*, *RET* and *NTRK*, **Figure 2A**). Third-
455 generation *EGFR* inhibitors such as osimertinib demonstrated impressive response in

456 patients with EGFR T790M-positive NSCLC after progression on early-generation TKIs,
457 receiving FDA-approval in 2017 [165]. Due to its ability to spare wild-type EGFR, inhibit EGFR
458 19Del/L858R/T790M and CNS penetration, osimertinib is approved as first-line treatment
459 since 2018 [166]. Unfortunately, new resistance mechanisms have emerged like the tertiary
460 C797S mutation affecting the covalent binding of the drug [167, 168] or the development of
461 T790 wild-type clones [169].

462 *ALK* rearrangements are observed in 5% of NSCLC, being *EML4-ALK* the most prevalent. At
463 least 15 *EML4-ALK* variants have been identified so far, with some expressed as multiple
464 isoforms [170]. All contain the *ALK* entire intracellular kinase domain (exons 20-29) but differ
465 in the breakpoint with the *EML4* gene. First-generation crizotinib received FDA approval in
466 2011, becoming the first approved *ALK* inhibitor for NSCLC [171]. Almost one third of
467 crizotinib-treated patients acquire resistance by kinase domain mutations, being L1196M
468 gatekeeper and G1269A mutations the most frequent. In 2014, second-generation *ALK*
469 inhibitor ceritinib was approved after confirmation of its efficacy in both crizotinib-naïve and
470 crizotinib-resistant patients with L1196M and G1269A/S mutations [172, 173]. In
471 approximately half of cases, resistance is caused by emergence of additional *ALK* mutations,
472 the most common being the solvent-front substitution G1202R. Therefore, two other
473 second-generation *ALK* inhibitors — alectinib and brigatinib — were granted accelerated
474 FDA approval for *ALK*-positive patients who had failed on crizotinib treatment,
475 demonstrating superior inhibitory profile against all known 17 secondary *ALK* mutations
476 [174, 175]. Both alectinib and brigatinib were later approved also as first line therapy in
477 treatment-naïve patients, although alectinib has become the preferred agent. Recently, the
478 third-generation *ALK/ROS1* inhibitor lorlatinib, specifically designed to target resistance
479 mutations and to penetrate the blood-brain barrier, received accelerated FDA approval for
480 the treatment of patients with *ALK*-rearranged advanced NSCLC after progression on
481 crizotinib and at least one other *ALK* inhibitor [176]. The phase III trial CROWN comparing
482 lorlatinib with crizotinib as first-line therapy is currently ongoing^{vi}.

483 **Box 2. BRAF non-V600 mutations in NSCLC**

484 While more than 90% of *BRAF*-altered melanoma bear a V600 mutation, *BRAF*-positive
485 NSCLC are equally divided in V600 and non-V600 mutations and, therefore, represent one of
486 the cancers with the higher proportion of non-V600 mutations. The tumor-initiating

487 potential of many of the rare BRAF mutations has yet to be demonstrated *in vivo*. In
488 addition, data demonstrating clinical activity of MAPK-directed therapies in non-V600 BRAF-
489 mutant lung cancers are lacking. Therefore, there is currently no consensus on how to
490 optimally manage patients with class 2 and 3 BRAF mutations. In the EURAF retrospective
491 series that included 6 NSCLC patients with BRAF mutations other than V600E, only one
492 patient (G596V) achieved a partial response to Vemurafenib [105]. These findings are
493 consistent with the statement that class 2 and 3 mutants signal as RAF dimers rather than
494 monomers [103], making them resistant to the BRAF monomer inhibitors. However, *in vitro*,
495 both class 2 and 3 mutated cell lines are sensitive to MEK inhibition [177]. Additionally, the
496 combination of BRAF and MEK inhibitors enhanced MAPK inhibition and cell proliferation
497 reduction in both class 2 and 3 BRAF-mutant NSCLC preclinical models compared to MEK
498 inhibitor alone [178-181]. Interestingly, oncogenic signaling triggered by class 3 BRAF
499 mutants depends on a variety of RTKs that should be identified per patient [103].
500 Alternatively, the inhibition of SHP2, a scaffold protein downstream of RTKs promoting RAS
501 activation, or the use of pan-RTK inhibitors (such as afatinib) could be considered [182].
502 Incidentally, concomitant SHP2 and BRAF/MEK inhibition showed synergistic effects in a
503 class 3 BRAF-mutant cell line [183]. Additionally, allosteric inhibitors targeting the
504 heterodimer interface between BRAF class 3 mutants with CRAF may represent an
505 alternative approach [184]. Further studies are required to (1) precise the molecular
506 mechanisms of each BRAF mutants (i.e. homo versus heterodimer), (2) define the
507 importance of the additional molecular determinants that may play a role in modulating
508 therapeutic response (i.e. expression level of CRAF and concomitant genetic alterations) and
509 (3) identify the most promising strategies with potential drug combination to achieve
510 successful clinical response in patients with non-V600 BRAF mutations.

511 **Competing interests**

512 E. N. participated in advisory boards from Bristol Myers Squibb, Merck Sharpe & Dohme,
513 Lilly, Roche, Pfizer, Takeda, Boehringer Ingelheim, Amgen and AstraZeneca. E. N. has
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524

525 **Resources**

526 ⁱ <https://clinicaltrials.gov/ct2/show/NCT02279433>

527 ⁱⁱ <https://clinicaltrials.gov/ct2/show/NCT02675491>

528 ⁱⁱⁱ <https://clinicaltrials.gov/ct2/show/NCT03215511>

529 ^{iv} <https://clinicaltrials.gov/ct2/show/NCT01813734>

530 ^v <https://clinicaltrials.gov/ct2/show/NCT04161391>

531 ^{vi} <https://clinicaltrials.gov/ct2/show/NCT03052608>

532

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1062

1063 **Table 1: Comparative clinical efficacy of targeted therapies in *ROS1*, *MET*, *RET*, *NTRK*, *HER2***
 1064 **and *BRAF*-altered lung cancers.**

Driver	Drug	Clinical trial identifier ³ /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/AccelerRET (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-	10	57 (pan cancer)	11.2 (pan cancer)		2019	[7]

		000148-88/ALKA-372-001 (I)						
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]
		NCT02535507 (II)	15	53.3	6.4			[195]
	Pyrotinib	NCT02834936 (II)	ongoing					
		Moboracetinib (TAK-788)	NCT02716116 (I/II)	21				
Pozotinib	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 (BRAF _i /MEK _i naïve)	25		1/12 (8%)		[114]
LXH254 and LLT462	NCT02974725 (I)	ongoing						

1065

1066 ^awww.clinicaltrials.gov or www.umin.ac.jp

1067

1068 **Figure legends**

1069

1070 **Figure 1: Comparative clinical efficacy of targeted therapies in *ROS1*, *MET*, *RET*, *HER2* and**
1071 ***BRAF*-altered lung cancers.** Each circle on the plot represents the efficacy of the indicated
1072 inhibitor in patients for each specific driver (indicated with the different colors). Inspired by
1073 Figure 5 in Drilon A. and colleagues [57]. X and Y axis represent the objective response rate
1074 and the median progression-free survival duration, respectively, as reported from phase I
1075 and II clinical trials (see main text and Table 1 for details and references).

1076

1077 **Figure 2: Schematic representation of the on-target resistance mutations and activity**
1078 **profile of kinase inhibitors targeting these specific resistance mutations among the**
1079 **different oncogenic drivers in NSCLC. A.** The different types of mutations affecting the
1080 solvent-front, the gatekeeper residue, the activation loop or the DFG motifs are represented.
1081 Most resistance mutations seen in uncommon driver oncogenes have analogous resistance
1082 mutations identified in EGFR and ALK. **B.** Blue boxes indicate kinase inhibitor for which anti-
1083 tumoral activity against the indicated mutants has been reported in preclinical models
1084 (preclinical validation). Orange boxes designate kinase inhibitor that failed to show any
1085 inhibitory activity *in vitro* and/or *in vivo* (preclinical invalidation). Green boxes highlight
1086 reports of clinical activity (tumor shrinkage) while red dots indicate agents that failed to
1087 achieve an objective response in patients. Asterisks (*) indicate FDA approved drugs.
1088 Abbreviations: GK, gatekeeper; SF, solvent-front; AL, activation loop. References [36, 60, 75,
1089 117, 120, 129, 197-207].

1090

1091 **Figure 3: Signaling pathways driving resistance to targeted therapies in *ROS1* (A), *RET* (B)**
1092 **and *NTRK* (C) fusions-positive NSCLC and *MET* (D), *HER2* (E) and *BRAF* (F)-mutated NSCLC.**
1093 Oncogenic drivers and their downstream signaling pathways are represented in blue and
1094 green, respectively. On-target resistance mutations as well as histological transformation are
1095 indicated (boxes). Protein alterations that have been implicated in the resistance to targeted
1096 agents are shown in orange. Potential therapeutic strategies are also highlighted in red.

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?

Highlights

- Lung cancer is responsible of 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 is not always capturing 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.

Figure 1

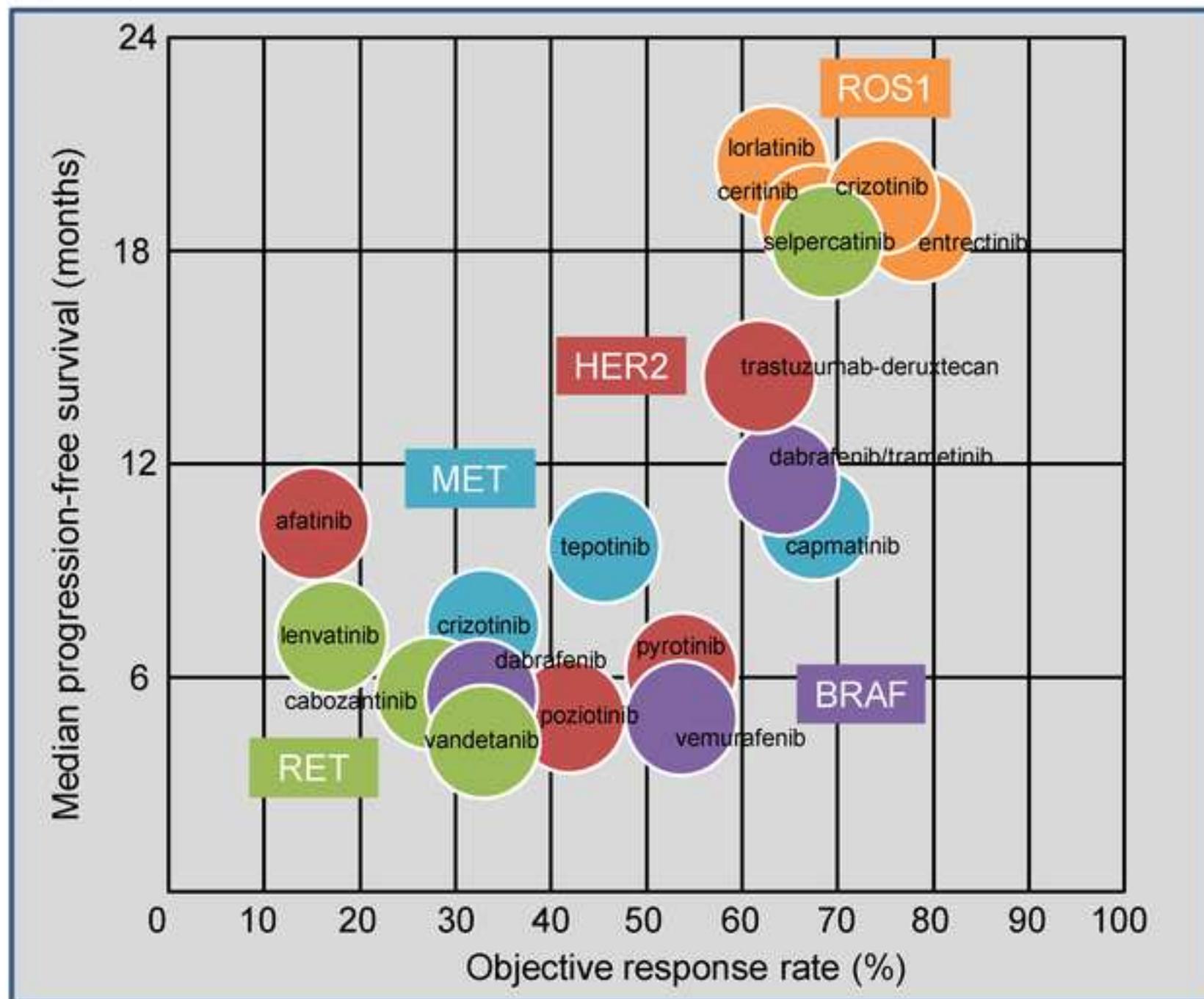


Figure 2

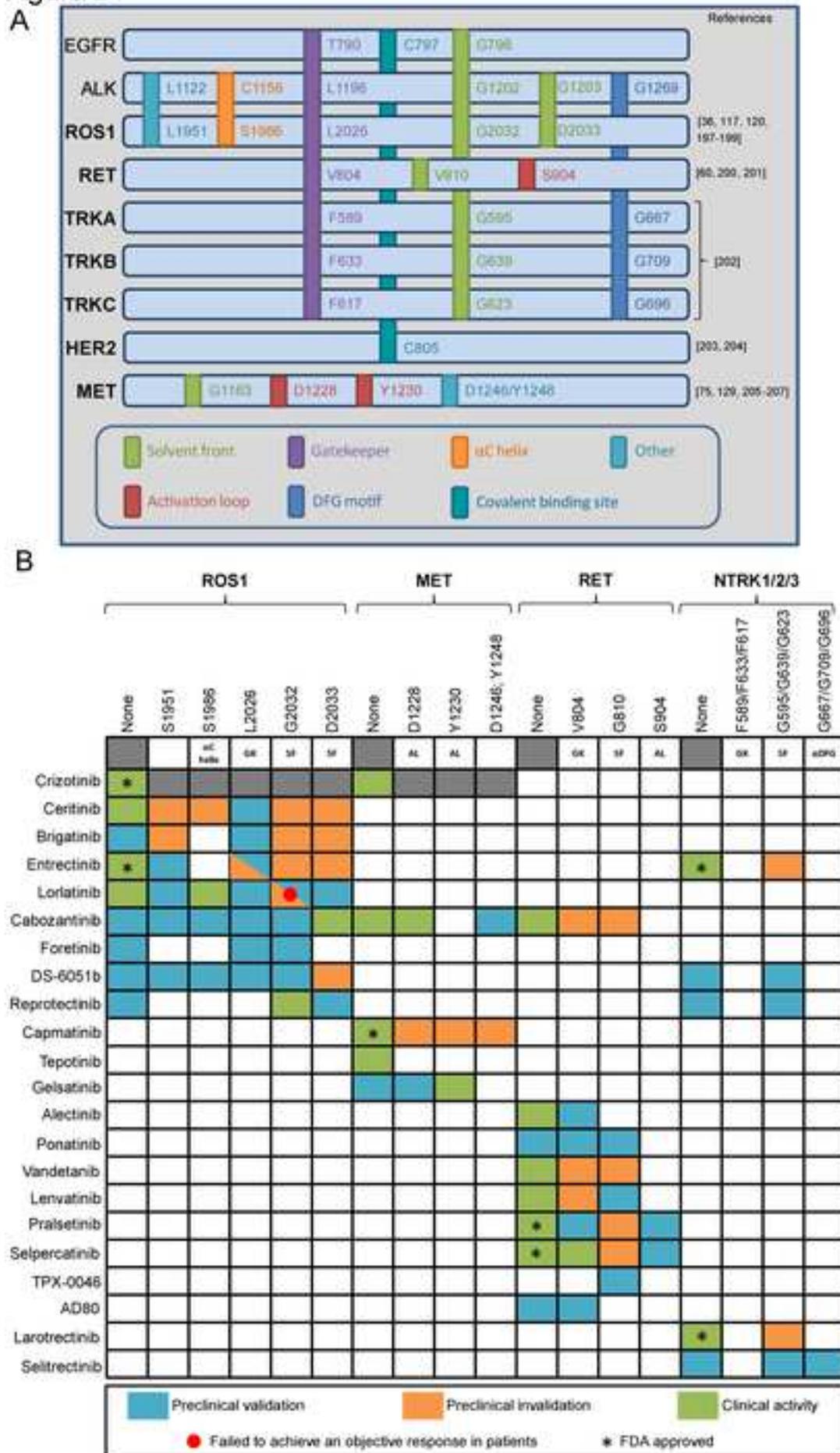


Figure 3

